NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal

Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276]

Committee papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

MULTIPLE TECHNOLOGY APPRAISAL

Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276]

Contents:

- British Society of Interventional Radiology

9. Expert personal statements from:

- Dr Teik See – Consultant Interventional Radiologist, nominated by BTG International
- Mark Thornberry – patient expert, nominated by the British Liver Trust

Any information supplied to NICE which has been marked as confidential has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma (ID1276)

Multiple technology appraisal

Pre-meeting briefing

Information on slide set

- This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:
  - the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
  - the Assessment Group (AG) report
- It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal.
- Please note that this document is a summary of the information available before comments on the assessment report have been received.
- The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Key issues for consideration – clinical

Positioning of SIRT in treatment pathway	What is the most appropriate position of SIRT in the treatment pathway?
	Are there clinically identifiable subgroups that might benefit from SIRT more than others?
Clinical effectiveness of SIRT	Are the results for SIR-Spheres generalisable to the UK population?
	Is it appropriate to assume that SIRTs have equal effectiveness?
	What proportion of people fail work-up and do not have SIRT?
Clinical effectiveness of systemic therapies	Is it appropriate to assume that sorafenib and lenvatinib have equal effectiveness?
NMA analysis for comparative clinical effectiveness	Does the clinical evidence support NMA analyses?

Key issues for consideration – cost effectiveness

Cost-effectiveness model	What is the most appropriate model to extrapolate OS and PFS?
	Should the base-case model allow for downstaging of disease?
	What is the most appropriate comparator?
Model suitability	Are the models suitable for decision-making?
ICER plausibility	What are the most plausible ICERs?
End of life	Are End of life criteria met?
Innovation	Are SIRTs innovative?
Equality	Are there any equality issues?

Disease background

Hepatocellular carcinoma (HCC) is the most common form of liver cancer

2,700 new cases of HCC in the England in 2017

Incidence is higher in men than women

Incidence increases with age

50% of people with HCC are diagnosed with advanced stage HCC and have poor prognosis with median survival of **less than 12 months**

HCC is commonly associated with cirrhosis

Related NICE guidance for treating HCC

TA474 (2017)

Sorafenib is recommended as an option for treating advanced hepatocellular carcinoma:

- only for people with Child-Pugh grade A liver impairment
- only if the company provides sorafenib within the agreed commercial access arrangement.

TA551 (2018)

Lenvatinib is recommended as an option for untreated, advanced, unresectable hepatocellular carcinoma in adults, only if:

- they have Child-Pugh grade A liver impairment and an ECOG performance status of 0 or 1 and
- the company provides it according to the commercial arrangement.

TA555 (2019)

Regorafenib is recommended as an option for treating advanced unresectable hepatocellular carcinoma in adults who have had sorafenib, only if:

- they have Child-Pugh grade A liver impairment and an ECOG performance status of 0 or 1 and
- the company provides it according to the commercial arrangement.

Others

Medtech innovation briefings

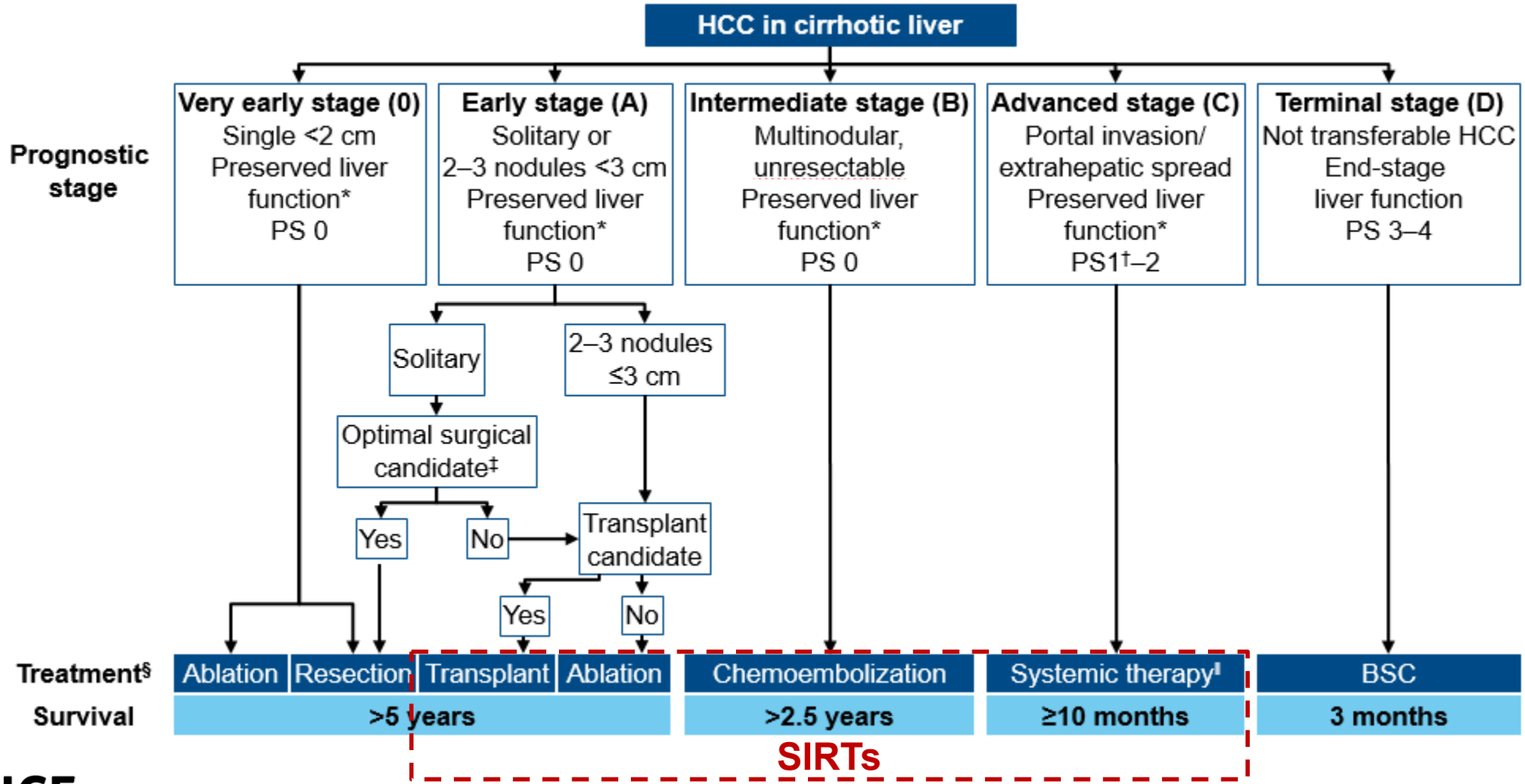
- MB62 TheraSphere for treating operable and inoperable hepatocellular carcinoma
- MB63 SIR-Spheres for treating inoperable hepatocellular carcinoma

Interventional procedures

- SIRT for primary HCC
- Microwave ablation of HCC
- Radiofrequency ablation of HCC

Current UK treatment pathway

This appraisal considers selective internal radiation therapies for people with unresectable early (BCLC stage A), intermediate-stage (BCLC stage B) and advanced (BCLC stage C) HCC (with or without portal vein thrombosis/involvement).



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HCC EASL clinical practice guideline

Selective internal radiation therapy (SIRT)

SIRT is a way of using radiotherapy to control cancers in the liver that can't be removed with surgery

Internal radiotherapy using small radioactive beads that are injected into the tumour's blood supply and damage the tumour and the blood vessels it needs to survive

A work-up procedure including an angiogram is used to assess suitability for SIRT

SIRT is also called radioembolisation or transarterial radioembolisation (TARE)

Interventions: MTA will appraise 3 SIRTs

	SIR-Spheres	TheraSphere	QuiremSpheres
Company	SIRTEX	BTG	Terumo Europe
License	CE-marked class III active medical device	CE-marked class III active medical device	CE-marked class III active medical device
Indication	Treatment of inoperable liver tumours	Treatment of hepatic neoplasia	Treatment of unresectable liver tumours
Design	Resin microspheres	Glass microspheres	Poly-L-lactic acid (PLLA) microspheres
Active substance	Yttrium-90	Yttrium-90	Holmium-166
List price	£8,000	£8,000	£9,896

MTA flowchart

Company submissions

All companies submitted their clinical evidence

2 companies submitted a cost-effectiveness model

Assessment group report

Assessment group (AG)

- Reviewed the company submissions and models
- Undertook own evidence review and synthesis
- Developed cost-effectiveness model that included data provided by the companies and from other sources
- AG report consulted on for 4 weeks
- *AG can respond to consultation comments but is not compelled to do so*

Committee decision making

Will be informed by AG report & model, company submissions and expert testimonies

Decision problem

	NICE	Assessment group
Population	People with unresectable early (BCLC stage A), intermediate-stage (BCLC stage B) and advanced (BCLC stage C) HCC (with or without portal vein thrombosis/involvement).	Looked at full population **BUT** available evidence restricted analysis to people who are ineligible for conventional transarterial therapies
Comparator	Unresectable HCC • Other SIRTs • Transarterial embolisation (TAE) • Transarterial chemoembolisation (TACE) • Drug-eluting bead transarterial chemoembolisation (DEB-TACE) For people for whom any transarterial embolisation is inappropriate • Established clinical management without SIRT including systemic therapies and best supportive care	
Intervention & outcomes	Intervention and outcomes align with scope	

Comments from patient experts

Patient expert submissions provided by 1 patient expert and British Liver Trust

	Patient experts comments
Unmet need	• Diagnosis often at later stages; few symptoms in early disease • Poor prognosis for advanced HCC • Few treatment options for advanced HC • Treatment options for advanced are non curative • Liver disease often complicates treatment • High incidence of recurrence
Quality of life	• People with HCC and their carers feel emotionally overwhelmed by diagnosis • People with HCC and carers live with uncertainty, hopelessness and often stigma and isolation
Advantages	• Life prolonging with less side effects and fast recovery • Might downstage tumour to allow transplant
Side effects	• Fewer side effects than TACE • Manageable side effects • Side effects less severe than for TACE or liver resection surgery

Comments from clinical experts – current management

Clinical expert submissions provided by 1 clinical expert and British Society of Interventional Radiology

	Clinical expert
Current disease management	• HCC is managed by multidisciplinary team • Treatment options include: – Transplantation – Resection – Loco-regional therapies (such as ablative techniques, transarterial chemo-embolisation or embolisation – TACE/TAE) – Sorafenib or immune mediated approaches – Best supportive care – Sometimes stereotactic body radiotherapy
Possible position in treatment pathway	• In early and intermediate stage HCC as an alternative to TACE to prolong survival or downstage to curative therapies such as resection or transplantation • In advanced BCLC stages as an alternative to sorafenib with similar outcomes but better side effect profile to palliate those without metastatic disease and offer prolonged survival comparable to sorafenib • Unmet need in patients who are not good TACE candidates (lesion size ≥7cm) who have unilobar disease within the intermediate stage of BCLC

Comments from clinical experts – experience with SIRT

Clinical expert submissions provided by 1 clinical expert and British Society of Interventional Radiology

	Clinical expert

Availability of SIRTs	• Not routinely funded, access is limited and managed locally
	• Might be available to:
	  • People whose tumour might be 'downstaged to resection'
	  • People whose disease is too advanced for standard TACE, and for whom sorafenib is not suitable (because of presence of a portal vein thrombosis)
	  • People after unsuccessful loco-regional therapies
	• Work-up procedure is required
	• 10 centres in England are commissioned to provide SIRT for metastatic colorectal cancer

Advantages	Survival benefit for younger people
Side effects	• Non-target radio-isotope delivery and radiation induced liver disease can be minimised by careful planning, dosimetry and delivery • Better tolerated than sorafenib, manageable side effects

Clinical evidence

There is some RCT evidence for SIR-Spheres and TheraSphere, but limited evidence for QuiremSpheres

Type of evidence	SIR-Spheres	TheraSphere	QuiremSpheres
Comparative studies versus conventional transarterial therapies			
RCTs	5 • 2 vs. sorafenib • 2 vs. TACE/DEB-TACE • 1 SIR-Spheres followed by sorafenib vs. sorafenib	2 • 1 vs. TACE • 1 vs. TheraSphere with sorafenib	0
Non-RCTs – prospective	0	7	0
Non-RCTs – retrospective	4	3	0
Comparative studies SIRT versus SIRT			
Non-RCTS - retrospective	5 SIR-Spheres versus TheraSphere		0
Non-comparative studies			
Non-comparative studies	0	0	1

SIR-Spheres – 2 good quality large RCTs compared SIR-Spheres with established therapies

	SARAH*	SIRveNIB*
Trial characteristics		
Location	France (25 centres)	Asia-Pacific region (11 countries)
Inclusion criteria	Locally advanced HCC (BCLC stage C), or new HCC not eligible for surgery/ablation after previously cured HCC, or HCC with 2 unsuccessful rounds of TACE. Life expectancy >3 months, ECOG PS 0 or 1, Child-Pugh class A or B score ≤7.	Locally advanced HCC (BCLC stage B or C without extrahepatic disease) with or without PVT, not amenable to curative treatment modalities.
Intervention	SIR-Spheres (n=237) Patients underwent angiography, protective coiling and MAA-SPECT/CT scan, SIRT 1 or 2 weeks later. Second SIRT possible. 53/237 (22%) did not get SIRT.	SIR-Spheres (n=182) Patients underwent angiographic and MAA assessment of suitability for SIRT. Single SIRT. 52/182 (29%) did not get SIRT.
Comparator	Sorafenib (n=222)	Sorafenib (n=178)
Primary outcome	Overall survival	Overall survival

*designed as superiority studies

SIR-Spheres – Baseline characteristics between groups in SARAH and SIRveNIB were similar

	SARAH		SIRveNIB	
Baseline patient characteristics (ITT population)				
	SIR-Spheres	**Sorafenib**	**SIR-Spheres**	**Sorafenib**
Number of patients	237 (ITT) 174 (per protocol)	222 (ITT) 206 (per protocol)	182 (ITT) 130 (per protocol)	178 (ITT) 162 (per protocol)
Median/Mean age	66 (IQR: 60-72)	65 (IQR: 58-73)	59.5 (SD: 12.9)	57.7 (SD: 10.6)
Proportion male	89%	91%	81%	85%
Cirrhosis present	211 (89%)	201 (91%)	NR	NR
HCC caused by alcohol*	147 (62%)	124 (56%)	NR	NR
Non-alcoholic steatohepatitis*	49 (21%)	60 (27%)	NR	NR
Hepatitis B*	13 (5%)	15 (7%)	93 (51%)	104 (58%)
Hepatitis C*	55 (23%)	49 (22%)	26 (14%)	19 (11%)
Hepatitis B & C*	NR	NR	4 (2%)	5 (3%)
Other/unknown*	45 (19%)	41 (18%)	NR	NR

* aetiology of HCC is different in Europe and Asia

SIR-Spheres – Baseline characteristics between groups in SARAH and SIRveNIB were similar

	SARAH		SIRveNIB	
Baseline patient characteristics (ITT population)				
	SIR-Spheres	**Sorafenib**	**SIR-Spheres**	**Sorafenib**
BCLC				
Stage A	9 (4%)	12 (5%)	0	1 (<1%)
Stage B	66 (28%)	61 (27%)	93 (51%)	97 (55%)
Stage C	162 (68%)	149 (67%)	88 (48%)	80 (45%)
Child-Pugh classification	A: 196 (83%) B7: 39 (16%) Unknown: 2 (1%)	A: 187 (84%) B7: 35 (16%) Unknown: 0 (0%)	A: 165 (91%) B: 14 (8%)	A: 160 (90%) B: 16 (9%)
Previously received TACE	106/237 (45%)	94/222 (42%)	NR	NR

SIR-Spheres – No evidence of differences in OS or PFS

	SARAH		SIRveNIB	
Trial results with 95% CIs				
	SIR-Spheres	**Sorafenib**	**SIR-Spheres**	**Sorafenib**
Median overall survival (months)	8.0 (6.7-9.9)	9.9 (8.7-11.4)	8.8	10.0
	HR: 1.15 (0.94-1.41) **ITT** HR: 0.99 (0.79-1.24) **Per protocol**		HR: 1.12 (0.9-1.4) **ITT** HR: 0.86 (0.7-1.1) **Per protocol**	
Median progression-free survival (months)	4.1 (3.8-4.6)	3.7 (3.3-5.4)	5.8	5.1
	HR: 1.03 (0.85-1.25) **ITT**		HR: 0.89 (0.7-1.1) **ITT** HR: 0.73 (0.6-0.9) **Per protocol**	
Time to progression	Not reported		6.1 **ITT**	5.4 **ITT**
Tumour response rate	36/190 (19%) n=5 complete n=31 partial	23/198 (12%) n=2 complete n=21 partial	17% **ITT**	2% **ITT**

SIR-Spheres – Mixed HRQoL results, but more adverse events with sorafenib

	SARAH		SIRveNIB	
Trial results				
	SIR-Spheres	**Sorafenib**	**SIR-Spheres**	**Sorafenib**
Rates of subsequent liver transplantation or resection	6/237 (3%) ablation 3/237 (1%) surgery 2/237 (1%) transplant	2/222 (1%) ablation 1/222 (<1%) transplant	1/182 (<1%) ablation 2/182 (1%) surgery	2/178 (1%) ablation 1/178 (1%) surgery
Health-related quality of life*	Significant difference in global health status sub-score between SIRT and sorafenib groups (group effect p=0.0048; time effect p<0.0001)		No statistically significant differences in EQ-5D between the SIRT and sorafenib groups throughout the study	
# patients with TRAE	173/226 (77%)	203/216 (94%)	78/130 (60%)	137/162 (85%)
# patients with Grade 3 or worse AE	92/226 (41%)	136/216 (63%)	36/130 (28%)	82/162 (51%)

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*proportion of people completing the questionnaires was low
AE: adverse events; TRAE: treatment-related adverse events,

SIR-Spheres – 2 small RCTs compared SIR-Spheres with TACE or DEB-TACE

	SIR-TACE		Pitton et al.	
Population	people with unresectable HCC without portal vein occlusion		people with unresectable intermediate (BCLC stage B) HCC with preserved liver function (Child-Pugh A-B7)	
Comparator	TACE		DEB-TACE	
Trial results				
	SIR-Spheres (n=13)	**TACE** (n=15)	**SIR-Sphere** (n=12)	**DEB-TACE** (n=12)
OS	46% (1 yr)	67% (1 yr)	No difference (medians)	
PFS	No difference		No difference (medians)	
Partial response	31%	13%	Not available	
HRQoL*	No difference		Not available	
TRAE	23%	33%	No AEs reported	
# patients with Grade 3 or worse AE	3	2		
# patients with serious AE	7	5		

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*proportion of people completing the questionnaires was low; 10/28 had missing baseline data
AE: adverse events; TRAE: treatment-related adverse events,

SIR-Spheres – The company provided a subgroup analysis which was included in their base-case model

Company:

- Selected subgroup of patients from the SARAH trial with ≤25% tumour burden and Albumin-Bilirubin (ALBI) grade 1 for their base-case analysis in the economic model

	SIR-Spheres (n=48)	Sorafenib (n=37)
Results for subgroup with 95% CI		
Median overall survival (months)	21.9 (15.2-32.5)	17.0 (11.6-20.8)
	HR 0.73 (0.44-1.21)	
Median progression free survival (months)	HR 0.65 (0.41-1.02)	

Assessment Group:

- Not a clinically recognised subgroup
- Based on a post-hoc analysis, breaks randomisation
- Explored in AG scenario analysis

Stakeholder comments:

- ALBI classification not routinely used
- People with ALBI 1 have good liver function – would be Child Pugh A
- People with tumour burden ≤25% and Child Pugh A are a recognisable groups
- Evidence in this group is emerging
- Group relevant to SIRTs in particular

SIR-Spheres summary – no evidence of difference to sorafenib or (DEB)-TACE, and evidence has limitations

Evidence

- No evidence of difference in OS/PFS versus:
  - Sorafenib: 2 RCTs (SARAH and SIRveNIB)
  - (DEB)-TACE: 2 small RCTs

Assessment group

- Results might not be generalisable to UK
  - Trials in France and Asia
  - People in trial might have poorer prognosis than those considered for SIRT in UK

Stakeholder comments

- SARAH and SIRveNIB conducted outside UK
  - included different patient groups that might not be comparable to UK patients
- In NHS current patient selection is more targeted using dosimetry

Are the results from SARAH and SIRveNIB generalisable to the UK population?

TheraSphere – 2 small RCTs compared TheraSphere with TACE or combination treatment to prepare for transplant

	PREMIERE	RCT by Kulik et al.
Trial characteristics		
Study design	Single centre open-label RCT	Single centre open-label RCT pilot study
Location	US	US
Inclusion criteria	Adults with BCLC stage A/B unablatable/unresectable HCC with no vascular invasion, Child-Pugh A/B	Adults with Child-Pugh ≤B8 and potential candidates for orthotopic liver transplant
Intervention	TheraSphere	TheraSphere
Comparator	TACE	TheraSphere with sorafenib*
Outcomes	Overall survival Time to progression Rate of liver transplant/resection Time to transplant/resection	Rate of liver transplant/resection Adverse events

*combination therapy is off label for sorafenib or CE mark for TheraSphere

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TheraSphere – Baseline characteristics in studies

	PREMIERE		RCT by Kulik et al.	
Baseline patient characteristics				
	TheraSphere (n=24)	**TACE (n=21)**	**TheraSphere (n=10)**	**TheraSphere with sorafenib (n=10)**
# of patients	24	21	10	10
Median age	62 (95% CI 58-65)	64 (95% CI 62-70)	60 (range 54-67)	58 (range 53-63)
Proportion male	71%	76%	50%	80%
Cirrhosis present	100%	95%		
HCC caused by **Alcohol** **Non-alcoholic steatohepatitis** **Hepatitis B** **Hepatitis C** **Other/unknown**	 5 1 3 13 2	 3 1 2 13 4	 2 1 6 2	 1 1 8 0
BCLC **Stage A** **Stage B** **Stage C**	 18 (75%) 6 (25%)	 17 (81%) 4 (19%)	 5 (50%) 1 (10%) 4 (40%)	 7 (70%) 1 (10%) 2 (20%)
Child-Pugh classification	A: 12 (50%) B: 12 (50%)	A: 15 (71%) B: 6 (29%)	A: 6 B: 4	A: 8 B: 2

TheraSphere – Results of studies

	PREMIERE		RCT by Kulik et al.	
Results				
	TheraSphere (n=24)	**TACE (n=21)**	**TheraSphere (n=10)**	**TheraSphere with sorafenib (n=10)**
Median overall survival (months)	18.6* (95% CI: 7.4-32.5)	17.7* (95% CI: 7.4-32.5)	3 deaths	2 deaths
Time to progression	Not reached (>26 months)	6.8 months	Not reported	
Rate of liver transplant/ resection	87%	70%	90%	90%
Time to transplant/ resection	8.8 months	7.6 months		
HRQoL	Not reported		Not reported	
Adverse events	Not reported		More common in TheraSphere than TheraSphere with sorafenib arm	

*censored to liver transplant

TheraSphere – AG identified 5 prospective studies for TheraSphere versus current therapies reporting OS/PFS

	Comparator	Location	#	Population	Results	
					Thera	Compar.
El Fouly 2015	TACE	Germany and Egypt	86	Adults with intermediate stage (BCLC B) un-resectable HCC & good liver function (Child-Pugh B<7)	OS 16.4 (7.9-25.3) TtP 13.3 (3.4-23.1)	OS 1.08 (12.1-25.5) TtP 6.8 (3.9-8.8)
Memon 2013	TACE	USA	96	Adults with HCC that progressed after intra-arterial loco-regional therapies (TACE and SIRT)	OS NR TtP 13.3 (9.3-25.0)*	OS NR TtP 8.4 (7.3-10.6)*
Hickey 2016	TACE	USA	765	Adults with unresectable HCC and bilirubin ≤3.0 mg/dL	OS reported for subgroups (BCLC and C-P): no diff.	
Maccaur 2014	TheraSphere + sorafenib	Italy	45	Adults with unresectable HCC (Child-Pugh A)	OS 10 PFS 7	OS 10 PFS 6
Woodall 2009	Best supportive care	USA	52	Adults with unresectable HCC (with and without portal vein thrombosis)	+PVT OS 13.9 -PVT OS 3.2	OS 5.2

*range

TheraSphere summary – no evidence of difference to comparators, and evidence has limitations

Evidence

- RCTs – no difference in transplant rate and OS versus:
  - TheraSphere with sorafenib
  - TACE
- Retrospective studies
  - No difference in OS versus:
    - TheraSphere with sorafenib
    - TACE
  - TheraSphere increased OS in people with PVT compared with people without PVT or people who got BSC
  - Longer TtP versus TACE

Assessment group

RCTs were small trials (n = 45 & 20)

- Imbalance in baseline characteristics
- Kulik et al. only includes people eligible for curative treatment

NICE technical team comments

- RCT and retrospective studies
  - Use of sorafenib in combination with TheraSphere is off label

Stakeholder comments

- Retrospective studies should be included in analysis

Are the results generalisable to the UK population?
Should retrospective evidence be taken into consideration when estimating clinical effectiveness for TheraSphere?

QuiremSpheres summary – very small and limited evidence base for effectiveness and safety

Evidence

- Retrospective case series
  - Conducted in Germany in 1 centre (n=9)
  - Response rate 56% (complete or partial response)

Assessment group

- Available data are too limited to draw any conclusions about the safety or efficacy of QuiremSpheres

Is it appropriate to include QuiremSpheres in the analysis?

Comparisons of SIRT options – 5 studies compared SIR-Spheres and TheraSphere

	Biederman 2015		Biederman 2016		Van der Gucht 2017		Bhangoo 2015		D'Abadie 2018	
Population	BCLC stage C HCC with PVT		Unresectable HCC with main or lobar PVT		Unresectable HCC, ECOG PS <2 & life expectancy >3 months		Unresectable HCC; failed or unsuitable for alternatives ECOG PS <2		HCC imaged by 90Y TOF-PET	
	Thera	**SIR**	**Thera**	**SIR**	**Thera**	**SIR**	**Thera**	**SIR**	**Thera**	**SIR**
# people	72	25	69	21	36	41	11	6	33†	25†
Median OS, months	15 (8.6-19.5)	4.1 (2.7-6.6)	9.5 (7.6-15.0)	3.7 (2.3-6.0)	7.0 (1.6-12.4)	7.7 (7.2-8.2)	8.4 (1.3-21.1)	7.8 (2.3-12.5)	Not reported¶	
Median TTP/PFS, months	9.1 (5.4-11.7)‡		5.9§ (4.2-9.1)	2.8§ (1.9-4.3)	5.0‖ (0.9-9.2)	6.1‖ (4.7-7.4)	Not reported		Not reported	
HRQoL	Not reported		Not reported		Not reported		Not reported		Not reported	
AE	Not reported for arms		No significant difference		Not reported		More frequent in Thera arm		Not reported	

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†procedures; ‡not reported for single arms; ¶Kaplan-Meier curves for different equivalent uniform doses presented; §time to progression; ‖progression-free survival

Most of these studies have high risk of bias

Trial	Biederman 2015	Biederman 2016	Van Der Gucht 2017	Bhangoo 2015	d'Abadie 2018
Inclusion criteria clearly defined	No	Yes	Yes	Yes	No
Population	Adults with unresectable HCC with PVT	Patients with unresectable HCC and main or lobar PVT	Subgroup of advanced stage HCC patients	Mixed pop.: unresectable HCC, either failed or not amenable to other loco-regional therapies	Appears to include both pts. eligible and ineligible for TACE
Representative sample from relevant population	Unclear	Yes	Yes	Yes	Unclear
Groups similar at baseline	Unclear	No	No Pts. with small-tumour more likely to get TheraSphere	Unclear	No
Overall judgement of risk of bias	**High**	**High**	**High**	**Unclear**	**High**

Evidence on comparison of SIRTs is limited with some studies favouring TheraSphere over SIR-Spheres

Evidence

- 5 retrospective studies compared TheraSphere and SIR-Spheres
  - In 2 studies TheraSphere showed longer OS for people with PVT
  - Conflicting results from other studies
- 1 small retrospective study compared all 3 SIRTs
  - No difference in OS at 6 and 12 months

Assessment group

- All studies are retrospective with high or unclear risk of bias
- Studies were generally small with less than 100 people

Stakeholder comments

- Conflicting opinion of whether SIRTs show similar effectiveness
- Conflicting opinion of whether non-RCT studies should be included in analysis

Is it appropriate to consider non-RCT?

Is there sufficient evidence to show that TheraSphere is more effective than SIR-Spheres?

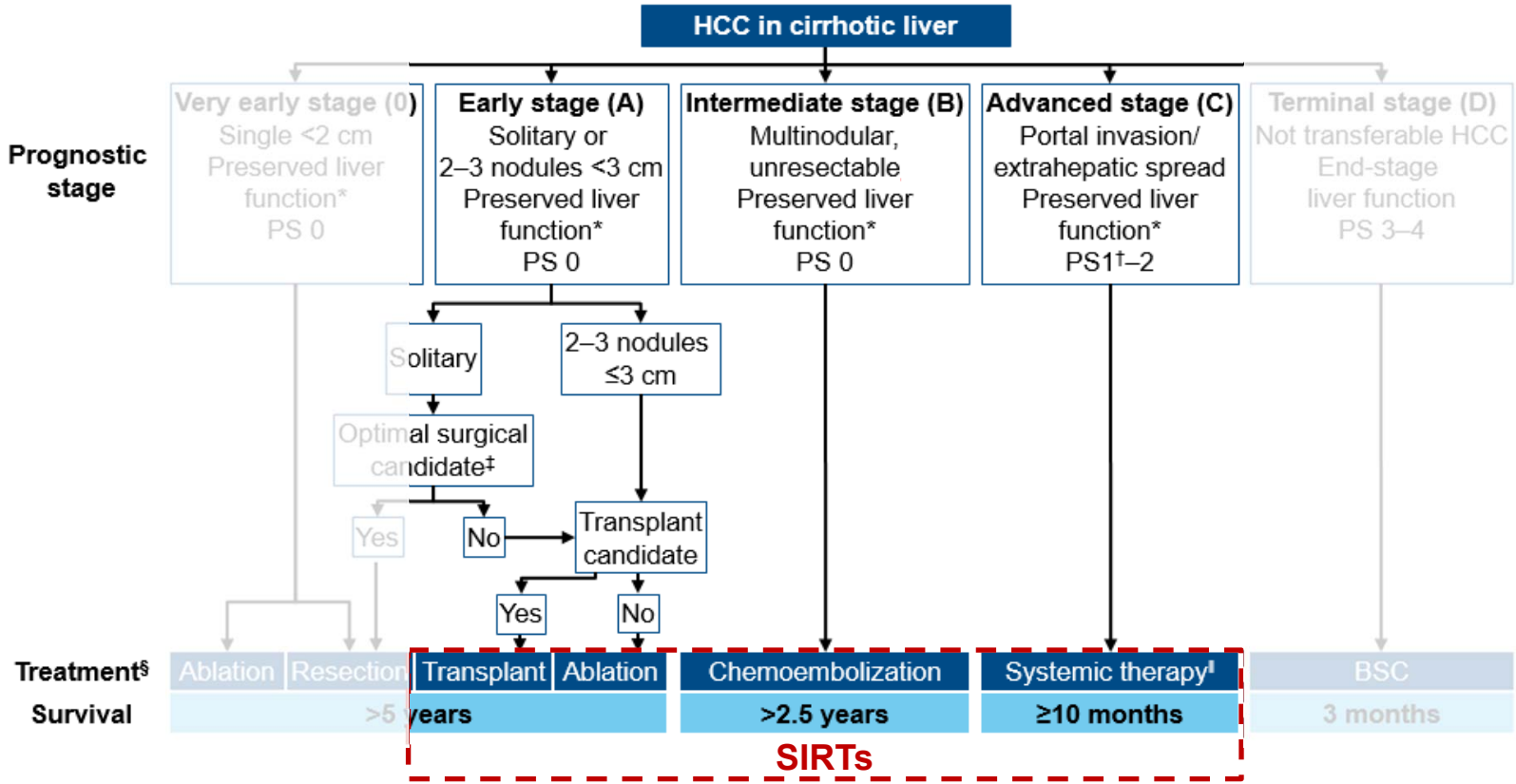
Is it reasonable to assume SIRTs are all similarly effective?

There are a number of ongoing studies for each SIRT

	SIR-Spheres	TheraSphere	QuiremSpheres
Company	SIRTEX	BTG	Terumo Europe
RCTs	None	STOP-HCC phase 3 trial comparing TheraSphere plus sorafenib and sorafenib alone	
Non-RCTs	• The Austrian CIRSE Registry for SIR-Spheres Therapy (CIRT) • RESIN tumour registry in the USA • RESIN tumour registry in Taiwan • VESPRO patient data retrospective meta-analysis of patients from the SIRveNIB and SARAH trials	BTG sponsored studies • LEGACY – retrospective study • TARGETA – retrospective study BTG supported studies • 10 prospective or retrospective studies	• HORA EST HCC • HEPAR primary – interventional phase 2 • Hope166 – observational

Network meta-analyses

3 subpopulations could potentially benefit from SIRT treatment



Adults with unresectable HCC		
Eligible for transplant	Eligible for conventional transarterial therapies	Ineligible for conventional transarterial therapies

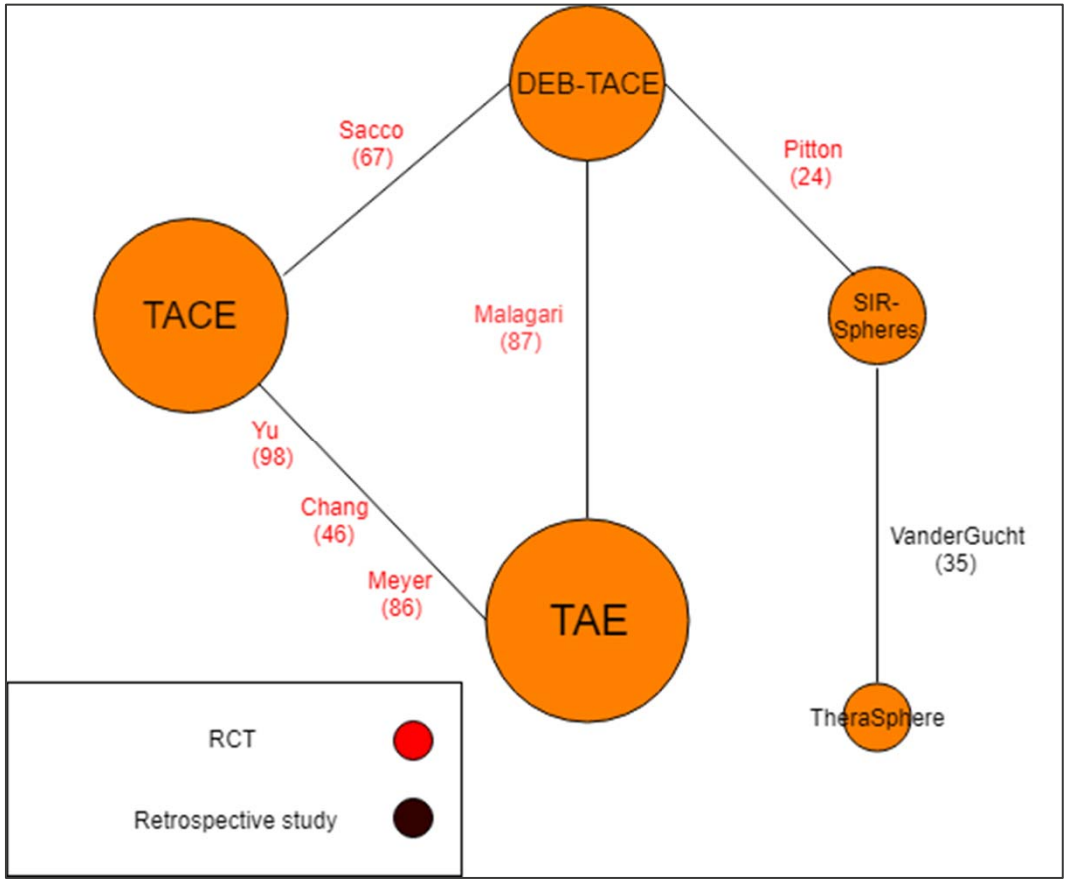
The AG planned 3 NMAs to estimate comparative effects

Aim of NMA is to compare effectiveness of two or more treatment options

Adults with unresectable HCC		
Eligible for transplant	Eligible for conventional transarterial therapies	Ineligible for conventional transarterial therapies
Network 1 • 2 small non-UK RCTs • Results might not be generalisable to UK population: transplant waiting times in studies longer than NHS • In UK, TACE rather than SIRT is often used during transplant waiting • **Not performed**	**Network 2** • 6 RCTs (5 compare CTTs with each other, 1 small trial of 24 people compares DEB-TACE and SIR-Spheres) • 1 retrospective comparative study • Weak link in network between CTTs and SIRTs • Results are uncertain • No evidence for downstaging identified	**Network 3** • 3 RCTs and 2 retrospective comparative studies • Most robust evidence • Complete network • Scenario analyses and sensitivity analyses provided

Network 2 – treatment effectiveness in adults with unresectable HCC who are eligible for CTT

- NMA performed following consultation
- CTT-eligible population includes:
  - people with intermediate stage HCC (BCLC B)
  - people with advanced stage HCC (BCLC C) if they do not have portal vein thrombosis (PVT)/portal vein involvement (PVI) or extra-hepatic spread
- SIR-Spheres connected by 1 trial (n=24)
- Base case analysis for OS and PFS
- No scenario or sensitivity analyses were performed



Base case results – No difference in OS and PFS between treatment options

- Treatment effect estimates for OS are uncertain
- Treatment effect similar for all treatment options

vs	*Comparator*				
Treatment	TACE	-	-	-	-
	1.06 (0.21-3.31)	SIR-Spheres	-	-	-
	1.02 (0.13-3.77)	0.96 (0.34-2.18)	TheraSphere	-	-
	0.88 (0.29-2.09)	0.95 (0.35-2.56)	1.41 (0.28-4.34)	DEB-TACE	-
	0.98 (0.61-1.57)	1.60 (0.27-5.25)	2.08 (0.24-8.01)	1.48 (0.42-3.77)	TAE

- Treatment effect estimates for PFS are uncertain
- Treatment effect similar for all treatment options

vs	*Comparator*				
Treatment	TACE	-	-	-	-
	1.20 (0.22-3.82)	SIR-Spheres	-	-	-
	1.14 (0.15-4.20)	0.95 (0.36-2.05)	TheraSphere	-	-
	0.86 (0.26-2.15)	0.92 (0.31-2.12)	0.94 (0.26-3.44)	DEB-TACE	-
	0.87 (0.61-1.20)	0.93 (0.21-4.05)	1.58 (0.20-5.97)	1.35 (0.38-3.50)	TAE

Network 2 – results show no difference between treatment options and are uncertain

Stakeholder comments

- NMA for CTT-eligible population should be done
- Network is complete if all evidence is considered
- Non-randomised and non-comparative evidence should be included

AG's NMA results for network 2 following consultation

Included evidence

- Weak evidence to connect SIRTs in the network
- Non-comparative evidence was not used because of low quality
- No evidence on downstaging identified

Results

- No difference between the treatment options
- Results are uncertain because of wide credible intervals

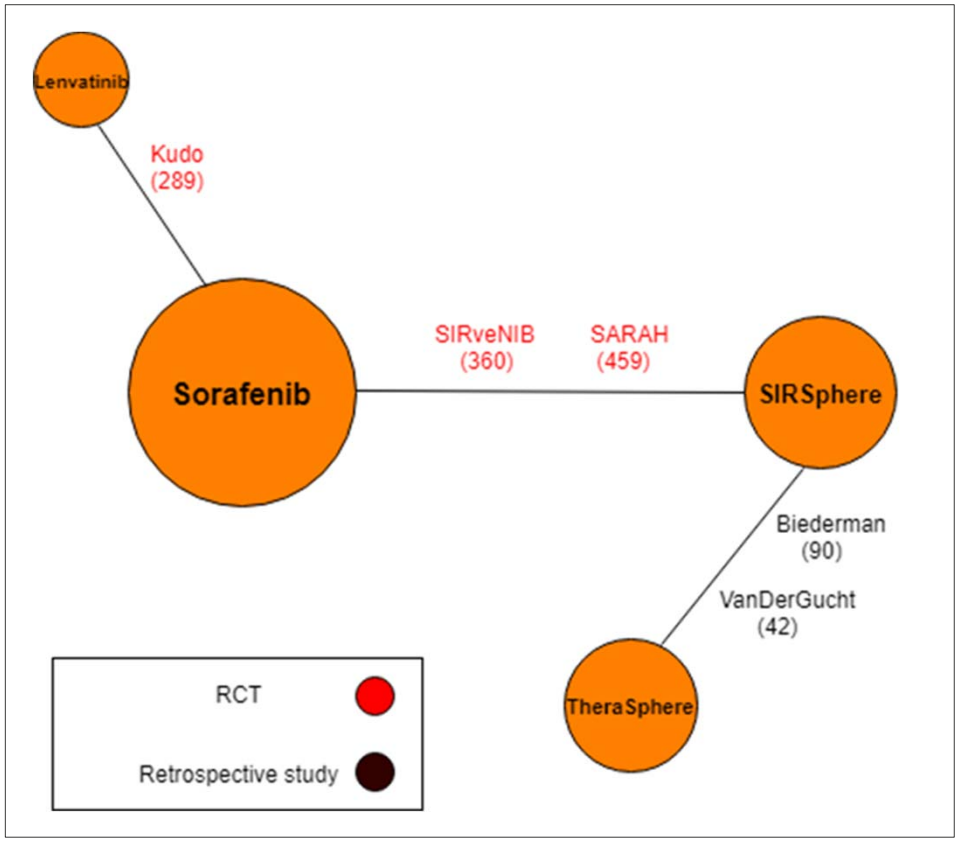
Is this network informative for decision making?

Network 3 – treatment effectiveness in adults with unresectable HCC who are ineligible for CTT

Base-case NMA – adults with Child-Pugh A

- SARAH and SIRveNIB trials (SIR-Spheres) included
- Per-protocol and intention-to-treat population

- Sensitivity analysis
  - SARAH trial only
  - Per-protocol and intention-to-treat population
- Scenario analysis 1
  - Includes Biederman et al. 2016 to add TheraSphere



Alternative NMA – all adults

- Intention-to-treat population
- Scenario analysis
  - Includes Biederman et al. 2016, and van der Gucht to add TheraSphere

Base case NMA – adults with Child-Pugh A per-protocol and ITT population

- Treatment effect estimates for OS are uncertain
- Treatment effect similar for the 3 treatment options
- PFS could not be assessed because it was not reported in SIRveNIB for people with Child-Pugh A

Hazard ratio estimates (95% CrI) for OS for each treatment comparison for *PP population*

vs	*Comparator*		
Treatment	**Sorafenib**	-	-
	0.94 (0.77-1.14)	**SIR-Spheres**	-
	1.06 (0.79-1.40)	1.14 (0.79-1.58)	**Lenvatinib**

Hazard ratio estimates (95% CrI) for OS for each treatment comparison for *ITT population*

vs	*Comparator*		
Treatment	**Sorafenib**	-	-
	1.13 (0.96-1.32)	**SIR-Spheres**	-
	1.06 (0.79-1.40)	0.92 (0.67-1.29)	**Lenvatinib**

Sensitivity analysis – excluding SIRveNIB study from base case NMA; PP and ITT population

- SIRveNIB was conducted in Asia
- Exclusion had some impact on the results for OS in the PP population
  - HRs got numerically higher (worse) for SIR-Spheres
- Exclusion had very little impact on the results for OS in the ITT population

Hazard ratio estimates (95% CrI) for OS for each treatment comparison for *PP population*

vs	*Comparator*		
Treatment	**Sorafenib**	-	-
	1.02 (0.79-1.29)*	**SIR-Spheres**	-
	1.06 (0.79-1.40)	1.06 (0.71-1.52)	**Lenvatinib**

Hazard ratio estimates (95% CrI) for OS for each treatment comparison for *ITT population*

vs	*Comparator*		
Treatment	**Sorafenib**	-	-
	1.14 (0.90-1.4)	**SIR-Spheres**	-
	1.06 (0.79-1.40)	0.94 (0.65-1.34)	**Lenvatinib**

* Higher than base case

Scenario analysis 1 – adults with Child-Pugh A inclusion of Biederman *et al*. study; PP and ITT population

- Biederman et al. 2016 is a retrospective, poor quality study, adds TheraSphere to the network
  - All people have portal vein thrombosis
- TheraSphere showed significant improvement in OS compared to SIR-Spheres, sorafenib and lenvatinib in both per protocol and ITT population

Hazard ratio estimates (95% CrI) for OS for each treatment comparison for *PP population*

vs	*Comparator*			
Treatment	**Sorafenib**	-	-	-
	0.94 (0.77-1.13)	**SIR-Spheres**	-	-
	1.06 (0.79-1.40)	1.13 (0.79-1.57)	**Lenvatinib**	-
	0.41 (0.20-0.77)	**0.44 (0.20-0.84)**	**0.40 (0.18-0.78)**	**TheraSphere**

Hazard ratio estimates (95% CrI) for OS for each treatment comparison for *ITT population*

vs	*Comparator*			
Treatment	**Sorafenib**	-	-	-
	1.13 (0.96-1.32)	**SIR-Spheres**	-	-
	1.06 (0.79-1.40)	0.95 (0.67-1.29)	**Lenvatinib**	-
	0.47 (0.21-0.88)	**0.41 (0.20-0.77)**	**0.45 (0.20-0.89)**	**TheraSphere**

Alternative NMA – all adults ITT population, no restriction to Child Pugh A

- SIR-Spheres showed significant improvement in OS compared with sorafenib

Base case (Child Pugh A) – Hazard ratio estimates (95% CrI) for OS for each treatment comparison for all patients ITT population

vs	*Comparator*		
Treatment	**Sorafenib**	-	-
	1.13 (0.96-1.32)	**SIR-Spheres**	-
	1.06 (0.79-1.40)	0.92 (0.67-1.29)	**Lenvatinib**

Hazard ratio estimates (95% CrI) for OS for each treatment comparison for all patients in ITT population

vs	*Comparator*		
Treatment	**Sorafenib**	-	-
	1.14 (1.01-1.28)	**SIR-Spheres**	-
	1.06 (0.79-1.40)	0.93 (0.67-1.25)	**Lenvatinib**

Scenario analysis 2 – all adults ITT population, no restriction to Child Pugh A

- Inclusion of Biederman et al. 2016 and Van der Gucht et al. showed significant improvement in OS with TheraSphere when compared to sorafenib, SIR-Spheres and lenvatinib

Hazard ratio estimates (95% CrI) for OS for each treatment comparison for *ITT population*

vs	*Comparator*			
Treatment	**Sorafenib**	-	-	-
	1.14 (1.01-1.28)	**SIR-Spheres**	-	-
	1.06 (0.79-1.40)	0.93 (0.67-1.25)	**Lenvatinib**	-
	0.53 (0.31-0.84)	**0.46 (0.28-0.72)**	**0.51 (0.28-0.86)**	**TheraSphere**

Network 3 – no difference between systemic treatments and SIR-Spheres if only high quality evidence is used

AG's NMA results for network 3

- *Child-Pugh A*
  - No difference between SIR-Spheres, sorafenib & lenvatinib in base case
  - Similar results when SIRveNIB is excluded
  - TheraSphere longer OS than SIR-Spheres, sorafenib and lenvatinib if retrospective evidence is included
- *All adults*
  - SIR-Spheres longer OS than sorafenib in base case network
  - TheraSphere longer OS than SIR-Spheres, sorafenib and lenvatinib if retrospective evidence is included

Stakeholder comments

- Non-randomised and non-comparative evidence should be included in analysis; TheraSphere should be included in base-case network
- Comparison should consider similar populations from REFLECT and SARAH
- No relevant evidence comparing TheraSphere or QuiremSpheres with comparators for CTT-ineligible patients
- SIRTs are not equally effective

Should non-randomised and non-comparative evidence be included?

Are SIRTs similarly effective?

Cost-effectiveness evidence

Existing cost-effectiveness evidence for SIRTs in advanced HCC is limited

Previous publications

3 full text publications and 4 abstracts were identified

SIRT versus sorafenib (1 full text and 4 abstracts)

- Inconsistencies in conclusion of results and limiting reporting of methods
- Only 1 abstract considered UK perspective

SIRT versus TACE (1 full text study)

- Limited and unclear reporting
- US Medicare perspective

Published NICE TAs

TA474 Sorafenib for advanced HCC in people with Child-Pugh A

- Markov model with 3 health states: progression-free, progressed and dead
- Comparator was BSC

TA551 Lenvatinib for untreated advanced unresectable HCC in people with Child-Pugh A

- Partitioned survival model with 3 health states: progression-free, progressed and dead
- Comparator was sorafenib

TA555 Regorafenib for previously treated advanced unresectable HCC in people with Child-Pugh A

- Partitioned survival model with 3 health states: progression-free, progressed and dead
- Comparator was BSC

2 companies included cost-effectiveness evidence in their submission

	SIR-Spheres	TheraSphere	QuiremSpheres
Company	SIRTEX	BTG	Terumo Europe
Economic evidence	CTT-eligible population – cost minimisation analysis to compare SIR-Spheres, TheraSphere, TACE and DEB-TACE	CTT-eligible population – cost-utility analysis to compare TheraSphere, SIR-Spheres and QuiremSpheres with TACE, DEB-TACE and TAE	Budget impact model
	CTT-ineligible population – cost-utility analysis to compare SIR-Spheres with sorafenib (and lenvatinib)	CTT-ineligible population – cost-utility analysis to compare SIRTs with systemic therapies	

SIR-Spheres models and AG critique

Model 1 – CTT-eligible population; cost-minimisation analysis

Company

- Comparison of SIR-Spheres, TheraSphere, TACE and DEB-TACE
- Costs included for initial treatment, hospitalisation and management of adverse events
- Scenarios presented using different assumptions and cost sources
- Ranges of costs associated with CTT, TheraSphere, and SIR-Spheres overlapped

	Cost (range)
TACE	£9,257 to £14,167
SIR-Spheres	£11,185 to [redacted]
TheraSphere	£12,026 to [redacted]

- No cost-utility analysis because of lack of comparative evidence

AG critique

- Choice of approach inappropriate and potentially misleading
- Insufficient evidence to demonstrate equivalence of treatments
- Excludes important outcomes regarding people who are downstaged after treatment and become eligible to receive curative therapy, or receive subsequent therapy after progression of disease
- Cost analysis of CTT highlighted significant uncertainties in the number of CTT treatments that are typically given, and the impact on the total costs

SIR-Spheres models and AG critique

Model 2 – CTT-ineligible population; cost-utility analysis

Company

- Comparison of SIR-Spheres versus sorafenib
- Base case was restricted to low tumour burden/ALBI 1 subgroup
- Downstaging was permitted
- Scenario analysis for broader population
- SIR-Spheres dominated sorafenib, producing more QALYs at a lower cost

	Incremental		
	QALYs	Costs (£)	ICER (£)
Probabilistic model			
SIR	0.682	-£1,979	Dominant
Sorafenib			
Deterministic model			
SIR	0.601	-£1,784	Dominant
Sorafenib			

AG critique

- Low tumour burden/ALBI 1 subgroup might not be clinical relevant
- Downstaging to curative therapies might not be clinical relevant in UK setting
- Modelling of OS and use of data which was not censored for downstaging to curative therapy
- Assumptions regarding the modelling of patients who underwent work-up but did not receive SIR-Spheres
- Number of SIRT treatments received; assumption bilobar tumours will be treated in one session
- Duration of subsequent treatments
- ICER very uncertain and company's estimate is probably optimistic

TheraSphere models and AG critique

Model 1 – CTT-eligible population; cost-utility analysis;

Company

- Comparison of TheraSphere with SIR-Spheres, QuiremSpheres, TAE, TACE and DEB-TACE
- Same efficacy of TheraSphere, SIR-Spheres and QuiremSpheres
- Same efficacy of TAE, DEB-TACE and TACE
- Key benefit of SIRT was increased proportion of patients who achieved downstaging after treatment and therefore receive curative treatment
- Cheapest strategy was DEB-TACE, which dominated TAE and TACE
- TheraSphere, QuiremSpheres and SIR-Spheres had a probabilistic ICER of **£25,052** per QALY gained, compared to DEB-TACE

AG critique

- Downstaging to curative therapies might not be clinical relevant in UK setting
- Use of a non-HCC specific dataset
- Failure to correctly account for patients who do not get SIRT after work-up
- Limitations in clinical evidence used to assume relative effectiveness
- Inappropriate implementation of age-adjusted utility values
- Inaccurate representation of patients in the pharmacological management health state
- ICER is uncertain; overall direction of uncertainty is not clear

TheraSphere models and AG critique

Model 2 – CTT-ineligible population; cost–utility analysis

Company

- Comparison of TheraSphere with SIR-Spheres, QuiremSpheres, and systemic therapies

	Incremental (to regorafenib)		
	QALYs	Costs (£)	ICER (£)
Probabilistic model (calculated by AG)			
Thera	0.185	£12,778	£69,070
Quirem	-0.030	£650	Dominated
SIR	-0.031	£610	Dominated
Sorafenib	0.000	£2,181	Dominated
Lenvatinib	0.030	£24,486	Dominated
Regorafenib			

- In response to AG critique BTG provided updated analysis without regorafenib and updated costs: TheraSphere ICER **£66,854** per QALY gained compared with sorafenib

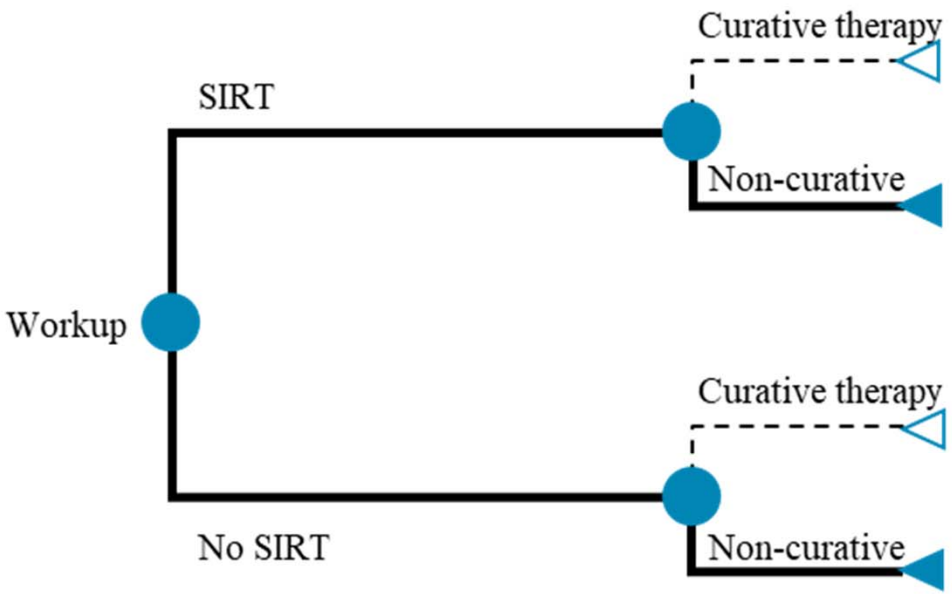
AG critique

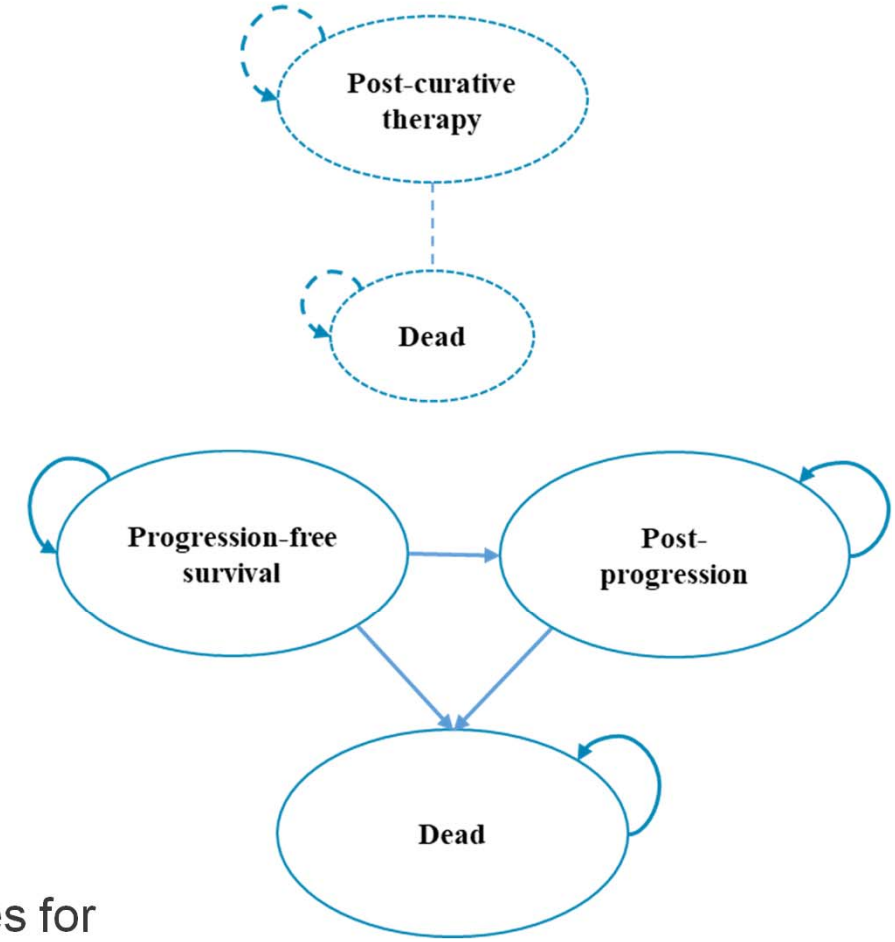
- Inclusion of regorafenib as direct comparator is not appropriate
- Failure to correctly account for patients who do not get SIRT after work-up
- Limitations in clinical evidence used to model the relative effectiveness
- Inappropriate and incorrect implementation of age-adjusted utility values
- Assumptions about time on treatment for systemic therapies
- Assumptions about subsequent therapies received following SIRT therapy
- ICER is uncertain; net effect on ICER is unclear because issues have opposite effects

AG proposed model for CTT-ineligible population

Model Component	Description
Population	Patients with unresectable intermediate (BCLC stage B) or advanced (BCLC stage C) HCC, • for whom any conventional transarterial therapy (TAE, TACE, DEB-TACE) is inappropriate • with or without macroscopic vascular invasion • without extrahepatic disease.
Intervention	• SIR-Spheres Y-90 resin microspheres • TheraSphere Y-90 glass microspheres • QuiremSpheres Ho-166 PLLA microspheres
Comparator	Established clinical management without SIRT: • Sorafenib • Lenvatinib
Analysis type	Cost-effectiveness (cost-utility) analysis
Economic outcome	Incremental cost per QALY gained, incremental net monetary benefit
Perspective	NHS and PSS
Time horizon	Lifetime (10 years)
Discount rate	Annual rate of 3.5% applied to costs and QALYs

The AG model is a hybrid decision tree & partitioned survival model with 3 health states





- Decision tree model enables separate outcomes for people who do not get SIRT after work-up procedure
- Curative therapy is considered in scenario analyses not base case
- Structure of partitioned survival model is similar to the company models

AG model input parameters

Model parameter	Evidence source
OS	• SIR-Spheres and sorafenib – parametric survival models fitted to pooled OS data (per protocol or intention to treat depending on trial arm) from the SARAH and SIRveNIB trials • TheraSphere and QuiremSpheres assumed to have same OS as SIR-Spheres (scenario analysis for alternative TheraSphere OS estimates) • Lenvatinib – hazard ratio to sorafenib OS curve from the NMA • Patients who received work-up but were ineligible to receive SIRT – observed KM data from SARAH
PFS	• SIR-Spheres and sorafenib – parametric survival models fitted to pooled PFS data (per protocol or intention to treat) from the SARAH and SIRveNIB trials • Lenvatinib – hazard ratio to sorafenib PFS curve from the NMA
Proportion receiving SIRT	• Based on the full SARAH trial population • Number of administrations of SIRT was based on the SARAH trial

AG model input parameters

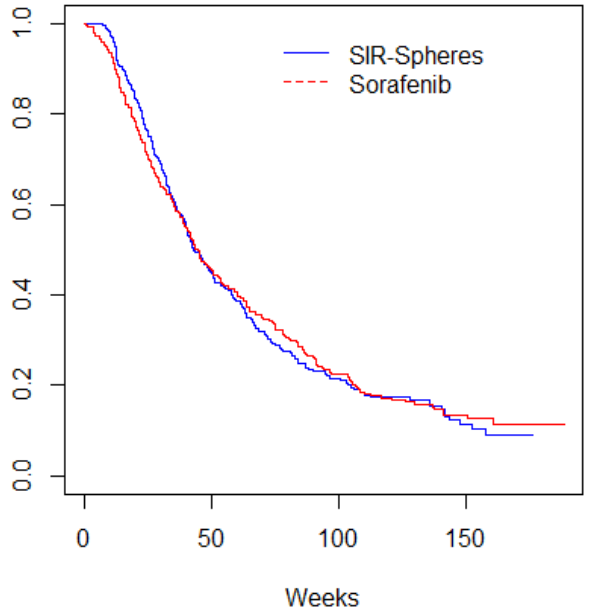
Model parameter	Evidence source
SIRT costs	Acquisition costs: Sirtex CS, BTG CS, Terumo CS Work-up costs: BTG-elicited values from The Christie NHS Foundation Trust Procedure costs: NHS Reference Costs 2017-18
Systemic therapy costs	Sorafenib and lenvatinib: BNF Dosing of sorafenib: SARAH trial Dosing of lenvatinib: REFLECT Western subgroup Duration of sorafenib: SARAH trial Duration of lenvatinib: PFS HR from REFLECT applied to SARAH, sorafenib ToT
Subsequent treatment costs	BNF, eMIT, TA555 (regorafenib)
AE costs	AEs ≥5% of the population were modelled with rates drawn from the SARAH and REFLECT trials. Unit costs based on TA474 and TA551.
Health state costs	Sirtex survey of clinical experts and NHS reference costs 2017/2018

Effectiveness – OS and PFS evidence

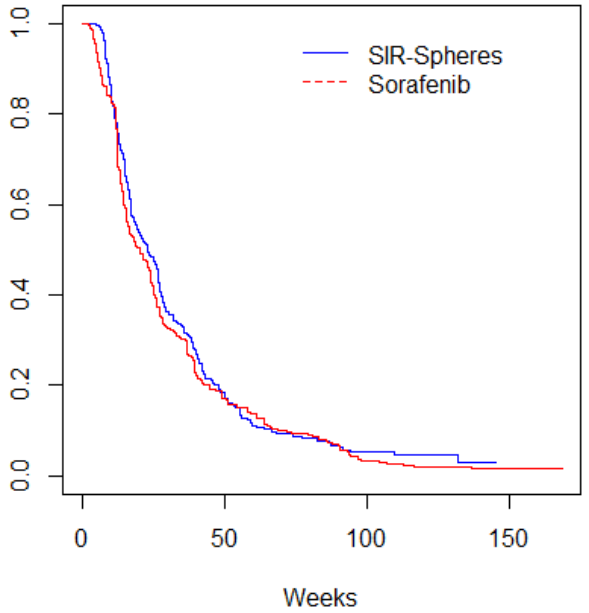
- Summary of observed survival estimates for SIR-Spheres and sorafenib, SARAH and SIRveNIB pooled dataset

	SIR-Spheres	Sorafenib
Overall survival		
Median (weeks)	42.9 (95% CI 39.9 – 51.1)	44.4 (95% CI 40.7 – 50.8)
Interquartile range	26.4 – 84.0	22.0 – 91.0
Progression-free survival		
Median (weeks)	23.0 (95% CI 19.0 – 26.8)	20.5 (95% CI 16.3 – 23.7)
Interquartile range	12.8 – 41.1	12.1 – 39.5

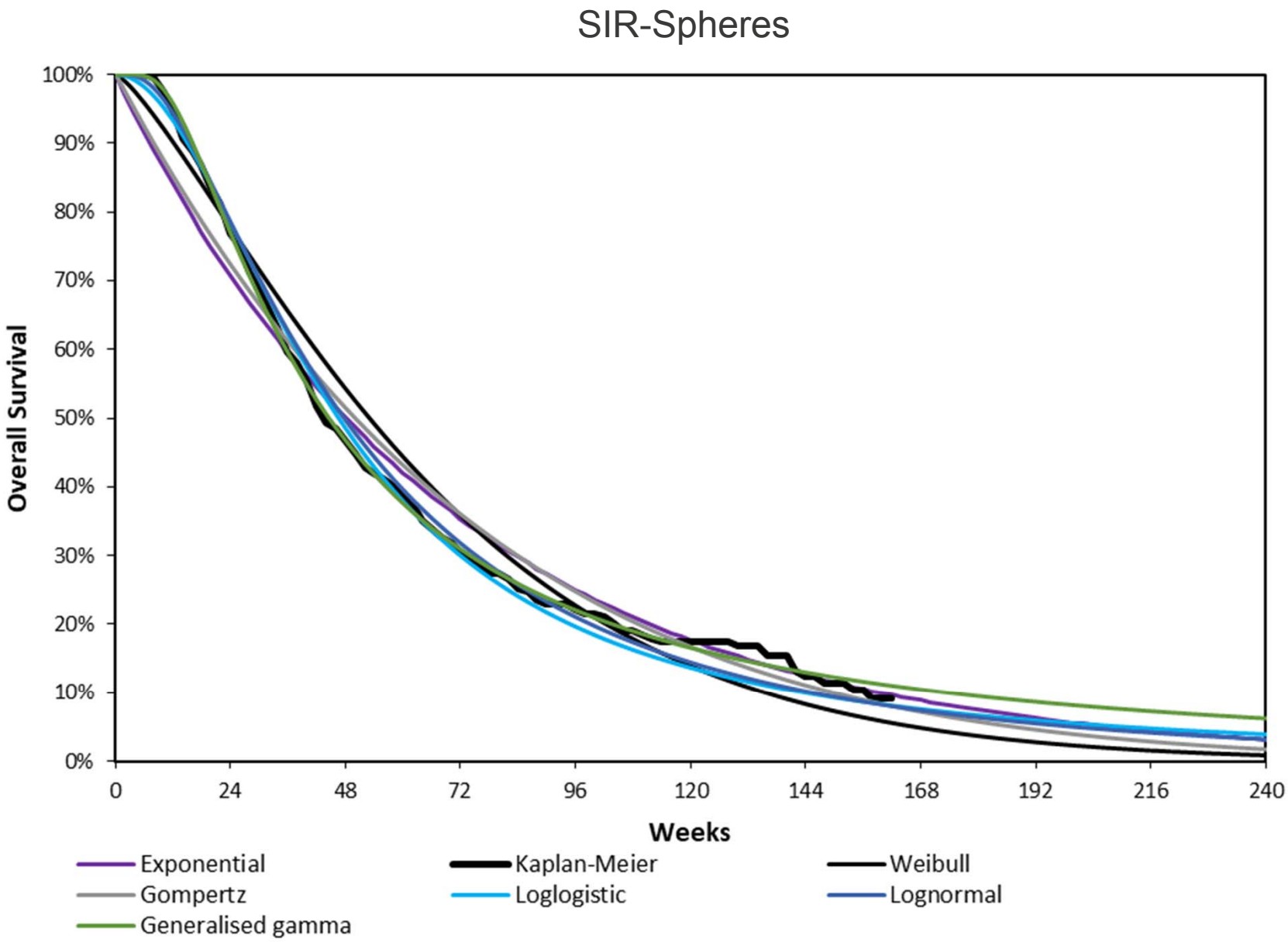
Overall survival



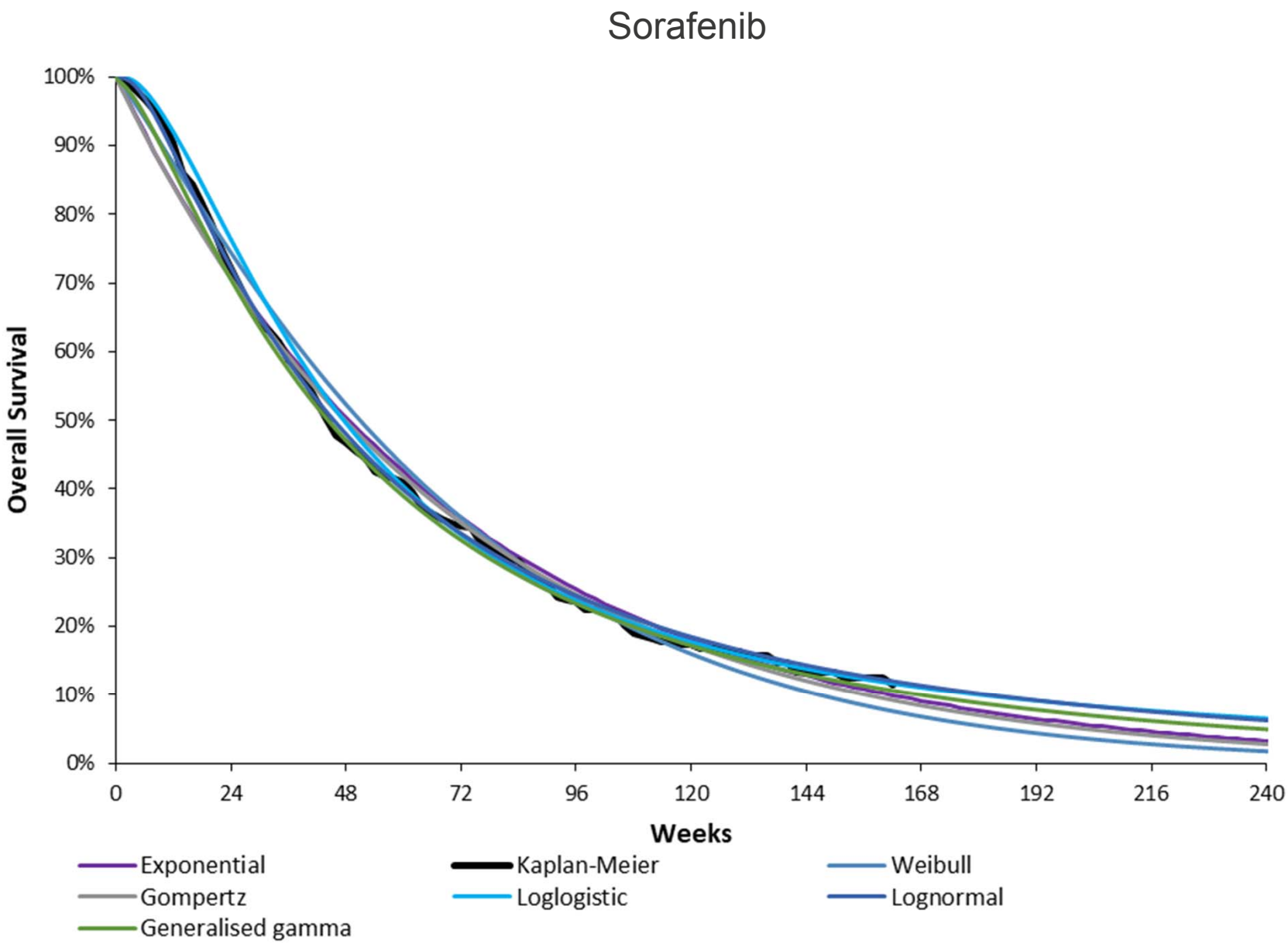
Progression-free survival



SIR-Spheres OS model fits

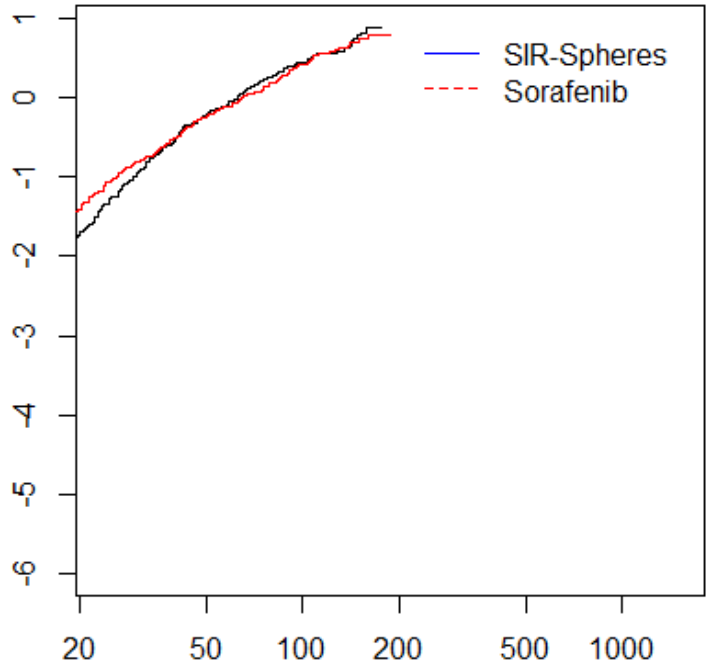


Sorafenib OS model fits



OS model choice for base case depended on model fit and model properties to allow HR use for lenvatinib

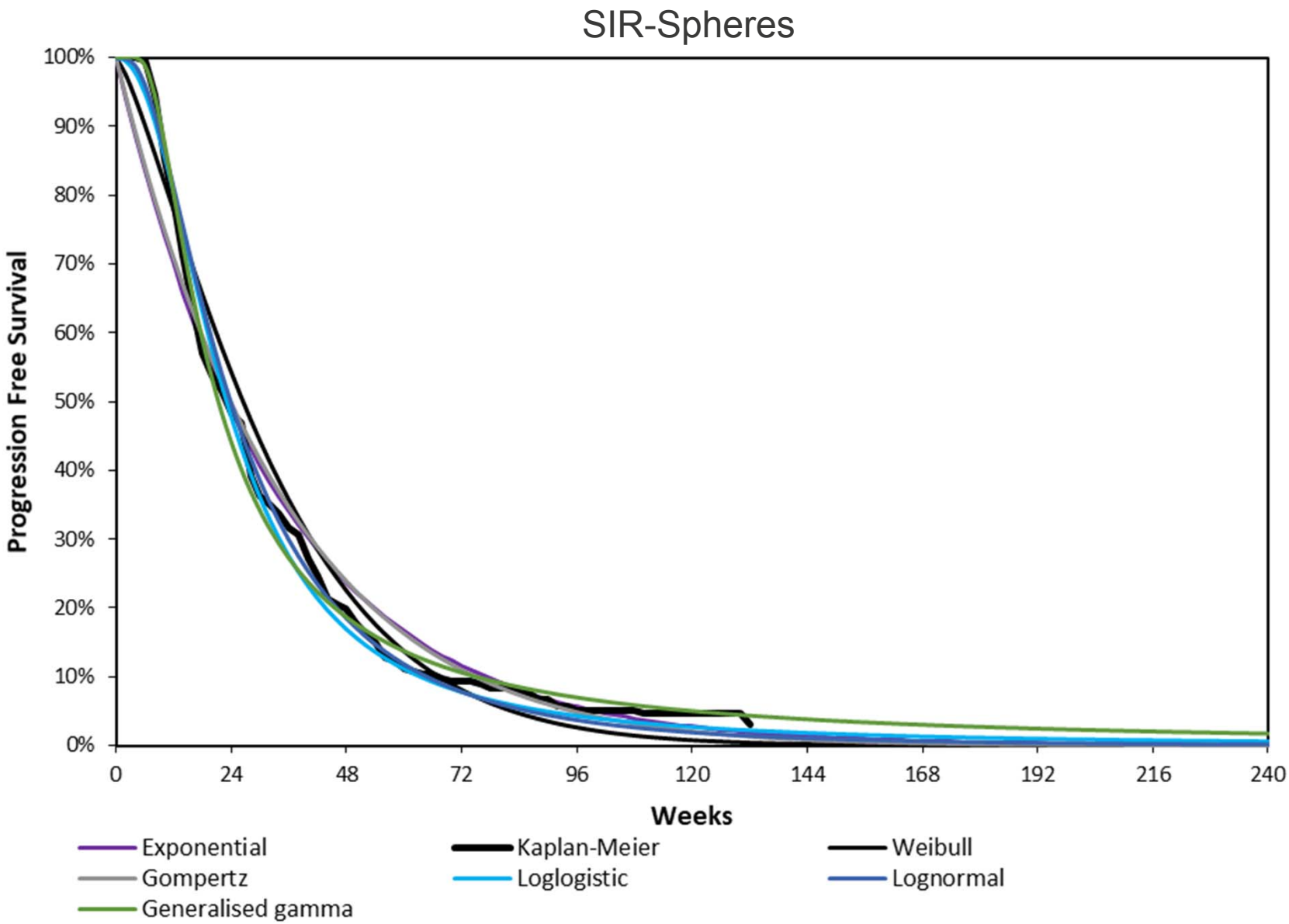
- Log-cumulative hazard plot of overall survival, for SIR-Spheres and sorafenib, from pooled SARAH and SIRveNIB dataset
  - Plot suggests that proportional hazard can be assumed and therefore HRs can be used
- AG used Weibull to fit OS and PFS curves in base case
  - Three better fitting curves not used because single HRs required to include lenvatinib and non-RCT TheraSphere studies
  - All 3 curve fits included in scenario analysis



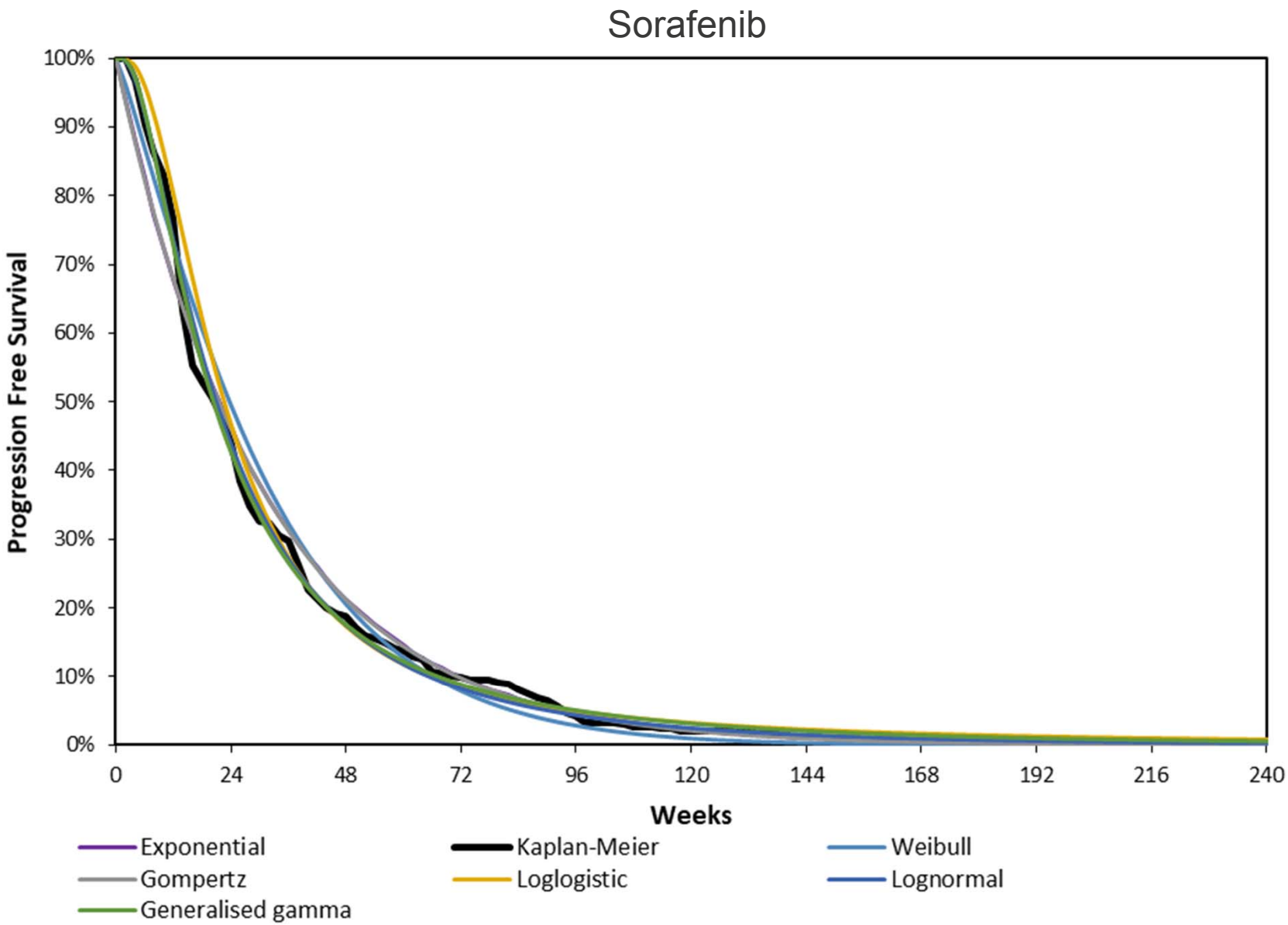
	SIR-Spheres		Sorafenib	
	AIC	BIC	AIC	BIC
Log-normal	2350	2358	3146	3154
Generalised gamma	2344	2355	3147	3159
Log-logistic	2358	2365	3144	3152
Weibull	2394	2401	3168	3176
Exponential	2412	2416	3173	3177
Gompertz	2413	2420	3175	3183

NICE

SIR-Spheres PFS model fits



Sorafenib PFS model fits



PFS model choice for base case depended on model fit and model properties to allow HR use for lenvatinib

- Log-cumulative hazard plot of overall survival, for SIR-Spheres and sorafenib, from pooled SARAH and SIRveNIB dataset
  - Plot suggests that proportional hazard can be assumed and therefore HRs can be used
- AG used Weibull to fit OS and PFS curves in base case
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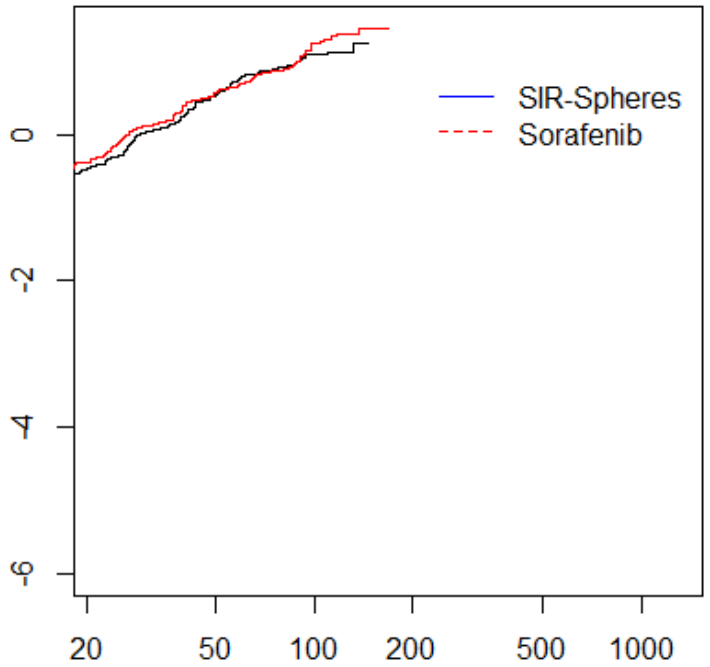
  - All 3 curve fits included in scenario analysis



	SIR-Spheres		Sorafenib	
	AIC	BIC	AIC	BIC
Generalised gamma	2226	2237	3120	3132
Log-normal	2246	2253	3120	3128
Log-logistic	2255	2262	3130	3138
Weibull	2313	2320	3182	3190
Exponential	2337	2341	3195	3199
Gompertz	2339	2346	3197	3205

Utility values and costs used in AG base case

Utility values

- Based on per-protocol population of SARAH, calculated by company (mapping EORTC-QLQ-C30 summary scores to EQ-5D using Longworth et al. algorithm)

Health State	Utility values		
	SIRT	Systemic therapy	Work-up no SIRT
Progression-free survival	0.71	0.70	0.70
Progressive disease	0.67	0.66	0.66
Post-transplant*	0.71	0.71	0.71

*AG Scenarios 6 & 10 only

Costs

- Derived from literature searches, previous NICE TAs, and company submissions
- Include:
  - treatment costs† (acquisition, procedures, and monitoring)
  - health service utilisation driven by disease status
  - adverse event management
- Cost for work-up procedure
  - £860.32 for SIR-Spheres and TheraSphere
  - [redacted] for QuiremSpheres (list price of QuiremScout)
- Disease management costs from company submission (resource survey 11 clinicians)

AG also explored sensitivity of using values from TA511

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†list price; results with PAS included are presented in part 2

Other base case assumptions

Downstaging to curative therapy not permitted

People who fail workup are modelled separately

SIRTs have similar efficacy

Bilobar treatments performed in two separate procedures

AG used a net benefit framework to present the relative cost-effectiveness of SIRTs with systemic therapies

- Net benefit framework used when there are a number of technologies under comparison, particularly when incremental costs and benefits are very similar
- Technologies with identical health outcomes and marginal differences in costs are often labelled as 'dominant/dominated' using incremental cost-effectiveness analysis with conventional decision rules
- NMB formula assigns a value to the additional QALYs generated by an intervention, and considers the opportunity cost associated with generating these health benefits

$$NMB = \lambda \times \Delta E - \Delta C$$

ΔE – difference in health effects
λ – threshold (here = £30,000 per QALY gained)
ΔC – difference in costs

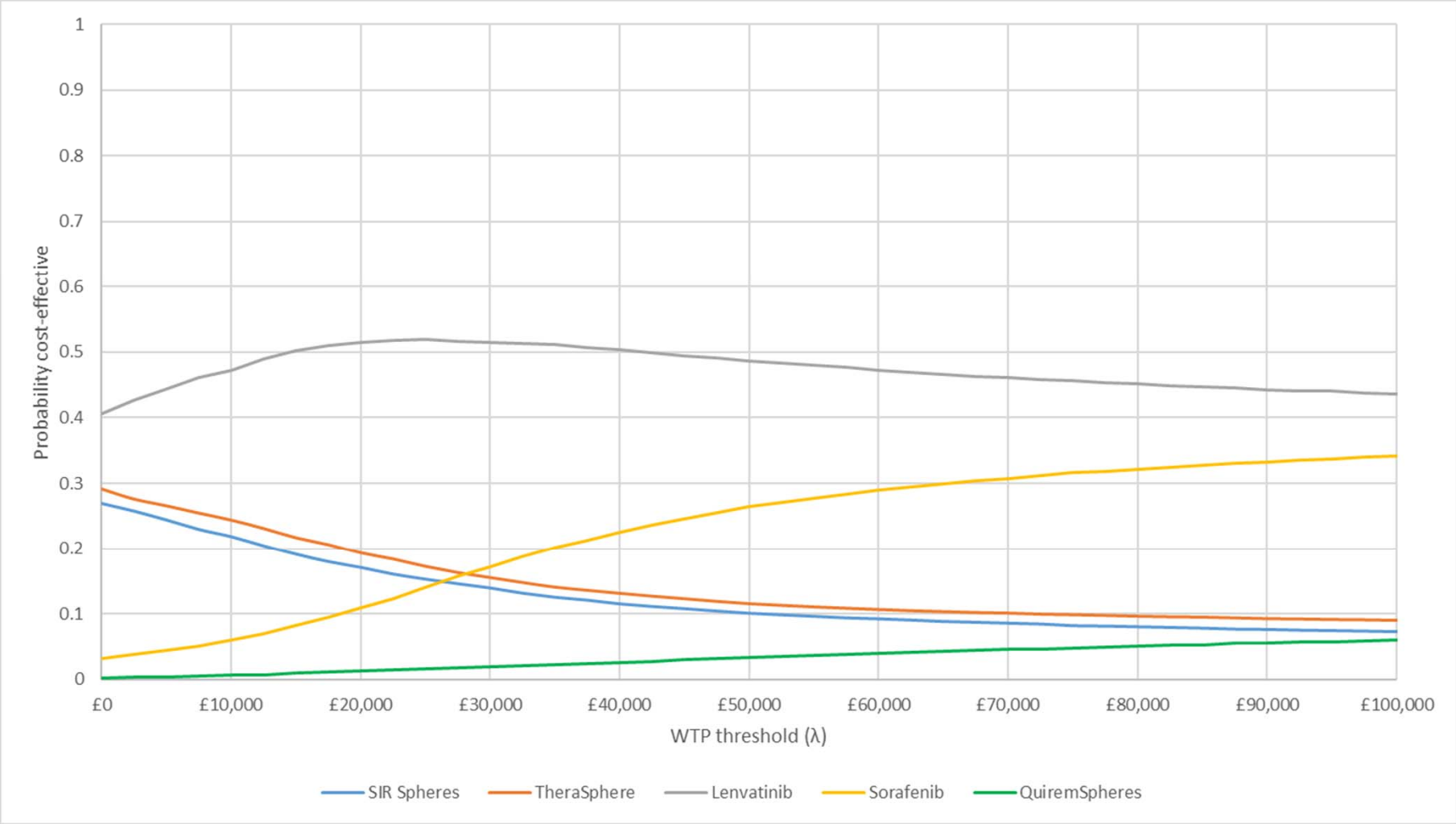
- If an intervention has an incremental NMB >0, then it would be considered more cost-effective than the baseline option, in this case, the least costly option
- NMB values can be directly compared, and show the monetary loss per patient of suboptimal strategies

AG base case results all treatment options (list price analysis)

Intervention	Total			Incremental (vs lowest cost)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB	
AG Deterministic base case								
TheraSphere	£29,888	1.110	0.764					
Lenvatinib	£30,005	1.183	0.805	£117	0.04	£2,911	£1,090	£2,911
SIR-Spheres	£30,107	1.110	0.764	£218	0.000	Dominated	-£218	Dominated
Sorafenib	£32,082	1.243	0.841	£2,194	0.076	£28,728	£97	£57,488
QuiremSpheres	£36,503	1.110	0.764	£6,614	0.000	Dominated	-£6,614	Dominated
AG Probabilistic base case								
Lenvatinib	£29,658	1.202	0.825					
TheraSphere	£30,014	1.111	0.765	£356	-0.060	Dominated	-£2,154	Dominated
SIR Spheres	£30,196	1.111	0.765	£538	-0.060	Dominated	-£2,323	Dominated
Sorafenib	£32,444	1.244	0.841	£2,786	0.016	£174,320	-£2,306	£174,320
QuiremSpheres	£36,613	1.111	0.765	£6,955	-0.060	Dominated	-£8,741	Dominated

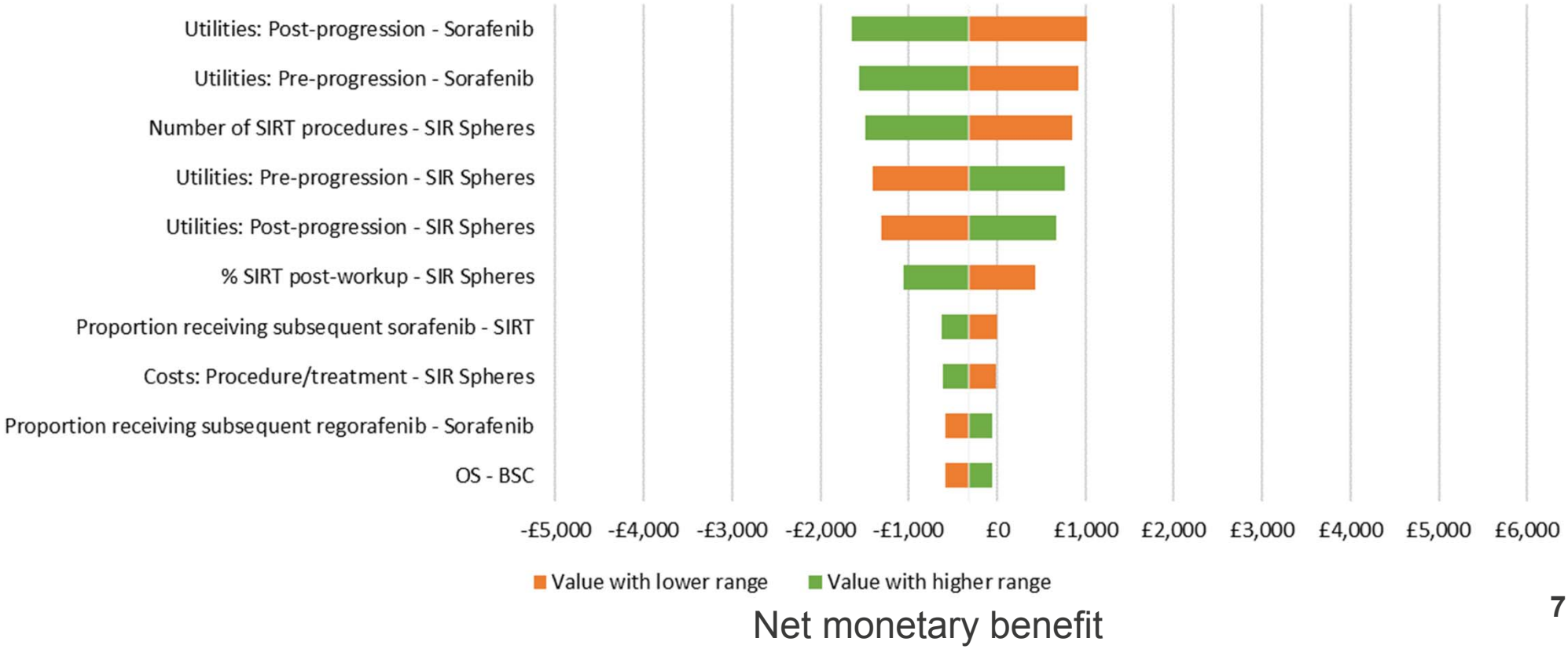
NMB, net monetary benefit

Cost-effectiveness acceptability curve for AG probabilistic base-case analysis



AG base case – deterministic scenario analyses when comparing SIR-Spheres with sorafenib (list price)

- AG considered sorafenib the most relevant comparator because of the existing direct evidence
- Most influential parameters – health state utilities, number of SIRT procedures and proportion of patients receiving SIRT after work-up



AG performed several scenario analyses

Scenario 1*	**Efficacy data from SARAH only** • Only data from SARAH included, might be more similar to UK population • SIRveNIB excluded (conducted in Asia)
Scenario 2*	**Low tumour burden/ALBI grade 1 subgroup** • Company's preferred post-hoc grouping of patients from the SARAH trial • Use of the higher low tumour burden/ALBI 1 subgroup utilities from the SARAH trial • Lower proportion of patients who receive work-up but not SIRT (8.1% vs 18.6%).
Scenario 3*	**No macroscopic vascular invasion (SARAH)** • Subgroup analysis – people who had no macroscopic vascular invasion (MVI) or portal vein invasion • Subgroup might benefit more from SIRT technologies because of more favourable positioning and spread of tumour • Subgroup identified in NICE's scope
Scenario 4*	**TheraSphere HR from Biederman and Van Der Gucht NMA scenario** • Hazard ratio derived from the AG's NMA scenario, inclusion of retrospective studies • Biederman et al. 2016 included only patients with MVI

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*AG provided deterministic and probabilistic sensitivity analyses

Other AG scenario analyses

Scenario 5	Utilities from lenvatinib TA511
Scenario 6	Downstaging to curative therapy possible (SARAH ITT proportions)
Scenario 7	Bilobar disease treated in same procedure
Scenario 8	Work-up costs from NHS Reference Costs (Sirtex assumption)
Scenario 9	Disease management costs taken from TA551
Scenario 10	Low tumour burden/ALBI 1 subgroup including possibility of downstaging
Scenario 11	Gompertz OS
Scenario 12	Exponential OS
Scenario 13	Generalised gamma OS (lenvatinib OS equal to sorafenib)
Scenario 14	Log-normal OS (lenvatinib OS equal to sorafenib)
Scenario 15	Log-logistic OS (lenvatinib OS equal to sorafenib)
Scenario 16	5% work-up/no SIRT
Scenario 17	SIRveNIB work-up/no SIRT (28.57%)

Incremental net monetary benefit at £30K WTP – lenvatinib almost always ranked first (list price analysis)

Intervention	Incremental NMB Rank																	
	Base case*	S1*	S2*	S3*	S4*	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14	S15	S16	S17
SIR-Spheres	4	4	2	4	4	4	2	3	4	3	2	4	4	3	4	4	4	3
TheraSphere	2	3	**1**	3	**1**	3	**1**	2	3	2	**1**	3	3	2	3	3	3	2
QuiremSpheres	5	5	5	5	5	5	5	5	5	5	3	5	5	5	5	5	5	5
Lenvatinib	**1**	**1**	3	**1**	2	**1**	3	**1**	**1**	**1**	4	**1**	**1**	**1**	**1**	**1**	**1**	**1**
Sorafenib	3	2	4	2	3	2	4	4	2	4	5	2	2	4	2	2	2	4

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*probabilistic analysis

Scenario 1 – Efficacy data from SARAH only (list price analysis)

Intervention	Total			Incremental (vs lowest cost)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB	
Deterministic Scenario 1								
TheraSphere	£29,395	0.976	0.671					
SIR Spheres	£29,614	0.976	0.671	£218	0.000	Dominated	-£218	Dominated
Lenvatinib	£29,893	1.150	0.782	£498	0.111	£4,475	£2,840	£4,475
Sorafenib	£31,951	1.209	0.817	£2,556	0.147	£17,424	£1,845	£58,080
QuiremSpheres	£36,010	0.976	0.671	£6,614	0.000	Dominated	-£6,614	Dominated
Probabilistic Scenario 1								
Lenvatinib	£29,413	1.171	0.805					
TheraSphere	£29,476	0.978	0.672	£62	-0.133	Dominated	-£4,044	Dominated
SIR Spheres	£29,660	0.977	0.671	£246	-0.134	Dominated	-£4,267	Dominated
Sorafenib	£32,300	1.213	0.818	£2,887	0.014	£212,505	-£2,479	£212,505
QuiremSpheres	£36,064	0.977	0.670	£6,650	-0.134	Dominated	-£10,684	Dominated

NMB, net monetary benefit

Scenario 2 – Low tumour burden/ALBI grade 1 subgroup (list price analysis)

Intervention	Total			Incremental (vs lowest cost)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB	
Deterministic Scenario 2								
Lenvatinib	£31,388	1.366	1.000					
Sorafenib	£33,388	1.420	1.037	£2,000	0.038	£53,320	-£875	Dominated
TheraSphere	£34,021	1.542	1.153	£2,633	0.153	£17,175	£1,966	£17,175
SIR Spheres	£34,267	1.542	1.153	£2,879	0.153	£18,783	£1,720	Dominated
QuiremSpheres	£40,931	1.542	1.153	£9,543	0.153	£62,257	-£4,945	Dominated
Probabilistic Scenario 2								
Lenvatinib	£31,233	1.397	1.024					
Sorafenib	£33,834	1.436	1.048	£2,601	0.024	£109,709	-£1,890	Dominated
TheraSphere	£34,086	1.552	1.161	£2,854	0.136	£20,926	£1,237	£20,926
SIR Spheres	£34,389	1.553	1.163	£3,156	0.139	£22,725	£1,010	£119,562
QuiremSpheres	£41,088	1.552	1.162	£9,855	0.138	£71,372	-£5,712	Dominated

NMB, net monetary benefit

Scenario 3 – No macroscopic vascular invasion (SARAH) (list price analysis)

Intervention	Total			Incremental (vs lowest cost)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB	
Deterministic Scenario 3								
TheraSphere	£29,949	1.272	0.740					
SIR Spheres	£30,167	1.326	0.740	£218	0.000	Dominated	-£218	Dominated
Lenvatinib	£30,399	1.078	0.865	£451	0.125	£3,594	£3,310	£3,594
Sorafenib	£32,452	1.078	0.897	£2,503	0.157	£15,923	£2,213	£64,437
QuiremSpheres	£36,563	1.078	0.740	£6,614	0.000	Dominated	-£6,614	Dominated
Probabilistic Scenario 3								
Lenvatinib	£29,983	1.296	0.893					
TheraSphere	£30,093	1.335	0.743	£110	-0.149	Dominated	-£4,585	Dominated
SIR Spheres	£30,287	1.083	0.744	£304	-0.149	Dominated	-£4,765	Dominated
Sorafenib	£32,852	1.082	0.905	£2,868	0.012	£23,195	-£2,507	£238,195
QuiremSpheres	£36,683	1.081	0.745	£6,699	-0.148	Dominated	-£11,134	Dominated

NMB, net monetary benefit;

Scenario 4 – TheraSphere HR from Biederman and Van Der Gucht NMA scenario (list price analysis)

Intervention	Total			Incremental (vs lowest cost)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB	
Deterministic Scenario 4								
Lenvatinib	£30,005	1.183	0.805					
SIR Spheres	£30,107	1.110	0.764	£101	-0.040	Dominated	-£1,308	Dominated
Sorafenib	£32,082	1.243	0.841	£2,077	0.036	£57,488	-£993	Dominated
TheraSphere	£33,373	1.883	1.297	£3,368	0.493	£6,835	£11,413	£6,835
QuiremSpheres	£36,503	1.110	0.764	£6,497	-0.040	Dominated	-£7,705	Dominated
Probabilistic Scenario 4								
Lenvatinib	£29,601	1.197	0.822					
SIR Spheres	£30,242	1.110	0.764	£641	-0.058	Dominated	-£2,387	Dominated
Sorafenib	£32,477	1.244	0.843	£2,876	0.021	£140,205	-£2,260	Dominated
TheraSphere	£33,670	1.931	1.330	£4,068	0.507	£8,017	£11,156	£8,017
QuiremSpheres	£36,616	1.111	0.765	£7,014	-0.058	Dominated	-£8,746	Dominated

NMB, net monetary benefit

Scenario 10 – Low tumour burden/ALBI 1 subgroup including downstaging (list price analysis)

Intervention	Total			Incremental (vs lowest cost)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB	
Deterministic Scenario 4								
Lenvatinib	£31,072	1.404	1.029					
TheraSphere	£31,255	1.752	1.316	£183	0.286	£639	£8,407	£639
SIR Spheres	£31,501	1.752	1.316	£429	0.286	£1,499	£8,160	Dominated
Sorafenib	£33,007	1.457	1.066	£1,935	0.037	£52,685	-£833	Dominated
QuiremSpheres	£38,166	1.752	1.316	£7,094	0.286	£24,775	£1,496	Dominated

NMB, net monetary benefit

Assessment Group comments on scenario 10:

- Low tumour burden/ALBI 1 is not a clinically recognised subgroup
- Based on a post-hoc analysis → breaks randomisation
- Downstaging is rare and is currently largely experimental

Responding to stakeholder comments AG conducted analysis with same work-up costs (list price analysis)

- Incremental net monetary benefit at £30K WTP
  - QuiremSpheres ranks 5th in 4 out of the 6 scenarios

Intervention	Incremental NMB Rank					
	Base case	S1	S2	S3	S4	S10
SIR-Spheres	4	4	2	4	4	2
TheraSphere	3	3	**1**	3	**1**	**1**
QuiremSpheres	5	5	4	5	5	3
Lenvatinib	**1**	**1**	3	**1**	2	4
Sorafenib	2	2	5	2	3	5

Base case results with same work-up costs (list price analysis)

Intervention	Total			Incremental (vs lowest cost)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB	
AG Deterministic base case								
TheraSphere	£29,888	1.110	0.764					
Lenvatinib	£30,005	1.183	0.805	£117	0.040	£2,911	£1,090	£2,911
SIR Spheres	£30,107	1.110	0.764	£218	0.000	Dominated	-£218	Dominated
QuiremSpheres	£31,868	1.110	0.764	£1,980	0.000	Dominated	-£1,980	Dominated
Sorafenib	£32,082	1.243	0.841	£2,194	0.076	£28,728	£97	£57,488

NMB, net monetary benefit

Scenarios same work-up – deterministic analyses (1/3)

Intervention	Total			Incremental (vs lowest cost)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB	
Scenario 1 – Efficacy data from SARAH only								
TheraSphere	£29,395	0.976	0.671					
SIR Spheres	£29,614	0.976	0.671	£218	0.000	Dominated	-£218	Dominated
Lenvatinib	£29,893	1.150	0.782	£498	0.111	£4,475	£2,840	£4,475
QuiremSpheres	£31,375	0.976	0.671	£1,980	0.000	Dominated	-£1,980	Dominated
Sorafenib	£31,951	1.209	0.817	£2,556	0.147	£17,424	£1,845	£58,080
Scenario 2 – Low tumour burden/ALBI grade 1 subgroup								
Lenvatinib	£31,388	1.366	1.000					
Sorafenib	£33,388	1.420	1.037	£2,000	0.038	£53,320	-£875	Dominated
TheraSphere	£34,021	1.542	1.153	£2,633	0.153	£17,175	£1,966	£17,175
SIR Spheres	£34,267	1.542	1.153	£2,879	0.153	£18,783	£1,720	Dominated
QuiremSpheres	£36,256	1.542	1.153	£4,868	0.153	£31,759	-£270	Dominated

NMB, net monetary benefit

Scenarios same work-up – deterministic analyses (2/3)

Intervention	Total			Incremental (vs lowest cost)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB	
Scenario 3 – No macroscopic vascular invasion (SARAH)								
TheraSphere	£29,949	1.078	0.740					
SIR Spheres	£30,167	1.078	0.740	£218	0.000	Dominated	-£218	Dominated
Lenvatinib	£30,399	1.272	0.865	£451	0.125	£3,594	£3,310	£3,594
QuiremSpheres	£31,929	1.078	0.740	£1,980	0.000	Dominated	-£1,980	Dominated
Sorafenib	£32,452	1.326	0.897	£2,503	0.157	£15,923	£2,213	£64,437
Scenario 4 – TheraSphere HR from Biederman and Van Der Gucht NMA Scenario								
Lenvatinib	£30,005	1.183	0.805					
SIR Spheres	£30,107	1.110	0.764	£101	-0.040	Dominated	-£1,308	Dominated
QuiremSpheres	£31,868	1.110	0.764	£1,863	-0.040	Dominated	-£3,070	Dominated
Sorafenib	£32,082	1.243	0.841	£2,077	0.036	£57,488	-£993	Dominated
TheraSphere	£33,373	1.883	1.297	£3,368	0.493	£6,835	£11,413	£6,835

NMB, net monetary benefit

Scenarios same work-up – deterministic analyses (3/3)

Intervention	Total			Incremental (vs lowest cost)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB	
Scenario 10 – Low tumour burden/ALBI 1 subgroup including 13.5% downstaging								
Lenvatinib	£31,072	1.404	1.029					
TheraSphere	£31,467	1.736	1.303	£395	0.274	£1,440	£7,826	£1,440
SIR Spheres	£31,713	1.736	1.303	£641	0.274	£2,339	£7,579	Dominated
Sorafenib	£33,007	1.457	1.066	£1,935	0.037	£52,685	-£833	Dominated
QuiremSpheres	£33,702	1.736	1.303	£2,630	0.274	£9,599	£5,590	Dominated

NMB, net monetary benefit

Assessment Group comments on scenario 10:

- Low tumour burden/ALBI 1 is not a clinically recognised subgroup
- Based on a post-hoc analysis → breaks randomisation
- Downstaging is rare and is currently largely experimental

Responding to stakeholder comments AG conducted analysis without lenvatinib (list price analysis)

- Incremental net monetary benefit at £30K WTP

Intervention	Incremental NMB Rank					
	Base case	S1	S2	S3	S4	S10
SIR-Spheres	3	3	2	3	3	2
TheraSphere	2	2	**1**	2	**1**	**1**
QuiremSpheres	4	4	4	4	4	3
Sorafenib	**1**	**1**	3	**1**	2	4

Base case results excl. lenvatinib (list price analysis)

Intervention	Total			Incremental (vs lowest cost)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB	
AG Deterministic base case								
TheraSphere	£29,888	1.110	0.764					
SIR Spheres	£30,107	1.110	0.764	£218	0.000	Dominated	-£218	Dominated
Sorafenib	£32,082	1.243	0.841	£2,194	0.076	£28,728	£97	£28,728
QuiremSpheres	£36,503	1.110	0.764	£6,614	0.000	Dominated	-£6,614	Dominated
AG Probabilistic base case								
TheraSphere	£30,017	1.111	0.765					
SIR Spheres	£30,230	1.111	0.765	£213	0.000	Dominated	-£217	Dominated
Sorafenib	£32,495	1.244	0.841	£2,478	0.077	£32,302	-£177	£32,302
QuiremSpheres	£36,618	1.111	0.765	£6,600	0.000	Dominated	-£6,604	Dominated
AG Deterministic base case with generalised gamma								
TheraSphere	£30,992	1.277	0.875					
SIR Spheres	£31,211	1.277	0.875	£218	0.000	Dominated	-£218	Dominated
Sorafenib	£32,854	1.357	0.916	£1,862	0.040	£46,103	-£650	£46,103
QuiremSpheres	£37,607	1.277	0.875	£6,614	0.000	Dominated	-£6,614	Dominated

NMB, net monetary benefit

- AG used Weibull and generalised gamma for base case analysis
- AG used Weibull in all scenarios

Scenarios excl. lenvatinib – deterministic analyses (1/2)

Intervention	Total			Incremental (vs lowest cost)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB	
Deterministic scenario 1 – Efficacy data from SARAH only								
TheraSphere	£29,395	0.976	0.671					
SIR Spheres	£29,614	0.976	0.671	£218	0.000	Dominated	-£218	Dominated
Sorafenib	£31,951	1.209	0.817	£2,556	0.147	£17,424	£1,845	£17,424
QuiremSpheres	£36,010	0.976	0.671	£6,614	0.000	Dominated	-£6,614	Dominated
Deterministic scenario 2 – Low tumour burden/ALBI grade 1 subgroup								
Sorafenib	£33,388	1.420	1.037					
TheraSphere	£34,021	1.542	1.153	£633	0.116	£5,466	£2,841	£5,466
SIR Spheres	£34,267	1.542	1.153	£879	0.116	£7,594	£2,594	Dominated
QuiremSpheres	£40,931	1.542	1.153	£7,544	0.116	£65,152	-£4,070	Dominated
Deterministic scenario 3 – No macroscopic vascular invasion (SARAH)								
TheraSphere	£29,949	1.078	0.740					
SIR Spheres	£30,167	1.078	0.740	£218	0.000	Dominated	-£218	Dominated
Sorafenib	£32,452	1.326	0.897	£2,503	0.157	£15,923	£2,213	£15,923
QuiremSpheres	£36,563	1.078	0.740	£6,614	0.000	Dominated	-£6,614	Dominated

NMB, net monetary benefit

Scenarios excl. lenvatinib – deterministic analyses (2/2)

Intervention	Total			Incremental (vs lowest cost)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB	
Deterministic scenario 4 – TheraSphere HR from Biederman and Van Der Gucht NMA								
SIR Spheres	£30,107	1.110	0.764					
Sorafenib	£32,082	1.243	0.841	£1,976	0.076	£25,870	£315	Dominated
TheraSphere	£33,373	1.883	1.297	£3,267	0.533	£6,130	£12,722	£6,130
QuiremSpheres	£36,503	1.110	0.764	£6,396	0.000	Dominated	-£6,396	Dominated
Deterministic scenario 10 – Low tumour burden/ALBI 1 subgroup with downstaging								
TheraSphere	£31,255	1.752	1.316					
SIR Spheres	£31,501	1.752	1.316	£246	0.000	Dominated	-£246	Dominated
Sorafenib	£33,007	1.457	1.066	£1,752	-0.250	Dominated	-£9,240	Dominated
QuiremSpheres	£38,166	1.752	1.316	£6,911	0.000	Dominated	-£6,911	Dominated

NMB, net monetary benefit

Assessment Group comments on scenario 10:

- Low tumour burden/ALBI 1 is not a clinically recognised subgroup
- Based on a post-hoc analysis → breaks randomisation
- Downstaging is rare and is currently largely experimental

AG model for CTT-ineligible population

Cost-effectiveness results (AG model – list price analysis)

- AG produced model for CTT-ineligible population only
- When all treatment options are included:
  - Lenvatinib is the least costly treatment and ranks first in most scenarios at a WTP of £30K
  - In probabilistic base case (Child-Pugh A population) SIRTs are more costly and less effective than lenvatinib
  - In low tumour burden and good liver function population (scenario 2) ICERs for TheraSphere and SIR-Spheres were £17,175 and £18,783 per QALY gained versus lenvatinib
  - In narrower population and downstaging (scenario 10) ICERs for TheraSphere, SIR-Spheres and QuiremSpheres were to £639, £1,499 and £24,775 per QALY gained versus lenvatinib
- When lenvatinib is excluded:
  - TheraSphere is the least costly treatment and ranks first in most looked-at scenarios

Stakeholder comments – base case assumptions

- Lenvatinib is not widely used in NHS; comparison to lenvatinib not relevant to UK
- Clinical evidence does not support equivalent effectiveness for SIRTs
- Downstaging should be included in base case; there is evidence that SIRTs increases use of curative treatments
- Bilobar disease can be treated with SIR-Spheres in single procedure

AG model for CTT-ineligible population

Stakeholder comments

Structure/modelling

- State occupancy is incorrectly modelled; some are modelled independently and others via relative effects
- Sorafenib OS data pooling is misleading as no detail is provided
- In base case OS and PFS should be modelled with lognormal
- Time to treatment should be fitted with lognormal function to patient level data

Inputs

- *Costs*
  - There are no additional imaging costs for SIR-Spheres
  - Similar work-up costs for all SIRTs should be assumed
- *Population*
  - Scenario analysis needed that aligns SARAH and REFLECT population (see NMA comment)

What is the most appropriate comparator for CTT-ineligible population?

Is it appropriate to assume that SIRTs have equal effectiveness?

Is it appropriate to include downstaging in base-case model (ineligible for CTT)?

Can bilobar disease be treated in a single procedure?

What is the most appropriate model to extrapolate OS and PFS?

Critique on missing AG models for population eligible for transplant and CTT-eligible population

Adults with unresectable HCC	
Eligible for transplant	Eligible for conventional transarterial therapies
AG • Did not conduct NMA because of lack of evidence in this population • Did not conduct cost-effectiveness analysis	**AG** • NMA results very uncertain • Weak link between CTTs and SIRTs • No evidence for downstaging in this population • Did not conduct cost-effectiveness analysis
Stakeholder comments • Agree with limited evidence • ESMO guidelines suggest SIRT as alternative • SIRT could be a potential treatment option in this population • Non-comparative evidence supports benefit in specific groups in this population	**Stakeholder comment** • Proportion of people might be unsuitable for CTT and this group is likely to benefit from SIRT • NMA and cost-effectiveness analysis provided by companies should be considered for decision making

Is there enough evidence to perform robust NMAs and cost-effectiveness analyses in these populations?
Should the company models be considered for the CTT-eligible population?

End of life criteria extension of life ≥3 months a not satisfied in most scenarios

Criterion		Evaluation
Life expectancy <24 months	✓	• Life expectancy for people ineligible for CTT is less than 24 months • Expected mean survival lenvatinib 14.72 months • Expected mean survival sorafenib 15.49 months
Extension of life ≥3 months	?	• Base case: SIRTs inferior to systemic therapies

Subgroup	Incremental undiscounted LYGs (months)	
	SIRT vs lenvatinib	SIRT vs sorafenib
AG base-case (no downstaging)	-0.95	-1.73
AG base-case (with downstaging)	0.11	-0.65
Low tumour/ALBI 1 subgroup (no downstaging)	2.80	2.11
Low tumour/ALBI 1 subgroup (with downstaging)	5.30	4.61
MVI subgroup (no downstaging)	-2.49	-3.18
MVI subgroup (with downstaging)	-1.51	-2.19

Innovation and equality

Innovation

Companies

- SIR-Spheres can alter treatment paradigm
- SIR-Spheres can offer chance of potentially curative therapy to people who would not otherwise have this option
- QuiremScout and QuiremSpheres enable more personalised procedure by improved patient selection

Patient organisation

- Targeted treatment option delivering small beads directly to tumours

Equality

Patient organisation

- Concerned about equality to access; needs clear referral pathway

Authors

Verena Wolfram
Technical Lead

Jamie Elvidge
Technical Adviser

with input from the Lead Team (Matt Stevenson, Richard Nicholas and Ugochi Nwulu) and committee chair (Stephen O’Brien)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Selective internal radiation therapies for treating hepatocellular carcinoma (ID1276)

Clarification questions

June 2019

File name	Version	Contains confidential information	Date
To BTG	Final for company	No	14.06.2019

Notes for company

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Section A: Clarification on effectiveness data

Trial data for STOP-HCC

A 1. Please provide any clinical effectiveness data available for the ongoing STOP-HCC trial including any available data on overall survival, progression free survival, time to down staging, proportion downstaged and adverse event data for the ITT and per protocol populations as well as the following subgroups of patients:

a) Patients with portal vein thrombosis or portal vein invasion.

b) Patients with Child-Pugh A

c) Patients with Child-Pugh A and no portal vein thrombosis or portal vein invasion.

d) Patients with ≤25% tumour burden and ALBI grade 1 (with and without portal vein thrombosis/portal vein invasion),

e) Patients who have previously failed treatment with chemoembolization,

f) Patients with Child-Pugh A and have previously failed treatment with chemoembolization.

[Company: please enter your answer to this question here]

A 2. Please also provide the requested overall survival and progression free survival data censored for downstaging, if applicable.

[Company: please enter your answer to this question here]

A 3. If these data are not available, can you please advise us on when any data from the STOP-HCC trial are likely to be available?

[Company: please enter your answer to this question here]

Clinician input

A 4. Please provide the following additional information regarding the elicitation of clinical expert opinion that was used to inform resource use inputs in the model (detailed in Appendix M of the submission):

a) **Please provide information on the clinical experts that are referred to. How many clinical experts were consulted? What were their titles, their specialties and experience in the treatment of patients with HCC?**

b) How was their opinion elicited (for example, through a survey, at an advisory board)?

c) If a survey was developed, please describe how these were developed and how they were completed by the clinicians. Please send completed questionnaires from the clinicians.

d) If any advisory board was undertaken, please describe what topics were covered.

e) We would specifically like to verify how the resource use data estimates were synthesised from the clinician responses – please provide estimates provided by the clinicians, and how these values were

combined to produce the values used in the submission (Table M1 to M9 in Appendix M).

[Company: please enter your answer to this question here]

A 5. Clinical expert opinion was referred to on a number of occasions in the submission (page 25 114, 127 of the submission). Please describe how this expert clinical advice was obtained, and provide transcripts of any discussions that were held.

[Company: please enter your answer to this question here]

Section B: Clarification on cost-effectiveness data

B1. The two executable cost-effectiveness models (TAE eligible and TAE ineligible) appear to contain a number of calculation errors and ambiguities. Please confirm these errors, and provide updated executable models.

a) In both models, health state utilities appear to be age-adjusted using an inappropriate method. A decrement was applied to the prior to the first cycle of model, which resulted in the baseline utilities being adjusted lower than they should have been (for example, the watch and wait utility was adjusted from 0.75 to 0.53). The utility values are from age-appropriate sources and age-adjustment should only apply from the first cycle of the model.

b) The process to derive transition probabilities for each treatment arm for the transitions to "Watch and wait", "Pharmacological management" and "Pre-Transplant" (the top table on the "Effectiveness" sheet) is unclear. Please describe how the mean time to downstaging was used to estimate these probabilities, why only the rate observed in the TheraSphere arm of the trial was applied to both arms, and whether it is reasonable to assume that the probability of remaining in the "Watch and wait" health state is the same in each arm. This concern is further supported by the fact that the model appears to

underestimate the total number of patients transitioning to the pre-transplant state in both treatment arms in the model, which should be equal to the total proportion who downstage (i.e. 58% and 38% for TheraSphere and cTACE respectively).

c) There are a number of calculations e.g. those relating to mortality, where it appears that the calculation was undertaken outside of the model. Please update the model so all model calculations are undertaken within the model.

[Company: please enter your answer to this question here]

B2. Please provide further information on the source of the SIRT work-up procedure cost (£467.91) used in the model, and the costs you anticipate will be associated with the work-up procedure for TheraSphere.

[Company: please enter your answer to this question here]

Section C: Textual clarification and additional points

C1. Please can the company provide the WinBUGS code used to conduct the network meta-analyses. Please provide all files required to run the NMA for all models presented. These should include all input data, initial values for each chain and the value of mx, and the centring constant.

[Company: please enter your answer to this question here]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Selective internal radiation therapies for treating hepatocellular carcinoma (ID1276)

Clarification questions

July 2019

File name	Version	Contains confidential information	Date
To SIRTEX	Final for company	No	05.07.19

Notes for company

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Section A: Clarification on effectiveness data

Trial data

A 1. Please provide overall survival and progression free survival data including numbers at risk for the SIRTACE RCT.

[Company: please enter your answer to this question here]

A 2. Please provide overall survival, progression free survival, time to down staging, proportion downstaged and adverse event data for the following subgroups of patients in the SARAH and SIRveNIB RCTs:

a) **Patients with portal vein thrombosis or portal vein invasion,**

b) **Patients with Child-Pugh A,**

c) **Patients with Child-Pugh A and no portal vein thrombosis or portal vein invasion,**

d) **Patients with ≤25% tumour burden and ALBI grade 1 (with and without portal vein thrombosis/portal vein invasion),**

e) **Patients who have previously failed treatment with chemoembolization,**

f) **Patients who are Child-Pugh and have previously failed treatment with chemoembolization.**

[Company: please enter your answer to this question here]

A 3. Please provide the requested overall survival and progression free survival data censored for downstaging for the SARAH and SIRveNIB RCTs.

[Company: please enter your answer to this question here]

A 4. Please provide further data on the patients who were downstaged in the SARAH and SIRveNIB RCTs; the proportion of patients in each treatment group who received transplant and the proportion of patients who received resection and the associated costs, for the 'ITT', 'per protocol' and '≤25% tumour burden and ALBI grade 1' subgroups.

[Company: please enter your answer to this question here]

A 5. Can you please provide further information on whether concomitant use of sorafenib or other systemic therapy was permitted in the SARAH and SIRVeNIB trials for patients who received SIR-Spheres. If this was permitted can you provide information on the proportion of patients which received systemic therapy and the duration of therapy.

[Company: please enter your answer to this question here]

A 6. Please provide overall survival, progression free survival (including numbers at risk), time to down staging, proportion downstaged, and adverse event data for the SORAMIC RCT, for the six subgroups listed in Question 2.

[Company: please enter your answer to this question here]

A 7. Please also provide the requested overall survival and progression free survival data from SORAMIC censored for downstaging, if applicable.

[Company: please enter your answer to this question here]

A 8. If the data requested in Questions 6 and 7 are not available, can you please advise us on when any data from the SORAMIC trial are likely to be available?

[Company: please enter your answer to this question here]

A 9. Please provide the audit data for reference 18 'Sirtex. Data on file. 2019'.

[Company: please enter your answer to this question here]

A 10. Please provide overall survival, progression free survival, proportion downstaged, and adverse event data for the ITT, and per protocol, and high function/low tumour burden populations of the SARAH and SIRveNIB trials.

[Company: please enter your answer to this question here]

A 11. Please provide overall survival, progression free survival, proportion downstaged, and adverse event data for the patients allocated to receive SIRT in SARAH and SIRveNIB who underwent a workup procedure but did not go on to receive SIRT.

[Company: please enter your answer to this question here]

Section B: Clarification on cost-effectiveness data

B1. Please provide an explanation of the calculations in cells AZ23:202 in the executable model and check that these are correct, as they appear to imply negative costs.

[Company: please enter your answer to this question here]

B2. The percentage of patients receiving subsequent therapy reported in Table 23 of the main submission do not add up to 100%. Can you please explain why?

[Company: please enter your answer to this question here]

B3. Please provide the following additional information regarding the advisory board data (references 5, 8, 39):

a) Completed questionnaires from clinicians (Appendix J, Section 2),

b) **We would specifically like to verify how the resource use data estimates were synthesised from clinician responses – please provide estimates provided by the clinicians and how these values were combined to produce the values used in the submission (Table 77 in Appendix O),**

c) **Transcripts of the three advisory board meetings,**

d) **In addition, we would also like additional details of the clinicians' discussions around the following: (i) discussion around the clinical relevance of the low tumour burden subgroup (page 39 of the submission), (ii) details of the SIRT work-up procedure and SIRT treatment eligibility (page 52-53 of the submission), (iii) number of work-up procedures (page 64 of submission).**

[Company: please enter your answer to this question here]

B4. Please provide further information about the source of the SIR Spheres work-up procedure cost used in the model, and detail the costs you would anticipate to be associated with work-up in practice

[Company: please enter your answer to this question here]

Section C: Textual clarification and additional points

C1. Please can the company provide the WinBUGS code used to conduct the network meta-analyses. Please provide all files required to run the NMA for all models presented. These should include all input data, initial values for each chain and the value of mx, and the centring constant.

[Company: please enter your answer to this question here]

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Selective internal radiation therapies for treating hepatocellular carcinoma (ID1276)

Clarification questions

June 2019

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Section A: Clarification on effectiveness data

Trial data for STOP-HCC

A 1. Please provide any clinical effectiveness data available for the ongoing STOP-HCC trial including any available data on overall survival, progression free survival, time to down staging, proportion downstaged and adverse event data for the ITT and per protocol populations as well as the following subgroups of patients:

a) Patients with portal vein thrombosis or portal vein invasion.

b) Patients with Child-Pugh A

c) Patients with Child-Pugh A and no portal vein thrombosis or portal vein invasion.

d) Patients with ≤25% tumour burden and ALBI grade 1 (with and without portal vein thrombosis/portal vein invasion),

e) Patients who have previously failed treatment with chemoembolization,

f) Patients with Child-Pugh A and have previously failed treatment with chemoembolization.

There is no outcome data available as the study is still ongoing at this time.

A 2. Please also provide the requested overall survival and progression free survival data censored for downstaging, if applicable.

There is no outcome data available as the study is still ongoing at this time.

A 3. If these data are not available, can you please advise us on when any data from the STOP-HCC trial are likely to be available?

The current anticipation for last patient last visit is February 2020. After this last visit, data needs to be cleaned and locked and analysed. However, since the outcome of the study is event driven, final results are not anticipated before at least December 2020.

Clinician input

A 4. Please provide the following additional information regarding the elicitation of clinical expert opinion that was used to inform resource use inputs in the model (detailed in Appendix M of the submission):

a) **Please provide information on the clinical experts that are referred to. How many clinical experts were consulted? What were their titles, their specialties and experience in the treatment of patients with HCC?**

Please refer to the list below for clinical experts consulted. All have experience in managing patients with HCC.

Delegate	Hospital	Speciality
Peter Littler	Freeman Hospital Newcastle upon Tyne	Consultant Interventional Radiologist
Matthew Hoare	Addenbrooke's Hospital	Consultant Hepatologist
Nadeem Shaida	Addenbrooke's Hospital	Consultant Interventional Radiologist
Phil Boardman	Oxford University Hospitals	Consultant Interventional Radiologist

Homoyon Mehrzad	University Hospitals Birmingham NHS Foundation Trust	Consultant Interventional Radiologist
Dan Palmer	Royal Liverpool University Hospital	Consultant Medical Oncologist
Derek Manas	Freeman Hospital Newcastle upon Tyne	Consultant Hepatobiliary and Transplant Surgeon
Andreas Prachalias	King's College Hospital, London	Consultant Liver and Pancreatic Surgeon
Aileen Marshal	Royal Free Hospital, London	Consultant Hepatologist
Gill Vivian	King's College Hospital	Consultant in Nuclear Medicine
Jonathan Evans	Royal Liverpool University Hospital	Consultant Radiologist
Sachin Modi	Southampton General Hospital	Consultant Interventional Radiologist
Tim Cross	Royal Liverpool	Consultant Hepatologist
Jon Bell	The Christie Manchester	Consultant Interventional Radiologist
Richard Hubner	The Christie Manchester	Consultant oncologist

b) **How was their opinion elicited (for example, through a survey, at an advisory board)?**

Opinion was elicited through advisory boards and one to one meetings.

c) **If a survey was developed, please describe how these were developed and how they were completed by the clinicians. Please send completed questionnaires from the clinicians.**

A survey was not developed.

d) **If any advisory board was undertaken, please describe what topics were covered.**

Advisory Board 1, 23rd January 2019, Manchester

Agenda Item	Task/Key Questions
Introductions Chair	• Understand background/role of expert physician • Share meeting objectives
The NICE MTA process	• Share brief background of NICE review, timelines and process

The patient pathway	• Outline on physician role within the patient pathway
Patient Definitions - Current thinking	• Brief summary on patient groups
Patient group definitions debate	• Which are the relevant patient profiles for SIRT intervention? • How realistic/clear are the different patient groups? • Do the definitions reflect current UK practice? • Which additions/amends could be suggested • Physicians to also comment on the correct test comparators • Which costings/micro costings would be relevant to reflect current practice? • Which route will NICE adopt for defining the patient groups? • Which UK physicians could be involved in the NICE process?
Final comments	• Final comments • What would you do differently?
The patient pathway	• Outline on physician role within the patient pathway
Final comments	• Final comments
CLOSE and next steps	Summary and close

Advisory Board 2, 18th March 2019, London

Agenda Item	Task/Key Questions
Welcome and Introductions	
Establish an understanding of current treatment pathways for HCC patients and best practice in the UK	• "Current treatment pathways. What works best?" • Followed by round table discussion
Discuss where SIRT could be used in the UK for HCC and why. Specifically;	• Palliative (advanced stage disease)

	• Curative intent- which patients and why • Followed by round table discussion
Current UK Experience with SIRT in HCC	• Experience from a practicing centre" • Followed by round table discussion and round table sharing of centre experience
SIRT in HCC: Where should it fit in the pathway?	• Followed by round table discussion
An Introduction to Health Economics and how TheraSphere will be modelled.	
Closing comments	

- **We would specifically like to verify how the resource use data estimates were synthesised from the clinician responses – please provide estimates provided by the clinicians, and how these values were combined to produce the values used in the submission (Table M1 to M9 in Appendix M)**

The resource use estimates were provided by a single clinical expert, whose role is consultant interventional radiologist at a leading cancer centre in the UK which uses SIRT.

Opinion was elicited via an unstructured phone conversation in which the inputs were described and explained in an intuitive way to the clinical expert, in order for estimates to be provided. The estimates were given verbally and were entered directly into the model; no transcripts of this conversation were maintained.

A 5. Clinical expert opinion was referred to on a number of occasions in the submission (page 25 114, 127 of the submission). Please describe how this expert clinical advice was obtained, and provide transcripts of any discussions that were held.

With regard to page 25 of the submission, please see the following response from Dr Riad Salem:

Clinical Expert Response:

I confirm that I provided clinical expertise to BTG, for the aforementioned meta-analysis and supported a 2004 lower limit cut off for the SLR used in this analysis. The justification for this lower limit cut-off date is as follows:

TheraSphere was first approved in the US in 1999 under an HDE designation. Early clinical experience using TheraSphere was published in 2000-2001 during a time in which the equipment, technique and patient selection criteria for TheraSphere treatment were still being refined. During this time, no drugs were approved for HCC and TACE had not yet been recognized as SOC (those papers were published in 2002) and patients were typically receiving systemic doxorubin for HCC.

After 2002, our angiographic equipment and microcatheter technology improved, enabling lobar and selective treatment with TheraSphere and further refinement of optimal patient selection criteria. Publications prior to 2004 included patients treated in 2001-2004 during a time in which technology and patient treatment practices were still evolving and often as part of a retrospective series.

Escalating clinical experience with TheraSphere led to Key Opinion Leaders (KOLs) in the field of HCC treatment with TheraSphere, and these KOLS continued to expand the knowledge around attainable outcomes with TheraSphere treatment, the radiology-pathology correlation, and who developed dosimetry techniques and expanded use of TheraSphere to earlier staged disease (e.g. transplant setting). Publications which expanded on TheraSphere knowledge, as opposed to establishing basic treatment technique, were published approximately 2004 and beyond. Therefore, a cut off date of 2004 (by inference including

patients between 2001-2004) was chosen for the SLRs for the meta-analysis and for the clinical section of the submission.

Riad Salem MD MBA
Professor of Radiology, Medicine and Surgery
Chief, Section of Vascular and Interventional Radiology
Vice-Chairman, Image-Guided Therapy
Department of Radiology
Northwestern University
676 N St Clair, Suite 800
Chicago, IL USA 60611
1-312-695-6371 office

On page 114 of the submission it was stated that “Based on a review of the literature and expert clinical opinion, a number of patients in [the TAE eligible group] would be expected to be subsequently treated with resection or transplant”. This advice was obtained via a clinical advisory meeting with four clinical experts, held during the model scoping phase to determine the relevant patient pathways. No formal transcripts were maintained.

On page 127 of the submission it was stated that “The absolute values for all states, with the exception of the post-transplant tunnel states and the no HCC other health state, were assumed to be the same as that for pre-progressed HCC as informed by the NICE lenvatinib submission [27]. This assumption has been validated by expert opinion.”. In this instance, the advice was obtained simply by stating the assumption and asking for comments from two clinical experts on its reasonableness. There was disagreement around the feasibility of this assumption, with one expert agreeing it was suitable and the other stating that they would expect a downstaging candidate to have superior utility to a lenvatinib patient (who are assumed to be advanced stage). Therefore, they believed we were underestimating the utility of patients in the model. However, due to lack of utility data specific to our constructed health states, we stood by the conservative assumption in question.

Section B: Clarification on cost-effectiveness data

B1. The two executable cost-effectiveness models (TAE eligible and TAE ineligible) appear to contain a number of calculation errors and ambiguities. Please confirm these errors, and provide updated executable models.

a) In both models, health state utilities appear to be age-adjusted using an inappropriate method. A decrement was applied to the prior to the first cycle of model, which resulted in the baseline utilities being adjusted lower than they should have been (for example, the watch and wait utility was adjusted from 0.75 to 0.53). The utility values are from age-appropriate sources and age-adjustment should only apply from the first cycle of the model.

It would appear, on review of our models that the TAG has misunderstood the approach used to include health related quality of life (HRQoL) into the analysis.

Firstly, the TAG have, we believe, incorrectly interpreted the assumptions underpinning the use of the absolute health state values (i.e. the 0.75 for the 'watch and wait' health state). We have made the simplifying assumption that these were generated using some form of time trade off or standard gamble method of elicitation and therefore, the baseline value used in the calculation is one.

As such, the health state utility decrement associated with having moderate to severe HCC was 0.25 (1-0.75), the utility decrement for having advanced, non-progressed HCC was 0.255 (1-0.745) and so on. These decrements were then applied to age and gender adjusted population norms to generate the utility value for an individual of a given age with moderate to advanced HCC (0.78 – 0.25 = 0.53), advanced, non-progressed HCCC (0.78 – 0.26 = 0.525) and so on. This approach is entirely consistent with many previous submissions to NICE in multiple therapy areas and is not, we believe, a construction or calculation error.

Secondly, we are unclear as to what changes are being requested by the TAG when they say that age adjustment should only apply from the first cycle of the

model. Using the 'watch and wait' health state for didactic purposes, our interpretation is that the ERG are advocating the following approach:

Cycle	Utility value	Rationale/ justification
0	0.75	Reported value is from and age appropriate source
1	0.53	Age adjustment should be applied to the reported value
2	0.53	Age adjustment should be applied to the reported value
Etc.		

In the context of our models where the cycle length is four weeks, we would question the clinical plausibility of such a sudden change in value without any substantive change in symptoms (since they do not move health state). We would also like to point out that if we have correctly interpreted the TAGs comments, the impact of using this approach on the relative cost-effectiveness of TheraSphere would be nominal at most since it would only be a small change applied to a single four week period of treatment. We maintain the position that this is not a calculation error but if we have misunderstood the TAGs position we will look to provide the requested analysis following more detailed clarification of what is required.

b) **The process to derive transition probabilities for each treatment arm for the transitions to "Watch and wait", "Pharmacological management" and "Pre-Transplant" (the top table on the "Effectiveness" sheet) is unclear. Please describe how the mean time to downstaging was used to estimate these probabilities, why only the rate observed in the TheraSphere arm of the trial was applied to both arms, and whether it is reasonable to assume that the probability of remaining in the "Watch and wait" health state is the same in each arm. This concern is further supported by the fact that the model appears to underestimate the total number of patients transitioning to the pre-transplant state in both treatment arms in the model, which should be equal to the total proportion who downstage (i.e. 58% and 38% for TheraSphere and cTACE respectively).**

The median time monitored for downstaging before "prognosis", reported by Lewandowski et al. (2009), was 3.1 months. Our first assumption in facilitating this

calculation was that this “decision point” happened at the same time whatever the prognosis (i.e. downstaged or not).

In terms of our 4-weekly cycles, this gave a median time of 3.38 cycles spent in watch & wait. Assuming an exponential distribution, this was calculated to be equivalent to a 18.56% probability of leaving watch & wait per cycle (and an 81.44% probability of staying).

Each cycle, the proportion of the cohort leaving watch & wait was further split into downstagers / non-downstagers. This split was informed by the downstaging rates reported in Lewandowski et al., i.e. 58/42 for SIRT and 31/69 for TA(C)E.

For example, in the first cycle in the SIRT arm, ~19% of the living cohort leave watch&wait. 58% of these go on to pre-transplant and the remaining 42% go to pharmacological management. That is, in the first cycle, 10.8% of the living cohort transition from watch & wait to pre-transplant and 7.8% transition from watch & wait to pharmacological management.

Mortality is calculated separately so these transition probabilities are all conditional on being alive. Therefore, it is true that a 58% share of patients going onto the transplant pathway is not achieved, as some patients die before leaving watch & wait.

Lewandowski et al. did not report on a median time to downstaging in the TACE arm because it was not reached. Thus, we made the assumption of equivalence in monitoring times across all treatments. We are unsure as to the robustness of this assumption, but were not able to find this data in the correct patient population for TACE.

Note that all of these calculations can be found in the off-piste section of the effectiveness sheet (row 84 and below).

c) There are a number of calculations e.g. those relating to mortality, where it appears that the calculation was undertaken outside of the model. Please update the model so all model calculations are undertaken within the model.

Please see the off-piste section of the mortality sheet (row 229 and below) for these calculations. The mortality inputs have now been linked to the off-piste calculations.

B2. Please provide further information on the source of the SIRT work-up procedure cost (£467.91) used in the model, and the costs you anticipate will be associated with the work-up procedure for TheraSphere.

The work-up procedure costs are sourced from the Christie NHS Foundation Trust, Manchester. Jill Tipping, a physicist at the hospital is the main point of contact. The work-up costs detailed in the model are the salary costs from the Christie hospital, which are based on national pay banding. The MAA body spect cost source is stated below Table 1 and Table 2. Since submission, it has come to our attention that further costs could be included in the work-up (coming from the same source, being what the Christie Hospital pay). A scenario using the alternative work-up figures, for each model, has been presented below.

Work up costs

Table 1: Work up factors - original

Work up factors - original	Cost
30 minutes band 6 technician (unit cost per hour £15.96)	£7.98
30 minutes band 7 clinical scientist (unit cost per hour £19.06)	£9.53
MAA body spect*	£353
Lung shunt calculation – 10 minutes band 7 clinical scientist (unit cost per hour £19.06)	£3.18
Volumetary 1 hour band 7 clinical scientist (unit cost per hour £19.06)	£19.06
Volumetary 1 hour band radiologist (unit cost per hour £75.16)	£75.16
TOTAL	**£467.91**

*Note: There is not currently an NHS tariff for an MAA body spect. However, it is thought that a sum of the RN codes (from the National Tariff Payment System) for the following is suitable for the total cost of an MAA body spect: A whole body spect for one area (RN04A - £147 minus the agent cost £26 = £121); a whole body spect for two areas (£180 minus the agent cost £22 = £158); MAA consumable agent (£74).

Table 2: Work up factors – alternative scenario

Work up factors - alternative costs	Cost
30 minutes band 6 technician (unit cost per hour £15.96)	£7.98
30 minutes band 7 clinical scientist (unit cost per hour £19.06)	£9.53
MAA body spect*	£353
Lung shunt calculation – 10 minutes band 7 clinical scientist (unit cost per hour £19.06)	£3.18
Volumetary 1 hour band 7 clinical scientist (unit cost per hour £19.06)	£19.06
Volumetary 1 hour band radiologist (unit cost per hour £75.16)	£75.16
2x radiologist 2 hrs (unit cost per hour £75.16)	£150.3
2 x band 6 nurse 3 hrs (unit cost per hour £23.82)	£142.92
1x band 6 radiographer 3 hrs (unit cost per hour £23.82)	£71.46
1x band 4 coordinator 1hr (unit cost per hour £16.30)	£16.30
Blood work	£11.35
TOTAL	**£860.32**

*Note: There is not currently an NHS tariff for an MAA body spect. However, it is thought that a sum of the RN codes (from the National Tariff Payment System) for the following is suitable for the total cost of an MAA body spect: A whole body spect for one area (RN04A - £147 minus the agent cost £26 = £121); a whole body spect for two areas (£180 minus the agent cost £22 = £158); MAA consumable agent (£74).

TAE eligible model

Table 3: Raw outputs when work-up cost is £860.32

Treatment	Costs	QALYs
TheraSphere	£57,731	2.119
QuiremSpheres	£57,753	2.119
SIR-Spheres	£57,753	2.119
cTACE	£43,488	1.393
DEB-TACE	£39,435	1.393
Bland embolisation	£43,470	1.392

Table 4: Ranked outputs (by cost) when work-up cost is £860.32

Intervention	∆ Costs	∆ QALYs	ICER
DEB-TACE	£0	0.000	Referent
Bland embolisation	£4,035	-0.001	Dominated
cTACE	£4,053	0.000	Dominated
TheraSphere	£18,295	0.726	£25,187
QuiremSpheres	£18,318	0.726	£25,187
SIR-Spheres	£18,318	0.726	£25,187

TAE ineligible model

Table 5: Raw outputs when work-up cost is £860.32

Intervention	QALYs (Disc)	Costs (Disc)
TheraSphere	0.715	£51,314
QuiremSpheres	0.489	£38,597
SIR-Spheres	0.489	£38,597
Sorafenib	0.518	£39,823
Lenvatinib	0.548	£63,085
Regorafenib	0.514	£37,885

Table 6: Ranked outputs (by cost) when work-up cost is £860.32

Intervention	∆ Costs	∆ QALYs	ICER
Regorafenib	£0	0.000	Referent
SIR-Spheres	£712	-0.024	Dominated
QuiremSpheres	£712	-0.024	Dominated
Sorafenib	£1,938	0.005	Ext dominated
TheraSphere	£13,429	0.202	£66,641
Lenvatinib	£25,201	0.034	Dominated

Section C: Textual clarification and additional points

C1. Please can the company provide the WinBUGS code used to conduct the network meta-analyses. Please provide all files required to run the NMA for all models presented. These should include all input data, initial values for each chain and the value of mx, and the centring constant.

Please find separate uploaded documents for the data files, the JAGS code, and an R script.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Selective internal radiation therapies for treating hepatocellular carcinoma (ID1276)

Clarification questions

June 2019

File name	Version	Contains confidential information	Date
Sirtex response to NICE	1.0	Redacted	10.07.2019

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Trial data

A 1. Please provide overall survival and progression free survival data including numbers at risk for the SIRTACE RCT.

The final patient-level dataset for the SIRTACE randomised control trial (RCT) is not available to Sirtex Medical. Please also note, that only 28 people were randomised to treatments in the trial (15 to TACE,13 to SIR-Spheres), therefore any analysis of survival data would be highly uncertain.

A 2. Please provide overall survival, progression free survival, time to down staging, proportion downstaged and adverse event data for the following subgroups of patients in the SARAH and SIRveNIB RCTs:

a) **Patients with portal vein thrombosis or portal vein invasion,**

b) **Patients with Child-Pugh A,**

c) **Patients with Child-Pugh A and no portal vein thrombosis or portal vein invasion,**

d) **Patients with ≤25% tumour burden and ALBI grade 1 (with and without portal vein thrombosis/portal vein invasion),**

e) **Patients who have previously failed treatment with chemoembolization,**

f) **Patients who are Child-Pugh and have previously failed treatment with chemoembolization.**

SARAH data are provided in the following files:

- *NICE_request_SARAH_OS.xlsx*
- *NICE_request_SARAH_PFS.xlsx*
- *NICE_request_SARAH_AE.xlsx*
- *NICE_request_SARAH_plots.docx*

For the location of the data requested, please see Table 1. Kaplan Meier (KM) and parametric survival curve plots have also been provided. Please note that for subgroup f) we have assumed that the request is for patients who are Child Pugh A.

Adverse event (AE) data have been reported as Grade 3+ treatment-related adverse events. Grades for AEs have been defined per the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) classification. Relation to treatment was determined by an independent data and safety monitoring board for the SARAH trial.

Table 1 Location of data requested

Data requested	**File**	**Worksheet name**
Overall survival	NICE_request_SARAH_OS	OS_KM
Progression free survival	NICE_request_SARAH_PFS	PFS_KM
Time to down-staging	NICE_request_SARAH_OS	OS_tx_summary. Downstaging IPD also provided in IPD_downstaging
Proportion down-staged	NICE_request_SARAH_OS	OS_tx_summary
Adverse event data	NICE_request_SARAH_AE	-
Additional data		
Plotted Kaplan Meier curves and parametric models	NICE_request_SARAH_plots	-
Diagnostic plots	NICE_request_SARAH_plots	-
Goodness-of-fit statistics	NICE_request_SARAH_OS and NICE_request_SARAH_PFS	OS_summary_stats, OS_excl_cure_summary_stats PFS_summary_stats, PFS_excl_cure_summary_stats

In addition to the KM data and parametric model plots, goodness-of-fit statistics (Akaike's Information Criterion [AIC] and the Bayesian Information Criterion [BIC]) and diagnostic plots have been provided, in order to aid with the selection of the model for the analysis. Based on these, lognormal distribution seems to provide the best fit for both OS and PFS (all patients and excluding patients down-staged to treatments with curative intent). This is in line with the submission (please see document: *Sirtex SIR-Spheres MTA ID1276 HCC Submission final AIC CIC 2019 05 28*).

The SIRveNIB RCT is an investigator-initiated trial sponsored by the Singapore General Hospital, which is the data owner for this trial. Overall survival, progression free survival and adverse events for SIRveNIB cannot be provided because the dataset available to Sirtex is incomplete due to some centres being unable to provide data.

Furthermore, there is evidence that treatment patterns for HCC differ largely between Europe and Asia, and that the SIRveNIB trial is not appropriate to inform subsequent treatments following SIRT or sorafenib.

The SIRveNIB trial mainly included patients from low- to upper-middle-income Asian countries (1) (n=243), including Myanmar (n=74), Philippines (n=57), Mongolia (n=39), Thailand (n=32), Indonesia (n=22), Malaysia (n=19). 117 patients came from high income countries (Singapore, South Korea, Taiwan, New Zealand, Brunei).

Treatment patterns for HCC in Asia are reported in the BRIDGE study, an international large-scale, longitudinal cohort study of treatment patterns for HCC, which reported these patterns for North America, Europe, China, Taiwan, South Korea and Japan. This study found significant differences in the management of patients with HCC between Europe and China: while TACE is the most common first-line treatment of HCC in both regions, there were variations in the proportion of patients receiving TACE as a first-line treatment (29% in Europe vs 51% in China). The proportion of patients receiving surgery as first-line treatment in China is double that observed in Europe (32% vs 16%). The most common second-line treatment after TACE for Chinese patients was palliative care, whereas patients becoming ineligible for TACE in Europe most frequently received sorafenib (2), as is described for the UK in the main body of the submission (please see: *Sirtex SIR-Spheres MTA ID1276 HCC Submission final AIC CIC 2019 05 28.*docx). These differences are also supported by analyses of the international OPTIMIS study (3), in which 82% of patients receiving TACE in China were considered to have too advanced disease and to be ineligible for this treatment according to the study protocol, mostly based on the BCLC staging system, compared to 40% in Europe and Canada (4).

These data support that patients with HCC considered unsuitable for TACE in China are heavily pre-treated, with patients receiving an initial or repeated TACE procedure

outside of accepted indications in Europe. These patients are unlikely to be down-staged to any treatment with curative intent after either SIRT or sorafenib, particularly due to the impact of treatments on liver function, which can condition the eligibility of patients to subsequent treatments with curative intent (5). A direct impact of TACE on liver function has been demonstrated (6,7), while repeated TACE beyond the point of refractoriness can also result in poor survival outcomes (3,6,8).

Assuming that treatment patterns in China, as an upper-middle-income economy (1), would be the most representative of those observed in the other low- to upper-middle-income countries represented in the SIRveNIB trial, these important differences in treatment patterns strongly limit the generalisability of findings from the SIRveNIB trial regarding subsequent treatments to the decision problem in the UK. The differences in treatment patterns are also reflected in European and Asian clinical guidelines, with different recommendations regarding TACE discontinuation (e.g. Asian guidelines do not consider a degradation in performance status as a relevant contraindication to repeated TACE (9–11) whereas this is considered in European guidelines (5,12)).

In addition to these differences in treatment patterns, previous randomised trials in HCC have also established that the prognosis of Asian patients with HCC is worse than that of Western patients, particularly for those patients receiving sorafenib (13–15). This may further limit the generalisability of the SIRveNIB trial to the UK setting.

In general, the Asian population of the SIRveNIB trial was not considered to be representative of the UK population with HCC so data from this study have not been used in the economic model, although headline results of this trial were similar to the SARAH trial.

A 3. Please provide the requested overall survival and progression free survival data censored for downstaging for the SARAH and SIRveNIB RCTs.

Overall survival and progression free survival data censored for downstaging from the SARAH RCT are provided in the following Excel files:

- *NICE_request_SARAH_OS*
- *NICE_request_SARAH_PFS*.

Please note, that only two out of the patients who received subsequent treatment with curative intent had died during the SARAH trial follow-up period, so the OS curves for are similar for the population including and excluding the down-staged patients.

Overall survival and progression free survival data censored for downstaging from SIRveNIB are not available (please see question A2).

A 4. Please provide further data on the patients who were downstaged in the SARAH and SIRveNIB RCTs; the proportion of patients in each treatment group who received transplant and the proportion of patients who received resection and the associated costs, for the 'ITT', 'per protocol' and '≤25% tumour burden and ALBI grade 1' subgroups.

The proportion of patients in each treatment group who received transplant and resection are provided in Table 2 for SARAH. The number receiving radiofrequency ablation is also included because ablation is considered a treatment with curative intent per available clinical guidelines (5,12).

Table 2 Treatment with curative intent in SARAH

Population	Treatment	Number downstaged	Transplant n (%)	Radiofrequency ablation n (%)	Resection n (%)
ITT	SIR-Spheres	12	2 (17%)	7 (58%)	4 (33%)
	Sorafenib	3	1 (33%)	2 (67%)	0 (0%)
PP	SIR-Spheres	11	2 (18%)	6 (55%)	4 (36%)
	Sorafenib	3	1 (33%)	2 (67%)	0 (0%)
'≤25% tumour burden and ALBI grade 1	SIR-Spheres	5	2 (40%)	2 (40%)	1 (20%)
	Sorafenib	1	0 (0%)	1 (100%)	0 (0%)

The SIRveNIB trial had few patients down-staged to receive potentially curative treatment. Chow et al (2018) report that in the ITT population of the SIRveNIB RCT, 3 patients in each of the randomisation groups received surgery or radiofrequency

ablation. Please see question A2 for a discussion of the differences in treatment patterns and patients characteristics between Western and Asian countries explaining the observed differences with the SARAH RCT. Furthermore, individual patient data from the SIRveNIB RCT was not available.

Only limited resource use data were collected in the SARAH trial. Limited hospital readmission data were collected. However, the corresponding length of stays were only observed for resection in 2 patients and for transplantation in 2 patients. These small sample sizes warranted using external data for the calculation of these costs. Information about the costs of these treatments and references are provided in the cost-effectiveness model [filename: *Sirtex SIR-Spheres MTA ID1276 HCC CEM final CIC 2019 05 28*, cell reference: Costs!C16:F18], in the submission body text [filename: *Sirtex SIR-Spheres MTA ID1276 HCC Submission final AIC CIC 2019 05 28*, section reference: 7.2.4.2.1], and in the appendices [filename: *Sirtex SIR-Spheres MTA ID1276 HCC Appendices final CIC 2019 05 28*, table 85].

A 5. Can you please provide further information on whether concomitant use of sorafenib or other systemic therapy was permitted in the SARAH and SIRVeNIB trials for patients who received SIR-Spheres. If this was permitted can you provide information on the proportion of patients which received systemic therapy and the duration of therapy.

The SARAH and SIRveNIB trial protocols did not allow for concomitant use of sorafenib or other systemic therapy. Both trials were designed as trials of SIRT using Y-90 resin microspheres versus sorafenib in monotherapy with 1:1 randomisation to either of the treatments until disease progression, no further response, complete regression or unacceptable toxicity (16,17): this design excludes the possibility for patients in the SIR-Spheres arm to receive concomitant sorafenib or another systemic therapy for the treatment of cancer. Previous systemic therapy of HCC was also an exclusion criterion in both trials.

A 6. Please provide overall survival, progression free survival (including numbers at risk), time to down staging, proportion downstaged, and adverse event data for the SORAMIC RCT, for the six subgroups listed in Question 2.

The SORAMIC RCT is an investigator-initiated trial sponsored by the University of Magdeburg, Germany, which is the data owner for this trial. Patient-level data for the SORAMIC RCT are not available to Sirtex Medical (see A 8).

A 7. Please also provide the requested overall survival and progression free survival data from SORAMIC censored for downstaging, if applicable.

The SORAMIC RCT is an investigator-initiated trial sponsored by the University of Magdeburg, Germany, which is the data owner for this trial. Patient-level data for the SORAMIC RCT are not available to Sirtex Medical (see A 8).

A 8. If the data requested in Questions 6 and 7 are not available, can you please advise us on when any data from the SORAMIC trial are likely to be available?

The SORAMIC trial (EudraCT Number: 2009-012576-27) is an investigator-initiated trial sponsored by the Medical Faculty of the University of Magdeburg, Germany. According to the information communicated by the trial investigators to Sirtex Medical, the primary manuscript for this trial is in development for publication in a peer-reviewed journal. The potential date for this publication is unconfirmed at this point in time. Patient-level data for the SORAMIC RCT are not available to Sirtex Medical.

A 9. Please provide the audit data for reference 18 'Sirtex. Data on file. 2019'.

The data were obtained from Royal Liverpool University Hospital. The dataset includes [redacted] consecutive patients, with HCC, who received TACE between 2010-2017. The data are routinely collected including gender, site of lesion, number of

HCC nodules, total TACE treatments received, date of first treatment and date of last treatment.

Patients received between [redacted] and [redacted] TACE procedures. The mean number of treatments per patient was [redacted]. However, [redacted] patients ([redacted]%) received 10 or more TACE treatments, and [redacted] patients ([redacted]%) received 5 or more TACE treatments.

The data are academic in confidence as Sirtex is not the data owner for this dataset and as these data will be subject to publication.

A 10. Please provide overall survival, progression free survival, proportion downstaged, and adverse event data for the ITT, and per protocol, and high function/low tumour burden populations of the SARAH and SIRveNIB trials.

SARAH data are provided in the following files:

- *NICE_request_SARAH_OS.xlsx*
- *NICE_request_SARAH_PFS.xlsx*
- *NICE_request_SARAH_AE.xlsx*
- *NICE_request_SARAH_plots.docx*

The location of the data requested is the same as Table 1, Question A2.

A 11. Please provide overall survival, progression free survival, proportion downstaged, and adverse event data for the patients allocated to receive SIRT in SARAH and SIRveNIB who underwent a workup procedure but did not go on to receive SIRT.

SARAH data are provided in the following files:

- *NICE_request_SARAH_OS.xlsx*
- *NICE_request_SARAH_PFS.xlsx*
- *NICE_request_SARAH_AE.xlsx*
- *NICE_request_SARAH_plots.docx*

The location of the data requested is the same as Table 1, Question A2.

Patients who underwent a workup procedure but did not go on to receive SIRT had poor survival outcomes which can be explained by the following factors:

- Among those patients, 16/42 patients in the SARAH RCT and 11/21 patients in the SIRveNIB RCT were reported not to receive any active treatment following their randomisation to the SIRT ITT arm. This does not reflect clinical practice according to clinicians consulted in the advisory boards for this submission, as patients enrolled in both trials should have been offered sorafenib as an alternative.

- Disease progression before the treatment or before the work-up are considered by clinicians to reflect the poor patient selection in the SARAH trial (*Sirtex Advisory Board – Meeting minutes 26th April 2.0*). Some of the patients enrolled in the SARAH RCT (e.g. with Child-Pugh B liver disease) would not have been considered suitable to receive any active treatment in routine clinical practice in the UK. Impaired liver function also carries an important and independent risk of mortality that could also have precluded patients to receive further treatment.

Although the subgroup of patients with a tumour burden <25% and a well-preserved liver function (ALBI grade 1) is derived from the ITT population of the SARAH RCT, this analysis does include 3 patients (8%) who did not go on to receive SIRT after the work-up. This proportion is similar to that observed in other real-life studies in HCC (UK clinicians survey, Sancho et al. study (18)).

The above suggests that the high proportion of dropouts observed in the overall SARAH ITT population, in which 19% of patients, does not reflect clinical practice in the UK or in Europe. In all alternative data sources, the proportion of patients considered ineligible for SIRT after the work-up was estimated between 3-10%. This latter proportion reflects some patients being considered unsuitable for SIRT due to anatomical or vascular constraints and is observed in all settings.

Patients not considered suitable for SIRT after the work-up should be offered systemic treatment with sorafenib or lenvatinib in UK clinical practice.

Section B: Clarification on cost-effectiveness data

B1. Please provide an explanation of the calculations in cells AZ23:202 in the executable model and check that these are correct, as they appear to imply negative costs.

The calculation in question is correct and the calculation logic does imply negative costs for the first couple of cycles.

The model assumes, based on the resource use interviews, that costs for follow-up of patients during active subsequent treatments is much lower than on BSC when the patient no longer receives any active treatment. Due to the structure and assumptions of a partitioned survival model, other follow-up costs on BSC are accrued cycle by cycle until death, however, since given for a limited amount of time, costs associated with follow-up during subsequent active treatments are assigned as a lump sum at the time of progression. Therefore, the calculations in column AZ include two components:

=((S22-S23) * (K23/K22) + (AA22-AA23) * (P23/P22)) * (m_c_other_atprog_syst + m_prop_subs * dur_subs * (m_c_other_syst - m_c_other_post_syst)) + (AVERAGE(V22:V23) + AVERAGE(AD22:AD23)) * m_c_other_post_syst

The second part of the calculation assigns costs of follow-up during BSC to everyone who is in the post-progression health state. However, this would overestimate follow-up costs as those who receive subsequent active treatments require less frequent monitoring and therefore should accrue lower costs. Therefore, the first part of the equation corrects for this, i.e. subtracts the difference between the cost of follow-up during BSC and during subsequent active treatments for the entire duration of the subsequent treatments as a lump sum.

In the first few cycles, when there are yet relatively few patients in the post-progression health state, this implies negative costs as the total difference between follow-up costs during other active subsequent treatments and costs during BSC for the entire duration of the subsequent therapies outweigh the cycle costs of BSC follow-up for everyone in the post-progression health state.

B2. The percentage of patients receiving subsequent therapy reported in Table 23 of the main submission do not add up to 100%. Can you please explain why?

There are patients receiving the following treatment options in addition to the ones in the table:

- Clinical trial
- Treatments with curative intent
- In four cases, the responses sent by email for the short survey have not indicated any specific treatments in the 'Other section', while the indicated specific treatments do not add up to 100%

Please see below Table 3 with these options added. Patients who are in clinical trial or receive 'Other' palliative treatments, accrue the same BSC follow-up costs as all patients not receiving active treatment, and as for patients with BSC, no additional active treatment costs. These patients together with their health benefit and cost consequences are included in the model, just not emphasized in Table 23 of the main submission.

Table 3. Revision of Table 23. Subsequent treatment use, excluding treatments with curative intent

Treatments	After SIR-Spheres		After sorafenib	
	% of patients receiving	Length of treatment (months)	% of patients receiving	Length of treatment (months)
Sorafenib	42.08%	3.7	-	-
Lenvatinib	-	-	1.00%	8.2
Regorafenib	1.50%	3.6	18.94%	3.6
Gemcitabine+oxaliplatin	-	-	-	-
BSC	32.17%	Not applicable	55.63%	Not applicable
Treatments with curative intent	5.6%	Not applicable	0.07%	Not applicable
Clinical trial	0%	Not applicable	24.65%	Not applicable
Other*	18.65%	Not applicable	0%	Not applicable

Source: Resource use survey

*Includes where clinicians/nurses have not indicated any other treatment (four cases) in the section 'Other', but percentages of treatments indicated did not add up to 100%.

B3. Please provide the following additional information regarding the advisory board data (references 5, 8, 39):

a) Completed questionnaires from clinicians (Appendix J, Section 2),

Please see completed questionnaires added as separate documents. The numbering of the KOLs match the numbering in the Excel file of the results.

The first clinician to fill out the Resource use survey provided feedback that the questionnaire required simplification. As a result, the following changes were made:

- List of assumptions (Section III.) was deleted, since these assumptions can be added into the resource use tables themselves, which was done in the subsequent interviews.
- AE table (Section VII.) was deleted, since hepatologists / oncologists / radiologists are not the ones to treat many of these AEs, and AE costs data is available from previous technology appraisals
- Differentiation between complete/partial response and stable disease have been deleted, as this differentiation was deemed to have high uncertainty (19)

KOL1-5 have filled out the Resource use questionnaire on a telephone or face-to-face interview. KOL6-10 filled out the short survey independently and sent it through email. The last survey (KOL11) was conducted over the phone and concentrated on the questions of the short survey and micro-costing for the procedure and work-up. Files are listed in Table 4.

Table 4. List of the files with the resource use and short survey responses

Data requested	File type	File name
Completed resource use questionnaire from clinician 1	Word document	*NICE_request_HCC physician survey KOL1*
Completed resource use questionnaire from clinician 2	Word document	*NICE_request_HCC physician survey KOL2*
Completed resource use questionnaire from clinician 3	Word document	*NICE_request_HCC physician survey KOL3*
Completed resource use questionnaire from clinician 4	Word document	*NICE_request_HCC physician survey KOL4*

Data requested	File type	File name
Completed resource use questionnaire from clinician 5	Word document	*NICE_request_HCC physician survey KOL5*
Completed short survey from clinician 6	PDF document	*NICE_request_HCC validation survey – anonymised KOL6*
Completed short survey from clinician 7	PDF document	*NICE_request_HCC validation survey – anonymised KOL7*
Completed short survey from clinician 8	PDF document	*NICE_request_HCC validation survey – anonymised KOL8*
Completed short survey from clinician 9	PDF document	*NICE_request_HCC validation survey – anonymised KOL9*
Completed short survey from clinician 10	PDF document	*NICE_request_HCC validation survey – anonymised KOL10*
Completed interview from clinician 11	PDF document	*NICE_request_HCC interview – anonymised KOL11*

b) We would specifically like to verify how the resource use data estimates were synthesised from clinician responses – please provide estimates provided by the clinicians and how these values were combined to produce the values used in the submission (Table 77 in Appendix O),

Individual answers were inputted into a separate Excel file, then mean resource use was estimated and multiplied by the relevant unit cost. Please see resource use by clinicians and how values were combined in the separate document listed in Table 4 (Excel file called: *NICE_request_Resource use for TACE ineligible patients*). The KOLs numbers match the numbering on the individual surveys.

Table 5. Files describing detailed resource use

Data requested	File type	File name
How resource use data was combined	Excel document	*NICE_request_Resource use for TACE ineligible patients*
Details of resource use for work-up and procedure	Excel document	*NICE_request_SIRT Resource use for work-up and procedure*

c) Transcripts of the three advisory board meetings,

Transcripts have not been recorded; however, we have included the minutes from the three advisory board meetings, that were also reviewed by the invited clinical and HTA experts. These are the following files listed in .

Table 6.

Table 6. List of files for the advisory board meetings

Data requested	File type	File name
Transcript of the first advisory board	Word document	*Sirtex Advisory Board – Meeting minutes 11th Jan 1.0*
Transcript of the second advisory board	Word document	*Sirtex Advisory Board – Meeting minutes 14th March 1.0*
Transcript of the third advisory board	Word document	*Sirtex Advisory Board – Meeting minutes 26th April 2.0*

Advisory board meeting minutes are provided by Sirtex as CIC materials as these include key elements on the company strategy in the UK and globally, the publication of which would pose a significant commercial risk for Sirtex operations.

d) In addition, we would also like additional details of the clinicians' discussions around the following: (i) discussion around the clinical relevance of the low tumour burden subgroup (page 39 of the submission), (ii) details of the SIRT work-up procedure and SIRT treatment eligibility (page 52-53 of the submission), (iii) number of work-up procedures (page 64 of submission).

Details around these discussions can be found in the following documents:

i) Initial discussion in *Sirtex Advisory Board – Meeting minutes 14th March 1.0*: pages 2-3, 6, Follow-up discussion based on all available data and analysis in *Sirtex Advisory Board – Meeting minutes 26th April 2.0* (files listed in .

ii) Table 6).

iii) Details of the SIRT work-up and eligibility is from data collected in the Short surveys and the Resource use surveys. Please see documents listed in question B3 for individual surveys. Summary of the relevant data is available in the Excel file listed in Table 5 (*NICE_request_SIRT Resource use for work-up and procedure*).

iv) Details of the number of work-up procedures was estimated from data collected in the Short surveys and the Resource use surveys. Please see documents listed in question B3 for individual surveys. Summary of the relevant data is available in the Excel file listed in Table 5 (*NICE_request_SIRT Resource use for work-up and procedure*)

B4. Please provide further information about the source of the SIR Spheres work-up procedure cost used in the model, and detail the costs you would anticipate to be associated with work-up in practice

In the base case for the cost-effectiveness, cost-minimisation and budget impact models the work-up and procedure cost calculation is based on the length of stay, number of procedures from the surveys and the relevant NHS Reference Costs (2017/2018). The following steps were used:

1. Mean resource use: The estimation of the mean length of stay and number of procedures is available in the attached Excel file (*NICE_request_SIRT Resource use for work-up and procedure*).

2. Cost for one work-up/procedure: For the work-up, since the mean length of stay is less than one day, the outpatient elective cost was used for the code YR57Z- Percutaneous, Chemoembolisation or Radioembolisation, of Lesion of Liver (£1,123.15). For the procedure, as the length of stay is longer than a day, the mean length of stay (1.19 days) was multiplied by the cost of a single day of the elective inpatient costs for the code YR57Z. The cost per day (£1,757.45) was estimated by dividing the elective inpatient cost (£2,764.70) by the average length of stay for that HRG (1.57 days).

3. Cost of work-up/procedure: the cost of one work-up/procedure was multiplied by the number of work-ups (1.05) and procedures (1.20).

The estimation of the costs can be seen in the cost-minimisation analysis (Excel file submitted originally: *Sirtex SIR-Spheres MTA ID1276 HCC CMA final CIC 2019 05 28*).

In practice these costs are expected to decrease as clinicians in the UK have reported increasing use of a transradial vascular approach instead of the transfemoral approach, allowing patients to be treated in the outpatient setting. These evolutions could speed up the time to receiving treatment and minimise costs to the patient and healthcare providers.

Section C: Textual clarification and additional points

C1. Please can the company provide the WinBUGS code used to conduct the network meta-analyses. Please provide all files required to run the NMA for all models presented. These should include all input data, initial values for each chain and the value of mx, and the centring constant.

WinBUGS code and required data are provided in files in the following folder: *WinBUGS code.*

References

1. World Bank. World Bank Country and Lending Groups – World Bank Data Help Desk [Internet]. 2019 [cited 2019 Jul 5]. Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups

2. Park J-W, Chen M, Colombo M, Roberts LR, Schwartz M, Chen P-J, et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. Liver Int. 2015 Sep;35(9):2155–66.

3. Peck-Radosavljevic M. OPTIMIS: Real-World Data in Patients with Hepatocellular Carcinoma Treated with Transarterial Chemoembolisation: Second Interim Analysis. Eur Med J. 2018;6(1):58–9.

4. Raoul J, Decaens T, Burak K, et al. Practice Patterns and Deterioration of Liver Function after Transarterial Chemoembolization (TACE) in Hepatocellular Carcinoma (HCC): Final Analysis. Ann Oncol. 2018;29(suppl_8):viii205–70.

5. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182–236.

6. Arizumi T, Ueshima K, Minami T, Kono M, Chishina H, Takita M, et al. Effectiveness of Sorafenib in Patients with Transcatheter Arterial Chemoembolization (TACE) Refractory and Intermediate-Stage Hepatocellular Carcinoma. Liver Cancer. 2015 Dec;4(4):253–62.

7. Miksad RA, Ogasawara S, Xia F, Fellous MM, Piscaglia F. Changes in liver function following real-world transarterial chemoembolization (TACE) in US patients (pts) with hepatocellular carcinoma (HCC): The LiverT study. J Clin Oncol. 2018 Feb 1;36(4_suppl):441–441.

8. Ogasawara S, Chiba T, Ooka Y, Kanogawa N, Motoyama T, Suzuki E, et al. Efficacy of sorafenib in intermediate-stage hepatocellular carcinoma patients refractory to transarterial chemoembolization. Oncology. 2014;87(6):330–41.

9. Park HC, Yu JI, Cheng JC-H, Zeng ZC, Hong JH, Wang MLC, et al. Consensus for Radiotherapy in Hepatocellular Carcinoma from The 5th Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE 2014): Current Practice and Future Clinical Trials. Liver Cancer. 2016 Jul;5(3):162–74.

10. Cheung TT-T, Kwok PC-H, Chan S, Cheung C-C, Lee A-S, Lee V, et al. Hong Kong Consensus Statements for the Management of Unresectable Hepatocellular Carcinoma. Liver Cancer. 2018;7(1):40–54.

11. al S group et. Management consensus guideline for hepatocellular carcinoma: 2016 updated by the Taiwan Liver Cancer Association and the Gastroenterological Societ... - PubMed - NCBI [Internet]. [cited 2019 Jul 5]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29074347

12. Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2018 Oct 1;29(Supplement_4):iv238–55.

13. Llovet JM, Hilgard P, de Oliveira AC, Forner A, Zeuzem S, Galle PR, et al. Sorafenib in Advanced Hepatocellular Carcinoma. N Engl J Med. 2008;13.

14. Kudo M, Finn RS, Qin S, Han K-H, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. The Lancet. 2018 Mar;391(10126):1163–73.

15. Cheng A-L, Kang Y-K, Chen Z, Tsao C-J, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009 Jan;10(1):25–34.

16. Vilgrain V, Abdel-Rehim M, Sibert A, Ronot M, Lebtahi R, Castéra L, et al. Radioembolisation with yttrium–90 microspheres versus sorafenib for treatment of advanced hepatocellular carcinoma (SARAH): study protocol for a randomised controlled trial. Trials [Internet]. 2014 Dec 3 [cited 2019 Jul 5];15. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4265525/

17. Gandhi M, Choo SP, Thng CH, Tan SB, Low ASC, Cheow PC, et al. Single administration of Selective Internal Radiation Therapy versus continuous treatment with sorafeNIB in locally advanced hepatocellular carcinoma (SIRveNIB): study protocol for a phase iii randomized controlled trial. BMC Cancer [Internet]. 2016 Nov 7 [cited 2019 Jul 5];16. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5100089/

18. Sancho L, Rodriguez-Fraile M, Bilbao JI, Beorlegui Arteta C, Iñarrairaegui M, Moran V, et al. Is a Technetium-99m Macroaggregated Albumin Scan Essential in the Workup for Selective Internal Radiation Therapy with Yttrium-90? An Analysis of 532 Patients. J Vasc Interv Radiol. 2017 Nov;28(11):1536–42.

19. Visible Analytics. NICE_request_Sirtex Advisory Board – Meeting minutes 11th Jan 1.0. 2019.

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Assessment Group's Report
Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma

Produced by	CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York
Authors	Matthew Walton, Research Fellow in Health Economics, CRD Ros Wade, Research Fellow, CRD Lindsay Claxton, Research Fellow in Health Economics, CRD Sahar Sharif-Hurst, Research Fellow, CRD Melissa Harden, Information Specialist, CRD Jai Patel, Consultant Interventional Radiologist, Leeds Teaching Hospitals NHS Trust Ian Rowe, Honorary Consultant Hepatologist, Leeds Teaching Hospitals NHS Trust Robert Hodgson, Research Fellow in Health Economics, CRD Alison Eastwood, Professor of Research, CRD
Correspondence to	Ros Wade, Centre for Reviews and Dissemination, University of York, Heslington, York YO10 5DD
Date completed	06/09/2019

Source of funding

This report was commissioned by the NIHR HTA Programme as project number 17/109/19.

Declared competing interests of the authors

Jai Patel attended a product training course for using TheraSphere in Essen, Germany in 2016 which was sponsored by Biocompatibles UK Ltd. None of the other authors have any potential competing interests to declare.

Acknowledgements

We would like to thank Dr Daniel Swinson, Consultant Clinical Oncologist, Leeds Teaching Hospitals NHS Trust for advice throughout the project. We would also like to thank Professor Sofia Dias for support with the network meta-analysis and Peter Murphy, who supported the development

of the economic analysis. We would like to thank the companies (BTG, Terumo Europe and Sirtex Medical) for responding to requests for additional data and NHS Blood and Transplant for providing data from the UK Transplant Registry for this project.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Walton M, Wade R, Claxton L, Sharif-Hurst S, Harden M, Patel J, Rowe I, Hodgson R, Eastwood A. Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma: A Multiple Technology Appraisal. CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York, 2019.

Contributions of authors

Matthew Walton contributed to the protocol and the review of economic analyses. He developed the economic model and undertook the analysis and interpretation of the results, and the writing of the report.

Ros Wade contributed to the protocol, study selection, data extraction, validity assessments and synthesis of the included studies. She also contributed to the interpretation of the results and the writing of the report, and had overall responsibility for the clinical effectiveness sections.

Lindsay Claxton contributed to the protocol and undertook the review of economic studies. She developed the economic model and contributed to the analysis and interpretation of the results, and the writing of the report.

Sahar Sharif-Hurst contributed to the protocol, study selection, data extraction and validity assessments. She developed the synthesis models and undertook the analysis. She also contributed to the interpretation of the results and the writing of the report.

Melissa Harden contributed to the protocol development, developed the search strategies, conducted a range of searches to locate studies, and wrote the sections of the report relating to the literature searches.

Jai Patel provided expert clinical advice, contributed to the protocol, interpretation of the results and commented on drafts of the report.

Ian Rowe provided expert clinical advice, contributed to the protocol, interpretation of the results and commented on drafts of the report.

Robert Hodgson contributed to the development of the protocol and all aspects of the cost-effectiveness work. He also contributed to the interpretation of the results and the writing of the report, and had overall responsibility for the cost-effectiveness sections.

Alison Eastwood contributed to the protocol, study selection, validity assessments and synthesis of the included studies. She also contributed to the interpretation of the results and the writing of the report, and had overall responsibility for the project.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, all academic-in-confidence (AIC) data have been highlighted in yellow and underlined.

Keywords

Hepatocellular carcinoma, liver cancer, selective internal radiation therapy, TheraSphere, SIR-Spheres, QuiremSpheres.

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List of abbreviations

AE	Adverse event
AFP	Alpha-fetoprotein
AG	Assessment Group
BCLC	Barcelona Clinic Liver Cancer
BNF	British National Formulary
BSC	Best supportive care
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost-effectiveness analysis
CEACs	Cost-effectiveness acceptability curves
CENTRAL	Cochrane Central Register of Controlled Trials
CG	Clinical Guideline
CI	Confidence interval
CINAHL	Cumulative Index to Nursing & Allied Health
CIRT	CIRSE Registry for SIR-Spheres Therapy
CMA	Cost minimisation analysis
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTT	Conventional transarterial therapies
DARE	Database of Abstracts of Reviews of Effects
DEB-TACE	Drug-eluting bead transarterial chemoembolization
DIC	Deviance information criterion
DSA	Deterministic sensitivity analysis
EASL	European Association for the Study of the Liver
ECOG	Eastern Cooperative Oncology Group
ENRY	European Network on Radioembolisation with Yttrium-90 Resin Microspheres register
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
HCC	Hepatocellular carcinoma
HR	Hazard ratio
HRQoL	Health-related quality of life

HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
ITT	Intention to treat
KM	Kaplan-Meier
LYG	Life years gained
MCMC	Markov Chain Monte Carlo
MELD	Model for End-Stage Liver Disease
MeSH	Medical Subject Heading
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MTA	Multiple Technology Appraisal
MVI	Macroscopic vascular invasion
NHS EED	NHS Economic Evaluation Database
NMA	Network meta-analysis
NMB	Net monetary benefit
NR	Not reported
PAS	Patient Access Scheme
PFS	Progression-free survival
PLLA	Poly-L-lactic acid
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	The international database of prospectively registered systematic reviews in health and social care
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PVI	Portal vein involvement
PVT	Portal vein thrombosis
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
REILD	Radioembolisation induced liver disease
RR	Relative risk
SAE	Serious adverse event
SD	Standard deviation
SIRT	Selective internal radiation therapies
SmPC	EMA Summary of product characteristics

SPECT	Single-photon emission CT
STA	Single Technology Appraisal
TA	Technology Appraisal
TACE	Transarterial chemoembolisation
TAE	Transarterial embolisation
TARE	Transarterial radioembolisation
ToT	Time on treatment
TTP	Time to progression
WTP	Willingness-to-pay

Glossary

Adverse effect: An adverse outcome that occurs during or after exposure to a drug or other intervention and which may or may not be caused by the intervention.

Confidence Interval (CI): A measure of uncertainty around the results of a statistical analysis that describes the range of values within which we can be reasonably sure that the true effect lies. For example a 95% confidence interval is based on the notion that if a study were repeated many times in other samples from the same population, 95% of the confidence intervals from those studies would include the true value of the effect being measured. Wider intervals indicate lower precision; narrow intervals, greater precision.

Conventional transarterial therapies (CTT): CTT includes transarterial chemoembolization (TACE), drug-eluting bead transarterial chemoembolization (DEB-TACE), and transarterial embolization (TAE) without chemotherapy. All three forms of CTT work by administering an embolising agent into the hepatic artery to block blood vessels feeding the tumours within the liver. In the case of TACE, also known as conventional TACE (cTACE), lipiodol is combined with a chemotherapy agent, typically doxorubicin or cisplatin, which is administered directly to the tumour. In DEB-TACE, drug-eluting beads typically bound with doxorubicin or epirubicin are administered to the tumour via the hepatic artery. TAE, or bland TACE, involves only the physical occlusion of blood vessels, with no addition of chemotherapy.

Cost-benefit analysis: An economic analysis that converts the effects or consequences of interventions into the same monetary terms as the costs and compares them using a measure of net benefit or a cost–benefit ratio.

Cost-effectiveness acceptability curve (CEAC): A cost-effectiveness acceptability curve (CEAC) is a graph describing the impact of uncertainty on the result of a cost-effectiveness model. The graph plots a range of cost-effectiveness thresholds on the horizontal axis against the probability that the intervention will be cost-effective at that threshold on the vertical axis. It can usually be drawn directly from the results of a probabilistic sensitivity analysis.

Cost-effectiveness model: A cost-effectiveness or decision model seeks to answer questions about how to deploy resources in a healthcare system. A model is a simplified representation of a real world condition and treatment pathway, which aims to estimate the costs and consequences arising from making a particular policy decision, i.e. whether or not the NHS should fund a new procedure or drug. All relevant alternative courses of action and their long-term costs and consequences are compared to inform a decision on which option to adopt.

Cost-effectiveness threshold: A cost-effectiveness threshold represents the maximum amount a healthcare system is willing to pay for to provide a new technology or intervention. NICE guidance typically considers interventions with an incremental cost-effectiveness ratio (ICER) of between £20,000 to £30,000 per QALY as cost-effective.

Cycle: The time horizon within a model is split into cycles which represent the smallest period of time measured within the economic model.

Cost–utility analysis: The same as a cost-effectiveness analysis, but the effects or consequences of interventions are expressed in generic units of health gain, usually quality-adjusted life-years (QALYs).

Credible interval: In Bayesian statistics, a credible interval is a posterior probability interval estimation that incorporates problem-specific contextual information from the prior distribution. Credible intervals are used for the purposes similar to those of confidence intervals in frequentist statistics.

Deterministic sensitivity analysis: Deterministic sensitivity analysis explores the impact on model results of varying one or two input parameters at a time.

Dominance: In the field of health economics a treatment option is said to be ‘dominant’ when it is both less costly and produces better health outcomes than the comparator strategy. Thus, a treatment that is both more expensive and results in poorer health outcomes is referred to as ‘dominated’.

European Quality of Life Five Dimensions (EQ-5D): A generic measurement of quality of life used in many clinical trials. This instrument is easy to use and has been extensively validated across many disease areas. The benefit of EQ-5D is the availability of utility scores (generated through large population surveys) for each possible combination of questionnaire responses, these can be combined with the time individuals reside in particular health states to calculate the quality-adjusted life-years (QALYs) associated with an intervention.

Fixed effect model: A statistical model that stipulates that the units under analysis (e.g. people in a trial or study in a meta-analysis) are the ones of interest, and thus constitute the entire population of units. Only within-study variation is taken to influence the uncertainty of results (as reflected in the confidence interval) of a meta-analysis using a fixed effect model.

Heterogeneity: In systematic reviews, heterogeneity refers to variability or differences between studies in the estimates of effects. A distinction is sometimes made between "statistical heterogeneity" (differences in the reported effects), "methodological heterogeneity" (differences in study design) and

"clinical heterogeneity" (differences between studies in key characteristics of the participants, interventions or outcome measures).

Incremental cost-effectiveness ratio (ICER): The ICER is a measure which represents the economic value of an intervention compared with an alternative, and is generally the primary outcome of an economic evaluation. An ICER is calculated by dividing the difference in costs between two interventions by the difference in QALYs. The ICER is the cost of generating an additional QALY using the intervention we are interested in versus an alternative (usually current clinical practice).

Intention-to-treat (ITT): An intention-to-treat analysis is one in which all participants enrolled in a trial are analysed according to the intervention to which they were initially allocated, regardless of whether they went on to receive it or not.

Network meta-analysis (NMA): Network meta-analysis is a meta-analysis in which three or more treatments are compared using both direct comparisons of interventions within trials and indirect comparisons across trials, based on a common comparator.

Probabilistic sensitivity analysis: Probabilistic sensitivity analysis assesses the joint uncertainty across all input parameters in the model. This is done by assigning probability distributions to each input parameter and making random draws from each of these distributions. This process is then repeated many thousands of times resulting in a distribution of outputs that describe the uncertainty in the results of the model.

Quality of life: A broad concept incorporating all of the factors that might impact upon an individual's physical, mental, and social well-being. Health-related quality of life (HRQoL) refers to the specific impact a medical condition or treatment has on an individual's functioning and general well-being. HRQoL is generally measured in clinical trials alongside other outcomes to assess the impact of an intervention from a patient's perspective, typically using questionnaires completed by patients, their families, or clinicians, such as EQ-5D.

Quality-Adjusted Life Year (QALY): QALYs are an index of health gain where survival duration is weighted or adjusted according to the patient's quality of life over the time they are alive. QALYs are based on utilities, which are valuations of quality of life measured on a scale between full health (1) and death (0). These valuations are multiplied by the number of years that an individual spends in a health state with that particular utility score, and the QALYs are summed over the modelled time horizon.

Random effects model: A statistical model sometimes used in meta-analysis in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis.

Randomised controlled trial (RCT): An experiment in which investigators randomly allocate eligible people into groups which are each assigned a different intervention in order to compare their relative effectiveness and safety.

Relative risk (RR) (synonym: risk ratio): The ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability, or rate) is the ratio of people with an event in a group to the total number in the group. An RR of one indicates no difference between comparison groups. For undesirable outcomes, an RR of <1 indicates that the intervention was effective in reducing the risk of that outcome.

Scenario analysis: Scenario analysis is a process of exploring alternative future outcomes by selection of different assumptions used in the economic model. Scenarios can represent outcomes ranging from optimistic, where input variables are changed to their most optimistic values and to their most pessimistic. These types of analyses test the cost-effectiveness and safety of an intervention in the best and worst cases, and in other plausible 'alternative worlds'.

Statistical significance: A result is described as statistically significant when the reported p-value falls below the selected significance level; this value represents the probability that the observed result could have occurred due to chance alone if the 'null hypothesis' is true, i.e. there was no true difference between the groups.

Time horizon: The time horizon of an economic model is the duration over which costs and health outcomes are calculated. The choice of time horizon is important, and generally depends on the nature of the condition for which an intervention is being assessed. A long time horizon is preferred in chronic or long-term conditions for which there are likely to be important ongoing management costs and consequences well into the future. The use of a long-term time horizon often involves the extrapolation of short-term data into the future and the use of assumptions about the persistence of treatment effects due to a lack of long-term data.

1 Scientific summary

1.1 Background

Liver cancer is the fifth most common cancer and the second most frequent cause of cancer-related death globally. Hepatocellular carcinoma (HCC) is the most common type of liver cancer.[1]

Clinical management of HCC is complex; there is a range of treatment options available. The Barcelona Clinic Liver Cancer (BCLC) staging system is used to establish prognosis and enable the selection of appropriate treatment based on underlying liver dysfunction and cancer stage. Treatment options include surgery or ablation for early stage disease, conventional transarterial therapies (CTT) for intermediate stage disease, and systemic therapy for advanced stage disease. Best supportive care (BSC) is offered to patients when CTT or systemic therapy is not available or appropriate, including patients with terminal stage disease.[1]

Selective internal radiation therapies (SIRT) deliver radiation to liver tumours via microspheres that are injected into the hepatic artery. There are three SIRT technologies; TheraSphere®, SIR-Spheres® and QuiremSpheres®.

1.2 Objective

The aim of this project was to assess the clinical and cost-effectiveness of SIRT technologies for treating patients with unresectable early, intermediate, or advanced stage HCC.

1.3 Methods

1.3.1 Methods of clinical effectiveness review

A comprehensive search was undertaken to systematically identify clinical effectiveness literature relating to TheraSphere, SIR-Spheres, and QuiremSpheres, compared to each other, CTT or established clinical management without SIRT, in patients with HCC. Randomised controlled trials (RCTs) were eligible for inclusion. Where RCT evidence was insufficient to address the decision problem, non-randomised comparative studies and non-comparative studies were considered. In addition, a search for RCTs of comparator therapies was undertaken, in order to strengthen the network of evidence.

1.3.2 Methods of network meta-analysis

A network meta-analysis (NMA) was undertaken to estimate the relative effectiveness of the different treatments. Three NMA models were produced for the different populations of unresectable HCC patients: patients eligible for transplant; patients ineligible for transplant but eligible for CTT; and patients ineligible for CTT.

The NMA in patients eligible for transplant was not conducted. Clinical advice confirmed that there are short transplant waiting times in the UK, whereas these were much longer in the network trials. Therefore, the network may not be generalisable to UK practice. The NMA of patients eligible for CTT was also not conducted because of the lack of good quality evidence in this population.

Several network meta-analyses of patients who are ineligible for CTT were conducted for both overall survival (OS) and progression-free survival (PFS) outcomes in the per protocol and ITT populations.

1.3.3 Methods of economic modelling

Due to the limited clinical evidence in the early and intermediate patient groups, the focus of the AG's economic analysis was on an advanced HCC population, in which high-quality RCT evidence was available.

The AG built a fully probabilistic *de novo* model, which compared the three SIRT treatments with the systemic therapies lenvatinib and sorafenib. The model structure comprised a decision tree representing the outcome of the work-up procedure transitioning into a three-state partitioned survival model. The main model structure is similar to that adopted in previous appraisals in advanced HCC, consisting of health states representing progression-free survival, post-progression, and death. The time horizon was 10 years. Costs and benefits were discounted at a rate of 3.5% per annum. Costs were valued at 2017/18 prices.

The model drew on data from the SARAH[2] and SIRveNIB[3] trials to estimate the relative effectiveness of SIRT and sorafenib; the base-case assumed equivalence in efficacy for all SIRTs. A hazard ratio derived from the NMA was applied to the sorafenib survival curve to estimate the efficacy of lenvatinib. Health state utilities were derived from the per protocol subgroup of the SARAH trial[2] for SIRT and systemic therapy patients. Resource use and cost inputs were derived primarily from the included trials, targeted literature searches, estimates presented in the companies' evidence submissions, and previous NICE Technology Appraisals.

Confidential Patient Access Schemes (PASs) are available for a number of modelled technologies, including the comparator therapies lenvatinib and sorafenib and also for QuiremScout®. All results in this report are based on list prices; separate analyses which include relevant PAS discounts are presented in a confidential appendix to this report.

Results were presented in terms of incremental net monetary benefit (NMB) versus the least costly option in each scenario. Fully incremental, incremental cost-effectiveness ratios (ICERs) were also produced. Uncertainty was accounted for using probabilistic and deterministic sensitivity analyses, the base-case was based on 20,000 model iterations using Monte Carlo sampling methods.

1.4 Results

1.4.1 Results of clinical effectiveness review

Seven RCTs, seven prospective comparative studies, five retrospective comparative studies and one non-comparative case series were included in the review of clinical effectiveness.

Efficacy and safety of SIR-Spheres

Two large RCTs with a low risk of bias (SARAH[2] and SIRveNIB[3]) found no significant difference in OS or PFS between SIR-Spheres and sorafenib, despite statistically significantly greater tumour response rate in the SIR-Spheres arm of both trials (SARAH: 19% versus 12%, p=0.0421; SIRveNIB: 16.5% versus 1.7%, p<0.001). The SARAH trial reported a significant difference between groups in health-related quality of life, favouring SIR-Spheres, however the proportion of patients who completed the questionnaires was low. There was no significant difference in health-related quality of life between groups in the SIRveNIB trial. Adverse events, particularly grade ≥3 events, were more frequent in the sorafenib group in both trials.

The Sirtex company submission selected a subgroup of patients from the SARAH trial with ≤25% tumour burden and ALBI grade 1 for their base-case analysis in the economic model; this is not a clinically recognised subgroup and was based on a *post-hoc* analysis.

There were methodological differences between the trials, most notably SARAH was conducted in France, whilst SIRveNIB was conducted in the Asia-Pacific region. HCC in European patients is more likely to be caused by alcohol or hepatitis C, whereas in Asia it is more likely to be caused by hepatitis B. This has implications for the generalisability of the SIRveNIB trial results to the UK population, since the natural history of the disease and treatment options differ. Also the SARAH trial included patients with a poor prognosis who would only be considered for BSC in UK practice.

Three other RCTs of SIR-Spheres were included comparing SIR-Spheres with TACE,[4] and DEB-TACE[5] and SIR-Spheres followed by sorafenib with sorafenib alone.[6] Each of these small RCTs had either a high risk of bias or some concerns regarding bias. The trials comparing SIR-Spheres with TACE or DEB-TACE appeared to favour CTT over SIRT in terms of survival outcomes. The addition of SIR-Spheres to sorafenib did not appear to increase the number of treatment-emergent adverse events.

Efficacy and safety of TheraSphere

There were two small RCTs and seven prospective comparative studies of TheraSphere.[7-15] One of the RCTs (PREMIERE)[8] and all of the non-RCT studies had a high risk of bias, whilst the other RCT had some concerns regarding bias.[11] PREMIERE compared TheraSphere with TACE as a bridge to

transplant; outcomes were improved in the TheraSphere arm compared with the TACE arm.[8] The other RCT compared TheraSphere plus sorafenib with sorafenib alone as a bridge to transplant; outcomes were similar between treatment groups.[11]

Efficacy and safety of QuiremSpheres

Only one very small case series of QuiremSpheres has been completed in patients with HCC.[16] The available data are too limited to draw any conclusions about the safety or efficacy of QuiremSpheres.

Direct comparison of different SIRT technologies

Five small retrospective comparative studies, all with a high or unclear risk of bias, compared SIR-Spheres with TheraSphere.[17-21] Two studies included patients who had portal vein thrombosis (PVT) and appear to have included some of the same patients.[19, 20] OS was reported in four studies, including the two studies of patients with PVT; OS was longer in the TheraSphere arm in three of the studies.[17, 19, 20] One study assessed PFS, which was longer with SIR-Spheres,[18] whilst another study assessed time to progression, which was longer with TheraSphere (in patients with PVT).[19] Tumour response rate was higher in the TheraSphere arm than the SIR-Spheres arm in patients with PVT.[19]

Clinical toxicities were generally more frequent with SIR-Spheres than TheraSphere in one very small study.[17] In a study of patients with PVT there was no difference in the frequency of fatigue, but pain and nausea appeared more frequent with SIR-Spheres, whilst anorexia appeared more frequent with TheraSphere.[19]

No studies were identified that directly compared QuiremSpheres with either SIR-Spheres or TheraSphere. An addendum was received from Terumo Europe in August describing a very small pilot study with several methodological limitations.[22]

1.4.2 Network meta-analysis results

The base-case NMA was in adults with unresectable HCC who were Child-Pugh A and ineligible for CTT in the per protocol population. There were three studies included in the base-case analysis. Two RCTs comparing SIR-Spheres and sorafenib; SARAH and SIRveNIB[2, 3] and one RCT comparing lenvatinib and sorafenib; REFLECT.[23] The results provided no evidence that the random effects model should be preferred. Therefore, the results of the fixed effects model were used for the base-case and scenario analyses.

There were no meaningful differences in OS between any of the three treatments in the per protocol or ITT populations. In the per protocol population SIR-Spheres showed a non-significant marginal improvement in OS when compared to sorafenib (HR: 0.94, 96% CrI: 0.77-1.14) although the credible interval indicates that this result is uncertain. SIR-Spheres was ranked as the most efficacious

therapy, with a probability of being the best of 0.61. Sorafenib was ranked as the worst treatment, with a probability of being best of 0.16. Lenvatinib was ranked as the second best with a probability of 0.22.

To produce an efficacy estimate for TheraSphere, a sensitivity analysis included the only study that directly compared TheraSphere and SIR-Spheres for Child-Pugh A patients ineligible for CTT (Biederman *et al*.).[20] Adding this study had a substantial effect on the NMA results. In the per protocol population, TheraSphere showed a significant improvement in OS when compared to SIR-Spheres (HR: 0.44, 95% CrI: 0.20-0.84), sorafenib (HR: 0.41, 95% CrI: 0.20-0.77) and lenvatinib (HR: 0.40, 95% CrI: 0.18-0.78). However, these results may be biased and unreliable as the Biederman study is a low quality retrospective study reporting a very strong treatment effect on OS for TheraSphere compared to SIR-Spheres (HR: 0.40, 95% CrI: 0.20-0.78). A sensitivity analysis, excluding the Asia-Pacific SIRveNIB study from the NMA had very little impact on the results for OS in the per protocol and ITT populations compared to the base-case; there were no significant differences in treatment effects for any comparisons.

1.4.3 Results of economic modelling

The Sirtex and BTG company submissions (CS) each present the methods and results of two separate economic evaluations which split the population potentially eligible for SIRT into two groups: patients eligible for CTT and those ineligible for CTT. In the corrected version of the BTG CTT-eligible population, the probabilistic ICER for SIRT compared with DEB-TACE was £24,647. In the corrected version of the BTG CTT-ineligible population, the probabilistic ICER for TheraSphere compared with regorafenib was £69,070. The economic assessment in the CTT-eligible population submitted by Sirtex was a cost-minimisation analysis, and found that the costs of SIRT overlapped significantly with those of CTT. The base-case economic analysis submitted for the CTT-ineligible population by Sirtex was in a subgroup of patients with low tumour burden and preserved liver function, the results of the presented probabilistic analysis predicted that SIR-Spheres dominated sorafenib (lower costs and higher QALYs).

The results of the AG's base-case analysis (probabilistic) suggested TheraSphere is cost-saving relative to both SIR-Spheres and QuiremSpheres. However, incremental costs between TheraSphere and SIR-Spheres were small, and pairwise NMB was close to zero (-£182). QuiremSpheres was associated with substantial incremental costs of £6,615 relative to both TheraSphere and SIR-Spheres (exclusive of PAS). Pairwise NMB between QuiremSpheres and TheraSphere in the AG's base-case was therefore negative, at -£6,599. In analyses presented in the confidential appendix which include available PAS discounts, QuiremSpheres remained more costly than both TheraSphere and SIR-Spheres, as such, the pairwise NMB remained negative.

In a fully incremental analysis at list price, none of the three SIRT technologies were predicted to be cost-effective at any willingness-to-pay (WTP) threshold, being more costly and less effective than lenvatinib. Predicted NMB for lenvatinib compared with TheraSphere (the lowest costing SIRT) was -£2,154. In a pairwise comparison of sorafenib with TheraSphere, the ICER for sorafenib was £31,974 per QALY gained, with an estimated NMB of -£150 (implying TheraSphere is cost-effective compared to sorafenib at a WTP threshold of £30,000).

In a fully incremental analysis conducted including confidential PAS discounts, lenvatinib remained the most cost-effective therapy and dominated all SIRTs, generating greater health benefits at lower costs. In pairwise comparisons of sorafenib with each SIRT, sorafenib also dominated all SIRTs.

A number of scenarios were produced to explore the effect of using data from more restrictive but clinically effective sub-populations, downstaging to potentially curative therapy, different resource use, cost assumptions, and data sources. When the modelled population was limited to only those with a low tumour burden and preserved liver function, the ICERs for TheraSphere and SIR-Spheres were £22,420 and £23,617 per QALY gained versus the most cost-effective systemic therapy at list price. The most optimistic ICERs were produced when downstaging to curative therapy was permitted in this more selective population, ICERs for TheraSphere and SIR-Spheres decreased to £3,569 and £4,356 respectively. However, there was no scenario in which SIRT was predicted to be cost-effective at a WTP threshold of £30,000 when confidential PAS discounts were included.

1.5 Discussion

The AG's analyses predicted lenvatinib to be the most cost-effective in nearly all scenarios, while sorafenib was generally the most cost-effective alternative, producing more QALYs at a higher cost. The results of the AG's base-case analysis are robust to changes in a wide range of assumptions and across different scenarios.

Strengths of the AG model include: (i) high-quality RCT data were included to model the outcomes of the most relevant patient population to UK practice; (ii) analyses included all appropriate comparators; (iii) independent modelling of the costs and outcomes of patients who receive work-up but were ineligible to receive SIRT, and (iv) preserved randomisation and internal consistency with regards to the use of subsequent systemic and curative therapies.

Insurmountable limitations in the evidence base meant the AG were unable to address the question of SIRT's cost-effectiveness in patients with early and intermediate stage HCC. The evidence for TheraSphere and QuiremSpheres in advanced HCC was extremely limited, and a lack of head-to-head evidence prevented a meaningful comparison of SIR-Spheres, TheraSphere, and QuiremSpheres with

one another. This essentially limits this particular comparison to that of a cost-minimisation, although a full comparison of the cost-effectiveness of SIRT versus sorafenib and lenvatinib was possible.

1.6 Conclusions

Implications for service provision

The existing evidence cannot provide decision makers with clear guidance on the comparative effectiveness of treatments in early and intermediate stage HCC.

In the advanced stage HCC population, two large randomised trials have assessed the comparative effectiveness of SIR-Spheres with sorafenib, showing that SIRT has similar effectiveness to sorafenib.

None of the SIRT technologies are cost-effective at any WTP threshold, being more costly and less effective than lenvatinib; this is the case at both list price and with PASs.

Suggested research priorities

No strong conclusions can be drawn in the early and intermediate stage HCC populations owing to considerable uncertainty in estimates of effectiveness and high risk of bias. A priority for further research is therefore the conduct of studies in these populations.

The low tumour burden/ALBI 1 subgroup potentially represents a group of patients for which SIRT may be beneficial when compared with sorafenib. Future work considering this subgroup may therefore be useful.

There is currently very limited evidence on the comparative effectiveness of alternative SIRT technologies; future high quality studies evaluating alternative SIRTs would be beneficial.

Study registration

This study is registered as PROSPERO CRD42019128383

Funding details

This report was commissioned by the NIHR HTA Programme as project number 17/109/19.

Word count: 2570

2 Background

2.1 Description of health problem

Liver cancer is the fifth most common cancer and the second most frequent cause of cancer-related death globally. Hepatocellular carcinoma (HCC) is the most common type of liver cancer, representing around 90% of primary liver cancers.[1] Around 90% of HCCs are associated with a known underlying aetiology, most frequently chronic viral hepatitis B or C, or overconsumption of alcohol (alcoholic liver disease). Long periods of chronic liver disease, characterised by hepatic inflammation, fibrosis and aberrant hepatocyte regeneration, can cause scarring of the liver (cirrhosis).[24] One-third of patients with cirrhosis will develop HCC during their lifetime.[1]

In the UK, the underlying aetiology of HCC is commonly alcoholic liver disease and non-alcoholic fatty liver disease, with 50% of cases attributable to these factors. Hepatitis infection (hepatitis B or C) is also a common cause in the UK, but in contrast with non-western populations, represents only 15% of cases. Viral hepatitis is the primary cause of HCC in non-western populations, with up to 90% of cases directly attributable to the hepatitis B and C virus.[25]

Underlying liver cirrhosis and the burden of a growing tumour results in an often substantially reduced liver function in HCC patients, with consequences for morbidity and mortality. Liver dysfunction associated with chronic liver disease is commonly assessed using the Child-Pugh scoring system, which classifies patients into three groups: A, B, or C (least severe disease, moderate liver disease; severe/end stage liver disease). Treatment options available to HCC patients are in part dictated by liver function, with choices becoming more limited with increasing liver dysfunction. The Barcelona Clinic Liver Cancer (BCLC) staging system is used to establish prognosis and enable the selection of appropriate treatment based on both the underlying liver dysfunction and cancer stage.[1] A modified version of the BCLC staging system is presented in Table 1 in Section 2.2. The BCLC staging system classifies patients into five stages (0, A, B, C, and D) according to tumour burden, liver function, and ECOG performance status, which must all be considered when selecting appropriate treatment.

2.1.1 Epidemiology

The incidence of HCC is higher in men than women, with 2,128 men and 586 women diagnosed with HCC in England in 2017.[26] The majority of cases occur in adults over the age of 60.[26] The average age of patients at HCC diagnosis is 66 years, reflecting the long-term nature of most chronic liver disease underlying HCC.[27] Approximately 30% of European patients are diagnosed with early (BCLC stage 0 or A) HCC, approximately 10% with intermediate (BCLC stage B) HCC, approximately 50% with advanced stage HCC (BCLC stage C) and approximately 10% with terminal (BCLC stage D) HCC.[28]

The majority of patients are therefore diagnosed with advanced disease where treatment options are more limited, see Section 2.2 for details.

2.1.2 Prognosis

Prognosis of patients with HCC is heavily dependent on stage of disease and is summarised in Table 1 presented in Section 2.2. In very early and early stage disease, a range of potentially curative treatment options are typically available and as such, the long-term prognosis of these patients can be good. In very early stage disease, 5-year survival is between 70 to 90%, and 50 to 70% in early stage disease.[29] In intermediate and advanced stage disease, treatment options are more limited and are primarily delivered to prolong survival and reduce the burden of symptoms. Length of survival is therefore significantly shorter; prognosis in patients with advanced disease is particularly poor, with a median survival of less than 12 months.[29]

2.2 Current service provision

Clinical management of HCC is complex; there are a range of treatment options available which depend upon the location and stage of the cancer and liver function. Clinical practice guidelines published by The European Association for the Study of the Liver (EASL) summarise treatment recommendations according to BCLC classification.[1] These recommendations are reproduced in Table 1 with some modifications, reflecting entry criteria to pivotal clinical trials.

Table 1: Modified BCLC staging system and treatment strategy

Prognostic stage	Tumour burden	Liver function	Performance status	Recommended treatment	Survival
Very early stage (BCLC 0)	Single <2cm nodule	Preserved liver function	0	Ablation or resection	>5 years
Early stage (BCLC A)	Single or 2-3 nodules <3cm	Preserved liver function	0	Ablation, resection or transplant	>5 years
Intermediate stage (BCLC B)	Multinodular, unresectable	Preserved liver function	0-1	Conventional transarterial therapies (TAE, TACE, DEB-TACE)	>2.5 years
Advanced stage (BCLC C)	Portal invasion/ extrahepatic spread	Preserved liver function	0-2	Systemic therapy (sorafenib, lenvatinib or regorafenib (for patients who have previously had sorafenib))	≥10 months
Terminal stage (BCLC D)	Not transplantable HCC	End-stage liver function	3-4	Best supportive care	3 months

The primary aim of therapy in patients diagnosed with early stage HCC is typically curative, and there are a number of treatment options with curative potential available. These include radiofrequency

ablation (which uses the heat generated by alternating current to destroy solid tumour tissue), resection (where the tumour-containing portions of the liver are removed), and liver transplantation.[1] Owing to the limited availability of suitable donors, liver transplant is typically reserved for patients with a poor prognosis due to impaired liver function, and in whom resection is inappropriate, for example in patients with multifocal tumours. Suitability for transplant is assessed against the Milan criteria, which require patients to have a single lesion of <5 cm, or up to 3 lesions of <3 cm each, without macroscopic vascular invasion (MVI).[1] Typically, patients not meeting these criteria are ineligible for transplant, but increasingly patients whose disease has been 'downstaged' may be considered for transplant. Downstaging is where patients whose tumours fall outside of the limits permitted by the Milan criteria are brought within the criteria, typically through the use of conventional transarterial therapies (CTT; see below) to reduce tumour burden. Patients waiting for a transplant may also receive CTT as 'bridging therapy', where the intent is to control the progression of disease in order to keep patients within the Milan criteria. However, as transplant waiting times in the UK are typically relatively short, with a median time for HCC patients of approximately 50 days, the use of bridging therapy is limited.

Conventional transarterial therapies (CTT) are the standard care in intermediate HCC where resection or other curative treatment modalities are unsuitable. CTT includes transarterial chemoembolization (TACE), drug-eluting bead transarterial chemoembolization (DEB-TACE), and transarterial embolization (TAE) without chemotherapy. Blood is primarily supplied to the liver via the hepatic portal vein, while most tumours are supplied by the hepatic artery. All three forms of CTT work by administering an embolising agent into the hepatic artery to block blood vessels feeding the tumours within the liver. This process preferentially interrupts the blood supply to the tumours, while allowing blood to continue to reach the remaining healthy tissue. In the case of TACE, lipiodol is combined with a chemotherapy agent, typically doxorubicin or cisplatin, which is administered directly to the tumour, allowing for much higher concentrations of the drug to be achieved than could be tolerated systemically. In DEB-TACE, drug-eluting beads typically bound with doxorubicin or epirubicin are administered to the tumour via the hepatic artery. This allows the release of the chemotherapeutic agent over a prolonged period of time, thereby reducing systemic concentrations (and thus any side effects) compared with TACE.[30] TAE, or bland TACE, involves only the physical occlusion of blood vessels, with no addition of chemotherapy. Because the primary therapeutic effect of CTT is the embolization of the hepatic artery, the use of these techniques is typically limited to patients with good portal vein flow, so as to maintain a good blood supply to the liver. As such patients with portal vein thrombosis or tumour invasion of the portal vein are typically considered contraindicated to CTT.

In patients that have advanced HCC, or who have previously failed CTT, the current standard of care consists of systemic chemotherapy. Current NICE guidance in this population recommends sorafenib as an option for people with Child-Pugh grade A liver impairment (TA474).[31] Lenvatinib is also recommended as an option for people with Child-Pugh grade A liver impairment and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (TA551).[32] A recent technology appraisal on regorafenib for treating advanced unresectable HCC (TA555) recommends regorafenib as an option for people who have previously been treated with sorafenib and have Child-Pugh grade A liver impairment and an ECOG performance status of 0 or 1. Best supportive care (BSC) is offered to patients when conventional transarterial therapies or systemic therapy is not available or appropriate, including patients with terminal stage disease.

2.3 Description of technology under assessment

Selective internal radiation therapy (SIRT), also known as transarterial radioembolisation (TARE), is a complex intervention that delivers radiation directly to liver tumours via microspheres that are injected into the hepatic artery via a catheter inserted into the femoral artery. The most likely position for SIRT in the HCC treatment pathway is for patients with intermediate (BCLC stage B) or advanced (BCLC stage C) stage HCC as a non-curative option, as the use of SIRT is not precluded by reduced liver function as strictly as CTTs. However, SIRT is unlikely to be suitable for patients with more limited liver function (Child-Pugh B8+), or extrahepatic tumour spread. There may also be a role for SIRT as a bridging therapy for BCLC A patients awaiting transplant (see Section 2.2) as an alternative to conventional transarterial therapies.

NICE Interventional Procedures Guidance 460 states that current evidence on the efficacy and safety of SIRT for primary HCC was adequate to permit routine use of the technology.[33] However, significant uncertainties remain about its comparative effectiveness relative to conventional transarterial and systemic therapeutic options.[33] Clinicians have been encouraged by NICE to enter eligible patients into trials comparing the procedure against other forms of treatment and to enrol all patients into the UK SIRT registry (launched in 2013).[33]

The present appraisal concerns three SIRT technologies; SIR-Spheres®, TheraSphere®, and QuiremSpheres®. SIR-Spheres (manufactured by Sirtex Medical) is a CE marked class III active medical device comprising resin microspheres containing yttrium-90, indicated for the treatment of inoperable liver tumours. TheraSphere (manufactured by BTG) is a CE marked class III active medical device comprising glass microspheres containing yttrium-90, indicated for the treatment of hepatic neoplasia. QuiremSpheres (manufactured by Quirem Medical, distributed by Terumo Europe) is a CE marked class III active medical device comprising poly-L-lactic acid (PLLA) microspheres containing holmium-166, indicated for the treatment of unresectable liver tumours.

In preparation for SIRT, patients undergo preliminary angiography of the hepatic artery, and protective coiling of extrahepatic branches to reduce extrahepatic radiation uptake. For TheraSphere and SIR-Spheres, ^{99m}Tc-macroaggregated albumin is used as an imaging surrogate and injected into the hepatic artery using the same catheter position chosen for the scheduled SIRT session. Calculation of the radiation dose to the tumour, adjacent liver, hepato-pulmonary shunt fraction, and tracer distribution are evaluated with single-photon emission computerised tomography (SPECT-CT) imaging. This is known as the 'work-up' procedure, and is ultimately what decides whether patients are eligible to receive SIRT. A high level of lung shunt or extrahepatic uptake contraindicate the SIRT procedure. When SIRT is not contraindicated following work-up, patients are later readmitted for the SIRT procedure, which is performed in a lobar, sectorial or segmental approach according to tumour size and location.[1] When tumours are present in both lobes, patients may receive a separate administration of SIRT to each lobe on separate occasions (often several weeks apart), to allow clinicians to monitor the liver's response to radiation and prevent damage.

The work-up procedure for QuiremSpheres exploits the properties of holmium-166 microspheres, which unlike yttrium-90 can be visualised with SPECT and magnetic resonance (MR) imaging even at low concentrations. Therefore, a lower dose of holmium-166 is used for evaluating dose distribution (known as QuiremScout®), rather than a surrogate, which may allow for a more accurate assessment of radiation distribution and dosimetry.

Table 2 presents an overview of the main characteristics for each product.

Table 2: Main characteristics of SIR-Spheres, TheraSphere and QuiremSpheres

Technique	SIR-Spheres	TheraSphere	QuiremSpheres
Radioactive isotope	Yttrium-90	Yttrium-90	Holmium-166
Microsphere material	Resin	Glass	Poly-L-lactic acid
Therapeutic mode of action	Beta radiation	Beta radiation	Beta radiation
Mean diameter of the microsphere	32.5 μm	20-30 μm	30 μm
Half-life of the radioactive isotope	64.1 hours	64.1 hours	26.8 hours
Specific activity per microsphere	50 Bq	2500 Bq	350 Bq
Typical administered activity	1.4-2.0 GBq	-	-
Typical number of microspheres administered (x million)	30-40	4	20-30
90% of dose deposited	11 days	11 days	4 days

3 Definition of decision problem

3.1 Decision problem in terms of PICOS and other key issues

The decision problem relates to the use of the selective internal radiation therapies, TheraSphere, SIR-Spheres and QuiremSpheres, within their approved indications for the treatment of hepatocellular carcinoma. Relevant comparators are each other, conventional transarterial therapies (TAE, TACE, DEB-TACE) or, for people for whom any transarterial therapies are inappropriate, established clinical management without SIRT, such as systemic therapy (sorafenib, lenvatinib or regorafenib) or best supportive care.

3.2 Overall aims and objectives of assessment

This appraisal will assess the clinical and cost-effectiveness of the selective internal radiation therapies, TheraSphere, SIR-Spheres and QuiremSpheres, for treating hepatocellular carcinoma.

The objectives of the assessment are to:

- Evaluate the clinical effectiveness of each intervention
- Evaluate the adverse effect profile of each intervention
- Evaluate the incremental cost-effectiveness of each intervention compared against (i) each other, (ii) conventional transarterial therapies, (iii) systemic therapy, and (iv) best supportive care.

4 Assessment of clinical effectiveness

4.1 Methods for reviewing clinical effectiveness

A systematic review of the clinical effectiveness evidence on SIRTs was undertaken following the general principles outlined in CRD's guidance on undertaking systematic reviews[34] and reported according to the general principles of the PRISMA statement.[35] The research protocol is registered on PROSPERO, the international prospective register of systematic reviews in health and social care; registration number CRD42019128383.

4.1.1 Search strategy

A comprehensive search was undertaken to systematically identify clinical and cost-effectiveness literature relating to TheraSphere, SIR-Spheres and QuiremSpheres for HCC. In addition, a search for randomised controlled trials of comparator therapies was undertaken, in order to strengthen the network of evidence on SIRT.

Search strategy for selective internal radiation therapy (SIRT) studies

A search strategy was developed in Ovid MEDLINE by an Information Specialist (MH) with input from the review team. The strategy consisted of a set of terms for HCC combined with terms for SIRT, limited to studies from 2000 onwards. The 2000 date limit was applied as scoping searches had identified controlled studies of SIR-Spheres and TheraSphere published after the year 2000; earlier studies were preliminary uncontrolled studies so have limited value for addressing the decision problem. In addition, clinical advice confirmed that the treatment environment for patients with HCC was different prior to 2000 in terms of comparator treatment options. The searches were not limited by language or study design. The MEDLINE strategy was adapted for use in all other resources searched.

The following databases were searched on 28th January 2019:

- MEDLINE ALL (Ovid)
- EMBASE (Ovid)
- Cumulative Index to Nursing & Allied Health (CINAHL Plus)
- Science Citation Index (Web of Science)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)
- Cochrane Database of Systematic Reviews (CDSR) (Wiley)
- Database of Abstracts of Reviews of Effects (DARE) (CRD databases)
- Health Technology Assessment (HTA) database (CRD databases)
- NHS Economic Evaluations Database (CRD databases)

- EconLit (Ovid)

In addition, information on studies in progress, unpublished research or research reported in the grey literature was sought by searching a range of relevant resources:

- ClinicalTrials.gov
- WHO International Clinical Trials Registry portal
- EU Clinical Trials Register
- PROSPERO
- Conference Proceedings Citation Index – Science (Web of Science)
- ProQuest Dissertations & Theses A&I (ProQuest)

A search of the NICE website and NHS Evidence for relevant guidelines was undertaken on 8th May 2019.

Company submissions and relevant systematic reviews were also hand-searched to identify further relevant studies. Clinical advisors were consulted for any additional studies.

Search results were imported into EndNote® x9 and de-duplicated. Full search strategies can be found in Appendix 13.1.

Search strategy for comparator therapies

A search for randomised controlled trials (RCTs) of comparator therapies was undertaken, in order to strengthen the network of evidence on SIRT. In view of time and resource limitations, it was decided to identify RCTs of conventional transarterial therapies (TAE, TACE, DEB-TACE) by searching existing relevant systematic reviews and meta-analyses and undertaking update searches, if necessary.

Evidence on systemic therapies for HCC was identified from the recent NICE Single Technology Appraisals of sorafenib,[31] lenvatinib[32] and regorafenib.[36]

The search strategy for systematic reviews and meta-analyses of conventional transarterial therapies was developed in Ovid MEDLINE by an Information Specialist (MH) with input from the review team. The strategy consisted of a set of terms for HCC combined with terms for embolisation or chemoembolisation, limited to studies from 2010 onwards, in order to identify the most recent reviews. A search strategy to limit retrieval to systematic reviews or meta-analyses was added in MEDLINE and EMBASE.[37] The MEDLINE strategy was adapted for use in all resources searched.

The following databases were searched on 7th May 2019:

- MEDLINE ALL (Ovid)
- EMBASE (Ovid)
- Cochrane Database of Systematic Reviews (CDSR) (Wiley)
- Database of Abstracts of Reviews of Effects (DARE) (CRD databases)
- Health Technology Assessment (HTA) database (CRD databases)

In addition, PROSPERO was searched to identify any unpublished or ongoing systematic reviews or meta-analyses.

Search results were imported into EndNote x9 and de-duplicated. Full search strategies can be found in Appendix 13.2.

4.1.2 Inclusion criteria

Inclusion criteria were defined in line with the final scope provided by NICE and are outlined below. Studies were initially assessed for relevance using titles and abstracts. One reviewer examined titles and abstracts with a second reviewer checking 10% of records. Full manuscripts of any titles/abstracts that appeared relevant were obtained where possible and the relevance of each study assessed independently by two reviewers according to the criteria outlined below. Any discrepancies were resolved through consensus and, where necessary, a third reviewer was consulted. Relevant foreign language studies were translated and assessed for inclusion in the review. Studies available only as abstracts were included and attempts were made to contact authors for further data.

4.1.2.1 Study design

Randomised controlled trials (RCTs) were eligible for inclusion in the clinical effectiveness review. However, where RCT evidence was insufficient to address the decision problem, non-randomised comparative studies (including retrospective studies) and non-comparative studies of SIRT were considered for inclusion. The evidence was scoped before deciding what level of evidence would be included for data extraction and quality assessment.

4.1.2.2 Participants

Studies of people with early stage HCC where curative treatment is contraindicated (BCLC stage A), intermediate (BCLC stage B) or advanced (BCLC stage C) stage HCC, with or without portal vein thrombosis/involvement, were included in the review. Studies of people with secondary liver metastases or other types of liver cancer (such as cholangiocarcinoma) were not included unless they also included people with primary HCC and results were reported separately for people with HCC.

4.1.2.3 Interventions

The interventions under consideration were the selective internal radiation therapies TheraSphere, SIR-Spheres and QuiremSpheres. Studies in which more than one type of SIRT was used were only included if results were reported separately for the different types of SIRT. Where studies did not state which type of SIRT or radioembolisation technology was used authors were contacted to identify the specific technology used.

Evidence on combined treatments (e.g. SIRT plus sorafenib), was also considered for inclusion and evidence was scoped before deciding which trials would be included for data extraction and quality assessment.

4.1.2.4 Comparators

Relevant comparators were:

- Alternative SIRT interventions (TheraSphere, SIR-Spheres and QuiremSpheres)
- Conventional transarterial therapies (TAE, TACE and DEB-TACE)
- Established clinical management without SIRT, such as systemic therapy (sorafenib, lenvatinib and regorafenib) or best supportive care, for people for whom any transarterial embolisation therapies are inappropriate

In order to strengthen the network of evidence on SIRT, we considered undertaking comparisons of conventional transarterial therapies (TAE, TACE and DEB-TACE), systemic therapies (sorafenib, lenvatinib and regorafenib) and best supportive care, using RCT evidence. The evidence was scoped and criteria for inclusion were developed. Relevant RCTs were assessed for quality and key outcome data were extracted, based on requirements for the model.

4.1.2.5 Outcomes

The outcome measures to be considered included:

- Overall survival
- Progression-free survival
- Time-to-progression
- Response rates
- Rates of liver transplant or surgical resection
- Adverse effects of treatment
- Health-related quality of life (HRQoL)
- Time on treatment/number of treatments provided

4.1.3 Data extraction

Data were extracted by one reviewer using a standardised data extraction form and independently checked for accuracy by a second reviewer. Disagreements were resolved through consensus and, where necessary, a third reviewer was consulted. Where multiple publications of the same study were identified, data were extracted and reported as a single study.

4.1.4 Critical appraisal

The methodological quality of the included studies was assessed using criteria relevant to the study design. RCTs were assessed using the most recent version of the Cochrane risk of bias tool.[38] Quality assessment tools for other study designs were developed using relevant criteria such as those outlined in CRD's guidance on undertaking systematic reviews.[34] Quality assessment was undertaken by one reviewer and independently checked by a second reviewer. Any disagreements were resolved through consensus and, where necessary, a third reviewer was consulted. Details of the quality of the included studies are presented in descriptive tables and their impact on the reliability of results is discussed.

4.1.5 Methods of data analysis/synthesis

Characteristics of the included SIRT studies (such as participant and intervention characteristics, results and trial quality) were tabulated and described in a narrative synthesis. Where sufficient clinically and statistically homogenous data were available, data were pooled using appropriate meta-analytic therapies using WinBUGS software. Clinical, methodological and statistical heterogeneity was investigated, with sensitivity or subgroup analyses performed where appropriate, and where available data permitted.

Where the data allowed, a network meta-analysis (NMA) using Bayesian statistical methods with WinBUGS software was undertaken in order to estimate the relative effectiveness of the different treatments. Results are summarised using point estimates and 95% credible intervals (CrIs) of the effect of each treatment relative to the reference treatment. Where possible, consistency between direct and indirect estimates of treatment effect in the NMA was assessed. The results of the NMA are described in Section 5 of this report and were used in the economic model described in Section 8.

4.2 Clinical effectiveness results

4.2.1 Quantity and quality of research available

Studies of selective internal radiation therapy (SIRT)

The electronic searches for clinical effectiveness evidence on SIRT interventions (TheraSphere, SIR-Spheres and QuiremSpheres) identified a total of 4755 records (after de-duplication between databases). The 4755 records were inserted into an EndNote library. Reviewer one (RW) screened 2615 titles and abstracts and reviewer two (SS) screened 2617 titles and abstracts. A total of 477

records (10% of the library) were double screened; discrepancies were resolved through consensus, or in consultation with a third reviewer (AE).

Of the 4755 records in the library, 3670 were excluded from the clinical effectiveness review after title and abstract screening, as they did not include patients with unresectable HCC, did not assess TheraSphere, SIR-Spheres or QuiremSpheres, did not report relevant patient outcomes or were not a primary study. A total of 1085 records appeared to meet the study selection criteria based on title and abstract (where an abstract was available).

In view of the high number of potentially eligible records, the evidence was scoped before deciding which studies to order for full paper screening. Records were coded, using titles and abstracts (where available), in terms of the intervention (type of SIRT and whether the study focussed on the delivery of SIRT or the work-up procedure), the study design (prospective or retrospective, comparative or not) and the number of HCC patients included in the study. A large number of records were conference/meeting abstracts (n=603), rather than full publications (n=482); reviewer 1 (RW) coded the full publications and reviewer 2 (SS) coded the conference/meeting abstracts. Studies marked as 'RCT' (n=47; 43 full publications and 4 conference/meeting abstracts), 'prospective comparative' (n=26; 18 full publications and 8 conference/meeting abstracts) or 'retrospective comparative' (n=103; 61 full publications and 42 conference/meeting abstracts) studies were ordered for full paper screening as comparative studies (total n=176) were prioritised over non-comparative studies. However, it was clear that there were no comparative studies of QuiremSpheres, therefore, all studies considered to relate to QuiremSpheres (referring to holmium as the intervention) were ordered for full paper screening (n=11). In addition, large non-comparative studies that included over 500 patients were also ordered for full paper screening (n=6). One additional non-comparative study, where BCLC subgroups and subsequent treatments were reported and which was considered to be particularly relevant for the economic model, was ordered. Therefore, a total of 194 records were ordered for full paper screening.

Of the 194 records ordered, 130 were excluded based on full paper screening and 64 were considered to be potentially relevant records to be included in the clinical effectiveness review and/or network meta-analysis (55 studies plus 9 associated publications).

A total of 130 records were coded at the title and abstract stage as systematic reviews. Reviewer 1 (RW) screened systematic reviews from 2015 onwards for relevance; there were 25 relevant systematic reviews (plus one associated erratum). The reference lists of these systematic reviews were screened in order to check for additional potentially relevant studies; no additional studies were identified.

Separate searches of guideline databases (NICE website and NHS Evidence), conducted in May 2019, identified a total of 23 records after de-duplication against the original library; none of which were considered to be relevant for inclusion in the systematic review. The reference lists of relevant guidelines were screened in order to check for additional potentially relevant studies; no additional studies were identified.

Clinical advisors were not aware of any additional studies other than those already identified from electronic searches.

A PRISMA diagram is presented as Figure 1. Twenty-seven of the fifty-five studies were prioritised for data extraction, as they were considered to be the most relevant for the assessment of clinical effectiveness and/or the proposed network meta-analyses; these studies are summarised in Table 3. One non-comparative study was included in the clinical effectiveness review as this was the only study of QuiremSpheres,[16] the other 26 studies were comparative studies.

The twenty-eight lower priority studies are summarised in Appendix 13.7 along with the reason for not including them in the systematic review of clinical effectiveness or the proposed network meta-analyses, e.g. consultation with clinical advisors confirmed that the comparators used were not applicable to current UK practice.[39-42]

Figure 1: Flow diagram of the study selection process for the clinical effectiveness review

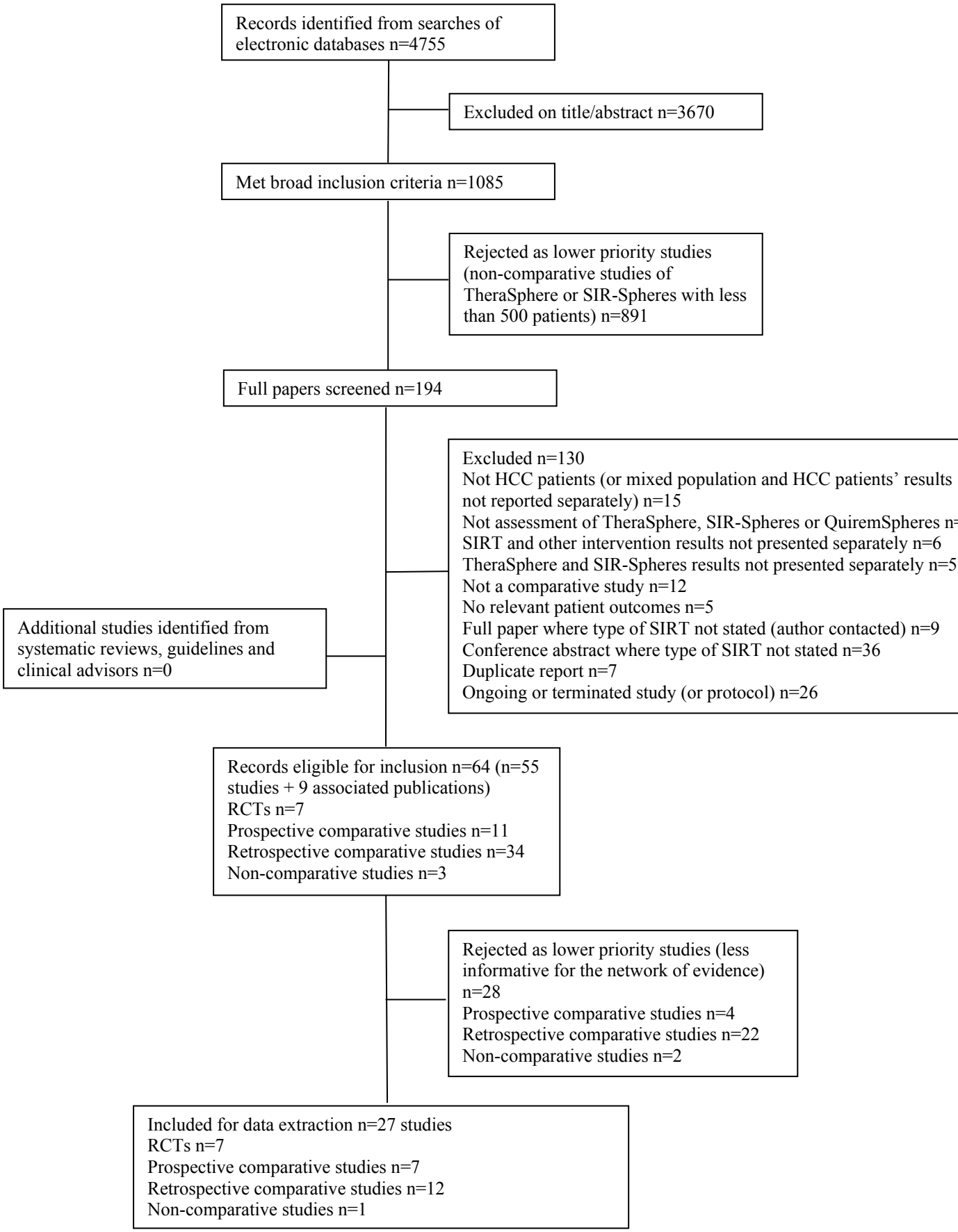


Table 3: Studies included in the systematic review of clinical effectiveness or considered for the network meta-analysis (n=27)

Study	Intervention	Comparator	Country	Population
RCTs of SIR-Spheres (n=5)				
Vilgrain, 2017[2, 43] SARAH	SIR-Spheres	Sorafenib	France	Adults with locally advanced HCC (BCLC C) or new HCC not eligible for surgical resection, transplant or thermal ablation after a previously cured HCC (cured by surgery or thermoablative therapy) or HCC with two unsuccessful rounds of TACE
Chow, 2018[3] SIRveNIB	SIR-Spheres	Sorafenib	Asia-Pacific region	Adults with locally advanced HCC (BCLC B or C) not amenable to curative treatment
Kolligs, 2015[4] SIR-TACE	SIR-Spheres	TACE	Germany and Spain	Adults with unresectable liver-only HCC (without portal vein occlusion)
Pitton, 2015[5]	SIR-Spheres	DEB-TACE	Germany	Adults with unresectable N0, M0 HCC (BCLC stage B)
Ricke, 2015[6] SORAMIC	SIR-Spheres + sorafenib	Sorafenib alone	Germany	Adults with unresectable intermediate or advanced HCC (BCLC stage B or C), with preserved liver function (Child-Pugh ≤B7) and ECOG <2, who were poor candidates for TACE (including those failing TACE)
RCTs of TheraSphere (n=2)				
Salem, 2016[8, 44, 45] PREMIERE	TheraSphere	TACE	USA	Adults with BCLC stage A/B unablatable/unresectable HCC with no vascular invasion, Child-Pugh A/B
Kulik, 2014[11, 46, 47]	TheraSphere	TheraSphere + sorafenib	USA	Adults with Child-Pugh ≤B8 and potential candidates for orthotopic liver transplant
Prospective comparative studies of TheraSphere (n=7)				
Kirchner, 2019[7]	TheraSphere	TACE/DEB-TACE	Germany	Adults with unresectable HCC
El Fouly, 2015[10]	TheraSphere	TACE	Germany and Egypt	Adults with intermediate stage (BCLC B) unresectable HCC and good liver function (Child-Pugh B <7)
Salem, 2013[12]	TheraSphere	TACE	USA	Adults with treatment naïve HCC with ECOG 0-2
Memon, 2013[13]	TheraSphere	TACE	USA	Adults with HCC that progressed after intra-arterial locoregional therapies (TACE and SIRT)
Hickey, 2016[9]	TheraSphere	TACE	USA	Adults with unresectable HCC and bilirubin ≤3.0 mg/dL
Maccauro, 2014[15]	TheraSphere plus sorafenib	TheraSphere alone	Italy	Adults with unresectable HCC (Child-Pugh A)
Woodall, 2009[14]	TheraSphere	Best supportive care	USA	Adults with unresectable HCC (including both patients with and patients without portal vein thrombosis)
Retrospective comparative studies of SIR-Spheres versus TheraSphere (n=5)				
Biederman, 2015[20]	SIR-Spheres	TheraSphere	USA	Adults with HCC with portal vein thrombosis

Biederman, 2016[19]	SIR-Spheres	TheraSphere	USA	Adults with HCC with portal vein invasion
Van Der Gucht, 2017[18]	SIR-Spheres	TheraSphere	Switzerland	Adults with unresectable HCC
Bhangoo, 2015[17]	TheraSphere	SIR-Spheres	USA	Adults with unresectable HCC
d'Abadie, 2018[21]	SIR-Spheres	TheraSphere	Belgium	Adults with HCC
Retrospective comparative studies of SIR-Spheres (n=4)				
Cho, 2016[48]	SIR-Spheres	Sorafenib	Korea	Adults with BCLC stage C HCC with portal vein thrombosis
De la Torre, 2016[49]	SIR-Spheres	Sorafenib	Spain	Adults with HCC with portal vein invasion
Gramenzi, 2014[50]	SIR-Spheres	Sorafenib	Italy	Adults with HCC unfit for other effective therapies, Child-Pugh A/B, performance status ≤1, no metastases and no previous systemic chemotherapy
Soydal, 2016[51]	TACE	SIR-Spheres	Turkey	Adults with BCLC B-C HCC
Retrospective comparative studies of TheraSphere (n=3)				
Salem, 2011[52]	TheraSphere	TACE	USA	Adults with unresectable HCC and bilirubin 3.0 mg/dL
Moreno-Luna, 2012[53]	TheraSphere	TACE	USA	Adults with unresectable HCC
Akinwande, 2016[54, 55]	TheraSphere	DEB-TACE	USA	Adults with unresectable HCC (with or without portal vein thrombosis)
Non-comparative studies of QuiremSpheres (n=1)				
Radosa, 2019[16]	QuiremSpheres	N/A	Germany	Adults with HCC

Thirty-four records were coded at the title and abstract stage as potentially relevant economic studies (seven of which were also coded as includes for the clinical effectiveness review). A separate flow diagram of the study selection process for these economic studies is presented in Section 6.1.2.

Studies of comparator therapies

Randomised controlled trials (RCTs) of comparator therapies were sought, in order to strengthen the network of evidence on SIRT (see Section 5). The search for systematic reviews and meta-analyses of conventional transarterial therapies (TAE, TACE, DEB-TACE) identified 989 records. The records were inserted into an EndNote library and one reviewer (RW) screened the titles and abstracts. Records were put in reverse date order and screened starting at the year 2019 and working backwards until no new relevant RCTs were identified from the reviews and meta-analyses. A total of 319 records were screened, published between 2017 and 2019. Twenty-four of the 319 records were relevant systematic reviews or meta-analyses; full papers were obtained and reference lists were

checked for RCTs comparing TAE, TACE or DEB-TACE with each other. Eleven relevant RCTs (reported in 12 publications) were identified, summarised in Table 4. In view of the recency of the relevant systematic reviews and meta-analyses and the age of the RCTs of conventional transarterial therapies (published between 1992 and 2016) it was decided that update searches were not necessary.

Table 4: RCTs of conventional transarterial therapies (n=11)

Study	Intervention	Comparator	Population
Lammer, 2010[56] and Vogl, 2010[57] PRECISION V	DEB-TACE	TACE	Adults with HCC unsuitable for resection or percutaneous ablation (BCLC A/B without portal invasion or extrahepatic spread)
Golfieri, 2014[58]	DEB-TACE	TACE	Adults with HCC unsuitable for curative treatment or had failed/recurred after resection/ablation
Sacco, 2011[59]	DEB-TACE	TACE	Adults with previously untreated unresectable HCC not suitable for ablative treatment, Child-Pugh A or B and ECOG score of 0/1, absence of portal vein thrombosis (PVT) and extrahepatic metastases
Van Malenstein, 2011[60]	DEB-TACE	TACE	Adults with HCC who were not candidates for curative treatments, Child-Pugh A or B cirrhosis and an ECOG score of 0 or ECOG <3 if the restriction in status was not due to the HCC
Llovet, 2002[61]	TACE	TAE	White patients with unresectable HCC not suitable for curative treatment, or Child-Pugh class A or B and Okuda stage I or II
Kawai, 1992[62]	TACE	TAE	HCC patients
Chang, 1994[63]	TACE	TAE	Untreated patients with inoperable HCC
Meyer, 2013[64]	TACE	TAE	Patients ≥16 years old with HCC not eligible for surgical resection
Yu, 2014[65]	TACE	TAE	Unresectable HCC
Malagari, 2010[66]	DEB-TACE	TAE	HCC patients unsuitable for curative treatments, with potentially resectable lesions but at high risk for surgery and patients with HCC suitable for RFA but of high risk due to location.
Brown, 2016[67]	DEB-TACE	TAE	Adults with HCC with ECOG score of 0 to 1 and Okuda stage I or II

Evidence on systemic therapies for hepatocellular carcinoma was identified from the recent NICE Single Technology Appraisals of sorafenib,[31] lenvatinib[32] and regorafenib.[36]

4.2.2 Assessment of clinical effectiveness

This section describes the seven RCTs and seven prospective comparative studies of SIR-Spheres and TheraSphere, the five retrospective comparative studies comparing SIR-Spheres versus TheraSphere and the non-comparative case series of QuiremSpheres. The additional seven retrospective comparative studies of SIR-Spheres or TheraSphere (see Table 3) and studies of comparator therapies (see Table 4) that were selected, as they were considered to be potentially relevant for the network meta-analyses, are described in Section 5.

4.2.2.1 Risk of bias

Results of the risk of bias judgements are presented in Appendix 13.5.

The SARAH and SIRveNIB RCTs both had a low overall risk of bias.[2, 3, 43] There were some concerns regarding bias for the trials undertaken by Pitton *et al*.[5] and Kulik *et al*.[11] Concerns related to the randomisation process for the study by Pitton *et al*.[5] There were concerns related to the randomisation process, potential deviations from the intended interventions and measurement of the outcome for the study by Kulik *et al*.[11] The SIR-TACE, SORAMIC and PREMIERE trials all had a high overall risk of bias; the SIR-TACE trial had a high risk of bias arising from the randomisation process, missing outcome data and measurement of the outcome,[4] the SORAMIC trial had a high risk of bias in relation to deviations from the intended interventions as well as some concerns arising from the randomisation process,[6] and the PREMIERE trial had a high risk of bias arising from the randomisation process and concerns arising from deviations from the intended interventions.[8, 44, 45]

The prospective comparative studies all had a high risk of bias.[7, 9, 10, 12-15] In particular, allocation to treatment groups was either inadequately described or inappropriate, resulting in differences in prognostic factors between treatment groups at baseline. Outcome assessors do not appear to have been blinded in any of the prospective comparative studies.

Four of the retrospective comparative studies had a high risk of bias.[18-21] The two studies by Biederman *et al*.[19, 20] appear to have included many of the same patients, although one of the studies was only reported as a conference abstract, with very limited study details.[20] Each of the studies at a high risk of bias appeared to include patients with different prognostic characteristics at baseline in the two different treatment groups. It was unclear whether outcome assessors were blinded in any of the studies. The study by Bhangoo *et al*. had an unclear risk of bias; it was unclear whether treatment groups were similar at baseline, whether outcome assessors were blinded or whether missing outcome data were balanced across treatment groups.[17]

The small case series undertaken by Radosa *et al*. should be considered to be at a high risk of bias; it is unclear whether patients were representative of all those who would be eligible for SIRT in clinical practice, outcome assessors were not blinded to the participants' intervention and outcome measures were not consistently assessed.[16]

4.2.2.2 Efficacy and safety of SIR-Spheres

As discussed in Section 4.1.2.1, randomised controlled trials were eligible for inclusion in the clinical effectiveness review, with non-randomised comparative studies and non-comparative studies considered for inclusion, in the absence of sufficient RCT evidence. Five RCTs of SIR-Spheres were identified, comparing SIR-Spheres with established therapies available to patients with intermediate

(TACE/DEB-TACE) and advanced (sorafenib) HCC. Other studies of SIR-Spheres identified also compared against sorafenib or TACE (see Table 3), therefore, they were not included in the review.

This section focusses on the two large good quality RCTs (SARAH and SIRveNIB) and also presents a brief summary of the three lower quality RCTs of SIR-Spheres.

SARAH and SIRveNIB RCTs

Two large RCTs compared SIR-Spheres with sorafenib in patients who were not suitable for curative treatments; the SARAH trial was conducted in France[2, 43] and the SIRveNIB trial was conducted in the Asia-Pacific region.[3] Both trials were considered to have a low overall risk of bias (see Appendix 13.5. Further details of these trials are presented in Table 5.

Table 5: Details of SARAH and SIRveNIB RCTs

	SARAH[2]	**SIRveNIB[3]**
Trial characteristics		
Study design	Multicentre open-label RCT	Multicentre open-label RCT
Location	France (25 centres)	Asia-Pacific region (11 countries)
Source of funding	Sirtex Medical	Sirtex Medical
Inclusion criteria	Locally advanced HCC (BCLC stage C), or new HCC not eligible for surgery/ablation after previously cured HCC (cured by surgery or thermoablative therapy), or HCC with two unsuccessful rounds of transarterial chemoembolization. Life expectancy >3 months, ECOG PS 0 or 1, Child-Pugh class A or B score ≤7.	Locally advanced HCC (BCLC stage B or C without extrahepatic disease) with or without PVT, not amenable to curative treatment modalities.
Intervention	**SIR-Spheres (n=237)** Patients underwent angiography, protective coiling and MAA-SPECT/CT scan and were readmitted for SIRT 1 or 2 weeks later. In bilobar tumours the first treatment was delivered to the hemiliver with the greatest tumour burden and the contralateral hemiliver was scheduled for treatment 30-60 days after the first treatment. If the tumour progressed SIRT could be repeated. 184/237 patients received SIR-Spheres: 1 (unilobar) treatment = 115 patients 2 (ipsilateral) treatments = 17 patients 2 (contralateral) treatments = 41 patients 3 (ipsilateral) treatments = 2 patients 3 (contralateral) treatments = 9 patients 53/237 (22%) patients did not receive SIRT.	**SIR-Spheres (n=182)** Patients underwent angiographic and MAA assessment of suitability for SIRT. Eligible patients received a single delivery of SIRT. 52/182 (28.6%) patients did not receive SIRT.
Comparator	**Sorafenib (n=222)** Continuous oral sorafenib (400mg twice daily)	**Sorafenib (n=178)** Continuous oral sorafenib (400mg twice daily)

Primary outcome	Overall survival		Overall survival	
Secondary outcomes	Progression-free survival Tumour response Adverse events Quality of life (EORTC QLQ-C30 version 3 and the specific HCC module QLQ-HCC18)		Progression-free survival Tumour response Adverse events Quality of life (EQ-5D)	
Baseline patient characteristics (ITT population)				
	SIR-Spheres	**Sorafenib**	**SIR-Spheres**	**Sorafenib**
Number of patients	237 (ITT) 174 (per protocol)	222 (ITT) 206 (per protocol)	182 (ITT) 130 (per protocol)	178 (ITT) 162 (per protocol)
Median/Mean age	66 (IQR: 60-72)	65 (IQR: 58-73)	59.5 (SD: 12.9)	57.7 (SD: 10.6)
Proportion male	89%	91%	80.8%	84.8%
Cirrhosis present	211 (89%)	201 (91%)	NR	NR
HCC caused by alcohol Non-alcoholic steatohepatitis Hepatitis B Hepatitis C Hepatitis B and C Other/unknown	147 (62%)* 49 (21%)* 13 (5%)* 55 (23%)* NR 45 (19%)*	124 (56%)* 60 (27%)* 15 (7%)* 49 (22%)* NR 41 (18%)*	NR NR 93 (51.1%) 26 (14.3%) 4 (2.2%) NR	NR NR 104 (58.4%) 19 (10.7%) 5 (2.8%) NR
BCLC classification Stage A Stage B Stage C	 9 (4%) 66 (28%) 162 (68%)	 12 (5%) 61 (27%) 149 (67%)	 0 93 (51.1%) 88 (48.4%)	 1 (0.6%) 97 (54.5%) 80 (44.9%)
Child-Pugh classification	A5+A6: 196 (83%) B7: 39 (16%) Unknown: 2 (1%)	A5+A6: 187 (84%) B7: 35 (16%) Unknown: 0 (0%)	A: 165 (90.7%) B: 14 (7.7%)	A: 160 (89.9%) B: 16 (9.0%)
ECOG performance status 0 ECOG performance status 1	145 (61%) 92 (39%)	139 (63%) 83 (37%)	135 (74.2%) 47 (25.8%)	141 (79.2%) 37 (20.8%)
Single tumour Multiple tumours	110 (46%) 127 (54%)	96 (43%) 126 (57%)	NR	NR
Unilobar tumour involvement Bilobar tumour involvement	187 (79%) 50 (21%)	187 (84%) 35 (16%)	NR	NR
Macroscopic vascular invasion	149 (63%)	128 (58%)	NR	NR
Portal vein thrombosis	NR	NR	56 (30.8%)	54 (30.3%)
Portal venous invasion Main portal vein Main portal branch (right or left) Segmental	 49/143 (34%) 65/143 (46%) 29/143 (20%)	 38/118 (32%) 59/118 (50%) 21/118 (18%)	NR	NR
Portal vein occlusion – complete Portal vein occlusion – incomplete	18/48 (38%) 30/48 (62%)	18/38 (47%) 20/38 (53%)	NR	NR
Previously received TACE	106/237 (45%)	94/222 (42%)	NR	NR
Trial results				

Median overall survival (months)	8.0 (95% CI: 6.7-9.9)	9.9 (95% CI: 8.7-11.4)	8.8	10.0
	HR: 1.15, 95% CI: 0.94-1.41, p=0.18 (ITT) HR: 0.99, 95% CI: 0.79-1.24 (per protocol)		HR: 1.12, 95% CI: 0.9-1.4, p=0.36 (ITT) HR: 0.86, 95% CI: 0.7-1.1, p=0.27 (per protocol)	
Median progression-free survival (months)	4.1 (95% CI: 3.8-4.6)	3.7 (95% CI: 3.3-5.4)	5.8	5.1
	HR: 1.03, 95% CI: 0.85-1.25, p=0.76 (ITT)		HR: 0.89, 95% CI: 0.7-1.1, p=0.31 (ITT) HR: 0.73, 95% CI: 0.6-0.9, p=0.0128 (per protocol)	
Time to progression	Not reported		6.1	5.4
Tumour response rate	36/190 (19%) evaluable patients achieved a complete (n=5) or partial (n=31) response	23/198 (12%) evaluable patients achieved a complete (n=2) or partial (n=21) response	16.5% (all partial response, 0% achieved a complete response)	1.7% (all partial response, 0% achieved a complete response)
Rates of subsequent liver transplantation or resection	**6/237 (2.5%) had tumour ablation **3/237 (1.3%) had liver surgery 2/237 (0.8%) had liver transplantation	2/222 (0.9%) had tumour ablation 1/222 (0.5) had liver transplantation	1/182 (0.5%) had radio frequency ablation 2/182 (1.1%) had surgery	2/178 (1.1%) had radio frequency ablation 1/178 (0.6%) had surgery
Health-related quality of life (note: HRQoL assessment had missing values for a high proportion of patients at most timepoints for SARAH and at some timepoints for SIRveNIB)	Global health status subscore was significantly better in the SIRT group than in the sorafenib group (group effect p=0.0048; time effect p<0.0001) and the between group difference tended to increase with time (group-time interaction p=0.0447)		There were no statistically significant differences in the EQ-5D index between the SIRT and sorafenib groups throughout the study in either the ITT or per protocol populations	
Number of patients reporting treatment-related adverse events	173/226 (77%)	203/216 (94%)	78/130 (60%)	137/162 (84.6%)
Number of patients reporting ≥Grade 3 adverse events	92/226 (41%)	136/216 (63%)	36/130 (27.7%)	82/162 (50.6%)

*The same patient could have several causes of disease

**Further information provided by Sirtex Medical in response to clarification questions stated that 7/237 patients had radiofrequency ablation and 4/237 patients had resection.

As shown in Table 5, there were methodological differences between the SARAH and SIRveNIB trials. In the SIRveNIB trial patients could only receive one SIRT delivery, whilst in the SARAH trial patients could receive more than one delivery of SIRT; 69/184 (37.5%) patients who received SIRT received more than one delivery, either to the ipsilateral or contralateral lobe.

The SARAH trial was conducted in France, whilst the SIRveNIB trial was conducted in the Asia-Pacific region. This has implications for the generalisability of the SIRveNIB trial results to the UK population. HCC in European patients is more likely to be caused by alcohol or hepatitis C, whereas in Asia it is more likely to be caused by hepatitis B. The natural history of these diseases is different. Treatment options are also different, as hepatitis B-related liver disease is often less advanced than in

alcohol-related or hepatitis C-related disease, therefore, patients may have had more treatment prior to receiving systemic therapy.

The Sirtex Medical submission stated that patient selection in the SARAH trial does not reflect UK clinical practice, as the trial included patients with a poor survival prognosis who would only be considered for systemic therapy or best supportive care (BSC), e.g. due to a high tumour burden, main portal vein thrombosis or impaired liver function (Child-Pugh B). Therefore, this has implications for the generalisability of the SARAH trial results to the UK population who would be eligible for SIRT in clinical practice.

In both trials patients were assessed for suitability for SIRT after randomisation. In the SARAH trial 53/237 (22.4%) patients allocated to SIR-Spheres did not receive SIRT, 26 of whom were treated with sorafenib. In the SIRveNIB trial 52/182 (28.6%) patients allocated to SIR-Spheres did not receive SIRT, 3 of whom were treated with sorafenib (where reported; subsequent treatments were not reported for 31/52 patients). Results were presented for both the ITT and per protocol populations; patients who did not receive their allocated treatment were excluded from the per protocol analysis (those who received sorafenib instead of SIRT were not included in the sorafenib arm in the per protocol analysis).

The SARAH and SIRveNIB trial publications reported baseline characteristics for both the ITT and per protocol populations.[2, 3] The SIR-Spheres and sorafenib groups were generally similar at baseline in the ITT populations (see Table 5). However, in the per protocol population patients in the sorafenib arm appeared to have slightly worse disease characteristics in the SARAH trial (BCLC stage C: 69.4% versus 65.5%; Child-Pugh B7: 14.6% versus 11.5%; median tumour burden: 20% versus 12.5%) and in the SIRveNIB trial (BCLC stage C: 45.1% versus 38.5%; portal vein thrombosis: 29.6% versus 23.1%; tumour size >50% of liver: 21.6% versus 17.7%).

Overall survival

Neither trial found a statistically significant difference in overall survival between SIR-Spheres and sorafenib in either the ITT or per protocol analyses, as shown in Table 5.

Both trials undertook subgroup analyses according to baseline characteristics. The SIRveNIB trial reported a statistically significant difference in overall survival favouring SIR-Spheres in the subgroup of patients with BCLC stage C disease in the per protocol analysis (9.2 versus 5.8 months; HR 0.67, 95% CI: 0.4-1.0, p=0.0475). The SARAH trial demonstrated a statistically significant difference in overall survival favouring sorafenib in the subgroup of patients with complete occlusion in the main portal vein in the per protocol analysis (HR 2.44, 95% CI: 1.01-5.88), however, the

number of patients included in this subgroup analysis was very small, so the result should be interpreted with caution.

Progression-free survival

In the SARAH trial progression-free survival was defined as the time from the closest date of radiological examination before first administration of study treatment to disease progression, according to RECIST 1.1 criteria, or death. In the SIRveNIB trial progression-free survival was defined as the time from the date of randomisation to tumour progression at any site in the body or death, whichever is earlier. Tumour progression was assessed according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria.

Progression-free survival was not statistically significantly different between treatment groups in the ITT analyses of either the SARAH or SIRveNIB trials. However in the SIRveNIB trial, progression-free survival was statistically significantly improved with SIR-Spheres in the per protocol analysis (HR: 0.73, 95% CI: 0.6-0.9, p=0.0128).

Tumour response rate

Tumour response was statistically significantly greater in the SIR-Spheres arm than the sorafenib arm in both the SARAH and SIRveNIB trials (SARAH: 19% versus 12%, p=0.0421; SIRveNIB: 16.5% versus 1.7%, p<0.001). However, in the SARAH trial only 190 SIR-Spheres patients and 198 sorafenib patients were evaluable and included in the analysis.

Rate of liver transplantation or resection

A very small proportion of patients in both treatment arms of the SARAH and SIRveNIB trials went on to have subsequent liver transplantation (<1%), liver surgery (0.6-1.3%) or tumour ablation (0.5-2.5%).

Quality of Life

The SARAH trial reported statistically significantly better health-related quality of life (HRQoL) in the SIR-Spheres treatment group than the sorafenib group for both the ITT and per protocol populations, assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30. However, the proportion of patients who completed questionnaires was 71% in the SIR-Spheres group (169/237) and 84% (186/222) in the sorafenib group at baseline, reducing with time to only 29% (26/90 patients at risk) in the SIR-Spheres group and 32% (29/92 patients at risk) in the sorafenib group at 12 months follow-up. There was no statistically significant difference in HRQoL between the treatment groups in the SIRveNIB trial, assessed using the EQ-5D index.

Adverse events

The proportion of patients reporting at least one treatment related adverse event and the proportion reporting at least one grade ≥3 adverse event was higher in the sorafenib group than the SIR-Spheres group in both trials, as shown in Table 5.

In the SARAH trial the most frequent grade ≥3 adverse events were fatigue (SIR-Spheres 9% vs sorafenib 19%), liver dysfunction (11% vs 13%), increased laboratory liver values (9% vs 7%), haematological abnormalities (10% vs 14%), diarrhoea (1% vs 14%), abdominal pain (3% vs 6%), increased creatinine (2% vs 6%) and hand-foot skin reaction (<1% vs 6%).

In the SIRveNIB trial the most frequent grade ≥3 adverse events of interest were anaemia (SIR-Spheres 0% vs sorafenib 2.5%), fatigue (0% vs 3.7%), diarrhoea (0% vs 3.7%), abdominal pain (2.3% vs 1.2%), ascites (3.8% vs 2.5%), hypertension (0% vs 1.2%), upper gastrointestinal haemorrhage (0.8% vs 1.9%), jaundice (0.8% vs 1.2%), radiation hepatitis (1.5% vs 0%) and hand-foot skin reaction (0% vs 16.7%).

The adverse event profiles of SIRT and sorafenib are very different. Sorafenib is a continuous treatment, whilst most patients only receive one delivery of SIRT (37.5% patients in the SARAH trial received more than one delivery, either to the ipsilateral or contralateral lobe (primarily due to bilobar tumours or a large central tumour requiring bilateral treatment), whilst in the SIRveNIB trial patients only received one delivery). Adverse event rates were not reported separately for patients who received more than one delivery of SIRT, therefore, it is not possible to compare adverse event rates for patients who received one delivery with those who received more than one delivery. In the SARAH trial, patients with bilobar tumours received the first treatment in the hemiliver with the greatest tumour burden and treatment of the contralateral hemiliver was scheduled 30-60 days after the first treatment. No patient had a whole liver treatment approach in one session. Clinical advisors confirmed that this is reflective of their experience, where patients would not receive whole liver treatment in one session, in order to reduce the risk of radioembolisation induced liver disease (REILD). However, the Sirtex Medical submission states that SIR-Spheres can be administered to both lobes of the liver during the same procedure (based on observational data in which 95.9% patients in the European Network on Radioembolisation with Yttrium-90 Resin Microspheres (ENRY) register received whole-liver treatments in a single session[68]); neither the SARAH nor the SIRveNIB trials administered SIR-Spheres to both lobes during the same procedure. This variance is likely to be due to the clinical indication for SIRT; the ENRY register is likely to include a majority of patients with colorectal cancer liver metastases, who do not have underlying cirrhosis, whereas in HCC patients the cirrhotic liver is likely to be more susceptible to REILD.

A relatively large proportion of patients who undergo work-up for SIRT, to assess their suitability for the procedure, are unable to receive SIRT, e.g. due to liver-to-lung shunting or unfavourable hepatic arterial anatomy (42/226 (18.6%) in SARAH and 37/182 (20.3%) in SIRveNIB). The work-up of patients who are unable to undergo SIRT delivery has cost implications.

SARAH RCT subgroup analysis (low tumour burden/low ALBI grade)

The Sirtex Medical company submission selected a subgroup of patients from the SARAH trial with ≤25% tumour burden and ALBI grade 1 for their base-case analysis in the economic model; the company stated that these patients are considered the most appropriate candidates for SIR-Spheres in clinical practice, as they are the most likely to benefit from SIRT. This is not a clinically recognised subgroup and was based on a *post-hoc* analysis; therefore, these results should be prospectively validated before being considered relevant for clinical practice.

This subgroup included 37 (16%) patients in the SIRT group and 48 (22%) patients in the sorafenib group; 92% of those allocated to SIRT received treatment after work-up. Baseline characteristics were relatively well balanced between treatment groups, although more patients in the SIRT arm had BCLC stage B disease, single tumours and had received previous TACE (these patients generally have a better prognosis than patients who are diagnosed at a later stage and are not eligible for TACE) than in the sorafenib arm. More patients in the sorafenib arm had ECOG performance status of 0 and unilobar liver involvement. Table 6 presents baseline characteristics and results for the full ITT population and the low tumour burden/low ALBI grade subgroup of the SARAH trial.

Table 6: Details of ITT population and low tumour burden/low ALBI grade subgroup of SARAH

	ITT population		**Low tumour burden/low ALBI grade subgroup**	
Baseline patient characteristics				
	SIR-Spheres	**Sorafenib**	**SIR-Spheres**	**Sorafenib**
Number of patients	237	222	37	48
Age, years (median) ≥65 <65	66 NR NR	65 NR NR	NR 43% 57%	NR 48% 52%
BCLC classification Stage A Stage B Stage C	 4% 28% 68%	 5% 27% 67%	 3% 43% 54%	 6% 35% 58%
Child-Pugh classification	A5+A6: 83% B7: 16% Unknown: 1%	A5+A6: 84% B7: 16% Unknown: 0%	A: 95% B: 5%	A: 98% B: 2%
ECOG performance status 0 ECOG performance status 1	61% 39%	63% 37%	62% 38%	79% 21%

Single tumour Multiple tumours	46% 54%	43% 57%	43% 57%	33% 67%
Unilobar tumour involvement Bilobar tumour involvement	79% 21%	84% 16%	76% 24%	85% 15%
Macroscopic vascular invasion	63%	58%	54%	52%
Portal venous invasion Main portal vein Main portal branch Segmental	 49/143 (34%) 65/143 (46%) 29/143 (20%)	 38/118 (32%) 59/118 (50%) 21/118 (18%)	11%	10%
Previously received TACE	45%	42%	51%	44%
Trial results				
Median overall survival (months)	8.0 (95% CI: 6.7-9.9)	9.9 (95% CI: 8.7-11.4)	21.9 (95% CI: 15.2-32.5)	17.0 (95% CI: 11.6-20.8)
	HR: 1.15, 95% CI: 0.94-1.41, p=0.18		HR: 0.73, 95% CI: 0.44-1.21, p=0.22)	
Median progression-free survival (months)	4.1 (95% CI: 3.8-4.6)	3.7 (95% CI: 3.3-5.4)	NR	NR
	HR: 1.03, 95% CI: 0.85-1.25, p=0.76		HR: 0.65, 95% CI: 0.41-1.02, p=0.06	
Tumour response rate	36/190 (19%) evaluable patients achieved a complete (n=5) or partial (n=31) response	23/198 (12%) evaluable patients achieved a complete (n=2) or partial (n=21) response	NR	NR
Rates of subsequent liver transplantation or resection	*6/237 (2.5%) had tumour ablation *3/237 (1.3%) had liver surgery 2/237 (0.8%) had liver transplantation	2/222 (0.9%) had tumour ablation 1/222 (0.5) had liver transplantation	14% (subsequent curative therapy)	2% (subsequent curative therapy)
Health-related quality of life (note: HRQoL assessment had missing values for a high proportion of patients at most timepoints for SARAH and at some timepoints for SIRveNIB)	Global health status subscore was significantly better in the SIRT group than in the sorafenib group (group effect p=0.0048; time effect p<0.0001) and the between group difference tended to increase with time (group-time interaction p=0.0447)		NR	
Number of patients reporting treatment related adverse events	173/226 (77%)	203/216 (94%)	NR	NR
Number of patients reporting ≥Grade 3 adverse events	92/226 (41%)	136/216 (63%)	NR	NR

*Further information provided by Sirtex Medical in response to clarification questions stated that 7/237 patients had radiofrequency ablation and 4/237 patients had resection.

As shown in Table 6, median overall survival and progression-free survival appeared better in the SIR-Spheres arm than the sorafenib arm in the *post-hoc* subgroup analysis, although the difference between treatment groups was not statistically significant. The proportion of patients who went on to have potentially curative therapy was higher in the SIR-Spheres arm than the sorafenib arm, although numbers were very low (5 and 1 patients, respectively). Tumour response rate, HRQoL and adverse events were not reported separately for the low tumour burden/low ALBI grade subgroup.

Prespecified and *post-hoc* subgroup analysis results were presented in the SARAH trial publication for overall survival.[2] Tumour burden was included as a *post-hoc* subgroup. However, neither ALBI grade, nor the combination of low tumour burden and low ALBI grade, were presented.

The SIRveNIB trial did not report subgroup analysis results for the subgroup of low tumour burden/low ALBI grade patients. However, ALBI grade was included in the overall survival subgroup analysis. Results favoured SIR-Spheres in the subgroup of ALBI 1 patients (HR: 0.89, 95% CI: 0.6-1.4; p=0.58) whilst results favoured sorafenib for the subgroup of patients with ALBI grade 2/3 (HR: 1.24, 95% CI: 0.9-1.7, p=0.14).

Other RCTs of SIR-Spheres

SIR-TACE is a small RCT with a high risk of bias that compared SIR-Spheres (n=13) with TACE (n=15) in patients with unresectable HCC without portal vein occlusion.[4] A higher proportion of patients in the SIRT group had BCLC stage A disease (38.5% versus 26.7%) and Child-Pugh liver function class A (92.3% versus 86.7%) than in the TACE group. The average number of tumour nodules was higher in the TACE group (5.0 versus 3.5). Therefore, patients in the SIR-Spheres treatment arm had a better prognosis than those in the TACE arm.

At 6 months 69.2% SIRT patients and 86.7% TACE patients were still alive. At 12 months 46.2% SIRT patients and 66.7% TACE patients were still alive. Progression-free survival, disease control rate and the proportion of patients who went on to have potentially curative therapy were similar between treatment groups. The proportion of patients with a partial response was higher in the SIRT group than the TACE group (30.8% versus 13.3%); although patient numbers were very low.

There were no statistically significant differences between treatment groups in HRQoL by week 12, despite FACT-Hep scores being lower in the SIRT group at baseline (indicating lower quality of life). However, 10/28 patients had missing baseline data and were excluded from HRQoL analyses. The proportion of patients reporting treatment-related adverse events was higher in the TACE group than the SIRT group (33.3% versus 23.1%), although the proportion of patients reporting at least one adverse event was higher in the SIRT group (92.3% versus 66.7%), as was the number of patients with grade ≥3 adverse events (3 versus 2 patients) and serious adverse events requiring hospitalisation (7 versus 5 patients).

A small RCT by Pitton *et al*., with some concerns regarding bias, compared SIR-Spheres (n=12) with DEB-TACE (n=12) in patients with unresectable intermediate (BCLC stage B) HCC with preserved liver function (Child-Pugh A-B7).[5] Treatment groups appeared reasonably similar at baseline, although more patients in the SIRT group had received prior local ablation (4 versus 1) and more

patients in the DEB-TACE group had received prior resection (5 versus 3). Median overall survival and progression-free survival were longer in the DEB-TACE arm than the SIR-Spheres arm (788 days versus 592 days and 216 days versus 180 days, respectively), although the difference between groups was not statistically significant. Median time to progression was 371 days in the SIRT arm and 336 days in the DEB-TACE arm. Adverse events were not reported.

The SORAMIC RCT compared SIR-Spheres followed by sorafenib with sorafenib alone in patients with unresectable intermediate or advanced (BCLC stage B or C) HCC with preserved liver function (Child-Pugh ≤B7) and ECOG performance status <2, who were poor candidates for TACE. Only safety and tolerability data for the first 40 patients have been published to date, with a high risk of bias.[6] More patients in the sorafenib alone group had portal vein thrombosis (35% versus 15%) and BCLC stage C disease (70% versus 60%), indicating poorer prognosis in this group. There were 196 treatment-emergent adverse events reported in the SIRT plus sorafenib arm and 222 events in the sorafenib alone arm; of which 21.9% and 21.2% respectively were considered to be grade 3 or higher. The most common grade 3 or 4 adverse events (hypertension, hand-foot skin reaction and diarrhoea) were reported in a similar number of patients in both treatment arms. Grade 3 or 4 fatigue appeared more common in patients receiving SIRT plus sorafenib (20% versus 10%). Grade 3 or 4 infection and anorexia appeared more common in patients receiving sorafenib alone (20% versus 5% and 0% versus 10%, respectively). Grade 3 or 4 laboratory-related events were more common in patients receiving sorafenib alone (elevated gamma-glutamyltransferase 45% versus 30%, elevated aspartate aminotransferase 15% versus 0%, and alanine aminotransferase 10% versus 0%). One patient experienced a grade 3 gastric ulcer which was probably (but not proven) related to SIRT microspheres deposition.

Further details of each of these trials are presented in Appendix 13.6.

Ongoing studies

There are three ongoing studies of SIR-Spheres including patients with HCC: the Austrian CIRSE Registry for SIR-Spheres Therapy (CIRT),[69] the RESIN tumour registry in the USA[70] and the RESIN tumour registry in Taiwan.[71] The CIRSE Registry is due to complete in 2020, the RESIN tumour registry in the USA is due to complete in 2021 and the RESIN tumour registry in Taiwan is due to complete in December 2019.

There is also an ongoing individual patient data prospective meta-analysis of patients from the SIRveNIB and SARAH trials; VESPRO.[72]

4.2.2.3 Efficacy and safety of TheraSphere

As discussed in Section 4.1.2.1, RCTs were eligible for inclusion in the clinical effectiveness review. Non-randomised comparative studies (including retrospective studies) and non-comparative studies were considered for inclusion in the absence of sufficient RCT evidence. Only two small RCTs of TheraSphere were identified. Therefore, prospective non-randomised comparative studies were also included in the clinical effectiveness review; seven non-RCTs were included, most of which compared TheraSphere with TACE/DEB-TACE. The retrospective comparative studies of TheraSphere that were identified also compared against TACE/DEB-TACE (see Table 3), therefore, they were not included in the review as they were considered to be lower quality than the prospective comparative studies.

One small RCT with a high risk of bias (PREMIERE) compared TheraSphere (n=24) with TACE (n=21) as a bridge to transplant in patients with BCLC stage A or B unresectable HCC with no vascular invasion and Child-Pugh liver function class A or B.[8, 44, 45] The proportion of patients with Child-Pugh class A was much higher in the TACE arm than the TheraSphere arm (71% versus 50%) and the proportion of patients with portal hypertension was much lower in the TACE arm (52% versus 83%), suggesting better prognosis in the TACE arm. Overall survival was slightly longer in the TheraSphere arm (18.6 months versus 17.7 months) and the rate of liver transplant/resection was also higher in the TheraSphere arm (87% versus 70% of 'listed patients'), although time to transplant/resection was slightly longer in the TheraSphere arm (8.8 months versus 7.6 months). Time to progression was significantly longer in the TheraSphere arm: overall median time to progression was not reached in the TheraSphere arm (>26 months) versus 6.8 months in the TACE arm (HR: 0.112, 95% CI: 0.027-0.557, p=0.007); time to progression in the non-transplanted patients was also significantly longer in the TheraSphere arm (median >26 months versus 4.8 months). Adverse events and HRQoL were not reported.

One small RCT by Kulik *et al*., with some concerns regarding bias, compared TheraSphere plus sorafenib (n=10) with sorafenib alone (n=10) as a bridge to transplant in patients with Child-Pugh liver function class ≤B8 HCC who were potential candidates for liver transplant.[11, 46, 47] A higher proportion of patients in the TheraSphere plus sorafenib arm were male (80% versus 50%) and had BCLC stage A disease (70% versus 50%), with more patients in the TheraSphere alone arm having BCLC stage C disease (40% versus 20%). More patients in the TheraSphere plus sorafenib arm had ECOG performance status 0 (80% versus 60%) and Child-Pugh liver function class A (80% versus 60%). Three patients died in the TheraSphere arm versus two patients in the TheraSphere plus sorafenib arm. The proportion of patients receiving liver transplant or resection was 90% in each treatment arm. Most adverse events were more common in the TheraSphere alone arm (fatigue: 90%

versus 40%; diarrhoea 20% versus 10%; pain 50% versus 0%; nausea 70% versus 20%; vomiting 20% versus 0%), although grade ≥3 hand-foot skin reaction was more common in the TheraSphere plus sorafenib arm (20% versus 0%).

Five prospective comparative studies, all with a high risk of bias, compared TheraSphere with TACE/DEB-TACE in patients with HCC.[7, 9, 10, 12, 13] Two studies assessed overall survival. In one small study (n=86) overall survival appeared slightly longer with TACE than TheraSphere in patients with intermediate stage disease (median 18 months versus 16.4 months).[10] In a much larger study (n=765) in which survival outcomes were stratified by BCLC stage and Child-Pugh liver function class, survival was longer in the TACE arm for patients with early and intermediate stage disease but longer in the TheraSphere arm for patients with advanced stage disease.[9] Two small studies (n=86 and n=96) assessed time to progression, which was longer with TheraSphere than TACE (median 13.3 months versus 6.8 months and median 13.3 months versus 8.4 months).[10, 13] Two small studies (n=67 and n=86) assessed complete or partial response rate; results were conflicting, with one study favouring TACE (2.3% versus 0%, using RECIST criteria)[7] and the other favouring TheraSphere (75% versus 50%, using modified RECIST criteria).[10] Two small studies (n=67 and n=56) assessed HRQoL, both favouring TheraSphere.[7, 12] Only one study (n=86) reported adverse events; the most commonly reported adverse event (unspecific abdominal pain) was more frequent in TACE patients than SIRT patients (83% versus 5%).[10]

One small prospective matched case-control study by Maccauro *et al*., with a high risk of bias, compared TheraSphere plus sorafenib (n=15) with TheraSphere alone (n=30) in patients with predominantly BCLC stage C (due to portal vein thrombosis) unresectable HCC with Child-Pugh liver function class A.[15] The study was only published as a conference abstract, therefore, very limited data are available. Results were similar between treatment groups for overall survival (median 10 months in each treatment arm), progression-free survival (median 6 months versus 7 months in the TheraSphere plus sorafenib and TheraSphere alone arms, respectively) and response rate, using modified RECIST criteria (45.5% and 42.8%). However, response rate using European Association for the Study of the Liver (EASL) criteria was better in the TheraSphere alone arm (40% versus 10%).

One small prospective comparative study by Woodall *et al*., with a high risk of bias, compared TheraSphere in HCC patients without portal vein thrombosis (PVT) (n=20) with TheraSphere in HCC patients with PVT (n=15) and a no treatment control (BSC) in HCC patients who were not eligible for SIRT due to substantial extrahepatic disease or hepatic-pulmonary shunt or underlying liver insufficiency (n=17).[14] Overall survival was significantly longer in patients without PVT who received TheraSphere (median 13.9 months) compared with patients with PVT who received TheraSphere (median 3.2 months) and patients who received BSC (median 5.2 months). Adverse

events were more common in TheraSphere patients who had PVT than those who did not have PVT (33% versus 25%). No other outcomes were reported.

Further details of each of these studies is presented in Appendix 13.6.

Ongoing studies

There is one ongoing RCT of TheraSphere in patients with HCC: STOP-HCC, which has an estimated study completion date of February 2020, final results are not anticipated before at least December 2020.[73]

The BTG submission presents twelve additional ongoing or planned studies of TheraSphere.

4.2.2.4 Efficacy and safety of QuiremSpheres

Only one study of QuiremSpheres has been completed in patients with HCC; a small case series undertaken by Radosa *et al*.[16] Nine patients with HCC were retrospectively identified from a prospectively maintained database of patients who received QuiremSpheres between March 2017 and April 2018 at a single centre. It is unclear whether patients were representative of all those who would be eligible for SIRT in clinical practice. The available data are too limited to draw any conclusions about the safety or efficacy of QuiremSpheres. Study details are presented in Appendix 13.6.

Ongoing studies

There are three ongoing studies of QuiremSpheres including patients with HCC: HEPAR Primary,[74] HORA EST HCC[75] and Hope166.[76] All three studies are currently recruiting patients.

4.2.2.5 Direct comparisons of different SIRT technologies

Five small retrospective comparative studies, all with a high or unclear risk of bias, compared SIR-Spheres with TheraSphere. No studies were identified that directly compared QuiremSpheres with either SIR-Spheres or TheraSphere. Further details of each of the five studies are presented in Appendix 13.6. The two studies by Biederman *et al*. (n=97 and n=90) included patients who all had portal vein thrombosis and appear to have included some of the same patients, although one of the studies was only published as a conference abstract,[20] so it is unclear how much overlap there was.[19, 20] The study by d'Abadie *et al*. (n=58 procedures) aimed to investigate the difference in efficacy per Gy of resin versus glass spheres and whether the difference could result from the different degrees of heterogeneity in sphere distribution; limited patient outcomes were reported.[21]

Overall survival was reported in four studies (n=97, n=90 (possibly with some overlap), n=77 and n=17).[17-20] Overall survival was longer in the TheraSphere arm in three of the studies,[17, 19, 20] two of which included patients who all had portal vein thrombosis.[19, 20] Median overall survival in the SIR-

Spheres arm ranged from 3.7 to 7.7 months. Median overall survival in the TheraSphere arm ranged from 7.0 to 15 months.

Progression-free survival was reported in only one study (n=77), in which it was longer in the SIR-Spheres arm (6.1 months versus 5.0 months).[18] However, time to progression was reported for the two treatment arms separately in one other study (n=90 patients with portal vein thrombosis), in which it was longer in the TheraSphere arm (5.9 months versus 2.8 months).[19]

Tumour response rate was reported for the two treatment arms separately in only one study (n=90 patients with portal vein thrombosis), in which a higher proportion of evaluable patients had a complete (8.8% versus 0%) or partial (31.6% versus 13.3%) response in the TheraSphere arm.[19]

None of the studies reported HRQoL outcomes.

Adverse events were reported separately for the two treatment arms in two studies. The study by Biederman *et al*. (n=90 patients with portal vein thrombosis) reported no significant difference in pain (41.2% versus 30.8%), fatigue (17.6% versus 18.5%), nausea (17.6% versus 3.1%) or anorexia (0% versus 9.2%) between SIR-Spheres and TheraSphere, respectively.[19] In the very small study by Bhangoo *et al*. (n=17) all clinical toxicities reported were more frequent in the SIR-Spheres arm than the TheraSphere arm: fatigue 67% versus 45%; abdominal pain 33% versus 27%; nausea/vomiting 67% versus 55%; anorexia/weight loss 33% versus 9%; diarrhoea 17% versus 0%, gastric ulcer 17% versus 0%.[17]

An addendum, in the form of an academic-in-confidence manuscript, was received from Terumo Europe in August. The manuscript described a retrospective pilot study of [redacted] patients treated with QuiremSpheres, TheraSphere or SIR-Spheres at two centres in Germany and the Netherlands. Overall survival and response were assessed at 6 months for all three interventions and at 12 months for QuiremSpheres and SIR-Spheres. Median overall survival was similar between the treatment groups at 6 months [redacted] and 12 months [redacted] The most commonly reported adverse events were [redacted] abdominal pain, fatigue and nausea, other adverse events were rarely reported. This was a very small pilot study with unclear patient selection; patients in the TheraSphere group had poorer prognosis at baseline compared with the other two treatment groups. The authors acknowledge that the study carries several methodological limitations.[22]

4.3 Clinical effectiveness summary and conclusions

SIR-Spheres

There are two large good quality RCTs comparing SIR-Spheres with sorafenib (SARAH and SIRveNIB).[2, 3, 43]

There was no statistically significant difference in overall survival (HR=1.15, 95% CI: 0.94-1.41 and HR=1.12, 95% CI: 0.9-1.4) or progression-free survival (HR=1.03, 95% CI: 0.85-1.25 and HR=0.89, 95% CI: 0.7-1.1) in the SARAH or SIRveNIB trials in the intention-to-treat populations. However, tumour response rate was significantly greater in the SIR-Spheres arm than the sorafenib arm in both trials (of patients who were evaluable and included in the analyses). The SARAH trial reported significantly better HRQoL in the SIR-Spheres arm than the sorafenib arm, assessed using the EORTC QLQ-C30, although the proportion of patients who completed the questionnaires was low, particularly at later timepoints. The SIRveNIB trial found no significant difference in HRQoL assessed using the EQ-5D index. The adverse event profiles of SIR-Spheres and sorafenib are very different; although the most common adverse events generally occurred more frequently in the sorafenib arm in both trials.

There are some concerns regarding the generalisability of the SARAH and SIRveNIB trials to patients who would be eligible for SIRT in UK practice. The SIRveNIB trial was conducted in the Asia-Pacific region, where the aetiology of HCC differs from that in European patients; HCC is predominantly caused by hepatitis B in Asia, whilst it is predominantly caused by alcohol or hepatitis C in Europe. The SARAH trial included patients with a poorer prognosis than those who would be considered for SIRT in UK practice, e.g. high tumour burden, main portal vein thrombosis or impaired liver function.

Around a fifth of patients in the SARAH and SIRveNIB trials were not suitable for SIRT after work-up, e.g. due to liver-to-lung shunting or unfavourable hepatic arterial anatomy; a proportion of patients assessed for suitability for SIRT in clinical practice would also be considered unsuitable, with associated cost implications.

Patients with bilobar disease may require more than one administration of SIRT. In the SARAH trial, patients with bilobar tumours received the first treatment in the hemiliver with the greatest tumour burden and treatment of the contralateral hemiliver was scheduled 30-60 days after the first treatment. However, the Sirtex Medical submission states that SIR-Spheres can be administered to both lobes of the liver during the same procedure; neither the SARAH nor the SIRveNIB trials administered SIR-Spheres to both lobes during the same procedure. Clinical advisors confirmed that this is reflective of

their experience, where patients would not receive whole liver treatment in one session, in order to reduce the risk of REILD.

The Sirtex Medical company submission selected a subgroup of patients from the SARAH trial with ≤25% tumour burden and ALBI grade 1 for their base-case analysis in the economic model; the company stated that these patients are considered the most appropriate candidates for SIR-Spheres in clinical practice, as they are the most likely to benefit from SIRT. This is not a clinically recognised subgroup and was based on a *post-hoc* analysis; therefore, these results should be prospectively validated before being considered relevant for clinical practice. Median overall survival (HR=0.73, 95% CI: 0.44-1.21) and progression-free survival (HR=0.65, 95% CI: 0.41-1.02) appeared better in the SIR-Spheres arm than the sorafenib arm in the subgroup analysis, although the difference between treatment groups was not statistically significant. The proportion of patients who went on to have potentially curative therapy was higher in the SIR-Spheres arm than the sorafenib arm, although numbers were very low (5 and 1 patients, respectively).

Three very small poorer quality RCTs compared SIR-Spheres with TACE,[4] DEB-TACE[5] or SIR-Spheres plus sorafenib versus sorafenib alone.[6] The trials comparing SIR-Spheres with TACE or DEB-TACE appeared to favour the chemoembolization procedure over SIRT in terms of survival outcomes.[4, 5] The addition of SIR-Spheres to sorafenib did not appear to increase the number of treatment-emergent adverse events.[6]

TheraSphere

Two small RCTs[8, 11, 44-47] and seven prospective comparative studies [7, 9, 10, 12-15] of TheraSphere were included in the clinical effectiveness review; one of the RCTs (PREMIERE) and all of the non-RCT studies had a high risk of bias, whilst the other RCT had some concerns regarding bias. Therefore, all of these results should be interpreted with caution.

Both RCTs assessed TheraSphere as a bridge to transplant. The PREMIERE RCT reported longer time to progression, a higher proportion of patients undergoing transplant and slightly longer overall survival in the TheraSphere arm than the TACE arm.[8, 44, 45] Kulik *et al*. reported similar survival and transplant/resection rates between patients receiving TheraSphere plus sorafenib or sorafenib alone.[11, 46, 47]

Five prospective comparative studies compared TheraSphere with TACE or DEB-TACE; overall survival appeared better with TheraSphere in patients with early and intermediate stage disease.[9, 10] Time to progression was longer with TheraSphere than TACE.[10, 13] Results relating to response rates

were conflicting.[7, 10] HRQoL appeared better with TheraSphere.[7, 12] One study reported that the most common adverse event was more frequent with TACE than SIRT.[10]

One prospective comparative study compared TheraSphere plus sorafenib with TheraSphere alone, with similar results between treatment groups.[15] The other study compared TheraSphere in patients with or without PVT with no treatment in patients unsuitable for TheraSphere, overall survival was significantly longer in patients without PVT who received TheraSphere compared with those with PVT who received TheraSphere and those who received only BSC.[14]

QuiremSpheres

Only one study of QuiremSpheres has been completed in patients with HCC; a small case series undertaken by Radosa *et al*.[16] The available data are too limited to draw any conclusions about the safety or efficacy of QuiremSpheres.

Direct comparison of different SIRT technologies

Five small retrospective comparative studies, all with a high or unclear risk of bias, compared SIR-Spheres with TheraSphere. Two of the studies included patients who all had portal vein thrombosis and appear to have included some of the same patients.[19, 20] Overall survival was reported in four studies, including the two studies of patients with portal vein thrombosis; overall survival was longer in the TheraSphere arm in three of the studies.[17, 19, 20] One study assessed progression-free survival, which was longer with SIR-Spheres,[18] whilst another study assessed time to progression, which was longer with TheraSphere (in patients with portal vein thrombosis).[19] Tumour response rate was higher in the TheraSphere arm than the SIR-Spheres arm in patients with portal vein thrombosis.[19] One very small study reported more frequent clinical toxicities in the SIR-Spheres arm than the TheraSphere arm.[17] In patients with portal vein thrombosis there was no difference in the frequency of fatigue, but pain and nausea appeared more frequent with SIR-Spheres, whilst anorexia appeared more frequent with TheraSphere.[19]

No studies were identified that directly compared QuiremSpheres with either SIR-Spheres or TheraSphere.

The BTG submission described a systematic review by Kallini *et al*., supported by funding from BTG International, which aimed to compare the adverse event profiles of TheraSphere and SIR-Spheres for the treatment of unresectable HCC.[77] Twenty-two observational studies of TheraSphere and nine observational studies of SIR-Spheres were included in the review and the number of adverse events and number of patients across studies were summed in order to calculate the proportion of patients experiencing each adverse event. No studies directly comparing TheraSphere with SIR-Spheres were

included in the review. Adverse event reporting appears to have been variable between studies, with many adverse events being reported by very few of the included studies (e.g. hepatobiliary and respiratory adverse events). Baseline characteristics of patients were poorly reported in many of the included studies. Gastric ulcers were reported more frequently with SIR-Spheres than TheraSphere (3.1% (6 studies) versus 0.1% (9 studies)) but the proportion of patients reporting ascites was higher with TheraSphere than SIR-Spheres (9.2% (10 studies) versus 4.7% (5 studies)). Nausea (13 studies in total), fatigue (16 studies in total) and abdominal pain (18 studies in total) occurred in similar proportions of patients for both interventions.[77]

An addendum, in the form of an academic-in-confidence manuscript, was received from Terumo Europe in August. Overall survival and response were similar between the treatment groups. The most commonly reported adverse events were [redacted] abdominal pain, fatigue and nausea, other adverse events were rarely reported. This was a very small pilot study with several methodological limitations.[22]

Conclusions

There is a large body of evidence on the clinical effectiveness and safety of SIRT compared with sorafenib or transarterial chemoembolization. Only two studies were considered to have a low risk of bias; SARAH and SIRveNIB, which both compared SIR-Spheres with sorafenib. However, there are some concerns regarding the generalisability of the results of these two RCTs to the UK HCC population, particularly the SIRveNIB trial, which was conducted in the Asia-Pacific region, where the aetiology of HCC differs from that in Europe.

Both RCTs found no significant difference in overall survival or progression-free survival between SIR-Spheres and sorafenib, despite statistically significantly greater tumour response rate in the SIR-Spheres arm of both trials. The SARAH trial reported a significant difference between groups in HRQoL, favouring SIR-Spheres, however the proportion of patients who completed the questionnaires was low. Adverse events, particularly grade ≥3 events, were more frequent in the sorafenib group in both trials.

The Sirtex Medical company submission selected a subgroup of patients from the SARAH trial with ≤25% tumour burden and ALBI grade 1 for their base-case analysis in the economic model. Whilst results appeared more promising in this subgroup of patients with a better prognosis, these *post-hoc* subgroup analysis results should be prospectively validated before being considered relevant for clinical practice.

In studies comparing the different SIRT technologies, patients with portal vein thrombosis appeared to have better survival outcomes with TheraSphere than SIR-Spheres, however this result was from a small retrospective comparative study with a high risk of bias, therefore may not be reliable. Other studies comparing TheraSphere with SIR-Spheres that did not include only patients with portal vein thrombosis had conflicting results. The only study that compared QuiremSpheres with SIR-Spheres and TheraSphere was provided by Terumo Europe as an addendum in August. Clinical outcomes appeared to be similar between treatment groups, however, this was a very small pilot study with several methodological limitations.

5 Evidence synthesis to inform the relative efficacy of the interventions

5.1 Overview

Studies assessing the clinical effectiveness of SIRT for patients with unresectable HCC have been discussed and summarised in Section 4. The PRISMA diagram describing the selection process is shown in Figure 1 in Section 4.2.1. Treatment options vary greatly for patients with unresectable HCC according to the stage and severity of cancer and liver disease, as described in Section 2.2. Therefore, three network meta-analysis (NMA) models were produced to represent the different populations of unresectable HCC patients. The 26 comparative studies and RCTs included in the systematic review of clinical effectiveness (Table 3) and the 11 RCTs of conventional transarterial therapies (Table 4) were screened for inclusion in each of the three NMA models. Alongside this, two studies of systemic therapies were identified from recent NICE Single Technology Appraisals of sorafenib and lenvatinib: Llovet 2008[78] and Kudo *et al*. 2018.[23]Therefore, 39 studies were screened for inclusion in each of the three NMAs.

5.2 Network meta-analysis of adults with unresectable HCC who are eligible for transplant and of those eligible for conventional transarterial therapies

Meta-analysis using mixed treatment comparisons enables the estimation of different parameters when direct evidence on comparisons of interest is absent or sparse. The statistical synthesis method of network meta-analysis (NMA) enables the comparison of multiple treatment options using both direct comparisons of interventions from RCTs and indirect comparisons across trials based on a common comparator.[79] As suggested by the term, NMA needs a 'network of evidence' to be established between all the interventions of interest.

5.2.1 Network 1: Adults with unresectable HCC who are eligible for transplant

The first model (Network 1) included patients with early/intermediate stage unresectable HCC who were eligible for transplant. SIRT could potentially be used as a bridging treatment for patients awaiting transplant as described in Section 2.3. These patients are generally classed as BCLC stage A patients, with preserved liver function and performance status 0-1. To ensure consistency in the compared studies, studies were therefore only included if ≥ 70% of the recruited population had early stage HCC, or if results were split by disease stage. Only two out of 39 studies were selected for Network 1. This included two small RCTs: PREMIERE[8] and Kulik *et al*.[11] The main reason for the exclusion of studies was patients having advanced stage disease and therefore not eligible for transplant. The reasons for including and excluding each study are reported in Table 7.

However, clinical advice was that there are short transplant waiting times in the UK (<2 months), whereas the two trials in the network had transplant times of roughly 7 to 8 months (mean 7.8 months

in Kulik *et al*.[11] and median 8.8 months in Salem *et al*.[8]). Therefore, the network may not be generalisable to the UK and there may be limited opportunity for benefit in the UK given the short wait times. Clinicians advised that in the UK bridging treatment is also used during the work-up phase, before the patient goes on to the waiting list. However, TACE rather than SIRT is more commonly used in this context. Furthermore, the two RCTs included in the network have very small sample sizes and therefore any efficacy estimates produced would be highly uncertain. Therefore, Network 1 of patients with early/intermediate stage HCC was not conducted as it was deemed unsuitable for decision making.

Table 7: Network 1: Adults with unresectable HCC who are potentially eligible for transplant

First author/study name	N	Intervention	Comparator	Study Design	Reason for inclusion/exclusion
Studies included in the network (n=2)					
Salem, 2016[8, 44, 45] (PREMIERE)	45	TheraSphere	TACE	RCT	Patients with early/intermediate HCC with no vascular invasion. The intent of therapy was bridge to transplant.
Kulik, 2014[11]	20	TheraSphere	TheraSphere + Sorafenib	RCT	Adults with Child-Pugh ≤B8 and potential candidates for orthotopic liver transplant. BCLC C stage patients (30%) were symptomatic only.
Studies excluded from this network (n=37)					
Kolligs, 2015[4] (SIR-TACE)	28	SIR-Spheres	TACE	RCT	Mixed population of early and intermediate stage patients, without portal vein occlusion. Pilot trial funded by Sirtex Medical. Results split for transplantable patients was requested but not provided.
Chow, 2018[3] (SIRveNIB)	360	SIR-Spheres	Sorafenib	RCT	Adults with locally advanced HCC (BCLC B or C) not amenable to curative treatment.

First author/study name	N	Intervention	Comparator	Study Design	Reason for inclusion/exclusion
Vilgrain, 2017[2, 43] (SARAH)	459	SIR-Spheres	Sorafenib	RCT	Adults with locally advanced HCC (BCLC C) or new HCC not eligible for surgery/ablation after previously cured HCC or HCC with two unsuccessful rounds of TACE. Only a few patients received curative therapy.
Pitton, 2015[5]	24	SIR-Spheres	DEB-TACE	RCT	Adults with intermediate stage HCC (BCLC stage B). Patients eligible for curative therapy were excluded.
Ricke, 2015[6] SORAMIC	40	SIR-Spheres + Sorafenib	Sorafenib	RCT	Adults with unresectable intermediate or advanced HCC (BCLC stage B or C). No patients received transplant.
Kudo, 2018[23] (REFLECT)	289 (subgroup of 954 patients)	Lenvatinib	Sorafenib	RCT	Subgroup of adults with advanced stage HCC, majority had PVI or extra-hepatic spread – ineligible for transplant.
Llovet, 2008 (SHARP) [31]	602	Sorafenib	Placebo	RCT	Adults with intermediate and advanced stage HCC, majority had extra-hepatic spread/vascular invasion. Patients ineligible for transplant.
Malagari, 2010[66]	87	DEB-TACE	TAE	RCT	Patients unsuitable for curative treatments with potentially resectable lesions but at high risk for surgery.

First author/study name	N	Intervention	Comparator	Study Design	Reason for inclusion/exclusion
Brown, 2016[67]	101	DEB-TACE	TAE	RCT	Mixed population and some patients with PVI, ineligible for transplant.
Lammer, 2010 [56, 57](PRECISION)	212	DEB-TACE	TACE	RCT	No relevant outcomes reported.
Golfieri, 2014[58]	177	DEB-TACE	TACE	RCT	Adults with early, intermediate and advanced stage HCC without PVT. The population is too varied to include.
Sacco, 2011[59]	67	DEB-TACE	TACE	RCT	Patients with early and intermediate stage HCC, ineligible for transplant.
Van Malenstein, 2011[60]	30	DEB-TACE	TACE	RCT	No relevant outcomes reported.
Llovet, 2002[61]	112	TACE	TAE	RCT	Adults with intermediate and advanced stage HCC, ineligible for transplant.
Kawai, 1992 [62]	289	TACE	TAE	RCT	Patients with early/intermediate stage HCC but no relevant transplant results reported.
Chang, 1994[63]	46	TACE	TAE	RCT	Patients with inoperable HCC.
Meyer, 2013[64]	86	TACE	TAE	RCT	Patients with early, intermediate and advanced stage HCC, ineligible for transplant.

First author/study name	N	Intervention	Comparator	Study Design	Reason for inclusion/exclusion
Yu, 2013[65]	98	TACE	TAE	RCT	Adults with early, intermediate and advanced stage HCC, ineligible for transplant.
Kirchner, 2019[7]	94	TheraSphere	TACE/DEB-TACE	Prospective comparative	No relevant outcomes reported.
Hickey, 2016[9]	765	TheraSphere	TACE	Prospective comparative	Includes patients potentially eligible for transplant, but no transplant outcomes were reported.
El Fouly 2015[10]	86	TheraSphere	TACE	Prospective comparative	Adults with intermediate stage (BCLC B) unresectable HCC. Patients eligible for curative therapy were excluded.
Salem, 2013[12]	56	TheraSphere	TACE	Prospective comparative	No relevant outcomes were reported.
Woodall, 2009[14]	52	TheraSphere	BSC	Prospective comparative	Patients with advanced stage HCC, ineligible for transplant.
Memon, 2013[80]	96	TheraSphere	TACE	Prospective comparative	No relevant outcomes reported.

First author/study name	N	Intervention	Comparator	Study Design	Reason for inclusion/exclusion
Maccauro, 2014[15]	45	TheraSphere plus Sorafenib	TheraSphere	Matched case-control study	Patients with intermediate/advanced HCC with PVT, not appropriate for transplant.
Salem, 2011[52]	245	TheraSphere	TACE	Retrospective comparative	Majority of patients had early/intermediate stage HCC (88.1%) and 39% were within Milan transplant criteria (T2) but there were no relevant outcomes reported.
Bhangoo, 2015[17]	17	TheraSphere	SIR-Spheres	Retrospective comparative	Patients with intermediate/advanced unresectable HCC who either failed or had disease not amenable to alternative locoregional therapies.
Cho, 2016[48]	63	SIR-Spheres	Sorafenib	Retrospective comparative	Patients with BCLC stage C HCC with PVT, not appropriate for transplant.
De la Torre, 2016[49]	73	SIR-Spheres	Sorafenib	Retrospective comparative	Patients with HCC with PVI, not appropriate for curative therapy.
Van Der Gucht, 2017[18]	77	SIR-Spheres	TheraSphere	Retrospective comparative	Patients with early, intermediate and advanced HCC, not appropriate for curative therapy.
Biederman, 2016[19]	90	SIR-Spheres	TheraSphere	Retrospective comparative	Patients with unresectable HCC with main or lobar PVT, not appropriate for curative therapy.

First author/study name	N	Intervention	Comparator	Study Design	Reason for inclusion/exclusion
Akinwande, 2016[54, 55]	96 (matched cohort of 358 patients)	TheraSphere	DEB-TACE	Retrospective comparative	Adults with unresectable HCC (with or without portal vein thrombosis), unlikely transplant intent.
Soydal, 2016[51]	80	SIR-Spheres	TACE	Retrospective comparative	Patients with intermediate/advanced stage HCC, some patients with extrahepatic metastases.
Gramenzi, 2014[50]	137	SIR-Spheres	Sorafenib	Retrospective comparative	Patients with intermediate/advanced HCC, not appropriate for curative therapy.
Moreno-Luna, 2013[53]	116	TheraSphere	TACE	Retrospective comparative	Excluded patients eligible for curative therapy.
Biederman, 2015[20]	97	TheraSphere	SIR-Spheres	Retrospective comparative	Adults with advanced HCC with portal vein thrombosis, not eligible for curative therapy.
D'Abadie, 2018[21]	45	SIR-Spheres	TheraSphere	Retrospective comparative	Unclear population.

5.2.2 Network 2: Adults with unresectable HCC who are eligible for conventional transarterial therapies

The second model was for patients with unresectable HCC who are eligible for conventional transarterial therapies (CTT). Patients in this population tend to have intermediate stage HCC (BCLC B), however patients with advanced stage HCC (BCLC C) can also be eligible if they do not have portal vein thrombosis (PVT)/portal vein involvement (PVI) or extra-hepatic spread. Studies in which the majority of patients had intermediate stage HCC (BCLC B) and ≤ 30% of patients had advanced disease (BCLC C) were included. If studies reported results split by disease stage, they were included. A small proportion of patients in this population may also be eligible for downstaging to transplant. However, there was very little evidence to inform this. Furthermore, clinicians advised that the role of downstaging HCC for liver transplantation is currently under evaluation in the UK and SIRT is not specifically required for downstaging as this can be achieved using existing therapies, most commonly TACE.

After screening the 39 studies described in the previous section, 7 studies were identified as relevant for the population of patients who are eligible for CTT: 6 RCTs and 1 retrospective comparative study. The reasons for inclusion and exclusion are listed in **Table 8**. The main reason for exclusion was the population being substantially mixed in terms of stage of HCC disease or patients having advanced stage disease, which made them ineligible for CTT. SIR-TACE, which is an RCT comparing SIR-Spheres and TACE described in Section 4.2.2.2, included a mixed population of patients with early, intermediate or advanced stage HCC.[4] The trial was funded by Sirtex Medical; therefore, data split by disease stage was requested. However, Sirtex Medical were unable to provide the data as they did not have access to it, and it could not be included in the NMA.

The studies included in Network 2 were an RCT directly comparing SIR-Spheres to DEB-TACE (Pitton *et al.*),[5] 5 RCTs comparing different CTT therapies[59, 63-66] and one retrospective comparative study comparing SIR-Spheres and TheraSphere (Van Der Gucht *et al.*).[18] The RCT that compared SIR-Spheres and DEB-TACE (Pitton *et al.*)[5] included only 24 patients (described in more detail in Section 4.2.2.2) and was the only direct evidence between SIR-Spheres and CTT. There were no studies comparing TheraSphere and CTT. The retrospective study comparing SIR-Spheres and TheraSphere (Van Der Gucht *et al.*) had a high risk of bias, as described in Section 4.2.2.2.

The five RCTs comparing different CTTs, which were deemed relevant for this population, were included to inform the network. This includes, 3 RCTs comparing TACE and transarterial embolization (TAE): Yu *et al.*,[65] Chang *et al.*[63] and Meyer *et al.*[64] The risk of bias assessment reported some concerns regarding bias in the randomisation process for all three trials. The assessment also highlighted concerns regarding protocol deviations from the intended interventions for Chang *et al.*[63]

Both Yu *et al*. and Meyer *et al*. showed no significant differences in overall survival or progression-free survival. Chang *et al*. only reported survival rates between groups but did not find any significant differences.

There was one RCT comparing DEB-TACE and TAE: Malagari *et al*.[66] The risk of bias assessment reported some concerns with this study regarding bias in the randomisation process and in protocol deviations from the intended interventions. The trial was conducted in 95 patients and found that time to progression (TTP) was significantly longer in the DEB-TACE arm (42.4 ± 9.5 weeks) compared to the TAE arm (36.2 ± 9.0 weeks). The remaining RCT compared DEB-TACE and TACE: Sacco *et al*.[59] This trial had a high overall risk of bias, due to an open randomisation process. The trial found no significant differences in survival rates or other relevant outcomes between the two groups. Full results of the risk of bias judgements are presented in Appendix 13.9 and the study details and results are presented in Appendix 13.10.

The network diagram representing the model is shown in **Figure 2**. There are missing direct comparisons and there is no common comparator in the evidence base for both OS and PFS outcomes in this population, therefore it forms a 'disconnected network'. Implementing an NMA in this population would produce very uncertain results as it relies on a single small trial by Pitton *et al*. to connect SIR-Spheres in the network. Furthermore, it would not provide reliable evidence on TheraSphere comparisons with CTT as there is only one small, retrospective, low-quality study connecting TheraSphere in the network. Therefore, Network 2 of patients with unresectable HCC who are eligible for CTT was not conducted as it was deemed unsuitable for decision making.

Figure 2: Network 2: Patients eligible for conventional transarterial therapies

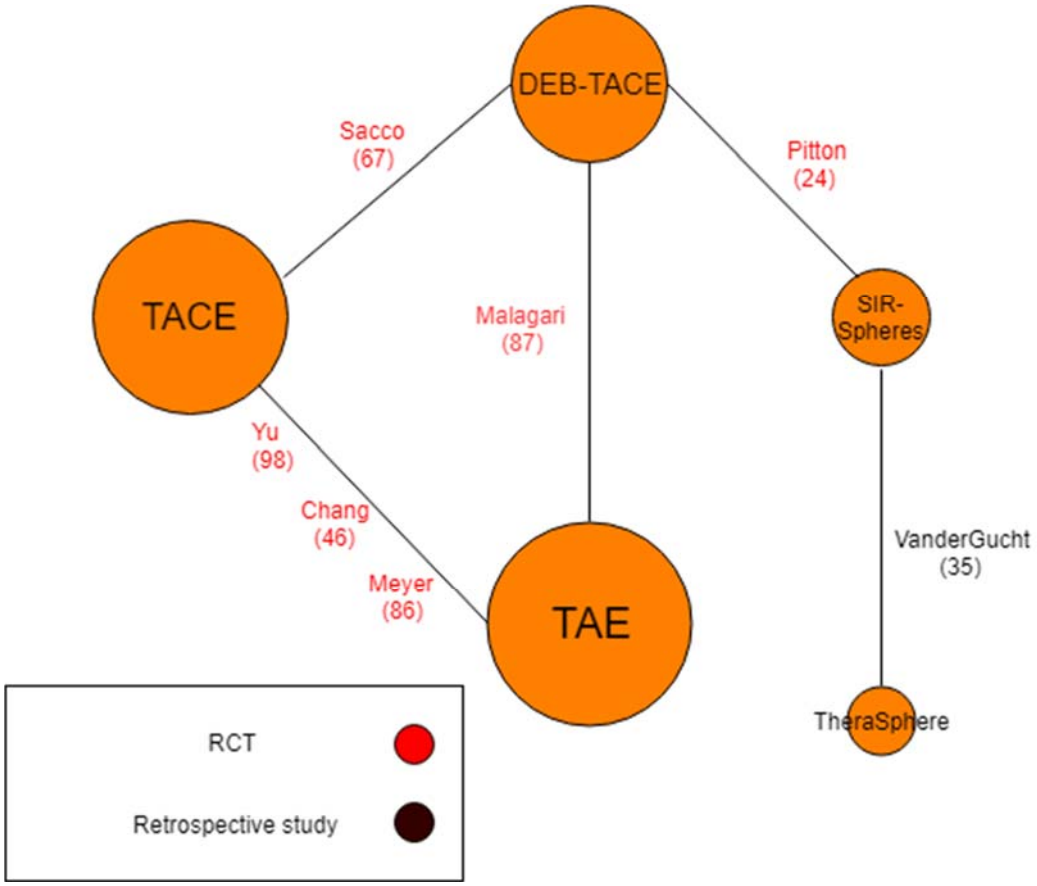


Table 8: Network 2: Adults with unresectable HCC who are eligible for conventional transarterial therapies

First author/study name	N	Intervention	Comparator	Study Design	Reason for inclusion/exclusion
Studies included in this network (n=7)					
Pitton, 2015[5]	24	SIR-Spheres	DEB-TACE	RCT	Patients with intermediate stage HCC (BCLC stage B).
Yu, 2013[65]	98	TACE	TAE	RCT	Patients with unresectable HCC, Child-Pugh A or B, ECOG <2.
Malagari, 2010[66]	87	DEB-TACE	TAE	RCT	Patients unsuitable for curative treatments with potentially resectable lesions but at high risk for surgery.
Sacco, 2011[59]	67	DEB-TACE	TACE	RCT	Patients with untreated HCC, Child-Pugh A or B, ECOG 0-1.
Chang, 1994[63]	46	TACE	TAE	RCT	Patients with inoperable HCC, Child-Pugh A or B.
Meyer, 2013[64]	86	TACE	TAE	RCT	Patients with untreated, unresectable HCC, Child-Pugh A or B, ECOG 0-2.
Van Der Gucht, 2017[18]	35 (subgroup of 77 patients)	SIR-Spheres	TheraSphere	Retrospective comparative	Subgroup of early/intermediate HCC patients.

First author/study name	N	Intervention	Comparator	Study Design	Reason for inclusion/exclusion
Studies excluded from this network (n=32)					
Kolligs, 2015[4] (SIR-TACE)	28	SIR-Spheres	TACE	RCT	Mixed population of early and intermediate stage patients, without portal vein occlusion. Pilot trial funded by Sirtex Medical. Data for intermediate patients was requested but not provided.
Vilgrain, 2017 (SARAH)[2, 43]	459	SIR-Spheres	Sorafenib	RCT	Patients with locally advanced HCC or new HCC not eligible for surgery/ablation after previously cured HCC or HCC with two unsuccessful rounds of TACE. Poor candidates for TACE.
Salem, 2016[8] (PREMIERE)	45	TheraSphere	TACE	RCT	Patients with early/intermediate HCC with no vascular invasion. The intent of therapy was bridge to transplant.
Kulik, 2014[11]	20	TheraSphere	TheraSphere + Sorafenib	RCT	Intent of therapy was bridge to transplant.
Chow, 2018 (SIRveNIB) [3]	360	SIR-Spheres	Sorafenib	RCT	Sorafenib is an irrelevant comparator in this population.
Lammer, 2010[56] [57](PRECISION)	212	DEB-TACE	TACE	RCT	No relevant outcomes reported.

First author/study name	N	Intervention	Comparator	Study Design	Reason for inclusion/exclusion
Ricke, 2015[6] (SORAMIC)	40	SIR-Spheres + Sorafenib	Sorafenib	RCT	Poor candidates for TACE.
Van Malenstein, 2011[60]	30	DEB-TACE	TACE	RCT	No relevant outcomes reported.
Brown, 2016[67]	101	DEB-TACE	TAE	RCT	Mixed population and some patients have PVI.
Golfieri, 2014[58]	177	DEB-TACE	TACE	RCT	Patients with early, intermediate and advanced stage HCC without PVT. The population is too varied to include.
Llovet, 2002[61]	112	TACE	TAE	RCT	Patients with intermediate/advanced stage HCC without PVI/extra-hepatic disease but no relevant outcomes reported.
Kawai, 1992 [62]	289	TACE	TAE	RCT	Patients with early/intermediate stage HCC but no relevant outcomes reported.
Kudo, 2018[23] (REFLECT)	289 (subgroup of 954 patients)	Lenvatinib	Sorafenib	RCT	Subgroup of patients with advanced stage HCC, majority had PVI or extra-hepatic spread – ineligible for TACE.

First author/study name	N	Intervention	Comparator	Study Design	Reason for inclusion/exclusion
Llovet, 2008[31] (SHARP)	602	Sorafenib	Placebo	RCT	Adults with intermediate/advanced stage HCC, majority had extra-hepatic spread/macroscopic vascular invasion. Patients ineligible for TACE.
Hickey, 2016[9]	765	TheraSphere	TACE	Prospective comparative	Adults with early, intermediate and advanced stage HCC but significant baseline imbalances in age, PVI, number of lesions and CP class.
Kirchner, 2019[7]	94	TheraSphere	TACE/DEB-TACE	Prospective comparative	No relevant outcomes reported.
Memom, 2013[13]	96	TheraSphere	TACE	Prospective comparative	No relevant outcomes reported.
Salem, 2013[12]	56	TheraSphere	TACE	Prospective comparative	No relevant outcomes reported.
El Fouly, 2015[10]	86	TheraSphere	TACE	Prospective comparative	Patients with intermediate stage HCC but systematic selection bias and baseline imbalances in age, tumour size and tumour number were detected.
Woodall, 2009[14]	52	TheraSphere	BSC	Prospective comparative	Patients with advanced stage HCC, ineligible for TACE.

First author/study name	N	Intervention	Comparator	Study Design	Reason for inclusion/exclusion
Maccauro, 2014[15]	45	TheraSphere + Sorafenib	TheraSphere	Matched case-control study	Patients with intermediate/advanced HCC, poor candidates for TACE.
Akinwande, 2016[54]	96 (subgroup of 358 patients)	TheraSphere	DEB-TACE	Retrospective comparative	Mixed population of patients with unresectable HCC with or without PVT, results not split by disease stage.
Bhangoo, 2015[17]	17	TheraSphere	SIR-Spheres	Retrospective comparative	Patients ineligible for TACE (patients had either failed or were not amenable to other locoregional therapies).
Moreno-Luna, 2013[53]	116	TheraSphere	TACE	Retrospective comparative	Patients with unresectable HCC not eligible for transplant but significant baseline imbalances between groups in ECOG status, Child-Pugh class, number of tumours and BCLC stage.
Cho, 2016[48]	63	SIR-Spheres	Sorafenib	Retrospective comparative	Patients ineligible for TACE.
De la Torre, 2016[49]	73	SIR-Spheres	Sorafenib	Retrospective comparative	Patients ineligible for TACE.
Biederman, 2016[19]	90	SIR-Spheres	TheraSphere	Retrospective comparative	Patients ineligible for TACE.
Gramenzi, 2014[50]	137	SIR-Spheres	Sorafenib	Retrospective comparative	Patients were ineligible or unsuitable for TACE.

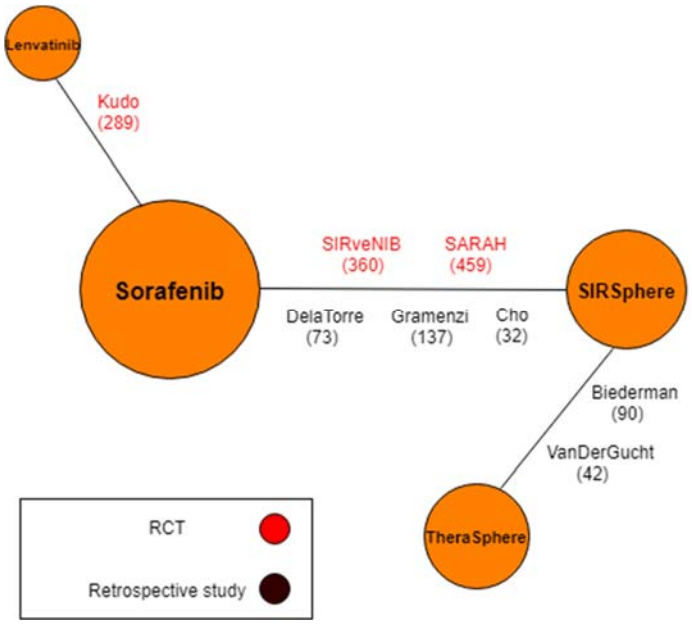
First author/study name	N	Intervention	Comparator	Study Design	Reason for inclusion/exclusion
Biederman, 2015[20]	97	SIR-Spheres	TheraSphere	Retrospective comparative	Patients with unresectable, advanced stage HCC with PVT, poor candidates for TACE.
D'Abadie, 2018[21]	45	SIR-Spheres	TheraSphere	Retrospective comparative	Population unclear. Appears to include both patients eligible and non-eligible for TACE.
Salem, 2011[52]	245	TheraSphere	TACE	Retrospective comparative	Mixed population of patients with HCC without PVT or extrahepatic metastases but results not stratified by BCLC stage.
Soydal, 2016[51]	80	TACE	SIR-Spheres	Retrospective comparative	Patients with intermediate/advanced stage HCC, some patients with extrahepatic metastases.

5.3 Network 3: Adults with unresectable HCC who are ineligible for conventional transarterial therapies

The third model was for patients with unresectable HCC who are ineligible for CTT. Patients in this population tend to have advanced stage HCC (BCLC C) with or without PVT/PVI. This population may, however, include some patients with intermediate stage disease (BCLC B) that are either ineligible for CTT or who have previously failed CTT.

There were 26 comparative studies included in the systematic review of clinical effectiveness, that were identified as potentially eligible for the third network; the 11 RCTs comparing different CTTs were not screened as they are not relevant for this population. A further two studies of systemic therapies identified from previous technology appraisals were additionally screened for inclusion in this network. Out of 28 studies, three RCTs and five retrospective comparative studies were initially selected as relevant for this population. Twenty studies were excluded, mainly due to irrelevant comparisons or not reporting relevant outcomes. The network meta-analysis diagram is illustrated in Figure 3.

Figure 3: Network 3: Adults with unresectable HCC who are ineligible for conventional transarterial therapies



The network includes robust direct evidence between SIR-Spheres and sorafenib from the two large RCTs SARAH[81] and SIRveNIB,[3] which are described in more detail in Section 4.2.2.2. There are also three smaller retrospective comparative studies comparing SIR-Spheres and sorafenib (De la Torre *et al*.,[49] Gramenzi *et al*.[50] and Cho *et al*.[82]). Upon closer examination, all three of these studies had a high risk of bias due to an imbalance in baseline characteristics, unclear reporting of missing data and unblinded outcome assessors (Appendix 13.8). Therefore, due to already having identified high quality RCTs comparing SIR-Spheres and sorafenib, these three retrospective studies were removed. Including low quality studies where there is already reliable evidence may invalidate the NMA and consequently the results. Furthermore, the two retrospective studies: Biederman *et al.*[19] and Van Der Gucht *et al.*[18] were also given a high risk of bias, as described in Section 4.2.2.5. However, these studies were included as a sensitivity analysis as they are the only studies with direct evidence between TheraSphere and SIR-Spheres.

The network was updated and the final NMA of patients ineligible for CTT has two RCTs comparing SIR-Spheres and sorafenib, one RCT comparing lenvatinib and sorafenib[23] and two retrospective comparative studies comparing SIR-Spheres and TheraSphere (included as a sensitivity analysis) (Figure 4). The decisions for including and excluding each study are detailed in **Table 9**. The study selection process for this NMA (Updated Network 3) is illustrated in Figure 5.

Figure 4: Updated Network 3: Adults with unresectable HCC who are ineligible for conventional transarterial therapies

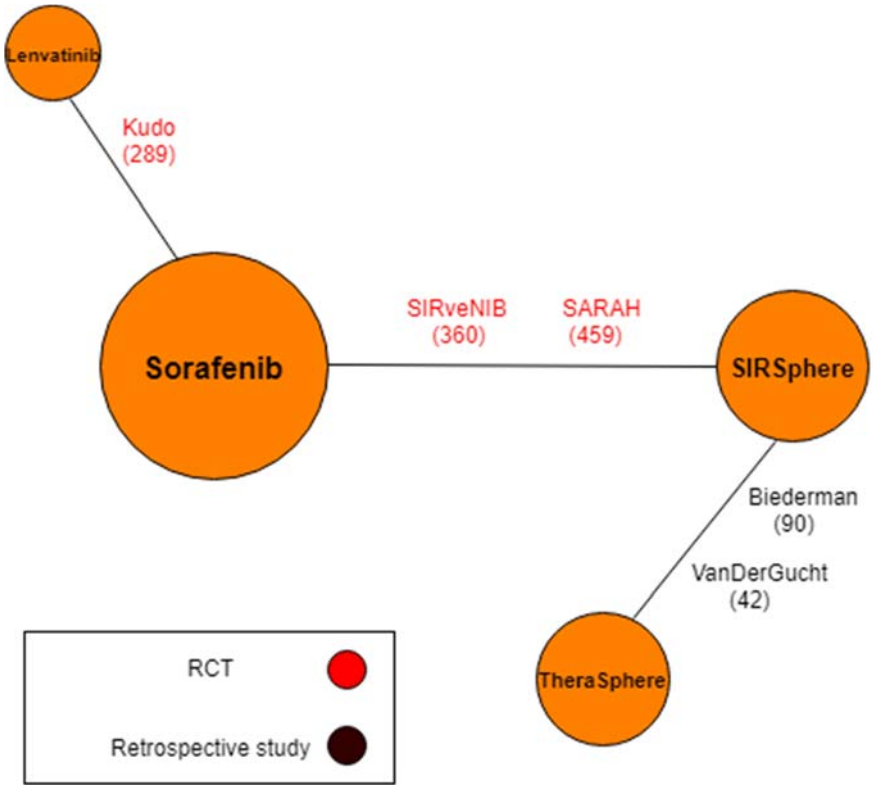


Figure 5: Flow diagram of the study selection process for the network meta-analysis of adults ineligible for conventional transarterial therapies

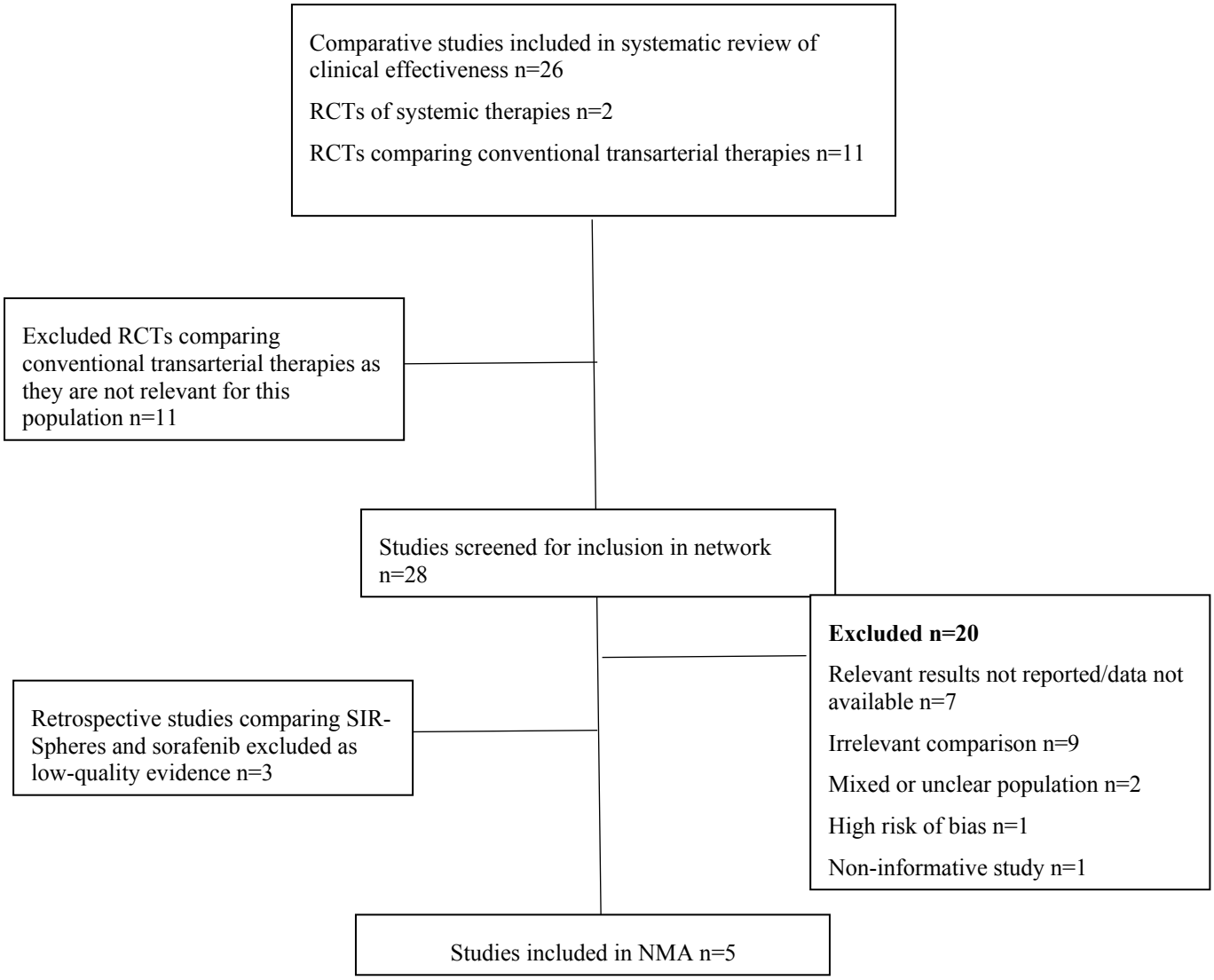


Table 9: Network 3: Adults with unresectable HCC who are ineligible for conventional transarterial therapies

First Author/ Study name	N	Intervention	Comparator	Study Design	Reason for inclusion/exclusion
Studies included in this network (n=5)					
Chow, 2018 [3] (SIRveNIB)	360	SIR-Spheres	Sorafenib	RCT	Patients with locally advanced HCC.
Vilgrain, 2017 [43, 81] (SARAH)	459	SIR-Spheres	Sorafenib	RCT	Adults with locally advanced HCC (BCLC C) or new HCC not eligible for surgery/ablation after previously cured HCC or HCC with two unsuccessful rounds of TACE.
Kudo, 2018[23] (REFLECT)	289 (subgroup of 954 patients)	Lenvatinib	Sorafenib	RCT	Subgroup of adults with advanced stage HCC, majority had PVI or extra-hepatic spread.
Van Der Gucht, 2017[18]	42 (subgroup of 77 patients)	SIR-Spheres	TheraSphere	Retrospective comparative	Subgroup of advanced stage HCC patients.
Biederman, 2016[19]	90	SIR-Spheres	TheraSphere	Retrospective comparative	Patients with unresectable HCC and main or lobar PVT.

First Author/ Study name	N	Intervention	Comparator	Study Design	Reason for inclusion/exclusion
Studies excluded from this network (n=23)					
Ricke, 2015[6], (SORAMIC)	40	SIR-Spheres + Sorafenib	Sorafenib	RCT	Adults with unresectable intermediate or advanced HCC, poor candidate for TACE. Only safety analyses are published. Data were requested from company but as it is an investigator-initiated trial, the data were not available.
Llovet, 2008[31] (SHARP)	602	Sorafenib	Placebo	RCT	Adults with intermediate/advanced stage HCC, majority had extra-hepatic spread/vascular invasion. This study was not required for the NMA as it did not provide any extra information and was not needed for the cost effectiveness model.
Salem, 2016[8] (PREMIERE)	45	TheraSphere	TACE	RCT	Compared TACE – irrelevant comparison in this population.
Kolligs, 2015[4] (SIR-TACE)	28	SIR-Spheres	TACE	RCT	Compared TACE – irrelevant comparison in this population.
Pitton, 2015[5]	24	SIR-Spheres	DEB-TACE	RCT	Compared DEB-TACE – irrelevant comparison in this population.
Kulik, 2014[11]	20	TheraSphere	TheraSphere +Sorafenib	RCT	Mixed population with the intent to bridge to transplant.

First Author/ Study name	N	Intervention	Comparator	Study Design	Reason for inclusion/exclusion
Kirchner, 2019[7]	94	TheraSphere	TACE/DEB-TACE	Prospective comparative	Compared TACE – irrelevant comparison in this population.
Hickey, 2016[9]	765	TheraSphere	TACE	Prospective comparative	Compared TACE – irrelevant comparison in this population.
El Fouly, 2015[10]	86	TheraSphere	TACE	Prospective comparative	Compared TACE – irrelevant comparison in this population.
Woodall, 2009[14]	52	TheraSphere	BSC	Prospective comparative	Patients with advanced stage HCC. Excluded due to systematic selection bias and significant baseline imbalances.
Memom, 2013[13]	96	TheraSphere	TACE	Prospective comparative	No relevant outcomes reported.
Salem, 2013[12]	56	TheraSphere	TACE	Prospective comparative	No relevant outcomes reported and compared TACE - irrelevant comparison in this population.
Maccauro, 2014[15]	45	TheraSphere plus Sorafenib	TheraSphere	Matched case-control study	Patients with intermediate/advanced stage HCC. No relevant outcomes reported.

First Author/ Study name	N	Intervention	Comparator	Study Design	Reason for inclusion/exclusion
Cho, 2016[48]	63	SIR-Spheres	Sorafenib	Retrospective comparative	Patients with BCLC stage C HCC and PVI. However, study of low quality and high risk of bias, therefore excluded from updated network.
De la Torre, 2016[49]	73	SIR-Spheres	Sorafenib	Retrospective comparative	Patients with unresectable HCC and PVI. However, study of low quality and high risk of bias therefore excluded from updated network.
Gramenzi, 2014[50]	137	SIR-Spheres	Sorafenib	Retrospective comparative	Patients with intermediate/advanced stage HCC unfit for other effective therapies. However, study of low quality and high risk of bias therefore excluded from updated network.
Akinwande, 2016[54]	96	TheraSphere	DEB-TACE	Retrospective comparative	Compared TACE – irrelevant comparison in this population.
Moreno-Luna, 2013[53]	116	TheraSphere	TACE	Retrospective comparative	Compared TACE – irrelevant comparison in this population.
Salem, 2011[52]	245	TheraSphere	TACE	Retrospective comparative	Compared TACE – irrelevant comparison in this population.
D'Abadie, 2018[21]	45	SIR-Spheres	TheraSphere	Retrospective comparative	Population unclear. Appears to include both patients eligible and non-eligible for TACE.

First Author/ Study name	N	Intervention	Comparator	Study Design	Reason for inclusion/exclusion
Bhangoo, 2015[17]	17	TheraSphere	SIR-Spheres	Retrospective comparative	Mixed population of patients with unresectable HCC, who had either failed or were not amenable to other locoregional therapies. No relevant outcomes reported.
Biederman, 2015[20]	97	SIR-Spheres	TheraSphere	Retrospective comparative	Adults with unresectable HCC with PVT. No relevant outcomes reported.
Soydal, 2016[51]	80	TACE	SIR-Spheres	Retrospective comparative	Compared TACE – irrelevant comparison.

5.3.1 Methods of data analysis

This section describes an NMA of all relevant RCTs (

Table **10**) and an NMA of RCTs which only included patients with Child-Pugh stage A liver function. Currently in the UK, systemic therapy such as sorafenib and lenvatinib is only licensed for Child-Pugh A patients with unresectable HCC.

In both the SARAH and SIRveNIB trials, 22.4% and 28.6% of patients allocated to SIR-Spheres did not receive SIRT. Patients who did not receive their allocated treatment were excluded from the per protocol analysis. Therefore, the NMA of Child-Pugh A patients with unresectable HCC who are ineligible for CTT in the per protocol population is the base-case scenario. However, the ITT results are used for the REFLECT trial. Therefore, the results for the ITT population are also reported. Both overall survival and progression-free survival (PFS) were assessed as outcomes. However, PFS in Child-Pugh A patients was not reported for the SIRveNIB study or for patients in the Biederman *et al*. study. Therefore, PFS could not be assessed in the base-case population or in the sensitivity analyses.

The NMA was estimated using Bayesian Markov Chain Monte Carlo (MCMC) techniques in WinBUGS, using code obtained from the NICE decision support unit, technical support document (DSU TSD).[83] An initial burn-in of at least 50,000 simulations was used, and convergence was confirmed through visual inspection of the Brook-Gelman Rubin diagnostic and history plots. This was followed by 100,000 simulations on three chains to estimate the sampled parameters. Where available, Kaplan-Meier (KM) data were extracted using methods reported by Guyot *et al.*[84] When KM data were not available, hazard ratios and their variance were extracted, and log-hazard ratios synthesised. In order to synthesise hazard ratios across studies, it is required that the proportional hazards assumption holds. Therefore, the deviation from proportional hazards was tested and the Schoenfeld residuals, survival curves and piecewise hazards visually inspected. It was decided to only conduct more complex time-varying models if simple models were not a good fit to the data. A model was chosen by first visually inspecting the development of the hazard over time for the different trials and then by comparing deviance information criterion (DIC) values for the competing models. It was decided that a hierarchical model with classes of treatments composed of individual treatments, which would allow each treatment effect to be estimated as well as the overall class mean, was not possible due to the small number of studies in the NMA.[83] Finally, both fixed and random effects models were evaluated and between-trial heterogeneity was assessed using the between study standard deviation. Inconsistency did not need to be examined, as there were no loops in the network.

5.3.2 Model selection

A Bayesian evidence synthesis approach was employed. With a Bayesian framework, prior belief about a treatment effect is combined with a likelihood distribution that summarizes the data to obtain a posterior distribution reflecting the belief about the treatment effect after incorporating the evidence.

Normal identity link models were used for this NMA.[83] The Schoenfeld residuals were visually inspected and statistically tested for each survival curve except for the REFLECT study because only a subgroup of the data was used, for which there was no Kaplan-Meier curve (Appendix 13.11). Although, the Kaplan-Meier curves for each study cross over, which suggests that there are some concerns about the proportional hazards assumption, there is no clear statistical evidence that the assumption is violated for all the included studies.[32] The viability of the network depends on the proportional hazards assumption. Therefore, hazard ratios were synthesised across studies. The choice of prior distributions for the between-study variance was explored. A half-normal (0, 0.19^2) prior was chosen as a uniform (0, 3) prior was too influential. The justification for the half-normal prior is that it expresses the prior belief that 95% of trials will give hazard ratios within a factor of 2 from the estimated median hazard ratio. However, due to the small number of studies, there was little evidence to inform the between-study heterogeneity. The half-normal prior was also influential, although less so than the uniform prior. According to deviance information criterion (DIC) and total residual deviance statistics, the fixed effects model provided a better fit to the data than the random effects counterpart. The fixed effects model had both a lower DIC and fewer parameters. This is again because of the small number of studies and the influence of the prior on the between-study heterogeneity. Due to both models having similar results, the fixed effects model was chosen as it is a simpler model. Results from both are presented for comparison.

5.3.3 Scenario and subgroup analyses

Scenario analyses including the two low quality retrospective studies: Biederman *et al*. and Van Der Gucht *et al*. were carried out, as discussed in Section 5.3. For the first scenario Biederman *et al*. was added to the base-case NMA; Adults with unresectable HCC who are Child-Pugh A and ineligible for CTT in both the per protocol and ITT population. There was no available data on Child-Pugh A patients in the Van Der Gucht *et al*. study, therefore it was not included. For the second scenario, both Biederman *et al*. and Van Der Gucht *et al*. were added to the NMA of all adults who are ineligible for CTT in the ITT population. Biederman *et al*. did not report PFS outcomes, therefore the second scenario was only done for the OS outcome.

A sensitivity analysis which excluded the RCT SIRveNIB was conducted. Patients in the SIRveNIB trial are from the Asia-Pacific region and thus have different HCC disease aetiology and consequently differing treatments. This is discussed in more detail in Section 4.2.2.2. Therefore, a scenario was conducted in which SIRveNIB was excluded from the base-case NMA.

It was not possible to conduct a subgroup analysis in Child-Pugh A patients with PVT or in patients with PVI. The only available data for this subgroup of patients was from the two RCTs comparing

SIR-Spheres and sorafenib: SARAH and SIRveNIB. However, SIRveNIB only reported results for the subgroup of patients with PVT, and SARAH only reported results for patients with PVI.

5.4 Results

5.4.1 Results of the base-case NMA in the per protocol population: Adults with unresectable HCC who are Child-Pugh A and ineligible for CTT

There were three studies included in the base-case analysis. Two RCTs comparing SIR-Spheres and sorafenib and one RCT comparing lenvatinib and sorafenib. The baseline characteristics of these studies are detailed in

Table **10**. The REFLECT trial[23], which compares lenvatinib and sorafenib included patients with extra-hepatic spread (61% in the lenvatinib arm and 62% in the sorafenib arm). All the other trials excluded patients with extra-hepatic spread, therefore the subgroup of patients without extra-hepatic spread or portal vein invasion was used for the REFLECT trial, a more appropriate subgroup was not reported.

The results of both the fixed effect and the random effects analysis are shown in Table 11.
The results provide no evidence that the random effects model should be preferred. The DIC is marginally higher; -0.40 for the random effects model, compared to -1.38 for the fixed effects model (lower DIC values are preferred, with differences of 2-5 considered important).[83] Additionally, the high level of uncertainty around the random effects credible interval indicates that there is little information to inform the random effect parameter. Therefore, the results of the fixed effects model will be used for the base-case and all scenario analyses. Both fixed effects and random effects results are reported in Appendix 13.12 for comparison.

There were no meaningful differences in overall survival in the per protocol population between any of the three treatments and all treatments appear to have a similar effect. SIR-Spheres shows a marginal improvement in OS when compared to Sorafenib (HR: 0.94, 95% CrI: 0.78-1.14) and lenvatinib (HR: 0.91, 95% CI: 0.63-1.26), however the treatment effects are uncertain as the credible interval crosses 1. Lenvatinib shows a marginal reduction in OS when compared to sorafenib (HR: 1.06, 95% CI: 0.79-1.40), although again the credible interval crosses 1. Figure 6 presents the cumulative ranking curves for each treatment, with rank 1 being the best and rank 3 being the worst. SIR-Spheres was ranked as the most efficacious therapy, with a probability of being the best of 0.61. Lenvatinib was ranked as the worst treatment, with a probability of being best of 0.22. Sorafenib was ranked as the second best, with a probability of being best of 0.16.

Table 10: Summary of studies included in the NMA

Study	Treatment	N	Age (median)	Male (%)	Portal vein thrombosis/invasion	BCLC classification		
						A	B	C
SARAH[2]	SIR-Spheres	174	66.3 ± 9.4	158 (90.8%)	29 (16.7%)[α]	7 (4.0%)	53 (30.5%)	114 (65.5%)
	Sorafenib	206	64.6 ± 9.5	186 (90.3%)	37 (18.0%)[α]	9 (4.4%)	54 (26.2%)	143 (69.4%)
SIRveNIB[3]	SIR-Spheres	130	60.9 (SD:11.5)	107 (82.3%)	30 (23.1%)[β]	0	79 (60.8%)	50 (38.5%)
	Sorafenib	162	57.5 (SD:10.6)	138 (85.2%)	48 (29.6%)[β]	1 (0.6%)	88 (54.3%)	73 (45.1%)
REFLECT [32∞]	Lenvatinib	369	-	-	0 (0%)	-	-	-
	Sorafenib	386	-	-	0 (0%)	-	-	-
Retrospective comparative studies								
Biederman *et al.*[19]	SIR-Spheres	21	60 ± 11.5	20 (95.2%)	100%[μ]	-	-	-
	TheraSphere	69	65.6 ± 11.3	54 (78.3%)	100%[μ]	-	-	-
Van Der Gucht *et al.*[18]γ	SIR-Spheres	24	-	-	-	0 (0%)	0 (0%)	24 (100%)
	TheraSphere	18	-	-	-	0 (0%)	0 (0%)	18 (100%)

IQR: inter-quartile range, SD: standard deviation [α]Main portal vein invasion, [β]Portal vein thrombosis, [∞]Subgroup of patients with no extrahepatic-spread or macroscopic portal vein invasion, [μ] Main and lobar portal vein thrombosis, γSubgroup of patients with advanced stage HCC

Table 11: OS results for the base-case NMA in the per protocol population

Intervention	Comparator	Hazard ratio (95% CrI) - fixed effects	Hazard ratio (95% CrI) – random effects
SIR-Spheres	Sorafenib	0.94 (0.78-1.14)	0.94 (0.68-1.26)
SIR-Spheres	Lenvatinib	0.91 (0.63-1.26)	0.92 (0.52-1.51)
Lenvatinib	Sorafenib	1.06 (0.79-1.40)	1.08 (0.68-1.64)

SD	-	0.13 (0.005-0.380)
DIC	-1.38	0.40
pD	2.0	2.5

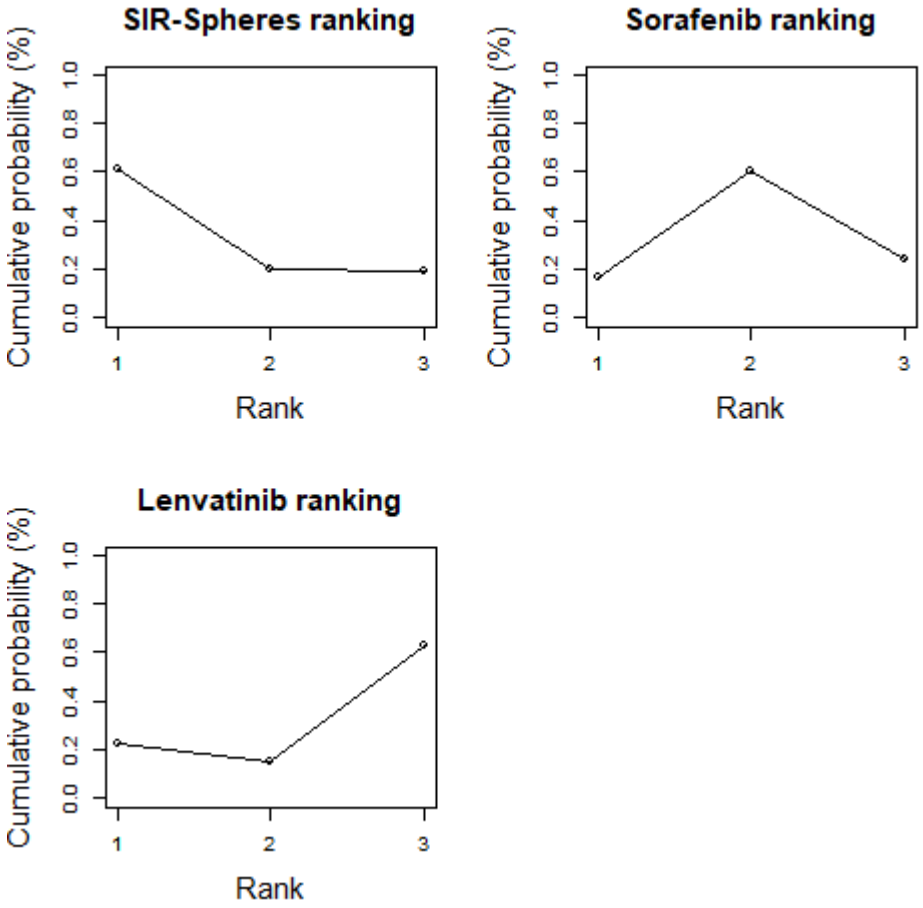
CrI: credible interval, SD: standard deviation, DIC: deviance information criterion, pD: number of parameters

Table 12: Hazard ratio estimates for OS for each treatment comparison for the base-case NMA in the per protocol population

Sorafenib	1.07 (0.88-1.29)	0.96 (0.72-1.27)
0.94 (0.77-1.14)	**SIR-Spheres**	0.91 (0.63-1.26)
1.06 (0.79-1.40)	1.14 (0.79-1.58)	**Lenvatinib**

Significant differences in the relative effects between a pair of agents are given in bold

Figure 6: Cumulative ranking probability plots for each treatment in the base-case NMA for the per protocol population



5.4.2 Results of the base-case NMA in the ITT population: Adults with unresectable HCC who are Child-Pugh A and ineligible for CTT

Similar to the per protocol population, there were no significant differences between treatments in the base-case NMA in the ITT population.

SIR-Spheres appear to increase mortality when compared to sorafenib and lenvatinib (HR: 1.13, 95% CrI: 0.96-1.32 and 1.09, 95% CrI: 0.77-1.48, respectively). Although, the credible intervals indicate that these results are uncertain. Lenvatinib also shows a reduction in OS when compared with sorafenib (1.06, 95% CrI: 0.79-1.40), however the 95% credible interval crosses 1, indicating that there is not a significant treatment effect.

Table 13: OS results for the base-case NMA in the ITT population

Intervention	Comparator	Hazard ratio (95% CI) - fixed effects	Hazard ratio (95% CI) – random effects
SIR-Spheres	Sorafenib	1.13 (0.96-1.32)	1.13 (0.86-1.47)
SIR-Spheres	Lenvatinib	1.09 (0.77-1.48)	1.10 (0.66-1.74)
Lenvatinib	Sorafenib	1.06 (0.79-1.40)	1.07 (0.70-1.59)
SD		-	0.11 (0.004-0.352)
DIC		-3.04	-0.86
pD		2.00	2.00

CrI: credible interval, SD: standard deviation, DIC: deviance information criterion, pD: number of parameters

Scenario 1: Inclusion of Biederman *et al.* into the base-case NMA

The Biederman *et al*. study was added to the base-case NMA in a scenario analysis, which allowed for a comparison to be made against TheraSphere. Biederman *et al*. reports a very strong treatment effect on overall survival with TheraSphere compared to SIR-Spheres (HR: 0.40, 95% CrI: 0.20-0.78). However, as discussed earlier, Biederman *et al*. is a retrospective, poor quality study, therefore these results may either in part or in full reflect the impact of bias. Furthermore, all patients in Biederman *et al*. have PVT, which is much higher than the proportion of patients in the other included studies that have PVT/PVI. Adding this study has a substantial effect on the NMA results. In the per protocol population, TheraSphere shows a substantial significant improvement in OS when compared to SIR-Spheres (HR: 0.44, 95% CrI: 0.20-0.84), sorafenib (HR: 0.41, 95% CrI: 0.20-0.77) and lenvatinib (HR: 0.40, 95% CrI: 0.18-0.78). There were no significant differences in OS between any of the other treatments

Table **14**.

Similarly, in the ITT population, there was a significant improvement in OS with TheraSphere compared to sorafenib (HR: 0.47 95% CrI: 0.21-0.88), SIR-Spheres (HR: 0.41, 95% CrI: 0.20-0.77) and lenvatinib (HR: 0.45, 95% CrI: 0.20-0.89). There were no significant differences in OS between SIR-Spheres, sorafenib and lenvatinib (

Table **14**).

Table 14: OS results adding Biederman *et al*. to the base-case NMA

Intervention	Comparator	Hazard ratio (95% CrI) fixed effects – Per protocol population	Hazard ratio (95% CrI) fixed effects –ITT population
SIR-Spheres	Sorafenib	0.94 (0.77-1.13)	1.13 (0.96-1.32)
SIR-Spheres	Lenvatinib	0.91 (0.63-1.26)	1.09 (0.77-1.48)
TheraSphere	SIR-Spheres	0.44 (0.20-0.84)	0.41 (0.20-0.77)
TheraSphere	Sorafenib	0.41 (0.20-0.77)	0.47 (0.21-0.88)
TheraSphere	Lenvatinib	0.40 (0.18-0.78)	0.45 (0.20-0.89)
Lenvatinib	Sorafenib	1.06 (0.79-1.40)	1.06 (0.79-1.40)
DIC		0.30	-1.32
pD		3.00	3.00

CrI: credible interval, SD: standard deviation, DIC: deviance information criterion, pD: number of parameters

5.4.3 Results of NMA for all patients in the ITT population

There were three studies included in the NMA of all adults with unresectable HCC who are ineligible for CTT; SARAH, SIRveNIB and Kudo *et al*.[85] Including all patients, and not just Child-Pugh A patients, in the NMA resulted in a marginal but significant reduction in OS with SIR-Spheres compared to Sorafenib (HR: 1.14, 95% CrI: 1.01-1.28). There were no significant differences in OS between the other treatments (

Table **15**) However, SIR-Spheres showed a non-significant improvement in PFS when compared to sorafenib (HR: 0.97, 95% CrI: 0.84-1.12). The credible intervals around the hazard ratios for lenvatinib compared to sorafenib and SIR-Spheres are wide and overlapped, indicating that there is uncertainty around these treatment effects. The hazard ratio estimates for each treatment comparison are presented in Appendix 13.12.

Table 15: OS and PFS results for all adults with unresectable HCC who are ineligible for CTT in the ITT population

Intervention	Comparator	Hazard ratio (95% CrI) OS	Hazard ratio (95% CrI) PFS
SIR-Spheres	Sorafenib	1.14 (1.01-1.28)	0.97 (0.84-1.12)
SIR-Spheres	Lenvatinib	1.10 (0.80-1.48)	1.56 (0.43-4.07)
Lenvatinib	Sorafenib	1.06 (0.79-1.40)	0.86 (0.24-2.22)
DIC		-3.94	0.34
pD		2.00	2.00

CrI: credible interval, SD: standard deviation, DIC: deviance information criterion, pD: number of parameters

Scenario 2: Inclusion of Biederman *et al.* and Van Der Gucht *et al.* into NMA for all adults in the ITT population

The two retrospective comparative studies: Biederman *et al*. and Van Der Gucht *et al*. were added to the NMA of all patients with unresectable HCC, who are ineligible for CTT, which allowed a comparison to be made with TheraSphere. A subgroup of 42 patients with advanced stage HCC was used from the Van Der Gucht *et al.* study. The fixed effects model was chosen as the DIC and the number of parameters was lower. There was a significant improvement in OS with TheraSphere when compared to sorafenib (HR: 0.53, 95% CrI: 0.31-0.84), SIR-Spheres (HR: 0.46, 95% CrI: 0.28-0.72) and lenvatinib (HR: 0.51, 95% CrI: 0.28-0.86). As discussed earlier, Biederman *et al*. and Van Der Gucht *et al*. both have large treatment effects and therefore, results in TheraSphere being significantly better for OS in the NMA. There were no notable differences between any of the other treatments for OS (

Table **16**).

Table 16: NMA results of all adults with unresectable HCC who are ineligible for CTT including studies Biederman *et al*. and Van Der Gucht *et al*.

Intervention	Comparator	OS Hazard ratio (95% CrI) fixed effects
SIR-Spheres	Sorafenib	1.14 (1.01-1.28)
SIR-Spheres	Lenvatinib	1.10 (0.80-1.48)
TheraSphere	SIR-Spheres	0.46 (0.28-0.72)
TheraSphere	Sorafenib	0.53 (0.31-0.84)
TheraSphere	Lenvatinib	0.51 (0.28-0.86)
Lenvatinib	Sorafenib	1.06 (0.79-1.40)

CrI: credible interval

5.4.4 Sensitivity analysis

Exclusion of the SIRveNIB study from the base-case NMA

The SIRveNIB trial, which compares SIR-Spheres and sorafenib, was conducted in the Asia-Pacific region. This has implications for the generalisability of the SIRveNIB trial results to the UK population. The aetiology of HCC and the consequent treatment in the Asia-Pacific region are different, as described in more detail in Section 4.2.2.2. A sensitivity analysis was therefore implemented in which the SIRveNIB study was excluded from the base-case NMA. Excluding SIRveNIB had very little impact on the results for OS in the ITT population compared to the base-case NMA. All treatment effects for all comparisons were similar to the base-case NMA (Table 17). The OS results in the per protocol population however, showed a slight change after excluding SIRveNIB. The treatment effect estimate for SIR-Spheres vs sorafenib increased (1.02, 95% CrI: 0.79-1.29) compared to the base-case NMA (0.94, 95% CrI: 0.77-1.14). This showed a reduction in OS with SIR-Spheres rather than an improvement as seen in the base-case per protocol population, although neither were statistically significant.

Table 17: Results of the base-case NMA excluding the SIRveNIB study

Intervention	**Comparator**	**OS Hazard ratio, ITT pop (95% CrI)**	**OS Hazard ratio, per protocol (95% CrI)**
SIR-Spheres	Sorafenib	1.14 (0.90-1.41)	1.02 (0.79-1.29)
SIR-Spheres	Lenvatinib	1.09 (0.75-1.55)	0.98 (0.66-1.40)
Lenvatinib	Sorafenib	1.06 (0.79-1.40)	1.06 (0.79-1.40)
DIC		-0.52	-0.34
pD		2.0	2.0

5.4.5 Summary of findings of relative efficacy from NMA

Treatment options and outcomes vary greatly for patients with unresectable HCC according to the severity of cancer and liver disease. Therefore, three network meta-analysis models were produced to represent the different populations of unresectable HCC patients; patients eligible for transplant, patients ineligible for transplant but eligible for conventional transarterial therapies (CTT) and patients ineligible for CTT.

The NMA in patients eligible for transplant was not conducted. Clinical advice was that there are short transplant waiting times in the UK, whereas these were much longer in the trials in the NMA. Therefore, the network may not be generalisable to the UK and there may be limited opportunity for benefit, given the short wait times. Furthermore, the two RCTs included in the network have very small sample sizes and therefore any efficacy estimates produced would be highly uncertain. The NMA of patients eligible for CTT was also not conducted because of the lack of good quality evidence in this population. There was only one RCT of 24 patients directly comparing SIR-Spheres and the comparator therapies of interest. There were no studies comparing TheraSphere and CTT. Therefore, with missing direct comparisons and only one small study to connect the network, results produced would be very uncertain and unsuitable for decision making.

Several network meta-analyses of patients who are ineligible for CTT were conducted for both overall survival and progression-free survival outcomes in the per protocol and ITT populations.

The base-case NMA was in adults with unresectable HCC who have Child-Pugh stage A liver disease and are ineligible for CTT in the per protocol population. There were three studies included in the base-case analysis. Two RCTs comparing SIR-Spheres and sorafenib and one RCT comparing lenvatinib and sorafenib. The results provided no evidence that the random effects model should be preferred. Additionally, the high level of uncertainty around the random effects credible interval indicated that there is little information to inform the random effect parameter. Therefore, the results of the fixed effects model were used for the base-case and scenario analyses.

There were no meaningful differences in overall survival between any of the three treatments in the per protocol or ITT populations. All treatments appear to have a similar effect. In the per protocol population SIR-Spheres showed a non-significant marginal improvement in OS when compared to sorafenib (HR: 0.94, 96% CrI: 0.77-1.14), although the credible interval indicates that this result is uncertain. SIR-Spheres was ranked as the most efficacious therapy, with a probability of being the best of 0.61. Lenvatinib was ranked as the worst treatment, with a probability of being best of 0.22. Sorafenib was ranked as the second best, with a probability of being best of 0.16.

To produce an efficacy estimate for TheraSphere, the only two studies which directly compared TheraSphere and SIR-Spheres for patients ineligible for CTT, Biederman *et al*. and Van Der Gucht *et al*. were included as a sensitivity analysis. Both are low-quality retrospective studies, which reported strong treatment effects on overall survival with TheraSphere compared to SIR-Spheres (HR: 0.40, 95% CrI: 0.20-0.78 and HR: 0.77, 95% C.I: 0.27-2.18, respectively). Adding these studies had a substantial effect on the NMA results. In the per protocol population, TheraSphere showed a substantial and statistically significant improvement in OS when compared to SIR-Spheres (HR: 0.44, 95% CrI: 0.20-0.84), sorafenib (HR: 0.41, 95% CrI: 0.20-0.77) and lenvatinib (HR: 0.40, 95% CrI: 0.18-0.78). In the ITT population, there was also a significant improvement in OS with TheraSphere when compared to sorafenib (HR: 0.53, 95% CrI: 0.31-0.84), SIR-Spheres (HR: 0.46, 95% CrI: 0.28-0.72) and lenvatinib (HR: 0.51, 95% CrI: 0.28-0.86). A sensitivity analysis, which excluded the SIRveNIB study from the base-case NMA was also conducted. The SIRveNIB trial, which compared SIR-Spheres and sorafenib, was conducted in the Asia-Pacific region. This has implications for the generalisability of the SIRveNIB trial results to the UK population. Excluding SIRveNIB, however, had very little impact on the results for OS and PFS in the per protocol and ITT populations compared to the base-case NMA. There were no significant differences in treatment effects for any comparisons.

6 Assessment of existing cost-effectiveness evidence

6.1 Systematic review of existing cost-effectiveness evidence

This section presents a systematic review of previous economic evaluations of SIRT and provides an overview of these assessments and a discussion of their relevance to the UK NHS. The findings from the review were used to help inform the development of a new decision-analytic model reported in Section 8 Independent economic assessment.

6.1.1 Methods

Systematic searches for relevant literature were completed as part of the search used to identify clinical effectiveness studies. These searches included a broad set of terms aimed at identifying any evidence relating to SIRT, including studies evaluating the cost-effectiveness of SIRTs. Details of the searches undertaken are reported in Section 4.1.1, and the full search strategy is reported in Appendix 13.1.

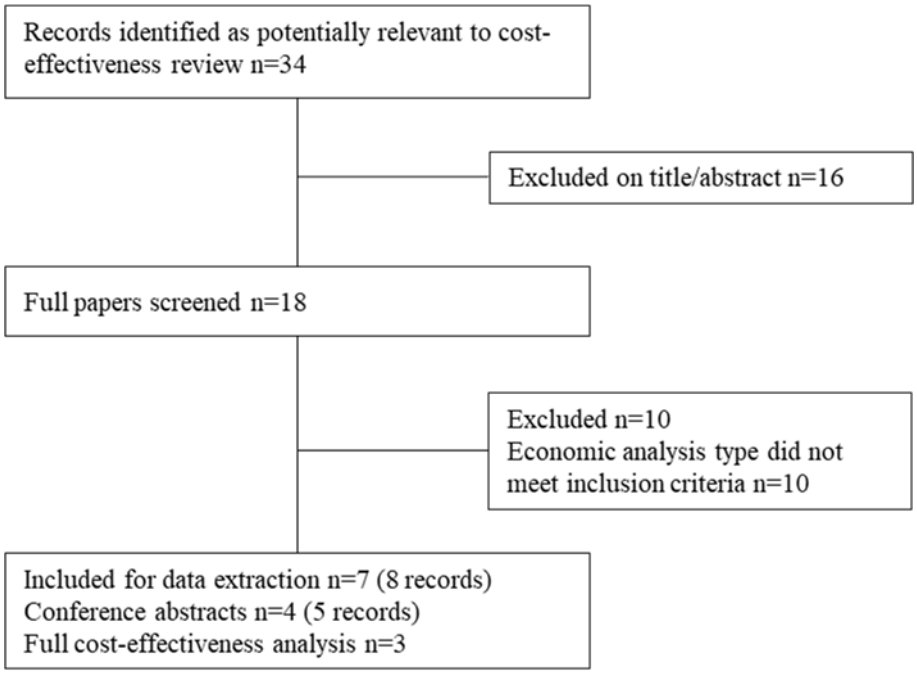
Study selection was conducted in two stages: (i) titles and abstracts identified by the search strategy were examined and screened as part of the clinical effectiveness review for any study potentially relevant to the cost-effectiveness review, (ii) full texts were then obtained and screened for inclusion. Screening of titles and abstracts therefore aligned with the selection approach outlined in Section 4.1.1; a single reviewer screened all studies, with 10% checked by a second reviewer. Full text screening was conducted independently by two reviewers, with disagreements resolved by consensus. All studies meeting the inclusion criteria were summarised and used to identify potential structural issues, assumptions, and key drivers of cost-effectiveness. The quality of the cost-effectiveness studies was assessed using a modified version of the Philips checklist.[86]

Studies were included in the review if they assessed the cost-effectiveness of a SIRT versus any other therapy in an HCC population. A broad range of studies was considered for inclusion in the review, including economic evaluations conducted alongside trials, modelling studies, and analyses of administrative databases. Only full economic evaluations comparing two or more options including both costs and consequences (cost-effectiveness, cost–utility or cost–benefit analyses) were included.

6.1.2 Results of review of existing cost-effectiveness evidence

As described in Section 4.2.1, a total of 34 records were identified as being potentially relevant to cost-effectiveness. The full text articles of these records were assessed for eligibility, with a total of seven studies (eight publications) found to meet the inclusion criteria. Three studies were reported as full papers and four as abstracts only. A PRISMA diagram of the review of studies identified in the main systematic review is presented in Figure 7.

Figure 7: Flow diagram of the study selection process for the cost-effectiveness review



The following sections provide a summary of the Assessment Group (AG)'s critique of the three studies[87-90]} reported in full paper format, including an assessment of the studies' quality and relevance to an NHS perspective. Details of the quality assessment implemented are included in Appendix 13.14. For the four studies identified which were only reported as conference abstracts,[91-94] a brief overview is presented along with reported results. Given the limited nature of the reporting of study details, no formal quality assessment of the abstracts was undertaken.

6.1.2.1 Review of Rognoni *et al.* (2017, 2018)

Overview

Two studies by Rognoni *et al.*[88, 95] reported on the cost-effectiveness of SIRT in HCC from an Italian heath service perspective. Both studies used the same basic model design and inputs, but investigated different treatment strategies. The first study[95] compared SIRT with sorafenib in two HCC sub-populations: intermediate (BCLC B) and intermediate-advanced (BCLC C) disease. The second study[88] compared SIRT followed by TACE and possibly sorafenib with SIRT followed by sorafenib in patients with intermediate disease (BCLC B).

Both studies presented a probabilistic Markov model consisting of up to five health states: stable disease, progression, post-transplant, death from disease, and death from other causes. The post-transplant health state was used only for the comparison of SIRT with sorafenib in patients with intermediate disease. Transition probabilities were drawn from three Italian oncology centres, which were compared using propensity score matching. HRQoL measures were not reported in this cohort;

utilities were therefore derived from cost-effectiveness analysis registries. Utilities were assumed to be the same across the patient populations. Italy-specific costs were used in the model, and were derived primarily from official local tariffs and reference costs.

For intermediate stage patients, the estimated ICER for SIRT compared with sorafenib was €3,302 per QALY gained. In advanced patients, SIRT was found to dominate sorafenib. These results appear to be driven primarily by the relatively low costs of the SIRT procedure relative to the acquisition costs of sorafenib, combined with significant clinical benefits of SIRT resulting in additional life-years gained. In the comparison of SIRT followed by TACE and possibly sorafenib, with SIRT followed by sorafenib, SIRT-TACE-sorafenib was found to dominate SIRT-sorafenib.

Commentary

The two studies appear to be comprehensive and well implemented, accounting for all major sources of costs and benefits, including long-term benefits in patients receiving liver transplant. However, the fitting and selection of parametric functions to survival data was poorly described and explored. Variability in cost-effectiveness estimates was explored using one-way sensitivity analysis, showing that the results were robust to a wide range of assumptions.

However, the two studies suffered from a number of potential limitations. Foremost amongst these is the use of non-randomised data to produce estimates of relative effectiveness. While propensity scoring was used to adjust for baseline imbalances, this process may have impacted the results. The comparison between SIRT and sorafenib in the BCLC C subgroup is of particular concern, as a significant survival benefit was predicted for patients receiving SIRT. This is inconsistent with the results of the SARAH[2] and SIRveNIB[3] trials reported in Section 4.2.2.2, which show no such benefit. The HRQoL values used were generally not reflective of the population under consideration, and matched poorly with those used in previous NICE TAs in this indication. The study was also limited in its capacity to inform the present appraisal as the costs and resource use evidence reflected an Italian healthcare setting, and the choice of comparators does not represent current UK practice.

6.1.2.2 Review of Rostambeigi *et al.* (2013)[89, 90 89, 90 89, 90]

Overview

The study by Rostambeigi *et al.*[89, 90] (also presented as a conference abstract) sought to assess the cost-effectiveness of SIRT versus conventional TACE in three subgroups (BCLC A, B, and C) of patients with HCC from a US Medicare perspective.

The model presented was a patient simulation which followed 750 patients (split evenly between BCLC A, B, and C) through a treatment pathway comprising treatment with either SIRT or TACE. The simulation was repeated for each treatment type and patient subgroup over a time horizon of 3 or

5 years. The model structure adopted is not clearly reported, but appeared to allow for disease recurrence, mortality, and liver transplant.

Probabilities for each outcome were drawn from the literature for each patient subgroup according to BCLC stage. Exponential curves were used to estimate survival based on reported survival rates, with a 10% increase in mortality for one month following recurrence of HCC and re-treatment. Transplant rates of 29%, 16%, and 5% were applied for patients in BCLC stages A, B, and C respectively, though is it unclear how this impacted on model outcomes. The model assumed disease 'recurrence' rates of 40%, 60%, and 80% every 10 months for SIRT patients, while TACE patients had a recurrence rate of 60%, and could receive 4 to 10 procedures. An assumed probability of 0.5 was used for SIRT re-treatment at the beginning of every 10-month treatment interval, and patients were assumed to receive a maximum of two or three SIRT treatments depending on the scenario. Costs applied in the model were obtained from Medicare reimbursement costs; HRQoL was not considered.

The ICERs presented were estimated using an unconventional approach, calculated by dividing the incremental mean cost per month of survival (i.e. total costs divided by OS in months) by the overall incremental survival in months. The authors did not account for dominance in their calculations, presenting a number of negative ICERs without sufficient interpretation of their different meanings. ICERs where SIRT was less costly and less effective, less costly and more effective, and more costly but less effective than TACE, were presented without further distinction.

In the main analysis where each procedure could be repeated every 10 months for up to 5 years, the AG calculated SIRT to increase mean survival by 3.80 months in BCLC C patients at a reduced cost. In the scenario in which procedures are repeated every 6 months for up to 3 years, SIRT was more effective (2.90 months incremental survival), with reduced costs compared to TACE in BCLC C patients. In all other patient groups and treatment regimens, SIRT was dominated by TACE.

Commentary

The limited reporting of the model structure and assumptions adopted prevents a detailed critique or discussion of the appropriateness of the model to estimate the relative costs and benefits of SIRT and sorafenib. A number of key structural assumptions appear to have been made arbitrarily, and poor reporting of model inputs limits the generalisability of this study to other settings. As the resource use and costs are specific to the USA, they are unlikely to be relevant to an NHS setting. The choice of comparators and outcome measures (life years gained [LYG]) further limits comparison with UK practice.

6.1.2.3 Review of Marqueen *et al.* (2018)

Marqueen *et al.*[91] (conference abstract only) estimated the cost-effectiveness of SIRT with yttrium-90 resin microspheres versus sorafenib in patients with advanced HCC, from a US Medicare perspective. The authors constructed a multi-state Markov model (health states not reported) to estimate incremental costs and QALYs over a 5-year time horizon. Hazard rates for disease progression and death were based on a pooled analysis of individual patient data from the SARAH and SIRveNIB RCTs. The clinical data used in the model were not summarised in the abstract, although the authors stated that there was no statistically significant difference in OS, and SIRT was better tolerated and with higher quality of life than sorafenib. Trial data were also used to inform the parameter values for adverse events, treatment adherence, and quality of life utility weights.

Costs were $135,256 vs $90,911 and QALYs were 0.63 vs 0.60 for sorafenib vs SIRT, respectively. The resulting ICER of sorafenib was $1,479,020 per QALY gained. A probabilistic sensitivity analysis (PSA) demonstrated that the likelihood that sorafenib would be cost-effective did not exceed 1% in cost-effectiveness thresholds up to $200k/QALY. If the monthly price of sorafenib decreased from $16,390 to $7,250, the ICER of sorafenib fell below $200k, and an ICER of < $100k was reached if the monthly price fell below $6,500. Similar results were found using SARAH and SIRveNIB results separately.

6.1.2.4 Review of Chaplin *et al.* (2015)

Chaplin *et al.*[92] (conference abstract only) conducted a cost-effectiveness analysis of TheraSphere versus sorafenib in patients with advanced HCC in the UK.[92] The authors constructed a Markov model comprising stable disease, progression and death health states, estimating incremental costs and QALYs over a 10-year time horizon. Clinical outcomes for TheraSphere and sorafenib were drawn from two separate RCTs. For TheraSphere, clinical outcomes were based on Salem *et al.*,[52] a non-randomised comparative effectiveness analysis of radioembolisation with TheraSphere (n=123) versus chemoembolisation (n=122). The study enrolled a range of patients, including 39% who were BCLC A, 50% who were BCLC B, and 9% who were BCLC C. For sorafenib, outcomes were based on Llovet *et al.*,[96] a Phase III RCT which included 299 sorafenib patients and 303 patients on placebo, who had not received previous systemic treatment: 82% patients were BCLC C and 18% were BCLC B. Details of data synthesis were not reported in the abstract, but a comparison of median PFS and OS reported in the trial manuscripts with the model predictions suggests the authors undertook adjustments to account for population differences.

The model estimated that TheraSphere increased time to progression (6.2 vs 4.9 months) and median survival (13.8 vs 9.7 months). Yttrium-90 was associated with higher QALYs than sorafenib (1.12 vs 0.85), with lower lifetime costs (£21,441 vs £34,050). The model also included a scenario where

overall survival and time to progression were assumed equivalent, in which TheraSphere remained a dominant treatment option.

6.1.2.5 Review of Parikh *et al.* (2018)

Parikh *et al.*[93] (conference abstract only) estimated the cost-effectiveness of SIRT with SIR-Spheres versus sorafenib in patients with unresectable HCC and Child-Pugh A cirrhosis, from a US payer perspective. The authors constructed a Markov simulation model. Clinical inputs for survival and adverse events were derived from the SARAH and SIRveNIB trials. Costs were derived from a literature review, Red Book pharmacy data, and SEER-Medicare data. While methods for estimating clinical outcomes were not reported, the authors stated that both trials failed to demonstrate a survival difference between SIRT and sorafenib, although patient-reported outcomes were superior in the SIRT groups. The authors reported results of the model using data from the SARAH trial only, the SIRveNIB trial only, and an analysis in which data from both studies were pooled.

In all scenarios, SIRT was associated with lower total QALYs compared with sorafenib. Using data from SARAH, [2] SIRT was associated with increased costs compared with sorafenib, and as such sorafenib was the dominant treatment option. Using data from SIRveNIB, [3] sorafenib was associated with an ICER of >$100,000, due to lower SIRT costs. When combining data from both trials, sorafenib was cost-effective compared to SIRT with an ICER of $19,534 per QALY gained. In the combined scenario, lifetime costs were $63,333 for sorafenib and $61,897 for SIRT, and there were 0.88 QALYs gained for sorafenib and 0.81 QALYs for SIRT. The authors concluded that sorafenib is cost-effective compared to SIRT for patients with unresectable HCC, and that SIRT should not be used as first-line therapy in patients with advanced HCC who are eligible for sorafenib.

6.1.2.6 Review of Palmer *et al.* (2017)

Palmer *et al.*[94] (conference abstract only) built a cost-minimisation model to evaluate the cost-effectiveness of SIR-Spheres versus sorafenib for patients with BCLC C HCC. This model assumed equal efficacy between SIR-Spheres and sorafenib based on data from the SARAH RCT. Adverse event data were collected from Llovet *et al.*[96] for sorafenib, and Sangro *et al.*[68] for SIR-Spheres. Costs were derived from 'standard UK sources' and data from a UK hospital.

SIR-Spheres dominated sorafenib in this analysis, generating 0.0079 (95% CI 0.0046 – 0.0111) more QALYs than sorafenib, and providing a cost-saving of £8,909 (95% CI £3,257 – £14,570). One-way sensitivity analyses showed the primary drivers were time on treatment for sorafenib, and the costs of work-up and administration for SIR-Spheres. The authors concluded that SIRT using SIR-Spheres is a cost-effective option for BCLC C HCC patients in the UK.

6.1.3 Discussion

The review of existing cost-effectiveness evidence identified three full studies along with four evaluations reported only in abstract form. The three studies reported as full texts compared SIRT with TACE, SIRT with sorafenib, and two alternative treatment sequences, SIRT followed by TACE and possibly sorafenib against SIRT followed by sorafenib. All studies reported in abstract form compared SIRT with sorafenib.

6.1.3.1 SIRT versus sorafenib

Only one study comparing SIRT with sorafenib was reported as a full text (Rognoni *et al*[87, 88].), with the remainder reported as conference abstracts (Chaplin *et al.*[92], Marqueen *et al.*[91] and Palmer *et al.*[94], Parikh *et al.*[93]).

The Rognoni study has a number of important limitations, most notably, the use of non-randomised evidence to estimate the relative effectiveness of SIRT and sorafenib. The survival gains achieved on SIRT in this study were not reflected in the much larger SARAH and SIRveNIB trials. A further limitation of the Rognoni study was the questionable source of utility values, which do not reflect HRQoL values used in a number of previous technology appraisals (TAs) in advanced HCC. The Rognoni study also adopts a non–UK perspective, which further limits the relevance of the model results to UK decision makers.

Except for Chaplin *et al*., which used non-randomised sources of efficacy data, the conference abstracts drew data from the SARAH and/or SIRveNIB trials. This may mean these studies are more relevant to NHS decision-making. However, their results were inconsistent – Marqueen *et al*.[91] and Palmer *et al.*[94] both reported small QALY gains in favour of SIRT with lower incremental costs. Parikh *et al.*[93] in contrast, reported sorafenib to be more clinically effective with higher costs for sorafenib. The source of this inconsistency is unclear given all three studies derived clinical effectiveness data from the same trials, but this may be reflective of differences in cost and HRQoL assumptions. In these three models, the differences in incremental QALYs between sorafenib and SIRT is small, suggesting that the results may be very sensitive to different assumptions around survival or HRQoL. Marqueen *et al.*[91] and Palmer *et al.*[94] noted that model predictions were sensitive to treatment cost assumptions. Palmer specifically highlighted SIRT work-up costs and time on treatment for sorafenib as particular drivers of cost-effectiveness.

Because of these inconsistencies, it is difficult to draw conclusions on the cost-effectiveness of SIRT based on existing analysis of the SARAH and SIRveNIB trials. Limited reporting also prevents meaningful validation of the assumptions and input parameters used in each model, and only Palmer *et al*. was conducted from a UK perspective.

6.1.3.2 SIRT versus TACE

One study, reported as a full text by Rostambeigi *et al.*[89, 90] evaluated the cost-effectiveness of SIRT versus TACE. However, the model structure and inputs used in the analysis were inadequately reported and justified. This is reflected in the AG's quality assessment (see Appendix 13.5), where the majority of elements were scored as unclear. In particular, the source of the clinical effectiveness data used to populate the model is unclear. The evidence identified in the systematic review presented in Section 4, however, suggests that it was likely to be based on non-randomised comparative studies, as little RCT evidence was identified in a CTT-eligible population.

6.2 Previous NICE guidance

There have been three previous NICE TAs in HCC, though none of which were for SIRT technologies. These include the evaluations of sorafenib (TA474[31]), lenvatinib (TA551[32]) and regorafenib (TA555[36]). These appraisals are all for systemic therapies for the treatment of advanced unresectable HCC, which forms a subpopulation of that outlined in the scope of the present appraisal of SIRT. This section discusses the key issues and sources of data in each appraisal.

A summary of relevant NICE technology appraisals completed prior to July 2019 is presented in Table 18 below.

Table 18: Summary of Previous Technology appraisals in HCC

	Sorafenib (TA474)[31]	**Lenvatinib (TA551)[32]**	**Regorafenib (TA555)[36]**
Model structure	Markov model, using three health states: progression-free, progressed and dead.	A partitioned survival model, using three health states: progression-free, progressed and dead.	A partitioned survival model, using three health states: progression-free, progressed and dead. Cycle length of 28 days.
Population	Patients with advanced stage HCC, who have failed or are unsuitable for surgical or locoregional therapies.	Untreated, advanced or unresectable HCC who had Child–Pugh class A status. This was in line with the NICE scope for this appraisal. The Evidence Review Group (ERG) evaluated efficacy results for the Western subgroup, but ultimately used the full population results.	Adults with advanced, unresectable HCC who had previously received sorafenib
Intervention and comparators	Sorafenib, administered orally at a dose of 400mg twice daily. The comparator was best supportive care. Dosing based on mean dose received in the SHARP trial,[68] assuming no wastage.	The intervention was lenvatinib, which is orally administered. The starting dose was 12mg for patients weighing >60 kg, and 8 mg for patients weighing <60 kg. Dosing was based on mean dose received by the Western subgroup of the REFLECT trial,[32] assuming no wastage. The ERG implemented dosing based on full pack usage (no wastage). The comparator was sorafenib, administered orally at a daily dose of 800 mg.	Regorafenib, administered orally at a dose of 160mg once daily for the first 21 days of each 28-day treatment cycle. The comparator was best supportive care, consisting of symptomatic therapies only. The company used mean doses from RESORCE[97] to estimate regorafenib usage. The ERG implemented dosing based on full pack usage (no wastage).
Perspective, time horizon and discounting	NHS perspective (personal social services (PSS) in sensitivity analysis). Time horizon of 14 years, discount rate of 3.5% applied to both costs and QALYs.	NHS and PSS perspective. Time horizon of 20 years, discount rate of 3.5% applied to both costs and QALYs.	NHS and PSS perspective. Time horizon of 15 years, discount rate of 3.5% was applied to both costs and QALYs.
Source of clinical outcomes data	SHARP trial.[68] A phase III trial comparing sorafenib with BSC, enrolling patients with an ECOG score of 0-2 and Child-Pugh class A liver disease.	REFLECT trial.[32] A phase III trial comparing lenvatinib with sorafenib enrolling patients with unresectable BCLC stage B (those who were ineligible for	RESORCE trial.[97] A phase III trial comparing regorafenib with BSC. This study excluded patients who discontinued treatment with sorafenib due to toxicity, those with Child-Pugh B liver disease, and

		TACE) or BCLC stage C HCC, and Child-Pugh Class A liver disease.	those with an ECOG performance score (PS) of 2 or more.
Effectiveness extrapolation	For PFS, the company fit a log-normal model. For OS, the company fit a log-normal model. Weibull was considered equally plausible by the Committee.	For PFS, the company fit a log-normal model to each treatment group independently. The ERG applied a gamma distribution for PFS in their base-case analysis. For OS, a log-logistic function was fitted to each treatment group independently. The ERG preferred adjusted OS analyses, controlling for rates of subsequent therapy.	For PFS, observed Kaplan-Meier curves were used directly. For OS, the company used a log-normal function fitted to IPD for regorafenib group in RESORCE,[97] with the relative effect for BSC modelled using a HR. The ERG preferred independent Weibull functions to model OS.
Health-related quality of life (HRQoL)	Mapping from FACT-G collected during the SHARP[68] study to a set of time trade-off utility values using a published algorithm. A treatment effect was not included.	Estimated based on EQ-5D-3L data collected in the REFLECT trial.[32] A linear mixed model was used to generate health state utilities from the EQ-5D data, controlling for prior treatment, age, sex, geographical region, baseline EQ-5D score and baseline ECOG-PS. A treatment effect was not included. Disutilities associated with AEs were not explicitly modelled.	Estimated based on EQ-5D-3L data collected in the RESORCE trial. A tobit regression model was fitted to the data: progression status and TEAEs were included as covariates. Treatment effect was not included as a covariate.
Resources and Costs	Costs and healthcare resource use considered included drug acquisition, disease management, and adverse events. Disease management costs were estimated from pooling two surveys used in the sorafenib appraisals (2007 and 2015).	Costs and healthcare resource use considered included drug acquisition, disease management, adverse events and end of life costs. Unit costs were from national sources. Disease management costs were estimated from pooling two surveys used in the sorafenib appraisals (2007 and 2015).	The company's model included costs of: (i) drug acquisition for regorafenib; (ii) health state resource use, and (iii) the management of AEs. Unit costs were from national sources. Resource use consisted of visits, tests and hospitalisations, and was estimated from the sorafenib resource use survey conducted in 2015, as no further sources of medical resource use data were identified. The ERG preferred the use of combined 2007 and 2015 survey costs.

Time on treatment and subsequent therapies	The cost of post-progression sorafenib treatment was removed from the model, but the analysis submitted for Cancer Drugs Fund (CDF) reconsideration included these costs. Patients received BSC after treatment discontinuation.	Time to treatment discontinuation (TTD) KM data were used directly in the model to estimate the proportion of patients on treatment at a given time. Subsequent therapies applied after discontinuation in the company model included sorafenib and regorafenib. The REFLECT trial[32] included other therapies post-progression. The ERG preferred a scenario whereby post-progression therapy costs were removed; however, the Committee concluded that it was reasonable to apply these costs as the benefits of post-progression treatment was reflected in the OS model.	Discontinuation probability applied for patients whilst progression-free and post-progression, from RESORCE.[97] Progression-free: based on proportion of patients discontinuing regorafenib for more than one cycle prior to disease progression and median PFS. Post-progression: based on proportion of patients who continued to receive regorafenib after disease progression and post-progression treatment rate. The ERG preferred to fit a log-logistic model to the TTD KM data. No subsequent therapies were applied after discontinuation.
Adverse events	Grade 3 or 4 treatment-emergent adverse events (TEAEs) occurring in ≥10% of patients in the sorafenib arm of SHARP.[68]	Grade 3 or 4 TEAEs occurring in ≥5% of patients in either arm of REFLECT[32], or if identified as being clinically or economically significant by UK clinical experts (diarrhoea, asthenia and fatigue)	Grade 3 or 4 TEAEs occurring in ≥5% of patients in either arm of RESORCE.[97]
Results (ICER, Δ£/ΔQALY)	Company base-case [TA189]: £64,754 Updated company base-case [TA474]: £39,162 DSU [TA474]: between £51,208 and £71,276	Company base-case: Lenvatinib dominated sorafenib ERG base-case: Lenvatinib dominated sorafenib	Company base-case: £33,437 per QALY gained. ERG base-case: £81,081 per QALY gained.

The modelling approach taken across all three appraisals was similar, with each using a model based on three health states: progression-free, progressed disease and death. The sorafenib appraisal differed slightly in its approach and used a Markov model, whereas a partitioned survival modelling approach was used in the other two appraisals.

Clinical data for TA474[31] (sorafenib), TA551[32] (lenvatinib) and TA555[36] (regorafenib) were drawn respectively from the relevant pivotal trials SHARP,[68] REFLECT[32] and RESORCE.[97] Because of the availability of directly relevant RCT data, no meta-analysis was undertaken in any of the three appraisals. Modelling of clinical effectiveness was therefore undertaken by extrapolating available Kaplan-Meier data. The Committee's preferred approach in all three appraisals was to independently fit parametric functions to each of the treatment arms on the grounds that proportional hazards did not hold. The parametric function adopted varied across appraisals, with the log-normal and Weibull functions considered the best fitting and most clinically plausible in the appraisal of sorafenib, while the log-logistic were considered the most appropriate in the lenvatinib appraisal. In the regorafenib appraisal, the Weibull function was considered the best fit, with the exponential and Gompertz functions being plausible alternatives.

Modelled HRQoL across all three appraisals was based on data collected in the respective pivotal trials. In each appraisal, health state utilities were determined by the presence/absence of progressive disease, with no treatment effect included. Progression-free utilities in TA474 and TA551 were similar (0.69 and 0.693 respectively). However, progressive disease values differed, with 0.71 used in TA474 and 0.63 in TA551. Utility values used in TA555 were generally higher than those in TA474 and TA551. The progression-free utility value used was 0.81, with a utility decrement of -0.048 applied in progression. The ERG questioned the face validity of the utility values used, noting the inconsistency with TA474 and TA551, which appraised first-line systemic therapy, while regorafenib is positioned as a second-line therapy used after discontinuation of sorafenib. Costs were broadly similar across each appraisal.

Time on treatment (ToT) was sourced from the relevant pivotal trials through extrapolation of KM data. In TA474, ToT was considered to be associated with significant uncertainty, as observational data collected during the cancer drugs fund period presented in the CDF reconsideration showed that median ToT was much shorter than observed in the SHARP trial. The Committee also heard from NHS England that patients are treated for a shorter period of time than was standard in 2007, trading a sizeable decrease in adverse events for a small drop in effectiveness. Despite this, the Committee preferred to model ToT based on that observed in the SHARP trial to retain consistency with other clinical inputs.

Health state resource use across all three appraisals were based on two surveys of clinical experts conducted in the appraisals for sorafenib (TA189 and TA474), with unit costs updated in subsequent appraisals. Health state costs included medical staff visits, laboratory and radiological tests, and inpatient costs (including general ward and ICU and A&E admission). The Committee preferred to pool the original and revised estimates of resource use, as it was noted that resource use data estimates varied widely.

6.3 Review of economic evidence submitted by companies

The Sirtex Medical (hereafter referred to as Sirtex)[98] and BTG[99] submissions included health economic evaluations assessing the cost effectiveness of SIR-Spheres and TheraSphere for the treatment of HCC, together with fully executable health economic models. The Terumo Europe (hereafter referred to as Terumo) submission[100] included a budget impact analysis but did not include any further economic evidence.

The Sirtex and BTG company submissions (CS) each present the methods and results of two separate economic evaluations which split the population potentially eligible for SIRT therapies into two main groups. The two populations considered in each submission were; (i) those eligible for conventional transarterial therapies (CTT) – referred to by Sirtex as TACE, and BTG as TAE, assumed to consist primarily of BCLC B patients, and (ii) those who are ineligible for CTT, assumed to consist primarily of BCLC C patients.

6.3.1 Sirtex submission – CTT-eligible analysis

A cost-minimisation analysis (CMA) was conducted by Sirtex to compare SIR-Spheres, TheraSphere, TACE (referred to by Sirtex as cTACE in their CS) and DEB-TACE in the CTT-eligible population. A summary of the key features of the Sirtex model is presented in

Table 19. A CMA assumes that the treatments being compared are equivalent in terms of their clinical effectiveness, and only considers the costs associated with each treatment. The presented analysis therefore only compares the respective costs associated with each technology. Sirtex's justification for implementing a CMA rather than a cost-utility analysis was the lack of comparative evidence available, and the uncertainty of the results of their NMA in this population.

Table 19: Sirtex model scope (CTT-eligible population)

Model Component	Description
Population	The patient population that is the focus of the cost-effectiveness analysis includes patients matching the following criteria: • People with intermediate-stage (BCLC stage B) HCC, who are eligible for treatment with CTT (conventional transarterial therapies)
Intervention	Selective internal radiation therapies (SIRT): • TheraSphere • SIR-Spheres
Comparator	Established clinical management without SIRT, consisting of conventional transarterial therapies (CTT). These are: • TACE (transarterial chemoembolization) • DEB-TACE (TACE with drug eluting beads)
Analysis type	Cost minimisation analysis
Economic outcome	Total treatment-related cost
Perspective	NHS and PSS
Time horizon	n/a
Discount rate	n/a

6.3.1.1 Evidence used to inform the company's model

The presented CMA considered the following costs: (i) initial treatment, (ii) hospitalisation, and (iii) management of adverse events.

Treatment costs of TACE and DEB-TACE

Sirtex provided three alternative scenarios for the cost of TACE and DEB-TACE. In one scenario, these costs were based on those estimated by Fateen *et al.* (2017),[101] a single centre retrospective database study from the UK. This study collected cost data for 101 procedures in 43 patients between 2006 and 2012 at a centre in Nottingham, UK. In this study, 25% of patients received DEB-TACE and the remaining 75% of patients received TACE. Costs reported in Fateen *et al.* were for the 2012 cost year: these were inflated to 2018 costs.[102]

A second scenario used unit costs from NHS Reference costs[103] for hospitalisation, applied to resource use as estimated in the Fateen *et al.* study. The mean cost per day of hospitalisation was estimated as £1,757 (from Elective Inpatient, Percutaneous, Chemoembolisation or Radioembolisation, of Lesion of Liver, YR57Z), and was assumed to include the cost of delivering TACE.

A third scenario incorporated the results of the resource use survey commissioned by Sirtex, which were used to estimate the number of TACE and DEB-TACE procedures received by each patient, and the proportion of patients receiving DEB-TACE and TACE. The resource use survey was completed

by five medical professionals from UK hospitals, including two oncologists, one hepatologist, and two specialist nurses. This scenario was presented to reflect that resource use might have changed since the time that the Fateen study was undertaken. The survey estimated that a greater proportion of CTT patients receive DEB-TACE in the survey than in the earlier-conducted Fateen study (63% vs 25%), and that on average there are fewer procedures performed for a given TACE patient (2.5 vs 3.03) but a greater number of DEB-TACE procedures (2.83 vs 1.43).

The costs of providing CTT, estimated as a weighted average of DEB-TACE and TACE costs, ranged from £8,792.59 in the scenario based on the Fateen study (Scenario 1), to £13,702.37 in the scenario incorporating the results of the resource use survey for the number of TACE and DEB-TACE procedures (Scenario 3). A full breakdown of costs is provided in Table 48 in Appendix 13.15.

Treatment costs of SIRT

Procedure costs relating to the administration of SIR-Spheres were assumed to comprise the device costs, the cost of work-up, and the SIRT administration procedure (see Table 49: Summary of cost of SIRT, Sirtex CTT-eligible model (adapted from Table 100 in Sirtex CS) in Appendix 13.15 for a detailed breakdown).

The acquisition cost for a single administration of SIR-Spheres and TheraSphere was assumed to be £8,000.

Sirtex provided a range of scenarios to explore work-up and procedure costs, using alternative sources and assumptions to provide a range of plausible costs. Work-up costs were based on the number of work-ups and the total length of hospital stay for a work-up. SIRT procedure costs were based on the number of procedures and the total length of inpatient stay. If the hospital stay was less than one day, the cost of an outpatient visit was instead applied.

Unit costs

Unit costs of outpatient visits and the inpatient cost for one night were obtained from two different sources. These were from either NHS Reference Costs,[103] or a microcosting derived from a specialist nurse interview. The inpatient cost from the microcosting exercise was lower than that from NHS Reference Costs (£1,178 compared with £1,757).

Work-up resource use

Two alternative sources of data were provided for the number of work-up procedures and the length of stay for the work-up. In one source, these figures were informed by a clinician survey, which did not differentiate between the resource use for TheraSphere and SIR-Spheres, which estimated a mean 1.05 work-ups required per patient. An alternative source was from The Christie NHS Foundation

Trust, which estimated a greater number of work-ups at [redacted] per patient for SIR-Spheres and [redacted] for TheraSphere, and longer length of stay for each SIRT technology, equivalent to an inpatient admission.

SIRT procedure resource use

Data were taken from the clinician survey and elicited from the Christie NHS Foundation Trust to define the number of procedures and length of stay involved in an average SIRT procedure. Sangro *et al.*[68] provided an alternative source for the number of SIR-Spheres procedures, while two studies by Salem and colleagues[8, 104] were used for TheraSphere. The mean number of procedures for TheraSphere ranged from 1.20 to [redacted], and from 1.08 to 1.20 for SIR-Spheres. While the SIRT procedure was provided on an inpatient basis in these scenarios, Sirtex also explored the provision of SIRT on an outpatient basis.

Adverse event costs

The unit costs applied in the CTT-eligible model are reproduced in Table 50 in Appendix 13.15. Sirtex derived the unit costs for treating each event from previous NICE TAs, and adverse event (AE) rates were obtained from Salem *et al.*,[8] a Phase II RCT which compared TheraSphere with TACE in a population of early stage HCC patients with intent to transplant. Rates of adverse events for SIR-Spheres were assumed equivalent to TheraSphere. This study estimated a higher burden of adverse events in CTT patients, in particular neutropenia and elevated aspartate aminotransferase. Consequently, a higher cost was applied in the model (£346 for CTT vs £109 for TheraSphere).

6.3.1.2 Results of the economic analysis

Sirtex provided three alternative scenarios for the costs of CTT, which estimated a total cost of providing CTT ranging between £9,257 and £14,167 per patient (Table 20).

A range of costing scenarios were presented for TheraSphere and SIR-Spheres based on the alternative methods for delivering the SIRT technologies. Total costs ranged from £12,026 to [redacted] for TheraSphere, and from £11,185 to [redacted] for SIR-Spheres. In the scenarios that differentiated costs between TheraSphere and SIR-Spheres, TheraSphere costs were slightly higher than SIR-Spheres due to an increased number of procedures per patient.

Rather than selecting a preferred scenario, Sirtex noted that the range of costs associated with CTT, TheraSphere, and SIR-Spheres overlapped, demonstrating the comparability of treatment costs. Total costs comprised mostly those directly related to the primary treatment, with treatment for adverse events and hospitalisation comprising a small proportion of total costs.

Table 20: Total costs associated with providing CTT and SIRT in the CTT-eligible population

Scenario	**Total costs**	
CTT costing		
CTT cost from literature	£9,257	
CTT resource use from literature with NHS Reference Costs	£11,919	
CTT resource use from survey, literature with NHS Reference Costs	£14,167	
	With microcosting	***With NHS Reference Costs***
SIR-Spheres costing		
Survey results	£12,279	£13,419
Survey results with outpatient procedures	£12,026	£12,261
The Christie NHS Foundation Trust results	[redacted]	[redacted]
Sangro 2011, Salem 2016 for # procedures, rest survey	£11,185	£12,222
Sangro 2011, Salem 2018 for # procedures, rest survey	£11,185	£12,222
TheraSphere costing		
Survey results	£12,279	£13,419
Survey results with outpatient procedures	£12,026	£12,261
The Christie NHS Foundation Trust results	[redacted]	[redacted]
Sangro 2011, Salem 2016 for # procedures, rest survey	£13,244	£14,474
Sangro 2011, Salem 2018 for # procedures, rest survey	£15,800	£17,269

6.3.1.3 AG critique of the Sirtex CTT-eligible model

Cost-minimisation analysis

The AG considered the presentation of a CMA for this population to be inappropriate and potentially misleading. Such an analysis is only appropriate if there is compelling and unambiguous evidence for equivalent efficacy between interventions. When a CMA is considered by NICE in other appraisals they are typically accompanied by an extensive and conclusive assessment of equivalence between treatment arms.[105-107] Clinical equivalence is a dynamic concept and any demonstration of clinical equivalence should be sustained over time. Therefore, it is important to assess whether the two therapies are equivalent not just in response rate, but that PFS and OS are also similar.

Results of the AG systematic review found no high quality evidence in this population. As discussed in Section 4.2, the RCTs directly comparing SIR-Spheres to TACE and DEB-TACE were very small and of poor quality, and appeared to favour the chemoembolization procedure over SIRT in terms of survival outcomes. While one RCT comparing TheraSphere to TACE reported longer time to progression, a higher proportion of patients undergoing transplant and a small but non-significant OS benefit in the TheraSphere arm, this study enrolled a small number of patients and was assessed as having a high risk of bias[4].

Therefore, while the AG acknowledges the cited limitation in the effectiveness evidence for this population, and agrees that the development of a cost-utility model is inappropriate, the AG does not consider the identified evidence sufficient to make the strong assumption of equivalence between CTT and SIRT. Further, a focus on treatment costs excludes possible important outcomes regarding people who are downstaged after treatment and become eligible to receive curative therapy, or receive subsequent therapy after progression of disease.

Cost of treatment with CTT

The cost analysis of CTT highlighted significant uncertainties in the number of CTT treatments that are typically given, and the impact on the total costs. The applicability of the available sources was limited, and included the only single UK centre collecting data between 2006 and 2012,[101] and a survey of five UK-based clinicians. These two sources were used to provide a range of the number of treatments that CTT patients might receive in practice. For TACE, the estimated range was narrow and estimated at between 2.5 and 3.03 treatments. A much wider range was, however, estimated for DEB-TACE (1.43 to 2.83). To consider the plausibility of the presented estimates the AG searched for alternative estimates of the number of TACE and DEB-TACE procedures. The AG identified two alternative sources of representative data: a UK-based multi-centre trial of DEB-TACE enrolling patients between 2010 and 2015 which found that a mean of 2.18 DEB-TACE treatments were given[4,] and clinicians at a centre in the UK with experience in delivering TACE reported that patients (up to 2010) received a mean of 2.56 treatments with TACE (Dr Jai Patel, Leeds Teaching Hospitals NHS Trust, 2019, personal communication). These estimates both fall between the ranges presented by Sirtex.

Number of SIRT procedures

Sirtex explored the cost impact from using a range of sources to estimate the number of procedures with SIR-Spheres and with TheraSphere. Patients receiving treatment with SIRT typically receive multiple procedures on the basis of their tumour burden, i.e. bilobar involvement requiring sequential treatment visits, with patients not typically re-treated with SIRT upon disease progression. Therefore, the number of procedures required would not be expected to differ between treatment arms, and the range of total treatment costs for SIR-Spheres and TheraSphere estimated by this analysis might be expected to be more similar.

6.3.2 Sirtex submission – CTT-ineligible analysis

The cost-utility model developed by Sirtex evaluates SIR-Spheres for the treatment of HCC in patients currently ineligible to receive TACE, and assesses the incremental cost-effectiveness of SIR-Spheres compared with sorafenib, as well as lenvatinib in a scenario analysis. Clinical inputs in the model are largely based on a subgroup analysis of the SARAH trial.[2] The scope of the company's

model is summarised in Table 21. The model uses a lifetime (15 year) time horizon and takes an NHS perspective. Costs and health outcomes are discounted at a rate of 3.5% per annum, with cost-effectiveness expressed in terms of the incremental cost per quality-adjusted life-year (QALY) gained as per the NICE reference case. Costs were valued at 2017/18 prices. The population considered within the company's model is limited to those patients who are currently ineligible to receive CTT, and focuses on a subgroup of patients with a low tumour burden and good liver function. Sirtex defines this as a maximum tumour size of 25% of the liver volume, with an ALBI grade of 1. The AG noted that this population is far narrower than the population who would be eligible for SIRT therapies within the 'CTT-ineligible' population, and it does not match the population defined in the NICE scope. It is also important to note that this subgroup represents a *post-hoc* subgroup analysis of the SARAH trial. [2] The CS also presented a health economic analysis of the broader CTT-ineligible population as a scenario analysis.

Table 21: Sirtex model scope (CTT-ineligible population)

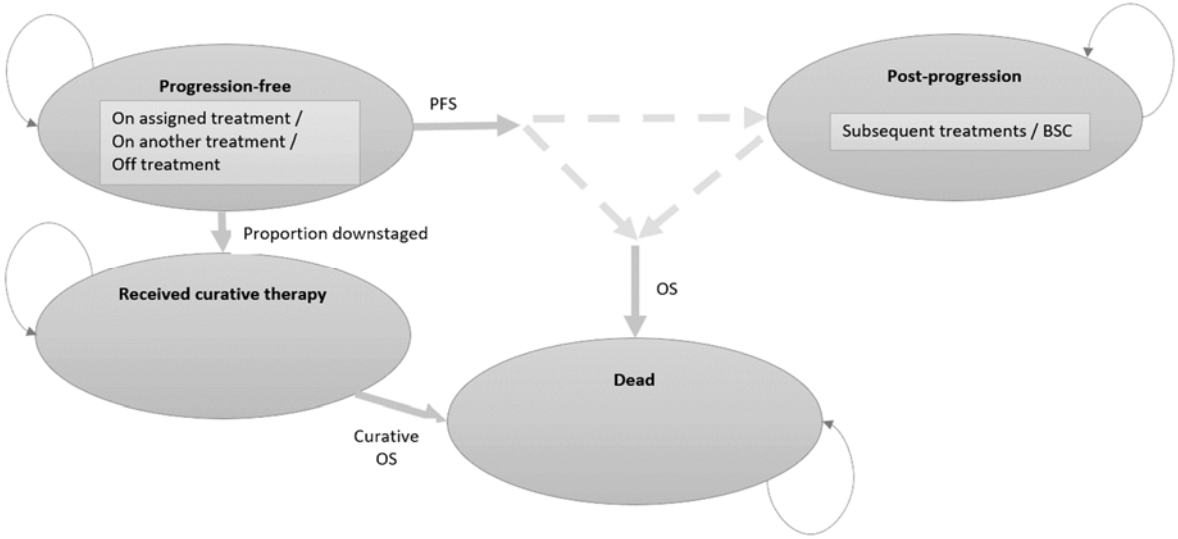
Model Component	Description
Population	The patient population that is the focus of the cost-effectiveness analysis includes patients matching the following criteria: • Patients with unresectable intermediate (BCLC stage B) or advanced (BCLC stage C) HCC, • for whom any transarterial embolisation therapies (TAE, TACE, DEB-TACE) are inappropriate, • with or without portal vein thrombosis / involvement, • without extrahepatic disease, • with a tumour burden ≤25%, • and with a preserved liver function (ALBI grade 1).
Intervention	Selective internal radiation therapies (SIRT): • SIR-Spheres Y-90 resin microspheres
Comparator	Established clinical management without SIRT (including but not limited to target chemotherapy). Established clinical management is limited to systemic therapy with sorafenib or lenvatinib in UK clinical practice.
Analysis type	Cost-effectiveness (cost-utility) analysis
Economic outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Time horizon	20 years
Discount rate	Annual rate of 3.5% applied to costs and QALYs

6.3.2.1 Model structure

The structure of the economic model developed by Sirtex takes the form of a cohort-level partitioned survival model. The main model includes three health states: (i) progression-free, (ii) post-progression and (iii) dead. In addition to the main partitioned survival component, the model also permits patients to receive curative therapy, assuming a proportion of patients are downstaged and receive liver

transplant, resection, or ablation. Patients who receive curative therapies do not enter the main model, but instead effectively move into a separate two-state model, which comprises the health states (i) alive/received curative therapy and (ii) dead. The proportion of patients downstaged to receive curative therapy is based on the numbers downstaged in the low tumour burden/ALBI 1 subgroup of the SARAH trial.[2] Figure 8 presents an overview of the model structure. Both sub-models use a lifetime time horizon of 15 years and monthly model cycle with a half-cycle correction applied.

Figure 8: Model structure for the CTT-ineligible population (Figure 17 in Sirtex CS)



In the partitioned survival sub-model, the transitions between the three health states were determined directly from the survival models of PFS and OS. Given the incomplete KM data available, parametric functions were fitted to KM curves for OS and PFS from the low tumour burden subgroup of the SARAH trial. [2] Log-normal functions were selected to model both OS and PFS, assuming independent (non-proportional) hazards between treatment groups.

In the partitioned survival model, health state utilities are determined based on the presence/absence of disease and the therapy received, with utility values drawn from the low tumour burden/ALBI 1 subgroup of the SARAH trial.[2] The model does not separately account for loss of QALYs as a result of AEs, as these were assumed to be accounted for through the direct use of trial based utility values. Utility values used for patients receiving curative therapy were the same as those for pre-progression in the SIR-Spheres arm of the main partitioned survival model.

The model includes the following costs: (i) procedural costs relating to the administration of SIR-Spheres and liver transplant, (ii) sorafenib/lenvatinib drug acquisition and administration costs, (iii) monitoring for participants receiving non-curative care, and (iv) costs associated with AEs.

The model employs the following structural assumptions:

- Health-related quality of life is determined according to the presence/absence of disease progression and the therapy received.
- Progression-free survival and OS are modelled using Weibull functions assuming independent (non-proportional) hazards.
- Survival models for PFS and OS were fitted to the low tumour burden/ALBI 1 subgroup of SARAH trial. [2]
- Adverse events are assumed to affect only costs, with HRQoL assumed to be captured by the use of trial based utility values.
- Utility values were assumed to differ according to therapy received both in the pre-progression and post-progression health state.
- Patients downstaged to receive curative therapy were assumed not to have recurrence of disease with mortality outcomes determined from a US cohort study comparing outcomes for patients receiving palliative and non-palliative care.[108]

6.3.2.2 Evidence used to inform the company's model

Overall survival

The modelling of OS for patients downstaged and in receipt of palliative care was modelled separately with the proportion of patients downstaged based on observed values in the low tumour burden/ALBI 1 subgroup of the SARAH trial.[2]

Overall survival for patients who are not downstaged to curative therapies in the economic model was based on observed survival in the SARAH trial,[2] using data on the low tumour burden/ALBI 1 subgroup of patients, including 37 SIRT patients and 48 sorafenib patients.

Before fitting parametric functions to the available KM data, diagnostic plots were used to assess the plausibility of assumption of proportional hazards. The plots revealed some evidence to suggest that the proportional hazards assumption may not hold, as the "lines in the plots are not parallel in all cases, with some lines crossing" (Sirtex CS Page 57). The Schoenfeld residuals, however, suggest no significant deviation from the proportion hazards assumption. Given this uncertainty, Sirtex opted to fit separate parametric functions to the KM data.

The following parametric survival models were fitted to the observed KM data: Weibull, log-normal, log-logistic, exponential, and gamma functions. Assessment of the most appropriate parametric extrapolation was made with reference to statistical goodness-of-fit, visual fit to the observed data and assumptions made in previous TAs.[31, 32, 36] Assessment of statistical fit (see Sirtex CS Appendix F) revealed a similar statistical fit for the majority of curves, with the exponential curve observed to have the highest statistical fit. In assessing visual fit, Sirtex noted that the generalised gamma, Weibull and

Gompertz curves crossed, which is not seen in the KM curves until the last few patients, while the log-normal and log-logistic curves did not cross. Sirtex further noted that in previous TAs of sorafenib (TA474[2]) and lenvatinib (TA551[32]), the log-logistic and log-normal curves were considered the most appropriate, and in the analysis of the SARAH ITT population the log-normal distribution fitted the best, both in terms of goodness-of-fit statistical criteria and visual inspection. On these grounds, Sirtex therefore selected the log-normal function for its base-case analysis. Assessment of uncertainty in curve selection was also partially explored in two scenario analyses considering the log-logistic and Weibull distributions.

Overall survival outcomes for patients downstaged to curative therapy was not drawn from the SARAH trial,[2] as OS data were censored upon receipt of curative therapy. Survival outcomes for these patients were therefore based on a US cohort study[108] which reported the outcomes for patients who did and did not receive curative therapy. The survival HR for downstaged patients was 0.29 (95% CI: 0.18-0.47). To model survival in the downstaged patients, this HR was applied to the treatment-specific survival curves for SIR-Spheres and sorafenib patients. Importantly, because this HR was applied to the individual survival curves for SIR-Spheres and sorafenib, the model implies differential OS following receipt of curative therapies depending upon the initial treatment received.

Progression-free survival

Progression-free survival was defined as the time from the closest date of radiological examination before the first administration of the study treatment to disease progression (per investigator assessment), or death from any cause. Because progression events were observed across patients who were and were not downstaged to receive curative therapy, a common PFS curve was assumed for all patients irrespective of whether or not they received subsequent curative therapy. Sirtex's base-case analysis drew PFS data from the low tumour burden/ALBI 1 subgroup of the SARAH trial.[2]

Assessment of the proportional hazards suggested a degree of uncertainty in whether this assumption it holds. Assessment of statistical fit based on AIC and BIC of the jointly fitted data, found the (assuming proportional hazards) log-logistic and log-normal, as well as the independently fitted (no proportional hazards) log-normal distribution had the best statistical fit. Aligning with assumptions made for OS, Sirtex's base-case analysis used independently fitted log-normal distributions. Uncertainty in curve selection was partially explored in a scenario analysis in which the log-logistic and Weibull distribution were used.

Health-related quality of life

The primary source of utility data used by Sirtex was the SARAH trial,[2] which measured HRQoL using the EORTC-QLQ C30 questionnaire. There were a significant number of missing responses

over the course of the study, ranging from 19% at baseline to 56.8% at 18 months, with an overall rate of missing data of 38.5%. To calculate health state utilities from this dataset, the mapping algorithm by Longworth *et al*.[109] was used to generate EQ-5D scores adjusted to reflect UK population weights. Sirtex did not consider the SARAH trial[2] to show evidence of an independent treatment effect upon utility, and there was no significant difference between the HRQoL of those treated with SIR-Spheres or sorafenib. The CS, however, also notes a statistically significant difference in reported global health scores between treatment arms, and applies treatment specific utility values based on the subgroup of patients with a tumour burden of ≤25% and an ALBI score of 1. The values used in the base-case model are reported in Table 51, Appendix 13.15.

SIRT procedure costs

Procedure costs relating to the administration of SIR-Spheres were assumed to comprise the device costs, and cost of the work-up and treatment procedures. All patients in the SIRT arm of the model were assumed to undergo at least one work-up procedure with 5% of patients also assumed to undergo a second work-up based on clinical opinion. To account for the fact that not all patients will go on to receive SIRT (e.g. due to excess shunting), only a proportion of patients were assumed to receive SIRT therapy. Sirtex's base-case used the low tumour burden/ALBI 1 subgroup of the SARAH trial[2] to derive this figure. The model also permitted SIRT patients to be re-treated with SIRT. Sirtex did not consider the average number of SIRT treatment rates in the SARAH trial[2] to represent likely UK practice, as the SARAH trial[2] mandated separate administrations where bilobar disease was present. Sirtex instead used data from the CIRSE European registry[110] (Belgium, France, Germany, Italy, Spain, Switzerland) as well as the ENRY study showing that patients with bilobar disease typically receive a single administration of SIRT with both lobes treated simultaneously.[68] The number of SIRT administrations was therefore based broadly on the CIRSE registry, with 1.20 treatments assumed per patient. Uncertainty in the number of SIRT administrations was also explored in scenario analyses based on the SARAH trial, [2] the SIRveNIB trial,[3] the ENRY study[68] and the Christie NHS Foundation Trust.[111]

Costs relating to the work-up and SIRT procedures were based on NHS Reference Costs 2017/2018,[103] with the cost of SIR-Spheres assumed to be £8,000 per administration. Table 52 in Appendix 13.15 summarises the assumptions and costs of the SIRT procedure.

Drug acquisition costs - systemic therapies

Drug acquisition costs for sorafenib and lenvatinib were taken from the British National Formulary (BNF).[112] Dosing of sorafenib was based on the SARAH trial,[2] assuming 24% received an 800mg dose, and 76% a 600mg dose. In scenarios where lenvatinib was included as a comparator, dosing was based on TA551[32] with 65% assumed to receive an 8mg dose and 35% a 12mg dose.[32] Duration of

sorafenib therapy was based on the time to discontinuation curve from the SARAH trial,[2] which was extrapolated using a log-normal function. Duration of lenvatinib therapy was estimated by applying a HR to the sorafenib TTD curve taken from TA551.[32]

Subsequent treatments

Modelled subsequent treatments without curative intent were based on expert elicitation, as the subsequent treatments received in the SARAH trial[2] were not considered reflective of NHS practice. Drug costs were taken from the electronic market information tool (eMIT) and BNF.[112, 113]

For patients downstaged to receive curative therapies, the modelled therapies were based on those received in the ITT population of the SARAH trial,[2] consisting of resection, liver transplantation, and tumour ablation. The proportion receiving each type of therapy is summarised in Table 53, Appendix 13.15. Costs of resection were based on NICE TA474,[31] while costs of ablation and liver transplantation were based on NHS reference costs 2017/2018.[103]

Health state costs

Resource use estimates were based on a survey of clinical experts, and included medical staff contacts (e.g. GP appointments), diagnostic procedures, inpatient care and Personal and Social Services contacts. Unit costs were derived from NHS Reference Costs 2017/18.[103] Total costs by health state are reported in Table 54, Appendix 13.15.

Adverse event costs

The costs of grade 3/4 treatment related AEs ≥5% of the population were modelled with rates drawn from the SARAH[2] and REFLECT[23] trials. Costs for each adverse event were sourced from previous TAs and inflated to the 2018 cost year as appropriate. See Table 55, Appendix 13.15 for a summary of included AE costs.

Model results

The headline results presented in the Sirtex CS[98] are based on the deterministic version of the model. Uncertainty surrounding model parameters was explored using DSA and PSA. Their probabilistic results were estimated from 1000 Monte Carlo samples. Uncertainty was represented using tornado diagrams, cost-effectiveness planes, and cost-effectiveness acceptability curves (CEACs).

Table 22 presents the base-case estimates of cost-effectiveness using the list price for sorafenib. Based on the probabilistic version of the company's model, SIR-Spheres are expected to generate an additional 0.682 QALYs at an incremental cost of -£1,979 compared with sorafenib; SIR-Spheres were therefore estimated to be dominant, producing greater health benefits at lower overall cost. The

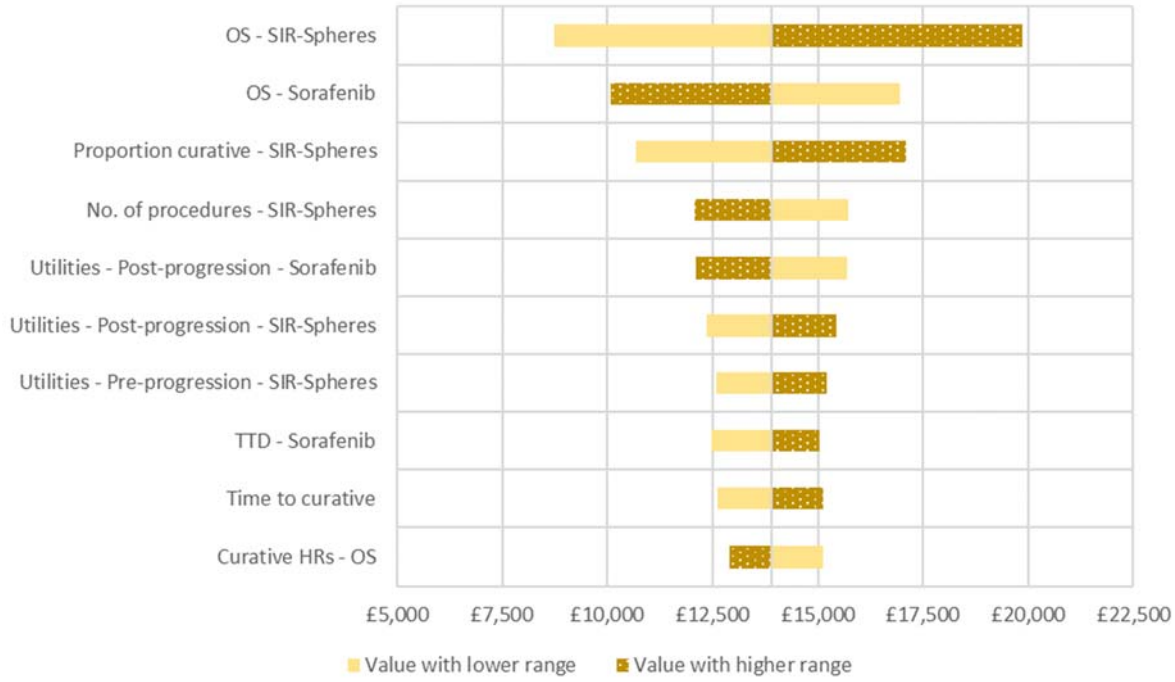
deterministic version of the model produces similar results with SIR-Spheres estimated to dominate sorafenib.

Table 22: Sirtex base-case results (CTT-ineligible population)

	Absolute		**Incremental**		
	QALYs	**Costs (£)**	**QALYs**	**Costs (£)**	**ICER (£)**
Probabilistic model					
SIR-Spheres	2.009	£24,456	0.682	-£1,979	Dominant
Sorafenib	1.408	£26,435			
Deterministic model					
SIR-Spheres	1.982	£29,143	0.601	-£1,784	Dominant
Sorafenib	1.381	£30,927			

Figure 9 presents the results of the company's deterministic sensitivity analysis. The most influential parameters (of those assessed by the company) relate to predicted OS (SIR-Spheres and sorafenib), and the proportion of patients downstaged to receive curative therapy. Additional scenario analyses presented by the company showed that the estimated ICER was generally robust to a range of alternative assumptions, including alternative extrapolations of survival data. However, this analysis also showed that estimated ICERs increased very significantly when the source of effectiveness estimates was changed from the low tumour burden/ALBI 1 subgroup to the ITT or per protocol population from the SARAH trial,[2] which yielded ICERs of £58,763 and £680,276 per QALY gained, respectively.

Figure 9: Sirtex deterministic sensitivity analysis – Tornado diagram (Sirtex CS Figure 21)



6.3.2.3 Critique of the Sirtex CTT-ineligible model

Relevance of modelled population

The company's health economic analysis is limited to a sub-population of patients with a tumour burden ≤25% and with preserved liver function (ALBI grade 1). The company cited clinical opinion and published literature in their justification for focusing on this group, stating that the ITT and per protocol population recruited to the SARAH trial[2] was unreflective of that eligible in the UK, while also highlighting that the trial included patients with high tumour volume, portal vein thrombosis, and poor liver function. The company also outlined that this sub-population increased the probability of receiving SIRT therapy, and the probability of going on to access curative therapy, citing figures from the SARAH trial.[2]

Consultation with the AG's clinical experts confirmed that this subgroup could be identified prospectively and treated with SIRT. However, they also noted that ALBI scores are not routinely used to assess liver function in UK practice, and that this definition did not represent a widely accepted clinically distinct subgroup of patients.

The AG is further concerned that the selection of this subgroup is based on a *post-hoc* analysis of a relatively small subgroup of the SARAH trial,[2] representing less than 20% of the total trial population. Comparison of the results for this subgroup on key outcomes such as PFS and OS revealed no statistically significant differences between this group and the remaining population. Furthermore, the

randomisation procedure for the SARAH trial[2] did not stratify by these baseline characteristics, increasing the risk of baseline imbalances. This can be observed in the sample size of this group between treatment arms, with 37 patients in the SIRT arm and 48 in the sorafenib arm. A further consequence of using this subgroup is that potentially relevant data from the SIRveNIB trial[3] cannot be used, as data on this subgroup were not available to the company. This is important for two reasons: (i) it reduces the available sample size with consequences for precision, (ii) it does not allow for a confirmatory analysis of the PFS and OS benefits observed in this subgroup.

The AG is therefore concerned that the purported treatment effects in this subgroup are potentially an artefact of imbalances in characteristics between treatment arms. Available data does not allow further analysis to establish the validity of the observed PFS and OS gains in this subgroup.

Model structure and clinical plausibility of downstaging

The company's model allows a proportion of patients to move on to receive curative therapy. This is a significant driver of the model results, as 66% of incremental QALYs are generated by patients who received curative therapies.

The SARAH trial[2] was used to support the downstaging paradigm used in the model, where a small number of patients went on to receive curative therapy. The plausibility of downstaging at such high rates in UK practice is unclear. The AG was advised that downstaging of patients with advanced HCC to transplant and other curative options is rare in UK clinical practice, with very few if any of these patients receiving curative therapies. It is also notable that the SIRveNIB trial,[3] which recruited a similar population, makes no mention of any patients going on to receive curative therapy. Similarly, none of the previous TAs which assessed systemic cancer treatments for advanced HCC modelled the possibility of curative therapies. The AG is therefore concerned that the very sizable benefits resulting from curative therapy would not be realised in practice, and that the rarity of downstaging means any resulting incremental benefits are subject to very considerable uncertainty.

Modelling of overall survival

The company fit independent parametric survival functions to the observed data from the SARAH trial. [2] This method makes fewer assumptions than a treatment-covariate based approach, and is in line with DSU guidance on survival analysis. [114] However, the AG does not accept the company's rationale for selecting the log-normal curve, which was based primarily on visual fit and its use in previous HCC appraisals. The AG notes that the log-normal is the most optimistic of all the fitted parametric curves, and has amongst the worst statistical fit. The log-normal also has a much longer tail, and in the AG's view, fits poorly to the tail of the observed data for the SIR-Spheres arm of the

SARAH trial.[2] Clinical advice to the AG indicated a preference for the Weibull function, which predicts substantially shorter survival gains and also has better statistical fit.

In addition to the above, the AG is concerned that the parametric functions were fitted to the observed data which had not been censored to exclude those patients downstaged to receive curative therapy. In the economic model, the outcomes for these patients are modelling independently, and therefore using the uncensored data means that the OS benefits experienced by these patients are double counted. The impact of this double counting is significant, and leads to a substantial overestimation of survival gain. For example, based on a log-normal extrapolation (used in the Sirtex base-case) and using the uncensored data, estimated OS gain on SIR-Spheres is 8.27 months. Using the log-normal function on the same data censored for downstaging results in a much reduced predicted OS gain of 1.55 months.

Further to the above issues regarding the plausibility of downstaging, the AG has concerns around the methods used to model the OS benefits associated with curative therapy. Post-curative OS is modelled by using the HR from the Kanwal *et al.*[108] cohort study to the OS curve for each treatment. This HR is assumed to reflect the improvement in survival outcomes post-curative therapy. The application of this HR is treatment specific, i.e. is applied to the SIR-Spheres OS curve for SIR-Spheres patients and to the sorafenib OS curve for sorafenib patients. This implies that OS post-curative therapy will differ depending on the initial treatment received, and thus favours SIR-Spheres. Expert advice received by the AG, however, considers this implausible and that outcomes will be the same post-curative therapy regardless of previous therapy received.

Furthermore, the application of an HR to log-normal curve is inappropriate, as the log-normal function is an accelerated failure time model and does not make assumptions about proportional hazard assumptions. Consequently, survival times are considerably overestimated. The AG also questions the appropriateness of the HR of 0.29 used by the company, noting that this figure was not based on the primary analysis presented in the cited study, but a scenario analysis in which classification of patients was based on both BCLC stage and ECOG performance status.

Modelling of progression-free survival

The company's approach to modelling PFS was similar to that of OS with independent parametric survival functions fitted to the observed data.

The AG is satisfied that the company's approach of using independent curves was appropriate given the presented evidence to support the non-proportionality of hazards. The AG, however, questions the appropriateness of fitting parametric functions to PFS data at all, given that the available KM data are all but complete; no patients remain at risk in the sorafenib arm and only one remained in the SIRT

arm. The company could therefore have used the observed data directly, avoiding any uncertainty in the choice of parametric function.

The AG is also concerned that the modelled data were not censored for downstaging events and therefore double counts patients who were downstaged to receive curative treatment. As with OS, this results in PFS gains being overestimated, though to a lesser degree than OS. Mean PFS gain assuming a log-normal function was 3.7 months using the uncensored data and 2.35 months using the censored data.

Concerns regarding costs of SIRT

It is assumed in the Sirtex model that patients with bilobar tumours receive SIRT in both liver lobes during the same treatment session. This is in contrast with how patients were treated in the SARAH trial[2] which mandated that patients receive separate treatments with a delay between the first and second administration. Sequential treatment is implemented to mitigate the risk of radioembolisation induced liver disease which is more likely to occur if both lobes are treated simultaneously. The company put forward evidence from the European CIRSE Registry for SIR-Spheres Therapy (CIRT), and suggested that [redacted].

The impact of this assumption is to reduce the costs of providing SIR-Spheres, as sequential treatment involves additional administration and acquisition costs. However, clinical advisors to the AG disagree with the assertion that simultaneous treatment would be implemented in the UK, and contend that in UK practice it is likely that sequential treatment would be used as per the SARAH trial.[2] Furthermore, the AG notes that while the company adjusts costs to account for the use of simultaneous treatment, no corresponding adjustment is made to health outcomes to account for the increased risks associated with simultaneous treatment.

Failed work-up procedures

In the Sirtex model, a proportion of patients are assumed to fail the work-up procedure and are thus ineligible to receive SIR-Spheres. The proportion of patients receiving work-up who do not go on to receive SIRT was drawn from the low tumour burden/ALBI 1 subgroup of the SARAH trial,[2] which was substantially lower than for the population as a whole (8.1% vs 18.6%). The AG is concerned about the appropriateness of this figure, given the *post-hoc* nature of the analysis. The primary reason patients become ineligible for SIRT following work-up is a high rate of shunting of radioactive material to the lungs. While this may be plausibly linked to tumour volume and liver status, any such association has not been demonstrated, and it is not clear that the proportion of patients who experience excessive lung shunt will vary substantially between patient groups.

Furthermore, the company's model assumes that patients who fail work-up will move to the sorafenib arm of the model. The AG considers this inappropriate as only 62% of patients in the SARAH trial[2] who failed work-up subsequently received sorafenib. The outcomes of patients in the SARAH trial[2] who received work-up but no SIRT were inferior to those who successfully received SIR-Spheres or were randomised to the sorafenib arm. Assuming that patients who fail work-up receive sorafenib outcomes is therefore likely to overestimate the PFS and OS for those allocated to receive SIR-Spheres.

Subsequent therapy costs

The company noted in their submission that the subsequent treatments received by patients in the SARAH trial[2] included a number of therapies (capecitabine and doxorubicin) not used in UK practice. The treatments received following primary therapy in the model was therefore based on a survey of 12 clinicians instead.

The AG considers the proportions of patients receiving subsequent therapies in the model to be subject to substantial uncertainty, and notes that these differ substantially from those reported in the SARAH trial. [2] The proportion of patients assumed to receive sorafenib following SIR-Spheres is higher than that observed in SARAH, [2] as is the proportion of patients receiving further treatments post-sorafenib. The AG also notes that post-sorafenib treatment is based on the ITT population of the SARAH trial, [2] and therefore does not reflect the modelled low tumour burden/ALBI 1 subgroup. Given the low tumour burden/ALBI 1 subgroup represents a particularly healthy population, it may be anticipated that a much higher proportion of these patients would go on to receive subsequent systemic therapies. As no figures on subsequent therapy in the low tumour burden/ALBI 1 subgroup are reported, this cannot be verified.

Duration of subsequent sorafenib and lenvatinib therapy were drawn from the REFLECT trial[32] while subsequent regorafenib was based on the RESORCE trial.[97] The approach taken to define ToT was inconsistent, as median values were used for sorafenib and lenvatinib, while a mean value was used for regorafenib. The AG considers mean values more appropriate than the medians used by the company, as the aim of the model is to calculate the mean costs of subsequent therapy. The AG is also concerned that the REFLECT trial[32] considers the use of sorafenib and lenvatinib in a first-line setting, particularly as this implies that patients receiving sorafenib as a subsequent therapy will receive treatment for much longer than those who received it as a first-line therapy. The AG therefore considers that these values are likely to overestimate ToT, and that it may be better to base duration of subsequent therapy on the RESORCE[97] trial which considers systemic therapy use in a second-line setting.

Omission of palliative care costs

The ERG notes that the company model does not include end-of-life costs to account for palliation at the end-of-life. However, the impact of this omission is small, as less than 1% of patients remain alive at the end of the modelled time horizon, meaning that nearly all modelled patients incur this cost.

6.3.3 BTG submission – CTT-eligible analysis

For the comparison with transarterial therapies, the company presented a cohort-based Markov model, comparing TheraSphere, SIR-Spheres and QuiremSpheres with TACE (referred to by the company as cTACE), DEB-TACE and TAE (referred to by the company as bland embolization). Outcomes were assessed over a time horizon of 20 years using 4-week cycles, and were discounted at a rate of 3.5%. The scope of the company's model is summarised in Table 23.

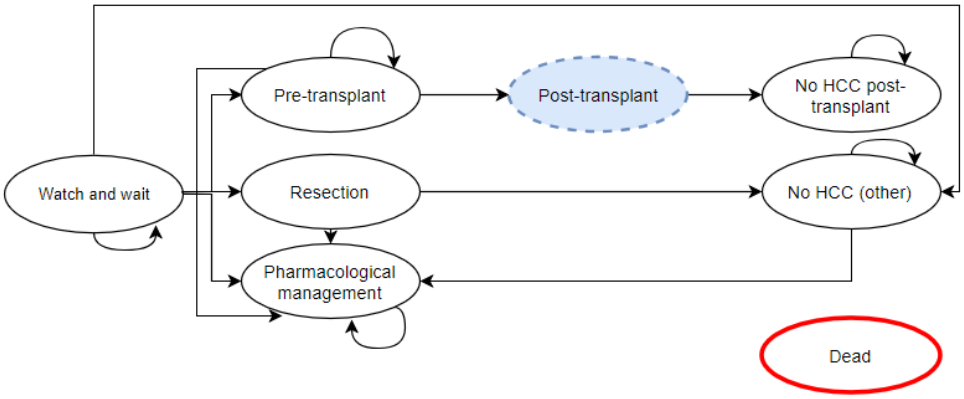
Table 23: BTG model scope (CTT-eligible population)

Model Component	Description
Population	The patient population that is the focus of the cost-effectiveness analysis includes patients matching the following criteria: • People with intermediate-stage (BCLC stage B) HCC, who are eligible for treatment with CTT (conventional transarterial therapies)
Intervention	Selective internal radiation therapies (SIRT): • TheraSphere • SIR-Spheres • QuiremSpheres
Comparator	Established clinical management without SIRT (including but not limited to target chemotherapy). The target chemotherapies are: • TACE (transarterial chemoembolization) • TAE (transarterial embolization) • DEB-TACE (TACE with drug eluting beads)
Analysis type	Cost-effectiveness (cost-utility) analysis
Economic outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Time horizon	20 years
Discount rate	Annual rate of 3.5% applied to costs and QALYs

6.3.3.1 Model structure

The model presented by BTG for the CTT-eligible population was based on a Markov structure, and contained the following health states: (i) watch and wait, (ii) pre-transplant, (iii) post-transplant (a series of three tunnel states), (iv) no HCC post-transplant, (v) pharmacological management, and (vi) dead. The model schematic is illustrated in Figure 10.

Figure 10: Model structure for the CTT-eligible population (Figure 6-1 in BTG CS)



Patients who are eligible for SIRT enter the model in the "watch and wait" health state, following initial treatment. Patients remain in this state until they (i) are downstaged and become eligible for transplant, moving on to the pre-transplant state (equivalent to a transplant waiting list), (ii) transition to the pharmacological management state due to not entering remission and being ineligible for liver transplant, or (iii) die.

While the model includes the functionality for patients to receive resection after being downstaged or achieving remission, these transitions are not included in the base-case analysis.

The pre-transplant state captures the time when patients are on the donor organ waiting list. Patients remain in this state until they (i) receive a transplant, and move to the post-transplant state, (ii) experience disease progression or become ineligible for a liver transplant, after which they move to the pharmacological management state, or (iii) die.

Following transplant, patients spend a single cycle in each of the post-transplant states before arriving in the no HCC post-transplant state, where they remain until death. The three tunnel states allow for differing resource use over the time following the transplant. Additionally, the model assumed that patients would not experience a tumour recurrence after transplantation.

Patients entered the pharmacological management pathway from either the "watch and wait" health state, or from the pre-transplant health state. Patients remain in this health state until death, although the impact of further disease progression is implicitly captured by assuming a 50:50 mix of patients who are in a pre-progressed or a progressed HCC state. This split is used to estimate the mean utility value and treatment-related costs. The patients in the pre-progression part of this health state received either sorafenib (33%) or best supportive care (BSC) (67%), and the patients in the progression portion of this health state received BSC.

6.3.3.2 Evidence used to inform the company's model

Downstaging outcomes

In this model, it was assumed that the impact of treatment with SIRT compared with CTT was limited to differences in the likelihood of patients being downstaged and becoming eligible for curative therapy.

Non-mortality outcomes for the "watch and wait" health state were estimated from a single-centre, non-randomised comparison of TACE and TheraSphere patients, Lewandowski *et al.* (2009).[115] The study was undertaken in a population of unresectable HCC patients who did not meet the Milan criteria at presentation, specifically including patients were of T3 United Network for Organ Sharing (UNOS) status. This is defined as patients with either a single nodule of greater than 5.0 cm, or with 2 or 3 nodules, at least one greater than 3.0 cm,[116] and downstaging was defined as a decrease in the maximal tumour dimension to 3.0 cm.

The probability of remaining in the watch and wait health state for all therapies was estimated by the company using the median time to downstaging in the TheraSphere arm of the Lewandowski study.[115] The company assumed that the median time to downstaging represented the median time to "prognosis", i.e. either to downstaging or to pharmaceutical management. The median time to downstaging in the study for TheraSphere patients was 3.1 months, median time to downstaging in the TACE arm of the study had not been reached. The company converted the median time of 3.1 months to a per-cycle probability of leaving the watch and wait health state of 18.6%, resulting in a per-cycle probability of remaining in this health state of 81.4%.

Of the proportion who leave the watch and wait health state in each cycle, the company used the probability of downstaging from the Lewandowski study to estimate the transition of patients to the pre-transplant state. The remaining living patients entered the pharmacological management health state. The study reported a probability of downstaging from TheraSphere treatment of 58% (25 of 43), compared to 31% (11 of 35) downstaged from TACE.

The efficacy of SIR-Spheres and QuiremSpheres were assumed to be equal to that of TheraSphere, and the efficacy of DEB-TACE and TAE were assumed to be equal to that of TACE.

Due to a lack of data specific to this outcome, the probability of death in each model cycle for the "watch and wait" health state was assumed to be equivalent to that of patients on the wait list which was estimated from a cohort of NHS patients awaiting liver transplant (see below). The mortality rate was assumed to be equal between all treatment arms. The greater predicted benefits of SIRT in this

model are therefore entirely attributable to a greater proportion of patients being successfully downstaged.

Table 56 and Table 57 in Appendix 13.15 summarise the transition probability values and mortality rates, respectively, used in the model.

Transplant wait list outcomes

The probability of successfully receiving a transplant once on the wait list was calculated by the company using the median wait time of 130 days for a liver transplant in the UK.[117] This dataset is based on a cohort of 2,706 NHS patients who were registered for a liver transplant between April 2013 and March 2016, and is not specific to an indication of HCC. This was converted to a per-cycle probability of 13.9%. The probability of transplantation was not conditional on initial treatment.

Patients could transition from the pre-transplant state to pharmacological management, in the case that a patient becomes ineligible for transplant whilst on the wait list. The probability of this occurring was informed by clinical advice to the company, with 16 cases of patients leaving the wait list due to disease progression for every 103 transplants (National Audit for Liver Transplant, incomplete source provided by the company).

Mortality in the pre-transplant wait list health state was estimated from a figure quoted in an NHS service specification for Liver Transplantation Service in Adults,[118] where "up to 18% of patients die whilst on the liver transplant waiting list" and converted to a per-cycle mortality rate using the median time to transplant of 130 days.

Pharmacological management outcomes

Patients entering the pharmacological management health state are assumed to remain there until death. The mortality rate applied was based on the median overall survival of BSC patients reported in the NICE sorafenib submission (34.4 weeks).[31] Per-cycle mortality was estimated assuming OS followed an exponential distribution; the applied per-cycle mortality rate was 7.7%. This rate was applied to patients in this health state regardless of their initial treatment.

Post-transplant outcomes

Mortality in the three cycles (12 weeks) following transplant was estimated using data from a study of early-stage HCC patients, Bellavance *et al.* (2008),[119] which reported a 30-day mortality probability of 1.5%.

The post-transplant mortality rate beyond these three cycles was assumed to be lower, and was estimated from NHS 5-year survival rates following transplantation[117] of liver patients transplanted

between 2010 and 2012, which was estimated at 81%. These data reflect a general liver transplant population and are not specific to those who have HCC. Further, for the patients in the population who did have HCC, they are also not specific to patients who had been downstaged after having previously been ineligible for transplant before active treatment for HCC. The company justified the assumption that the mortality rates for a downstaged population can be assumed equivalent to a population who were not originally downstaged, on the basis of a systematic review by Gordon-Weeks *et al.*(2011).[120]

Adverse events

For TheraSphere and SIR-Spheres, data on Grade 3 and 4 treatment-related adverse events (TRAEs) were sourced from a systematic review of adverse events.[77] Event rates for QuiremSpheres were assumed to be the same as SIR-Spheres. Rates of TRAEs for TACE and DEB-TACE were sourced from an RCT of DEB-TACE versus TACE in HCC.[58] The company's model included severe TRAEs that occurred in more than 5% of patients in at least one arm.

Total TRAE utility decrements and treatment costs were applied in the first model cycle. The estimates of utility decrements were based on the assumption that Grade 3 and 4 adverse events were associated with a utility decrement of 0.012, which was multiplied by AE rates reported for each event. The total TRAE disutility for TheraSphere, SIR-Spheres, QuiremSpheres and TACE was estimated as -0.002, with -0.009 for TAE, and 0.000 for DEB-TACE. Total TRAE costs ranged from £5.59 for DEB-TACE, to £111.33 for SIR-Spheres, and £384.15 for sorafenib. Further details of TRAE rates and associated costs are provided in Appendix 13.15.

Health-related quality of life

BTG drew upon a variety of external sources for the utility values in their economic model (Table 59 in Appendix 13.15). Utility values for all health states with the exception of the post-transplant tunnel states were the same as the pre-progression values used in the TA551[121] submission for lenvatinib (equal to 0.75), that were estimated from EQ-5D data collected from patients in the REFLECT trial.[23] The utility applied to the 'pharmacological management' state is taken to be an average of the pre-progression and post-progression health state values, as BTG state this population comprises patients in both progression states equally. Post-transplant utilities were derived from a study by Lim *et al.*,[122] which used an average of literature-derived utilities equal to 0.69. A scenario analysis was performed using significantly lower pre- and post-liver transplant utilities from Ratcliffe *et al.*;[123] however, these values were taken from a primarily non-HCC population.

Utilities were adjusted according to age and gender norms reported in Kind *et al.*;[124] however, this adjustment was applied incorrectly, which resulted in patients experiencing a much lower HRQoL than reported in the cited sources. When this was highlighted to the company, they stated that this was intentional, and considered the use of lower utility values appropriate and consistent with methods reported in Kind *et al*.

Costs of SIRT treatment

Procedure costs relating to the administration of SIRT therapies were assumed to comprise of microsphere (SIRT) acquisition costs, the cost of the work-up and procedure costs relating to the administration of SIRT. The mean number of SIRT treatments per patient was informed by an elicitation exercise undertaken by BTG. Each patient was estimated as having an average of 1.2 SIRT treatments, with one work-up per patient. Only patients who are eligible for SIRT enter the model, and so the cost of work-ups that did not result in treatment with SIRT were not included.

The work-up procedure costs were based on a microcosting from the Christie NHS Foundation Trust, Manchester, and were estimated as being £467.91. These costs included the time of the personnel involved with the work-up (a technician, clinical scientist, and radiologist) and a MAA body SPECT. The AG requested additional details of this microcosting; however, little further granularity was provided. Additionally, BTG identified further relevant cost items in the work-up procedure, which increased the cost to £860.32 per work-up. The company assumed that the resources required for the work-up associated with TheraSphere, SIR-Spheres and QuiremSpheres would be the same.

Costs relating to the administration of the SIRT work-up and the SIRT procedure were based on NHS Reference Costs 2017/2018,[103] and the cost of each SIRT therapy was assumed to be £8,000 per procedure. Further details are provided in Appendix 13.15, where Table 60 summarises the assumptions and costs of the SIRT work-up procedure, and Table 62 summarises the associated unit costs.

Treatment costs of CTT

Each patient in the TACE and TAE arms was assumed to have three initial treatments in their respective arms, whilst patients in the DEB-TACE arm had 1.5 initial treatments. The unit cost and the frequency of their use was informed by clinician input.

The cost of administration involved in each CTT was assumed to be captured in the HRG code for the embolisation procedure (£2,790, NHS Reference Costs 2017-2018, HRG code YR57Z).

Second-line treatment

After patients move into the pharmacological management health state, they were assumed to receive sorafenib (33% of patients) or BSC (67% of patients). Patients remain in this state until death. The unit cost of sorafenib was obtained from the BNF, with the total per-cycle cost estimated assuming a posology of 400mg twice daily. It was assumed that sorafenib would not be associated with administration costs and that patients would orally self-administer this treatment. It was unclear whether the costs of treating adverse events associated with sorafenib treatment were captured within the model. Costs associated with BSC were assumed to be captured within the health state resource use.

Health state resource use

Due to an absence of evidence from published literature for resource use for the CTT-eligible health states, expert opinion was sought from the Christie NHS Foundation Trust, Manchester (see Table 63 in Appendix 13.15 for a summary of health state costs). These consisted of the following:

- Physician visits (oncologist, hepatologist, Macmillan nurse, gastroenterologist, radiologist, clinical nurse specialist, palliative care physician)
- Laboratory tests (alpha-fetoprotein (AFP) test, liver function test, INR, complete blood count, biochemistry, endoscopy
- Radiological tests (CT scan, MRI scan, ultrasound scan)
- Hospitalisation
- Hospital follow-ups (specialist, GP, nurse)
- Transplant aftercare (immunosuppressants)

Unit costs for each of these items, plus the cost of a transplant procedure, were obtained from national sources.[102, 103]

The AG requested additional details of how these resource use estimates were obtained. BTG clarified that resource use estimates were provided by a single clinical expert whose role is consultant interventional radiologist at a centre in the UK that uses SIRT. Opinion was elicited via an unstructured phone conversation, the estimates were given verbally and were entered directly into the model; no transcripts of this conversation were collected. As such, the AG cannot verify the estimation of the resource use inputs.

Additional one-off costs were applied at the point of progression, relating to laboratory and radiological tests (estimated as £95.32 in total, and were obtained from TA555).[36]

Palliative care costs

The company's model also included a cost of £8,191 to account for costs of palliation at the end-of-life, which was applied upon death. This was derived from a joint Nuffield Trust and Marie Curie report into end-of-life cancer care and inflated to 2017/2018 prices.[125]

6.3.3.3 Model results

Base-case results

Results of the base-case analysis are summarised in Table 24. In the company's main analysis, TheraSphere, SIR-Spheres and QuiremSpheres were associated with virtually identical numbers of QALYs, due to the assumption of equal efficacy between interventions. They were all estimated to have similar total costs, with TheraSphere estimated to have marginally lower costs due to lower rates of adverse events requiring treatment.

Similarly, for TACE, DEB-TACE and TAE, marginal differences were observed due to assumed differences in adverse event rates and unit costs of treatment.

DEB-TACE was estimated as being the strategy with the lowest costs due to the fewer procedures required, and was used as the reference treatment in the incremental analysis. This resulted in an ICER of £24,647 for each of the SIRT technologies versus DEB-TACE, and TACE and TAE being dominated versus DEB-TACE.

The probabilistic version of the model produced similar results, with the ICER relative to DEB-TACE of £25,052 per QALY.

Table 24: Results of the CTT-eligible population analysis

Treatment	Total costs	Total QALYs	Δ Costs	Δ QALYs	ICER
Probabilistic analysis (estimated by AG)					
DEB-TACE	£39,505	1.377	-	-	-
TAE	£43,634	1.384	£4,129	0.007	£621,795
TACE	£43,525	1.373	£4,020	-0.004	Dominated
TheraSphere	£57,334	2.089	£17,829	0.712	£25,051.73
QuiremSpheres	£57,395	2.092	£17,890	0.715	£25,032.69
SIR-Spheres	£57,415	2.093	£17,910	0.716	£25,008.53
Deterministic analysis					
DEB-TACE	£39,435	1.393	-	-	-
TAE	£43,470	1.392	£4,035	-0.001	Dominated

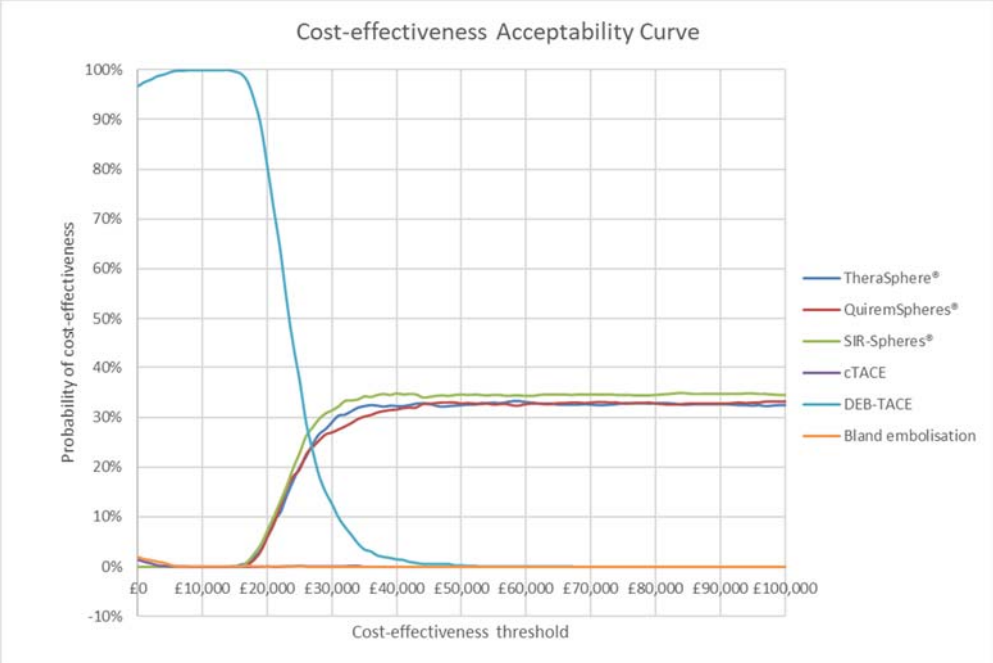
TACE	£43,488	1.393	£4,053	0.000	Dominated
TheraSphere	£57,338	2.119	£17,903	0.726	£24,647
QuiremSpheres	£57,361	2.119	£17,925	0.726	£24,647
SIR-Spheres	£57,361	2.119	£17,925	0.726	£24,647

Probabilistic results

Uncertainty surrounding model parameters was explored using scenario analyses and PSA, the executable model also included a number of DSA which were not presented in the CS or appendices. The company's probabilistic results were estimated from 1,000 Monte Carlo samples and were presented using CEAC and cost-effectiveness acceptability frontiers (CEAFs) only with no ICERs from the probabilistic model presented in the CS.

Figure 11 presents the results of the company's probabilistic sensitivity analysis. Up to a threshold of approximately £25,000 per QALY, the company model estimated the treatment with the highest likelihood of being cost-effective to be DEB-TACE. After this point, the probability of being cost-effective was highest for the three SIRT therapies, which had similar probabilities of cost-effectiveness.

Figure 11: Cost-effectiveness acceptability curve (CTT-eligible population) (Figure O1 in BTG CS)



Scenario analyses

Table 25 presents the results of the company's scenario analysis. The most influential parameters, of those assessed by the company, relate to the proportion of patients who transition to resection, and the proportion of patients who were downstaged after treatment with TheraSphere. While the amount by which the proportion of patients was varied was arbitrary, and the ICER does not specifically represent a potential upper bound, this analysis showed that the model was most sensitive to this parameter.

Table 25: Results of scenario analyses in the BTG CTT-eligible model (adapted from Table 6-20 in BTG CS)

Scenario	ICER
CTT-eligible scenarios - base-case	**£24,647**
50% discount on TheraSphere	£18,039
TheraSphere treatment free when more than one treatment needed	£21,676
50% of downstaged patients transition to resection rather than transplant	£31,112
Removal of SIRT work-up costs	£23,773
Alternative utility values	£25,003
Alternate downstaging rates for SIRT (relative efficacy of SIRT decreased vs. TACE/TAE)	£38,203
Alternate downstaging rates for SIRT (relative efficacy of SIRT increased vs. TACE/TAE)	£20,561
Alternate post-transplant mortality rates (increased)	£26,744

6.3.3.4 AG critique of the BTG CTT-eligible model

Downstaging and role of transplant in the UK

The company assumed that patients who are successfully downstaged become eligible for transplantation, and that no patients receive any other kind of curative therapy including resection or ablation. This was justified on the basis that few patients are expected to receive these latter therapies. The company provided two sources in support of this assumption: in these studies, of the patients who received radical curative therapy after downstaging, the proportion that received resection ranged from approximately 5.9%[126] to 10%.[115]

Clinical advice received by the AG also suggested that at least a proportion of these patients would go on to receive resection rather than transplant. This AG therefore considers the assumption that all patients will go on to receive transplant to be unreasonable and likely to favour SIRT, as outcomes following resection have been demonstrated to be associated with poorer outcomes (recurrence and survival) than those following transplantation.[119] The relevance of downstaging to transplant in UK practice is also unclear. Eligibility for transplantation in the UK has historically been defined by the Milan criteria,[127] and only recently has a service evaluation been introduced where eligibility criteria

have expanded to permit downstaged patients to receive transplant.[128, 129] Further, at the time of writing, this study has only recruited a small number of patients, and does not represent established national practice.

Modelling of pharmacological management

The progression status of patients in the pharmacological management health state was estimated as a 50:50 average of patients in pre-progressed and post-progression. This split is arbitrary and unlikely to accurately reflect the actual proportion of patients in each health state. A visual comparison of the PFS and OS extrapolation plots for sorafenib and BSC in the SHARP study appears to show a greater proportion of time is spent in the post-progressed health state, a more reasonable estimate of the ratio of patients in each group is likely to be 33:67. Further, given the PFS and OS plots for SHARP are available, time in state could have been explicitly modelled avoiding the need for such an assumption. The implications of this assumption are important and may lead to overly pessimistic estimates for patients in this health state, as this split is used to estimate utility and cost of active treatment. Based on the 50:50 split assumed, this will tend to overestimate total QALYs as too many patients are assumed to be in the pre-progressed state, as well as overestimating costs as time on sorafenib, where treatment duration is linked to progression.

Exclusion of patients who received SIRT work-up procedure but not treatment with SIRT

An important omission from the economic analysis is the costs and outcomes associated with patients who receive work-up associated with SIRT therapy, but who subsequently do not receive SIRT. These costs should be included in the economic analysis, since work-up costs will be incurred by the NHS if SIRT were to be implemented in practice. Further, patients who fail the work-up procedure are likely to be different from those who go on to receive treatment, as demonstrated in the SARAH trial,[2] where patients who failed work-up had significantly poorer outcomes than those that went on to receive SIRT. Excluding these patients from the analysis therefore underestimates total costs in the SIRT treatment arms and is likely to overestimate treatment benefits.

Modelling of comparator treatments

The company assumed equivalent efficacy between the SIRT treatments due to the paucity of comparative data, which the AG considered reasonable given the lack of data, and similarities in the treatment modalities. However, the BTG CS states that they consider this assumption to be conservative, and that it might be expected that TheraSphere would provide superior outcomes. The AG notes that no plausible clinical argument or clinical evidence was provided in support of this statement.

Downstaging outcomes

The key benefit of SIRT in this analysis was through the increased proportion of patients who achieved downstaging after treatment, which indirectly lead to increased numbers of patients receiving curative therapy. The probability of downstaging was estimated using data from a study of TheraSphere and TACE patients.[46] The AG had concerns relating to the robustness and generalisability of this study. The study was retrospective and single-centre, with non-randomised cohort arms, which could have left it open to confounding bias. Further, the study retrospectively identified patients that were most likely to be downstaged to curative therapies and therefore the modelled population is not representative of the broad CTT-eligible population in the scope of the analysis, and predicts higher rates of downstaging than would otherwise be observed for this broader population.

There are also issues regarding the generalisability of the downstaging criteria applied in the Lewandowski study which were based on tumour dimensions only. UK criteria, used in the UK service evaluation of downstaging however, also takes into account AFP level.[128] This may mean that there are differences between these patients and those considered eligible for transplant in the NHS.

To estimate the transition of patients to the pre-transplant wait list, the observed probability of downstaging from the Lewandowski study was applied to the proportion of patients who remained in the "watch and wait" health state, rather than being applied directly in the model. As a result, this method underestimated the proportion of patients who were downstaged: for TheraSphere, the model predicted that 48% patients were downstaged, compared with 58% reported by Lewandowski, and for TACE, the modelled versus observed proportion who were downstaged was 26% vs 35%.

The company assumed that the mortality rate of patients in the "watch and wait" health state was equivalent to that of the pre-transplant mortality rate, citing a lack of data to model this specific outcome. However, the Lewandowski study reported mortality rates that were censored to curative therapies, and it was unclear why these were not leveraged in the model. The same mortality rate was applied to both treatment arms, thereby assuming that the only impact of treatment on mortality is through the bridging of patients to transplant. Further, the data used to estimate pre-transplant mortality was from a cohort of patients[118], of which only a proportion had HCC. The Lewandowski study also reported progression outcomes, which again were not used in the economic analysis.

The use of different sources for downstaging, progression and mortality outcomes also means that the evidence were derived from very different study populations which lead to a lack of internal consistency, and made it more difficult to validate the predictions of the model.

Transplant wait list outcomes

The data source used to estimate the time spent on the transplant wait list was estimated for a cohort of patients not specific to HCC. Patients on the transplant wait list are prioritised by their MELD score;[130] however, the presence of HCC adds "exception points" to MELD, meaning that the wait list time is generally shorter for HCC patients. The AG obtained data from a report on the one-year outcomes following the introduction of the National Liver Offering Scheme, which was implemented on 20 March 2018. The median waiting time under the old offering scheme may not accurately reflect how long patients may wait under the new offering scheme. The median waiting time to transplant for HCC patients who received a transplant between 20 March 2018 and 19 March 2019 was 49.5 days, which is substantially lower than the value for the overall cohort.

The company provided an incomplete reference on the source of the data used to estimate the transition to pharmacological management, and so it was not possible to comment on the suitability of this source. In an interim report on a service evaluation of transplantation following downstaging of HCC patients in the UK,[129] of 27 patients enrolled in the programme to date, only one was removed from the wait list due to the deterioration of their condition. This provides a much lower estimate of drop out compared to that estimated by the company, although the AG acknowledges that it is based on a smaller subset of patients.

The AG questions whether it is appropriate to apply the same transition probabilities and mortality rate to patients regardless of their initial treatment; however, the AG is not aware of any directly applicable evidence for a differential rate. There are many factors that determine the rate at which patients receive transplant; some of these will not be treatment-dependent, including the availability of donor grafts, and some are dependent on treatment. Previous studies of SIRT and CTT with intent to downstage have demonstrated differential outcomes of transplantation and progression between treatment arms; while these are based on very small patient numbers, there does appear to be a small benefit in favour of SIRT.[8, 52] While TheraSphere and TACE were given as downstaging rather than bridging therapies in the Lewandowski study and so not directly applicable to outcomes for patients on the transplant waitlist, overall survival censored to curative therapies was also significantly different between arms in favour of SIRT, particularly after 2 and 3 years. Similarly, the rate at which patients receive curative therapy following downstaging is also likely to differ between arms, as evidenced in Lewandowski *et al*. As such, the AG considers it unlikely that outcomes would be equivalent across different treatment modalities, although it is not possible to estimate directly without estimates of survival conditional on downstaging.

Pharmacological management

Outcomes for patients in the pharmacological management health state were based on the BSC arm of the SHARP trial,[68] justified by the company as "to not bring the benefit of a particular HCC treatment into the model, as patients in the pharmacological management health state would be on different treatments". This is not representative of patients within this health state, as a proportion of these patients would receive further active therapy, assumed by the company to be sorafenib. Since patients receiving sorafenib experience better outcomes than patients on BSC (as demonstrated by a HR of 0.69 for OS in SHARP), this approach underestimates survival for patients in this health state. A more accurate approach would be to calculate outcomes separately for sorafenib and BSC and then weight according to the proportion of patients in the health state over time.

Further, the SHARP trial is unrepresentative of the patients who would receive BSC in this population for a number of reasons. Approximately 50% of patients in SHARP had extrahepatic spread, and would thus be contraindicated for SIRT treatment. A subgroup analysis of SHARP patients demonstrated that the sorafenib treatment effect was higher in patients with no extrahepatic spread (HR of 0.55 compared with 0.69 in the ITT population). Data from REFLECT[32] which compared lenvatinib to sorafenib also demonstrated that the prognosis of patients with extrahepatic spread is worse than in those without: in the ITT population, the median OS was 12.3 months, compared with 18.0 months in a population with no extrahepatic spread. Additionally, the SHARP trial only enrolled patients who had not received previous treatment with systemic therapy, so BSC patients in SHARP do not represent the patients in the pharmacological management health state who previously received TACE or SIRT. The AG was advised that patients who present with HCC and are eligible for sorafenib are typically associated with a more rapidly progressing form of the disease and will have a higher mortality rate.

As a result, the cost-effectiveness analysis is biased in favour of SIRT through the selection of unrepresentative comparator data. The use of this data from SHARP underestimates survival in the pharmacological management health state, thereby further inflating the relative treatment effect of SIRT, as fewer patients enter this health state than those on other therapies.

Post-transplant outcomes

The AG has concerns about the applicability of the sources used to estimate mortality following liver transplantation, and considers it uncertain whether the assumed treatment pathway is reflective of clinical practice.

Firstly, the dataset used to estimate long-term mortality after transplant is not specific to patients with HCC. Patients with HCC are at risk of tumour recurrence, which is linked to increased mortality.[119]

This can be illustrated by a comparison of survival in the general liver transplant population and in an HCC population. The AG obtained a HCC-specific dataset of survival outcomes for liver transplant recipients in the UK since 1994.[131] In this dataset, patients with HCC (restricted to over 60 years of age as a proxy for intermediate HCC patients) had a five year survival of 71%. This was lower than those in the general liver transplant dataset, whose five-year survival was estimated as 81%. As such, benefits estimated by the company model are likely to be overestimated.

By excluding tumour recurrences, the treatment pathway is also misrepresented by the model. Both the Bellavance and Lewandowski studies report on recurrences that occur after transplantation: approximately 20% in the Lewandowski study and 14% of patients in the Bellavance study experienced recurrence after transplantation, with a one-year relapse-free survival rate of between 73% and 89%. Additionally, the AG found that, in their analysis of the HCC-specific transplant dataset, over 10% of transplant recipients in the UK in this population experienced a recurrence within the first five years post-transplant. The patients who experience a recurrence are at an elevated risk of death,[119] and these patients often experience a reduced quality of life and additional treatment-related costs.[132] By excluding recurrence after transplant, the model overestimates the QALYs and underestimates costs generated for transplant recipients, which biases the results in favour of the SIRT arm due to a higher proportion of patients being downstaged.

Health-related quality of life

The total number of QALYs generated by the model are likely to be underestimated, due to the source chosen and an error in how age-related disutility was applied.

Health state utility values were estimated from a range of sources, but were primarily based on the NICE appraisal of lenvatinib (TA551),[32] which enrolled patients with advanced HCC, of whom approximately 60% had extrahepatic spread. This population therefore had more advanced disease and does not reflect the model population of intermediate HCC patients. As such, the utilities drawn from TA551 are likely to underestimate the quality of life for a CTT-eligible population, and disadvantages any treatment arm associated with increased life-years.

The AG also considers that the implementation of age-related disutilities in the model was incorrectly implemented, though the company contend that the application was appropriate. This "error" impacts upon all health states, and results in patients experiencing much lower utilities than observed in the cited sources. In the company's model, the decrement associated with aging is estimated by estimating an absolute utility decrement for each health relative to full health (i.e. 1 minus the reported health state utility) and then subtracting this decrement from the age- and gender-adjusted population norm from Kind *et al*.[124] For example, as patients enter the model at age 65, the age-

adjusted utility started at 0.78, and the literature-derived absolute utility for "watch and wait" patients was 0.75.[32] This meant the age-adjusted utility for patients in the "watch and wait" health state was 0.53 (0.78-0.25). The application of age-adjusted utilities in this way is inappropriate and ignores the fact that each health state utility is derived from an age-appropriate source, and thus already accounts for any age-related decline in HRQoL. Further, this method is inconsistent with previous TAs[133-135] in which age related disutilities have been applied, where age-related decrements are applied as a multiplier to health state utilities rather than as an absolute decrement.

Resource use estimates

Resource use was estimated in the model based on feedback from a single clinician at a centre in the UK that uses SIRT. As the company could not provide details of the questionnaire or transcript of the interview, it has not been possible to verify how these data were estimated. As such, there are a number of uncertainties regarding which treatment costs are included, such as adverse events relating to subsequent therapy (sorafenib) or to transplant, or whether any bridging therapy was provided for patients on the transplant wait list.

The company's clinical expert advised that TACE and TAE patients had around three initial treatments in their respective arms, whilst patients in the DEB-TACE arm had 1.5 initial treatments. As described in Section 6.3.1, there is apparent variation in the number of treatments that patients receive in practice, with values for DEB-TACE identified between 1.43 and 2.83 per patient and between 2.5 and 3.03 for TACE patients. The uncertainty in these numbers were not explored by the company. By implementing a single embolization cost for each CTT procedure, the company also did not explore any differences in the length of hospital stay between the different CTT treatments.

A proportion of patients in the pharmacological management health state receive sorafenib. This was estimated using data obtained from a survey of clinicians: as there were limited details provided on how the proportion was estimated, the underlying assumptions could not be validated. It appears that the cost of sorafenib was applied for the time that patients were in the pre-progression health state; however, this would overestimate the cost of treatment, since mean time on treatment with sorafenib is less than mean time to progression.[31] The analysis also excludes patients who receive lenvatinib instead of sorafenib, and the proportion of patients who progress on sorafenib and receive subsequent treatment with regorafenib; clinical advisors to the AG suggest this would be approximately 20% of patients.

The company assumed that the work-up procedure for each SIRT would be associated with the same resource use. This underestimates the costs for QuiremSpheres, as the use of QuiremScout is required and is associated with an additional procurement cost.

6.3.4 BTG submission – CTT-ineligible analysis

The second model submitted by the company assessed the incremental cost-effectiveness of SIRT therapies compared with systemic therapy for the treatment of HCC in patients ineligible for TACE. The SIRT therapies assessed in this analysis were TheraSphere, SIR-Spheres, and QuiremSpheres. The systemic therapies assessed were sorafenib, lenvatinib and regorafenib. Clinical inputs in the model were drawn primarily from an NMA of comparative studies and a single arm Phase 2 study of TheraSphere.[136] The scope of the company's model is summarised in Table 26. The time horizon considered in the model is 20 years and adopts a NHS and PSS perspective in line with the NICE reference case. Costs and health benefits in the model were discounted at a rate of 3.5%. The price year used in the model was 2017/2018. The BTG CS states that the model aimed to consider patients who are considered to have later stage HCC, which the company defines as patients who are either ineligible for, or have previously failed, TACE.

Table 26: BTG model scope (CTT-ineligible population)

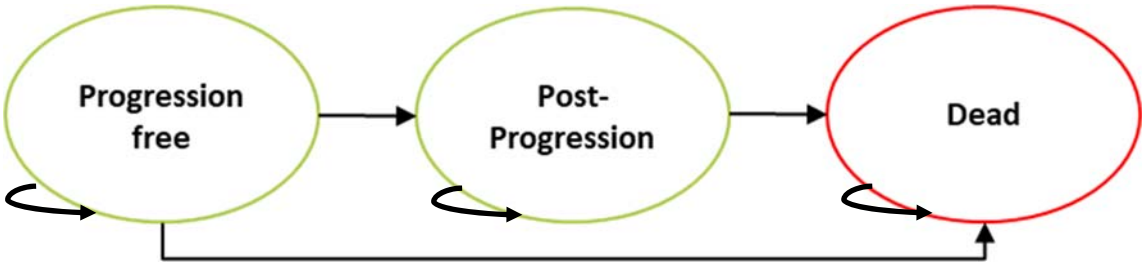
Model Component	Description
Population	The patient population that is the focus of the cost-effectiveness analysis includes patients matching the following criteria: • People with latter stage disease who are ineligible to receive CTT.
Intervention	Selective internal radiation therapies (SIRT): • TheraSphere • SIR-Spheres • QuiremSpheres
Comparators	Established clinical management without SIRT (including but not limited to target chemotherapy). The target chemotherapies are: • Sorafenib • Lenvatinib • Regorafenib
Analysis type	Cost-effectiveness (cost-utility) analysis
Economic outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Time horizon	20 years
Discount rate	Annual rate of 3.5% applied to costs and QALYs

6.3.4.1 Model structure

The model is a cohort-level partitioned survival model, which includes three health states: (i) progression-free, (ii) post-progression and (iii) dead. The model does not allow for downstaging to curative therapies. Figure 12 presents an overview of the adopted model structure. The proportion of patients in each health state is determined as a function of the TTP and OS. The proportion of patients in the progression-free health state was based on the TTP curve, while the post-progression state was

estimated as the difference between the OS and TTP curves. The proportion of patients in the dead state was determined by the OS curve.

Figure 12: BTG CTT-ineligible model structure (BTG CS, Figure 6-3)



For OS, the estimated treatment effect was drawn from a network meta-analysis of studies identified in the presented systematic review. This was then applied to parametric survival models fitted to Kaplan-Meier data from a single arm Phase 2 trial of TheraSphere.[136] A Weibull function was selected as the most appropriate survival model. Time to progression was modelled based on a naive comparison of relevant TTP data, and was assumed to follow an exponential survival function.

Health state utilities in the model are primarily determined by the presence/absence of disease progression, with values based on those used in TA551. The model also separately accounts for loss of QALYs as a result of AEs. The model attempts to account for the impact of aging by implementing an age adjustment factor, however, this was implemented incorrectly (see below for further discussion).

The model includes the following resource costs: (i) procedural costs relating to the administration of SIRT, (ii) drug acquisition and administration costs associated with systemic therapy, (iii) monitoring and disease management costs, (iv) costs associated with AEs, and (v) palliative care costs.

The model employs the following structural assumptions:

- Health-related quality of life is determined according to the presence/absence of disease progression and the therapy received.
- Patients were not permitted to be downstaged to receive curative therapy, all patients were therefore assumed to receive palliative care.
- Time to progression for TheraSphere was modelled using an exponential function fitted to a single arm study, comparator TTP was modelled based on median PFS extracted from trial and observational evidence identified as relevant by the company.
- Overall survival was modelled using a Weibull function fitted to a single arm study of TheraSphere with an HR derived from an NMA to determine OS for other therapies.

- Adverse events are assumed to affect both costs and HRQoL.
- Palliative care costs are assumed to be incurred only during the final month of life.

6.3.4.2 Evidence used to inform the company's model

Overall survival

Overall survival for patients receiving TheraSphere was based on a single arm Phase II study of 52 patients with intermediate and advanced HCC.[136]

The following standard parametric survival models were fitted to the observed data - Weibull, log-normal, log-logistic, exponential, and gamma functions. Assessment of the most appropriate parametric extrapolation was made with reference to statistical goodness-of-fit and clinical plausibility of survival estimates. The log-logistic and log-normal curves were eliminated on this basis, as they predicted that a small proportion of patients will not die within the time horizon of the model. The Weibull function was selected for the base-case analysis, no other extrapolations were explored in scenario analysis.

Estimation of overall survival for comparator therapies was based on an NMA of studies identified in the presented clinical effectiveness review. The NMA drew evidence from RCTs, as well as non-comparative studies. The primary NMA reported better survival for TheraSphere compared to sorafenib (HR: [redacted], 95% CrI: [redacted]), although not statistically significant.

Progression-free survival

Modelling of TTP for TheraSphere was implemented by fitting standard parametric functions to reported KM data from the same Phase II study used to model OS.[136] TTP was defined from first SIRT therapy to first progression at any site. TTP therefore excluded mortality events, as the model only permits death following progression. As with OS, standard parametric curves were fitted to available KM data and the exponential function was selected as the most appropriate survival model based on the clinical plausibility of predicted outcomes. No other parametric functions were explored in the presented scenario analyses.

Due to inconsistent reporting of TTP in the studies identified in the systematic review, an NMA for TTP was not feasible. Time to progression outcomes for comparator therapies were therefore based on a naive comparison, generated via median TTP and PFS data from relevant sources, which were converted to survival curves by assuming TTP followed an exponential function. Median TTP for SIR-Spheres was based on a retrospective cohort study of patients who received SIR-Spheres, [50] with TTP assumed to be the same for QuiremSpheres due to a lack of appropriate data. Median TTP for sorafenib was based on a weighted average of values reported in TA474,[31] TA551,[32] and a

retrospective cohort study.[50] Lenvatinib TTP was sourced from TA551,[32] while median TTP for regorafenib was sourced from TA555.[36] Note all values sourced from TAs were based on PFS not TTP.

Health-related quality of life

The primary source of utility data used by BTG was TA551, ,[32] which drew evidence from the REFLECT trial[23] comparing lenvatinib with sorafenib which collected EQ-5D-3L values from participants. The values used assume no differences in HRQoL between treatment arms, but do not attempt to account for differences in HRQoL as a result of AEs. This was done by applying a one-off utility decrement in the first cycle of the model which was estimated by applying a 0.012 decrement per grade 3/4 event. Note the BTG CS erroneously reports that a 0.014 decrement was applied in the model and miscalculates the decrement to be applied in the executable model.

In addition to the above, adjustments were also made to the health state utilities to account for the impact of aging. This is done by applying a decrement to every model cycle. The decrement applied was estimated by subtracting one from the age and gender adjusted population norm. Note the BTG CS erroneously reports the decrements applied as 0.26 for the progression health state and 0.32 for the progressive disease health state, when the model applies a common decrement to both health states which changes over time to reflect the increased age of the cohort. General population utility norms were sourced from Kind *et al*.[124] Utility values applied in the base-case analysis along with utility decrements are reported in Table 64 Appendix 13.15.

SIRT procedure costs

See review of CTT-eligible population model (Section 6.3.3.2) for details of SIRT procedure costs.

Drug acquisition costs - systemic therapies

Drug acquisition costs for sorafenib, lenvatinib and regorafenib were taken from the BNF. Respective dosing was 800mg, 12mg and 160mg per day. Dosing was based on those recommended for HCC patients, described in their respective EMA summary of product characteristics (SmPC). Duration of systemic therapy was based on progression with patients assumed to continue systemic therapy until either progressive disease or death. Table 65, Appendix 13.15 summarises the drug acquisition costs applied in the model.

Subsequent treatments

A proportion of the patients receiving SIRT were assumed to receive sorafenib therapy following SIRT, with patients assumed to receive sorafenib after cycle 1 until disease progression or death. In the base-case analysis, the proportion of patients assumed to receive sorafenib was 33% based on ‘data on file’. Patients not receiving concomitant sorafenib were assumed to receive BSC. No

subsequent therapies were modelled following disease progression in either model arm (SIRT or systemic therapy).

Health state costs

Resource use estimates were based on a survey of clinical experts conducted to inform resource use in the appraisals TA189,[137] TA474,[31] and TA551.[32] This included physician visits, laboratory and radiological tests, and hospital stays. Unit costs were derived from TA189 updated using NHS Reference Costs 2017/18.[103]

In addition to the above, a one-off cost was applied upon treatment progression based on the costs applied in TA551.[121] This comprised additional laboratory and radiological tests.

Total costs by health state are reported in Table 66, Appendix 13.15, along with a summary of one-off progression costs.

Adverse event costs

Unit costs associated with AEs were drawn from NHS reference costs 2017/2018 and are summarised in Table 68, Appendix 13.15. No information or justification was presented with regards to how the specific costs used were selected.

Palliative care costs

The company's model includes a cost of £8,191 to account for costs of palliation at the end of life. This was derived from a joint Nuffield Trust and Marie Curie report into end of life cancer care and inflated to 2017/2018 prices. This cost was applied upon a patient's death and was applied for all modelled interventions.

Model results

The headline results presented in the BTG CS are based on the deterministic version of the model. Uncertainty surrounding model parameters was explored using scenario analysis and a PSA. The executable model also included a number of DSA which were not presented in the CS or appendices. The company's probabilistic results were estimated from 1000 Monte Carlo samples and were presented using CEAC and CEAFs only, with no ICERs from the probabilistic model in the CS.

Table 27 presents the company's base-case estimates of cost-effectiveness using the corrected version of the model at the list price for sorafenib, lenvatinib and regorafenib. Based on the probabilistic version of the company's model, regorafenib was estimated to be the most cost-effective therapy. The results of the fully incremental analysis suggested that SIR-Spheres, QuiremSpheres and lenvatinib were dominated by one or more therapies while sorafenib was extendedly dominated by TheraSphere.

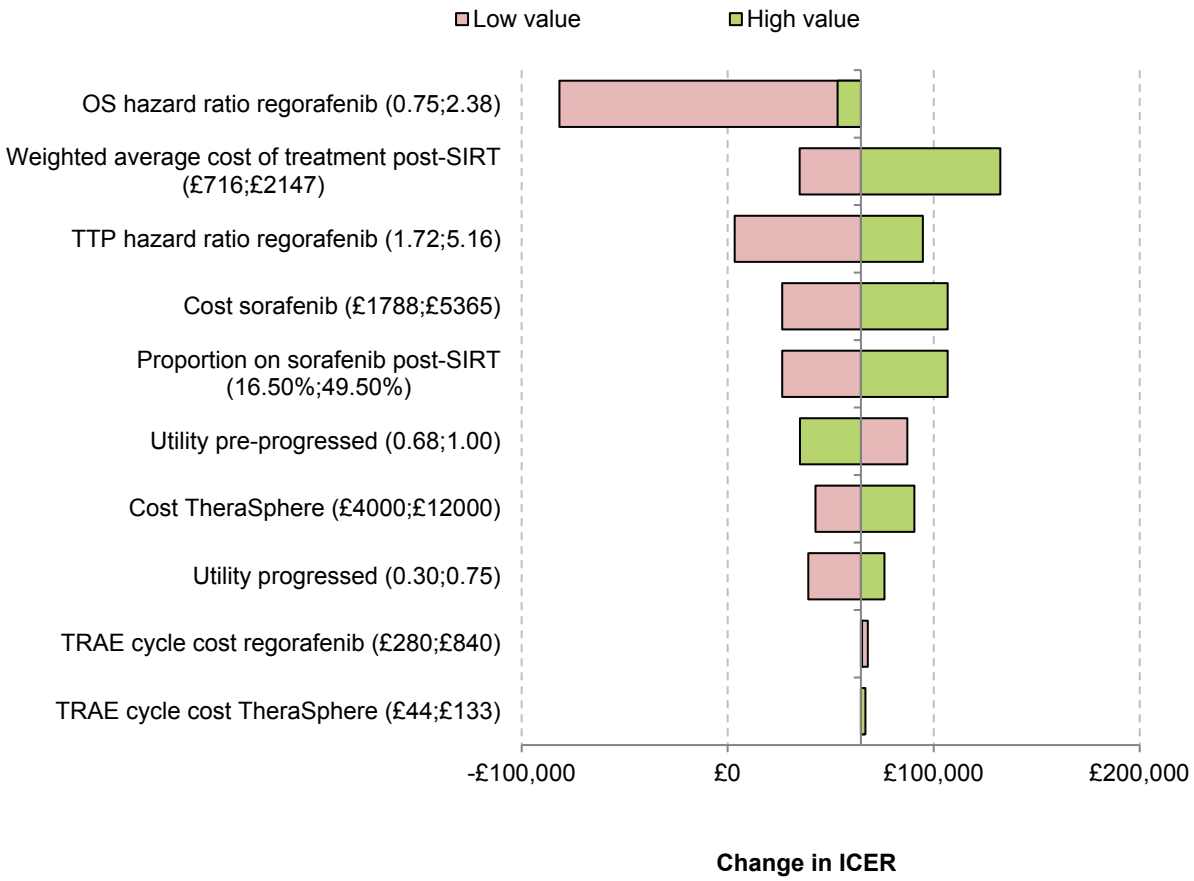
The estimated ICER for TheraSphere compared with regorafenib was £69,070 per QALY and estimated that TheraSphere generates an additional 0.185 QALYs at an additional cost of £12,778. The deterministic version of the model produces similar results with an ICER relative to regorafenib of £66,624 per QALY.

Table 27: Summary of base-case results BTG CTT-ineligible population

	Absolute		**Incremental (relative to regorafenib)**		
	QALYs	**Costs (£)**	**QALYs**	**Costs (£)**	**ICER (£)**
Probabilistic model (calculated by ERG)					
TheraSphere	0.681	£49,574	0.185	£12,778	£69,070
QuiremSpheres	0.466	£37,446	-0.030	£650	Dominated
SIR-Spheres	0.465	£37,406	-0.031	£610	Dominated
Sorafenib	0.496	£38,977	0.000	£2,181	Ext dominated
Lenvatinib	0.526	£61,282	0.030	£24,486	Dominated
Regorafenib	0.496	£36,796			
Deterministic model					
TheraSphere	0.695	£49,984	0.200	£13,331	£66,624
QuiremSpheres	0.470	£37,496	-0.025	£843	Dominated
SIR-Spheres	0.470	£37,496	-0.025	£843	Dominated
Sorafenib	0.500	£39,059	0.005	£2,406	Ext dominated
Lenvatinib	0.530	£62,647	0.035	£25,995	Dominated
Regorafenib	0.495	£36,653			

Figure 13 presents the results of the deterministic sensitivity analysis generated by the AG. The most influential parameters (of those assessed by the company) relate to OS hazard ratio for regorafenib and the proportion of patients assumed to go on to receive post SIRT sorafenib. Additional scenario analysis presented by the company showed that the estimated ICER was influenced significantly by assumptions made about post-SIRT therapy. In the presented scenario analysis in which no concomitant Sorafenib was assumed, TheraSphere was estimated to be the most cost-effective intervention with a deterministic ICER of £5,870 per QALY.

Figure 13: BTG deterministic sensitivity analysis – Tornado diagram (from BTG company model)



The AG questioned the face validity of the utility values applied, and were concerned that the company had made a calculation error with respect to the calculation of the utility decrements. After clarification from the company, BTG confirmed that the utility decrements applied in the model were as intended by the company, see below for further critique of the utility values applied.

6.3.4.3 Critique of the BTG CTT-ineligible model

Inappropriate inclusion of regorafenib as a comparator

The base-case analysis presented in the BTG economic analysis includes three systemic therapies sorafenib, lenvatinib, and regorafenib. The AG is of the view that regorafenib should not have been included as a comparator, as it is used only as a second-line therapy following sorafenib. This is stated in the SmPC for regorafenib and NICE's recommendation for regorafenib which restricts use to patients who have been previously treated with sorafenib. The AG considers it entirely reasonable to model subsequent regorafenib use following sorafenib, but it should not have been directly compared to SIRT and the other systemic therapies.

Work-up without SIRT procedure

An important omission from the BTG economic analysis is the costs associated with patients who received work-up but did not continue on to the SIRT procedure. In the SARAH[2] and SIRveNIB[3] trials, 18.6% and 28.6% of patients respectively received work-up but did not continue on to receive SIRT. The AG considers the cost of patients who do not proceed to SIRT treatment important, as they comprise part of the incremental costs of implementing SIRT n the NHS. The AG further notes that many of these patients will receive other active therapies instead of SIRT, and it is therefore appropriate to model the associated costs and outcomes. For example, in the SARAH trial[2] 62% of work-up failures went on to receive sorafenib. The AG therefore considers the costs associated with the administration of these alternatives should also be included in the economic analysis. The AG also notes that the clinical effectiveness data used to populate the model were based on the ITT population, and therefore the clinical outcomes of these work-up failures are implicitly included. This is inconsistent with BTG's stated position that only patients receiving therapy were considered.

Network meta-analysis and estimation of relative Overall Survival benefits

BTG conducted a network meta-analysis to compare TheraSphere to sorafenib for the treatment of unresectable HCC patients. Seven studies formed the primary network, which included two RCTs, one prospective study and four retrospective studies. There are differences in the studies included in the NMAs conducted by BTG and the AG. The BTG network only included studies conducted outside of Asia, due to known differences in both aetiology and treatment patterns in Asian populations. The AG also identified additional studies which the company did not include or identify in their systematic literature review [18]. Unlike the AG, the company did not split the NMA into different populations of patients with differing stages of HCC disease. Therefore, the baseline BCLC stage, Child-Pugh status, and the proportion of patients with PVT differed across studies. However, the population in the primary network was mostly advanced stage HCC patients.

The validity of results from the NMA relies on the quality of the studies that make up the evidence base. However, there are considerable concerns regarding the quality of the prospective and retrospective studies. The prospective observational study Woodall *et al.*,[14] which compared TheraSphere vs BSC, which was excluded from the AG NMA, presented significant baseline imbalances and evidence of selection bias, as patients who failed to meet the pre-treatment TheraSphere requirements formed the 'no treatment' arm. Additionally, the retrospective studies [19, 49, 50] were all associated with a high risk of bias as there are significant baseline imbalances, unclear reporting of blinding and missing outcome data, and were excluded from the AG's primary NMA for these reasons.

While the NMA reports better survival for TheraSphere compared to sorafenib, this appears to be on the basis of the inclusion of a particular retrospective study, Biederman *et al.*[19], which reports a very strong treatment effect on overall survival with TheraSphere compared to SIR-Spheres (HR: 0.40, 95% CrI: 0.20-0.78). As discussed earlier, the four retrospective studies (including Biederman *et al.*) and the prospective observational study are poor quality and have a high risk of bias, which reduces the reliability of the NMA results.

Limited exploration of uncertainty surrounding survival functions

The BTG CS does not include any consideration of the uncertainty surrounding the range of potentially plausible survival functions for OS. While a number of parametric functions were fitted to the available data for OS, the impact of alternative functions was not explored in the company's presented scenario analyses. Furthermore, there is no functionality within the presented executable model to implement alternative survival functions.

Omission of downstaging

The AG notes that the BTG economic model did not consider the possibility that patients may be downstaged to receive curative therapy. As stated in relation to the Sirtex CTT-ineligible model, the relevance of downstaging in an advanced HCC population is unclear, with the AG's clinical experts suggesting that this would be a very rare occurrence in UK practice. However, downstaging was observed in a small number of patients in the SARAH trial,[2] and as such the potential benefits of downstaging represent an important uncertainty. Therefore, while the AG recognises that the inclusion of downstaging in the company's base-case may be inappropriate, this uncertainty should have been explored in scenario analysis.

Modelling of progression-free survival

The BTG company submission states that it was not possible to obtain estimates of relative PFS from the NMA, and therefore PFS was based on a naive comparison of reported estimates from studies identified as relevant by the company. The AG considers there to be a number of significant weaknesses in the company's approach, and that the selected median PFS for TheraSphere lacks face validity. While the AG acknowledges that an NMA could not be run for PFS outcomes, based on the studies included in the company's network, the AG does not agree that a relevant network could not have been constructed (see Section 5). Importantly, as reported in Section 4 and 5, there are randomised comparisons of SIRT (SIR-Spheres) and systemic therapies (sorafenib) upon which estimates of median PFS could have been based. The AG would consider such an approach preferable to the company's naive comparison which used populations poorly matched with the modelled population. The AG further notes that this randomised evidence was ignored in favour of studies used in the relevant NICE appraisals which focused on populations including a significant proportion of

patients with extrahepatic spread, and with respect to regorafenib, had already failed previous sorafenib therapy.

Further to the above, the AG also questions the plausibility of the modelled median PFS for TheraSphere. The modelled value of 11 months is 3.5 times longer than the value used for SIR-Spheres (3 months) and longer than the median OS reported in the SARAH trial[2] for both SIR-Spheres and sorafenib. Given the broad clinical similarity between TheraSphere and SIR-Spheres, and the lack of high quality comparative evidence, the AG considers it is unreasonable to assume such a large disparity in PFS.

Dosing and time on systemic therapy

Dosing of systemic therapies in the BTG economic analysis was based on the relevant SmPC with a dose of 800 mg, 12 mg, and 160 mg assumed for sorafenib, lenvatinib and regorafenib respectively. These figures are likely to overestimate the dose received for all three drugs, as dose reductions and interruptions are common in patients receiving systemic therapy, and were observed in all relevant trial data. For example, the mean dose of sorafenib received in the SARAH trial[2] was 648 mg, not 800 mg. The company's model also does not account for the fact that the dosing of lenvatinib is weight dependent, with patients under 60 kg receiving 8 mg daily; 13% of patients in the Western subgroup of the REFLECT trial[23] weighed less than 60 kg.

Time on systemic treatment in the BTG economic analysis is assumed to align with PFS. This is consistent with the SmPC for both sorafenib and lenvatinib, both of which indicate that therapy should continue for as long as clinical benefit is observed, or until toxicity becomes unacceptable. However, sorafenib, lenvatinib, and regorafenib are all associated with significant tolerability issues, which means that many patients discontinue therapy prior to disease progression. This is seen in the pivotal trials, in which time on systemic therapy is always less than PFS. For example, median time on sorafenib in the SARAH trial[2] was 2.8 months while median PFS was 3.7 months. Using PFS as an indicator of treatment discontinuation therefore may produce overestimates of ToT and consequently total drug acquisition costs for sorafenib, lenvatinib, and regorafenib.

Subsequent therapy costs

The BTG economic analysis assumes that a proportion of patients receiving SIRT treatment (TheraSphere, SIR-Spheres or QuiremSpheres) move on to receive subsequent systemic therapy immediately following initial SIRT therapy. These patients are assumed to continue therapy until disease progression. The AG considers the modelling of subsequent therapy in this way to be inconsistent with likely NHS practice and the supporting trial evidence, and that typically initiation of systemic therapy following SIRT would occur following disease progression. The AG acknowledges

that within the SARAH trial,[2] a proportion 11/52 (21%) of patients did receive subsequent systemic therapy prior to progression. However, there is no evidence to suggest that this was initiated immediately following SIRT therapy; indeed, the SARAH and SIRveNIB trial protocols stipulated that further therapy should not commence until disease progression.

A further issue relating to the company's modelling of subsequent therapy is the assumption that patients receiving first-line sorafenib therapy will not receive further active therapy following progression. This is inconsistent with clinical practice where a proportion of patients will receive second line regorafenib as per NICE's recommendations. It is also not consistent with the modelled trial evidence as a proportion of patients in the SARAH and SIRveNIB trials went on to receive subsequent therapy following discontinuation of sorafenib.

Application of age-adjusted utilities

Similar to the BTG economic analysis in the CTT-eligible population, the estimation of age-related disutility was implemented incorrectly, resulting in health state utilities being applied that are inconsistent with values used in previous TAs, as well as values reported in the SARAH trial[2] . For further details of this error see Section 6.3.3.2.

Further to the above, the AG considers age adjustment unnecessary in an advanced population where the majority of patients are dead within 5 years, the application of age adjusted utilities is unnecessary and not in keeping with norms for this type of model.

Calculation errors

A small number of calculations errors were identified and corrected as part of the AG's assessment of the BTG economic analysis. These errors related to;

- The estimation of the comparator TTP which used incorrectly estimated HR;
- The calculation of per cycle mortality and progression which were estimated using monthly cycle, while the rest of the model used a 4 week cycle.

These errors have marginal effect on the reported ICER increasing the deterministic ICER from £64,693 to £66,624 per QALY.

6.3.5 Conclusions from the AG's assessment of the company's economic evidence

Conclusions from the company submissions provided by Sirtex and BTG are below. Please note that Terumo did not submit any economic evidence, and so a critique is not provided.

Sirtex submission – CTT-eligible population

The Sirtex submission included a cost-minimisation analysis (CMA) of SIR-Spheres, TheraSphere, TACE and DEB-TACE in the CTT-eligible population. A cost-utility analysis was not undertaken for the CTT-eligible population due to a lack of comparative evidence available for this group of patients. The CMA considered the costs of initial treatment, hospitalisation and management of adverse events. The company presented a range of scenarios for the costs of each treatment option, using alternative sources and assumptions to provide a range of plausible costs. Rather than selecting a preferred scenario, the company noted that the range of costs associated with CTT, TheraSphere, and SIR-Spheres overlapped, demonstrating the comparability of treatment costs.

The AG considered the presentation of a CMA for this population to be inappropriate and potentially misleading. Such an analysis is only appropriate if there is compelling and unambiguous evidence for equivalent efficacy between interventions. Results of the AG systematic review found very little high quality evidence in this population, and the data identified was not sufficient to demonstrate clinical equivalence or a clinical difference between treatments. A focus on treatment costs only excludes possible important outcomes regarding people who are downstaged after treatment and become eligible to receive curative therapy, or receive subsequent therapy after progression of disease.

Sirtex submission – CTT-ineligible population

The Sirtex submission also included a *de novo* model-based health economic evaluation of SIR-Spheres versus sorafenib in the restricted low tumour burden/ALBI 1 subgroup, for CTT-ineligible patients. An economic analysis for the broader population of patients with intermediate advanced HCC was also presented in scenario analysis. The company's model suggested that SIR-Spheres dominates sorafenib, producing more QALYs at a lower cost. The AG notes several concerns relating to the company's submitted model, in particular (i) the questionable relevance and validity of an analysis based on the low tumour burden/ALBI 1 subgroup, (ii) the relevance and methods used to model the downstaging of patients to curative therapies, (iii) the modelling of OS and in particular the use of data which was not censored for downstaging to curative therapy, (iv) questionable assumptions regarding the modelling of patients who underwent work-up but did not receive SIR-Spheres (v) the number of SIRT treatments received, particularly the assumption that patients with bilobar tumours will have both lobes treated in one session, and (vi) the duration of treatment on subsequent treatment.

Given the consistent direction of bias in the issues described in the sections above, the AG considers it probable that the incremental cost-effectiveness of SIR-Spheres compared to sorafenib is considerably higher than the estimates presented within the Sirtex CS.

BTG submission – CTT-eligible population

For the CTT-eligible population, the BTG submission included a *de novo* model-based health economic evaluation of TheraSphere compared with two other SIRT therapies, SIR-Spheres and QuiremSpheres, and with TAE, TACE and DEB-TACE. The key benefit of SIRT assumed by this analysis was through the increased proportion of patients who achieved downstaging after treatment, which indirectly lead to increased patients receiving curative therapy. These outcomes were based on Lewandowski *et al.* (2016), a retrospective analysis of TheraSphere and TACE in patients identified as being candidates for downstaging. SIR-Spheres and QuiremSpheres were assumed to have equivalent efficacy to TheraSphere, and TAE and DEB-TACE were assumed to be equivalent to TACE.

The model estimated that the cheapest strategy was DEB-TACE, which dominated TAE and TACE. TheraSphere, QuiremSpheres and SIR-Spheres had a probabilistic ICER of £25,052 per QALY gained, compared to DEB-TACE.

The AG notes several concerns relating to the company's analysis, in particular (i) the relevance of downstaging to transplant in this population to UK clinical practice and the use of a non-HCC specific dataset to model outcomes in these patients, (ii) the failure to properly account for patients who fail the work-up procedure and do not go on to receive SIRT therapy, (iii) significant limitations in the clinical evidence used to model the relative effectiveness of TheraSphere with other therapies, (iv) the inappropriate and incorrect implementation of age-adjusted utility values, and v) inaccurate representation of patients in the pharmacological management health state. The net effect of these issues on the estimated ICER is unclear, as many issues work in opposing directions.

BTG submission – CTT-ineligible population

For the CTT-ineligible population, the BTG submission included a *de novo* model-based health economic evaluation of TheraSphere compared with two other SIRT therapies, SIR-Spheres, and QuiremSpheres, and three systemic therapies (sorafenib, lenvatinib and regorafenib). The corrected version of the company's submitted model suggests that the probabilistic ICER for TheraSphere versus regorafenib is approximately £64,513 per QALY gained.

The AG has several concerns relating to the company's submitted model, which serve to critically undermine the validity of the presented model. Many of these concerns were also present in the CTT-eligible model presented by BTG. These concerns include (i) the inclusion of regorafenib as a direct comparator at first-line when it is only licensed for use following sorafenib therapy, (ii) the failure to properly account for patients who fail the work-up procedure and do not go on to receive SIRT therapy, (iii) significant limitations in the clinical evidence used to model the relative effectiveness of

TheraSphere with other therapies, (iv) the inappropriate and incorrect implementation of age-adjusted utility values, (v) questionable assumptions regarding the modelling of time on systemic therapies, and (vi) assumptions made regarding subsequent therapies received following SIRT therapy. As with the CTT-eligible model, the net effect of these issues on the estimated ICER is unclear, as many issues work in opposing directions.

7 Independent economic assessment - Scope of analysis

As described in Section 3, the scope of the systematic review conducted by the AG into the relative effectiveness of SIRT covered a broad population, which the AG split into three distinct populations based on the intent of treatment and the eligibility to receive conventional transarterial therapies (CTT). These three populations largely corresponded to early, intermediate and advanced HCC.

Assessment of the available clinical evidence to support an economic analysis in each of these three populations, however, revealed that much of the available evidence is from poor quality observational studies, with only a very small number of high quality randomised trials. These limitations in the availability of evidence have a number of important implications for the scope of the economic evaluation undertaken by the AG.

As described in Section 4.2, only three studies were identified for the population with early HCC (patients who are eligible for transplant and CTT). The intent of treatment in this population is primarily to act as a bridge to transplant, and therefore to control disease so as to allow patients to remain within transplant criteria until a donor organ becomes available. The primary benefit of SIRT or CTT in this population would therefore be through its capacity to sustain a greater proportion of patients through to receiving a transplant. In this context, waiting time to transplant is of crucial importance, and a determining factor in the proportion of patients who are ultimately likely to receive transplant. However, studies identified by the AG on bridging treatment efficacy were from a US setting, where waiting list residence times are significantly longer than in the UK; roughly 6 to 12 months in the USA,[8, 11, 44, 45] compared with an average waiting time of approximately 50 days for HCC patients in the UK.[131] The relevance of the available data on bridging to transplant was therefore limited, and basing estimates of the relative proportion of patients successfully bridged to transplant in this context would provide potentially misleading estimates of the relative effectiveness of SIRT and CTT. Furthermore, within the UK where wait times for transplant are relatively short, there is relatively limited scope for SIRT to offer significant health benefits and therefore it is unclear whether any additional costs associated with a SIRT procedure would be justified in this setting.

In the intermediate, CTT-eligible population, the evidence base was also considered too limited to inform a network meta-analysis (see Section 4.2), with only one available randomised study providing comparative evidence on the effectiveness of SIRT with CTT. This RCT recruited 24 patients and compared SIR-Spheres with DEB-TACE.[5] In the intermediate HCC population, the primary aim of therapy is to maintain locoregional control of the tumour to prevent progression to advanced disease, where treatment options are more limited and where survival outcomes are poor. There may also be a role for the use of locoregional therapy to downstage certain patients to make them eligible for potentially curative therapies such as liver transplant or resection. Key outcomes within this

population are therefore time to progression (TTP), as patient survival is largely dictated by progression to advanced disease, as well as the proportion of patients who are downstaged to curative therapy. However, the identified RCT[5] provided very limited data on TTP and PFS and did not report any downstaging events. Moreover, evidence on the relative effectiveness of alternative CTT was largely limited to survival outcomes. As a consequence, any economic analysis implemented in the CTT-eligible population would have had to rely on the Pitton RCT alone.[5] A model based on this single small study would, however, have generated significant challenges in populating key clinical inputs, and would not have permitted the model to address the potential role of downstaging in this population. Furthermore, any estimates of relative benefit would have been subject to very considerable uncertainty, meaning the results of any model would have limited value for decision making. The AG, therefore, considered it inappropriate to develop a full economic analysis in the CTT-eligible population. The AG notes that Sirtex reached a similar conclusion regarding the availability of evidence to inform a full economic analysis, and opted instead to present a cost-minimisation. As outlined in Section 6.3.1, the AG considers the value of such an approach limited, as a cost-minimisation relies on the assumption of equal efficacy, for which there was not sufficient evidence.

In contrast with early and intermediate populations, the systematic review identified two large RCTs comparing SIR-Spheres with sorafenib in the advanced HCC population.[2,3] The focus of the AG economic analysis is, therefore, on the CTT-ineligible population. Details of the AG's economic analysis are outlined in Section 8.

8 Independent economic assessment – CTT-ineligible population

A summary of the key features of the AG economic analysis for the CTT-ineligible population is presented in Table 28. The population covered by the AG base-case analysis is Child-Pugh A patients, who are ineligible or who have failed CTT. Scenario analysis considers two further subgroups; (i) patients who have a low-tumour burden and are ALBI grade 1 and (ii) patients with macroscopic vascular invasion (MVI).

It should be noted that these analyses are limited in that they do not include all patients who are ineligible to receive or have failed CTT, as they do not cover Child-Pugh B patients ineligible for CTT. In practice, these patients would be ineligible to receive systemic therapy as they are not covered by the relevant NICE recommendations and therefore in practice would receive BSC. The clinical evidence available comparing SIRT with BSC in an advanced HCC population is however, very limited, and as such it is not possible to extend the economic analysis to cover this population.

The interventions considered in the AG analysis were the three SIRT technologies (QuiremSpheres, SIR-Spheres, and TheraSphere) and the comparators were the systemic therapies sorafenib and lenvatinib. Regorafenib was not included as a comparator in the AG's analysis as the NICE recommendation and SmPC for regorafenib in HCC only permits use in patients who have previously failed sorafenib therapy. Patients in the AG model are however, permitted to move on to regorafenib following discontinuation of sorafenib.

In all analyses, cost-effectiveness is evaluated in terms of the incremental cost per QALY gained over a 10-year (lifetime) time horizon from an NHS and PSS perspective. In line with the NICE reference, case costs and health benefits were discounted at a rate of 3.5% per annum.[138] Costs in the model were based on the 2017/2018 price year.

Table 28: Summary of key features of the AG base-case model

Model Component	Description
Population	The patient population that is the focus of the cost-effectiveness analysis includes patients matching the following criteria: • Patients with unresectable intermediate (BCLC stage B) or advanced (BCLC stage C) HCC, • for whom any conventional transarterial embolisation therapies (TAE, TACE, DEB-TACE) are inappropriate, • with or without macroscopic vascular invasion, • without extrahepatic disease.
Intervention	Selective internal radiation therapies (SIRT): • SIR-Spheres Y-90 resin microspheres • TheraSphere Y-90 glass microspheres • QuiremSpheres Ho-166 PLLA microspheres
Comparator	Established clinical management without SIRT using the following targeted systemic therapies: • Sorafenib • Lenvatinib
Analysis type	Cost-effectiveness (cost-utility) analysis
Economic outcome	Incremental cost per QALY gained, incremental net monetary benefit
Perspective	NHS and PSS
Time horizon	Lifetime (10 years)
Discount rate	Annual rate of 3.5% applied to costs and QALYs

8.1 Model structure

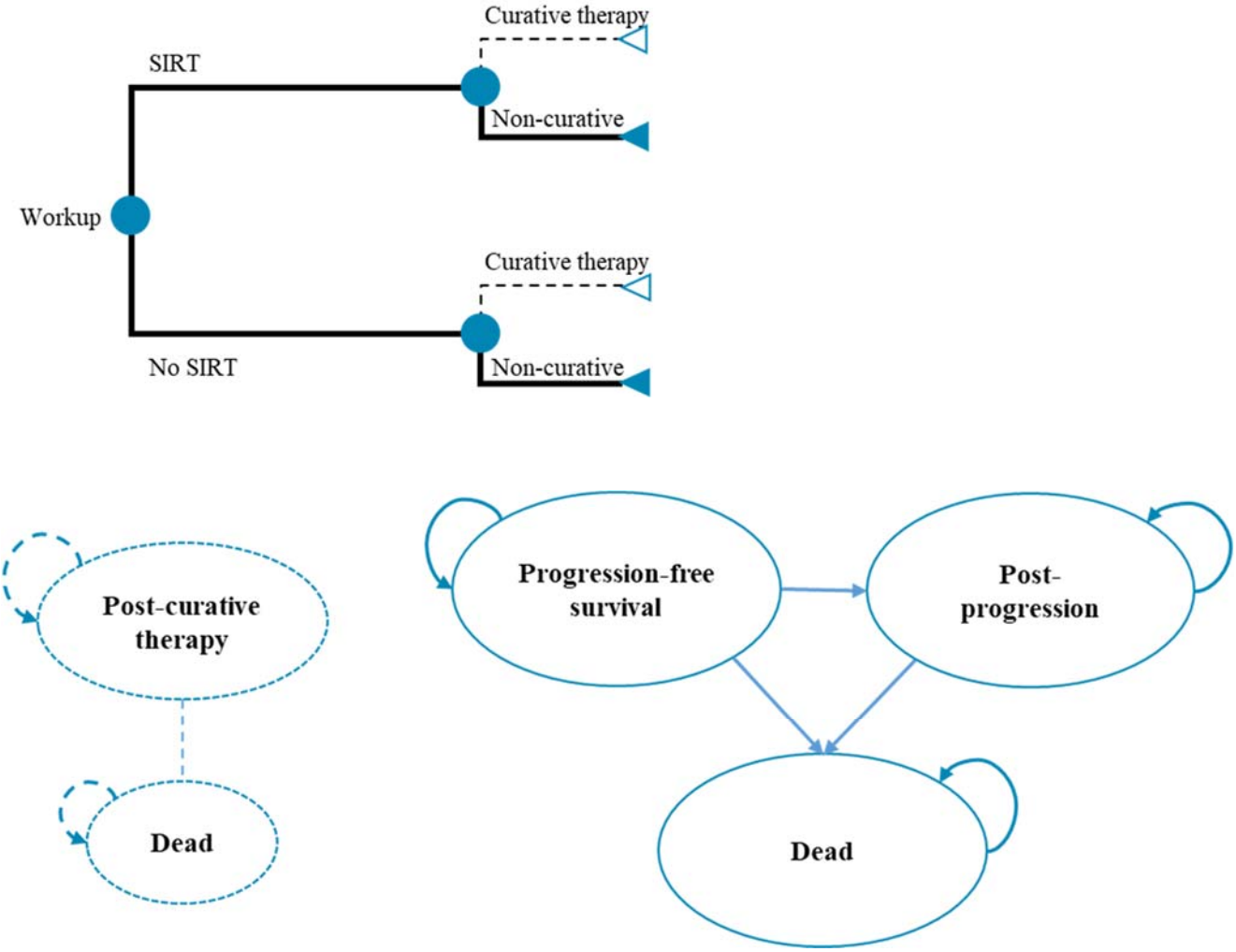
The structure of the AG model is presented in Figure 14. The AG model consists of a three-state partitioned survival model and decision tree for those intended to receive SIRT. Also presented is the structure of the downstaging scenario (see dashed lines), for whom the outcomes of patients successfully downstaged to receive curative therapy are modelled separately. In the AG model, those allocated to receive SIRT enter a decision tree representing the work-up procedure. A proportion of these patients go on to receive SIRT following work-up, while others are not considered suitable for SIRT or otherwise withdraw consent, so can either go on to receive BSC or a systemic therapy. In the AG base-case, patients then move into the main partitioned survival model.

The proportion of patients who receive work-up in the AG base-case is based on the SARAH trial, from which efficacy outcomes for these patients are drawn. Of the 226 patients who underwent work-up, 42 (18.6%) did not receive SIRT. Two further scenarios are presented in Section 8.4.2.1, which explore the effect of using the lower and upper bounds of work-up 'failure' identified in the literature (5% [139] - 28.6%[3]).

The model uses a lifetime (10 year) time horizon (<0.1% of patients alive at 10 years in most optimistic scenario), and takes an NHS and PSS perspective. Costs and health outcomes are discounted at a rate of 3.5% per annum, with cost-effectiveness expressed in terms of the incremental

cost per quality-adjusted life-year (QALY) gained, and incremental net monetary benefit (NMB). Costs were valued at 2017/18 prices.

Figure 14: Overview of CTT-ineligible AG model structure (with dashed curative therapy scenario)



As shown in Figure 14, the structure of the partitioned survival model is broadly similar to that adopted within both the BTG and Sirtex models (see Section 6.3) consisting of three health states: (1) progression-free, (2) post-progression and (3) dead. For any time, t, the probability that a patient is alive and progression-free is given by the cumulative survival probability for PFS, whereas the probability that a patient is alive is given by the cumulative survival probability for OS. The probability that a patient is in the post-progression state at any time, t is given by the difference between the cumulative survival probabilities for PFS and OS. Health and cost outcomes from the partitioned survival models for each intervention were multiplied by the proportion of patients who received each within the particular treatment arm per the decision tree.

As with the Sirtex model, HRQoL is defined according to the presence or absence of disease progression as well as treatment received. The model includes costs associated with SIRT procedures (work-up costs, acquisition costs, procedure costs) drug acquisition, health-state costs (consultant-led outpatient visits, nurse-led outpatient visits, ECG, blood tests and computerised tomography (CT) scans), costs associated with managing grade 3/4 AEs, BSC-related costs (consultant-led outpatient visits, CT scans, magnetic resonance imaging (MRI) scans, specialist palliative care visits, palliative radiotherapy) and end-of-life care costs.

8.2 Model input parameters

A summary of the data sources used to populate the AG's base-case model is presented in Table 29. These are discussed in greater depth over the following sections.

Table 29: Summary of sources of input parameters in the AG base-case economic model

Model parameter	Evidence source
OS	Parametric survival models fitted to pooled OS data from the SARAH[2] and SIRveNIB[3] trials for both SIR-spheres (per protocol) and sorafenib (intention-to-treat). A hazard ratio from the AG's NMA was applied to the sorafenib OS curve to estimate OS for lenvatinib. The OS for patients who received work-up but were ineligible to receive SIRT was modelled using the observed KM data from SARAH. [2]
PFS	Parametric survival models fitted to pooled PFS data from the SARAH[2] and SIRveNIB[3] trials for both SIR-spheres and sorafenib. A hazard ratio from the AG's NMA was applied to the sorafenib PFS curve to estimate OS for lenvatinib.
Health utilities	Utilities were generated by Sirtex from SARAH trial[2] data, and were applied by treatment class (SIRT/systemic therapy). Pre-progression: EORTC-QLQ C30 scores taken from the *post-hoc* analyses of the SARAH trial[2] for the per protocol population were mapped to EQ-5D using a mapping algorithm developed by Longworth *et al*.[109] Post progression: EORTC-QLQ C30 scores taken from the *post-hoc* analyses of the SARAH trial[2] for the per protocol were mapped to EQ-5D using the algorithm developed by Longworth *et al*.[109]
Proportion receiving SIRT	The proportion receiving SIRT after work-up was based on the full SARAH trial[2] population. Number of administrations of SIRT was based on the SARAH trial. [2]
SIRT costs	Acquisition cost: Sirtex CS, BTG CS, Terumo CS Work-up costs: BTG-elicited values from The Christie NHS Foundation Trust Procedure costs: NHS Reference Costs 2017-18[103]
Systemic therapies costs	Sorafenib and lenvatinib: BNF[112] Dosing of sorafenib: SARAH trial[2] Dosing of lenvatinib: REFLECT[23] Western subgroup Duration of sorafenib: SARAH trial,[2] Duration of lenvatinib: PFS HR from REFLECT.[23] applied to SARAH,[2] sorafenib ToT
Subsequent treatment costs	BNF, eMIT, TA555 (regorafenib)
AE costs	AEs ≥5% of the population were modelled with rates drawn from the SARAH[2] and REFLECT[23] trials. Costs were drawn NHS Reference Costs, with cost categories based on NICE TA474[31], and 551.[32]
Health state costs	Sirtex survey of clinical experts and NHS reference costs 2017/2018[103]

EORTC-QLQ C30, European Organization for Research and Treatment quality of life questionnaire

8.2.1 Treatment effectiveness

The base-case analysis used data from the SARAH,[2] SIRveNIB,[3] and REFLECT trials.[23] Scenario analyses also drew on a number of observational comparisons of SIR-Spheres and TheraSphere, see Section 5.3 for details.

The comparison of SIR-Spheres with sorafenib was based on pooled data from the SARAH and SIRveNIB trials. Modelled data from SARAH were supplied by Sirtex for both PFS and OS, while data were extracted from published literature sources from SIRveNIB.

The source of modelled survival data from the SARAH and SIRveNIB trials differed according to therapy received. For patients receiving sorafenib, OS and PFS outcomes were based on the ITT populations (sorafenib, n = 400), while OS and PFS outcomes for patients receiving SIR-Spheres are modelled based on the per protocol population of each trial (SIR-Spheres, n = 304). This is done to account for the proportion of patients who fail the SIRT work-up procedure, and subsequently do not undergo the main SIRT procedure. The outcomes of patients who fail the work-up procedure are modelled independently, and are based on near complete Kaplan-Meier data from the SARAH trial (work-up failures, n = 42). The proportion of patients failing the work-up procedure is based on the SARAH trial. The DSA included a range of estimates for work-up failure, based on the number of work-up failures reported in SARAH, SIRveNIB and other estimates provided by Sirtex. To avoid the double counting of patients who are downstaged to receive curative therapies, the data included from SARAH, for both SIR-Spheres and sorafenib are censored for downstaging. There was no downstaging reported in the SIRveNIB trial publication[3] and no patients received subsequent therapies that could be considered ‘curative’, so it was assumed that no patients were downstaged to receive curative therapies in these data.

The comparative effectiveness of lenvatinib was drawn from the NMA presented in Section 5.4. The hazard ratio (HR) for lenvatinib versus sorafenib was applied to the Weibull curve fitted to the sorafenib data drawn from the SARAH and SIRveNIB trials. Proportional hazards is therefore assumed between sorafenib and lenvatinib.

In the AG’s base-case analysis, equivalence is assumed between the SIRT technologies due to a lack of randomised evidence on the relative effectiveness of each SIRT. An exploratory scenario analysis is also presented in which the effectiveness of TheraSphere was based on two non-randomised comparative studies (SIR-Spheres, n = 34; TheraSphere, n = 78), with a HR versus SIR-Spheres drawn from the NMA. In this scenario, the HR is applied to the modelled parametric functions fitted to the pooled SIR-Spheres data, and therefore proportional hazards is assumed for this comparison, see Section 8.2.1.1 for consideration of the plausibility of this assumption.

In addition to the base-case analysis in which the modelled population was based on pooled analysis of the SARAH and SIRveNIB trials, additional scenario analysis was implemented in a number of alternative populations. To account for uncertainties in the relevance of the Asia-Pacific population to UK practice, a scenario was implemented using data only from the SARAH trial. Two further subgroup analyses based on the SARAH trial were also considered: the restricted low-tumour burden and ALBI grade 1 subgroup (SIR-Spheres, n = 28; sorafenib, n = 44), and patients with macroscopic vascular invasion (MVI); (SIR-Spheres, n = 64; sorafenib, n = 81). In both subgroup analyses, the comparison between SIR-Spheres and sorafenib is made using data drawn from the relevant subgroup of the SARAH trial only. Appropriate individual patient data (IPD) was requested by the AG for these subgroups of the SIRveNIB trial but Sirtex had only limited access to the IPD from the SIRveNIB trial and did not have subgroup data from all enrolling centres. Subgroup data were not available to support the comparative effectiveness of lenvatinib and TheraSphere. This scenario therefore only uses data for SIR-Spheres and sorafenib, assuming equivalent efficacy across SIRT technologies, and between lenvatinib and sorafenib.

8.2.1.1 Extrapolation of PFS and OS evidence

For each data set, model selection was conducted following the process described in the NICE Decision Support Unit Technical Support Document No. 14.[114] Log-cumulative hazard plots were produced to illustrate and assess the hazards observed in the trial to help inform which types of parametric model may be considered appropriate. Curve fitting was conducted in R using the 'survival' and 'flexsurv' packages. This was used to estimate the empirical hazard function. Exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma models were considered.

The AIC and BIC fit statistics were examined to assess the comparative internal validity of competing models. The final choice of models for the economic analysis was made on the basis of fit to the observed data as well as consideration of the clinical plausibility of candidate models.

Overall survival

The analysis of OS for the base-case analysis was based on time-to-event data from the SARAH trial supplied by Sirtex, and Kaplan–Meier curves from the SIRveNIB trial.[3]

Standard parametric survival functions were fitted to the survival data available for each of the considered populations and log-cumulative hazard plots were generated to assess any changes in hazards over time, see Figure 28 in Appendix 13.16. Plots of each of the fitted parametric models with the observed Kaplan-Meier OS curves are presented in Figure 15 (SIR-Spheres) and Figure 16 (sorafenib). Model fit statistics are summarised in Table 72, Appendix 13.16, which showed that the

generalised gamma model had the best fit; with the log-normal and log-logistic curves also having similar statistical fit, thereby providing little justification to discriminate between these models on this basis of fit statistics. The generalised gamma, log-normal, and log-logistic models are, however, all accelerated failure time models and as such, a hazard ratio cannot be applied to estimate outcomes for lenvatinib patients, and would likewise not permit scenarios in which differential outcomes are assumed for TheraSphere, which would similarly require the application of an HR. To accommodate the use of HRs, the AG base-case analysis therefore selected the Weibull function which has the best statistical fit from the remaining curves, and was considered the most clinically plausible. The AG considered this reasonable given the limited data to accommodate accelerated failure time (AFT) functions, and the small variation in predicted incremental survival across all six functions; but acknowledge this as a limitation of the presented base-case analysis. Scenario analysis is therefore presented in which the generalised gamma, log-normal and log-logistic functions are used to model OS. In these scenarios, equivalence is assumed between sorafenib and lenvatinib.

Figure 15: Extrapolation of OS SIR-Spheres

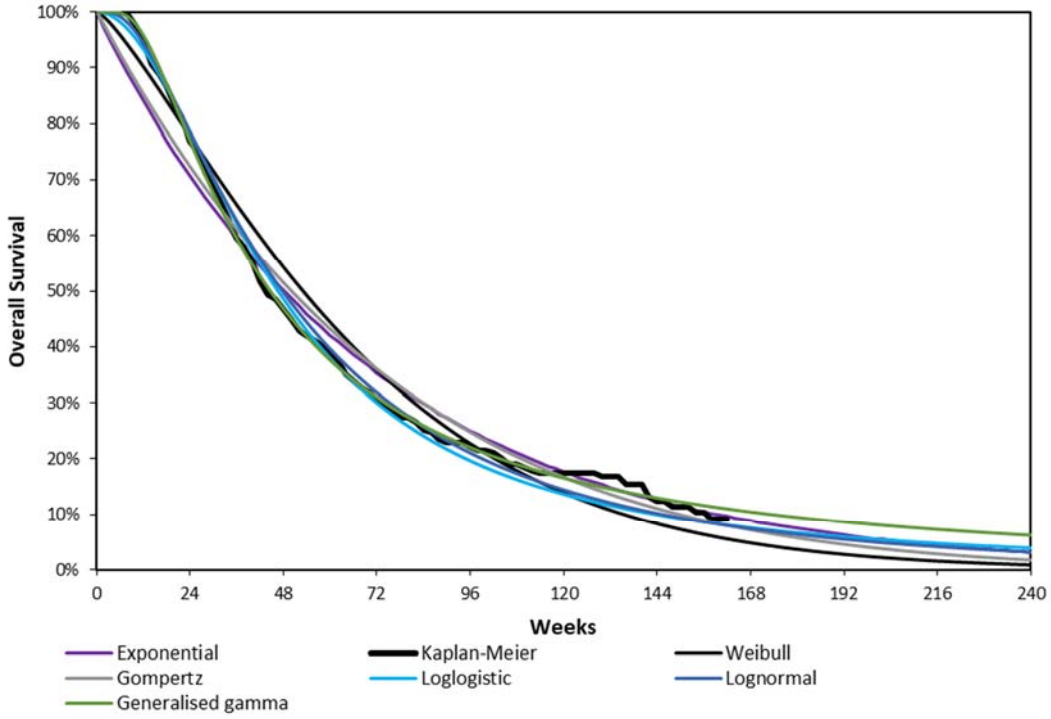
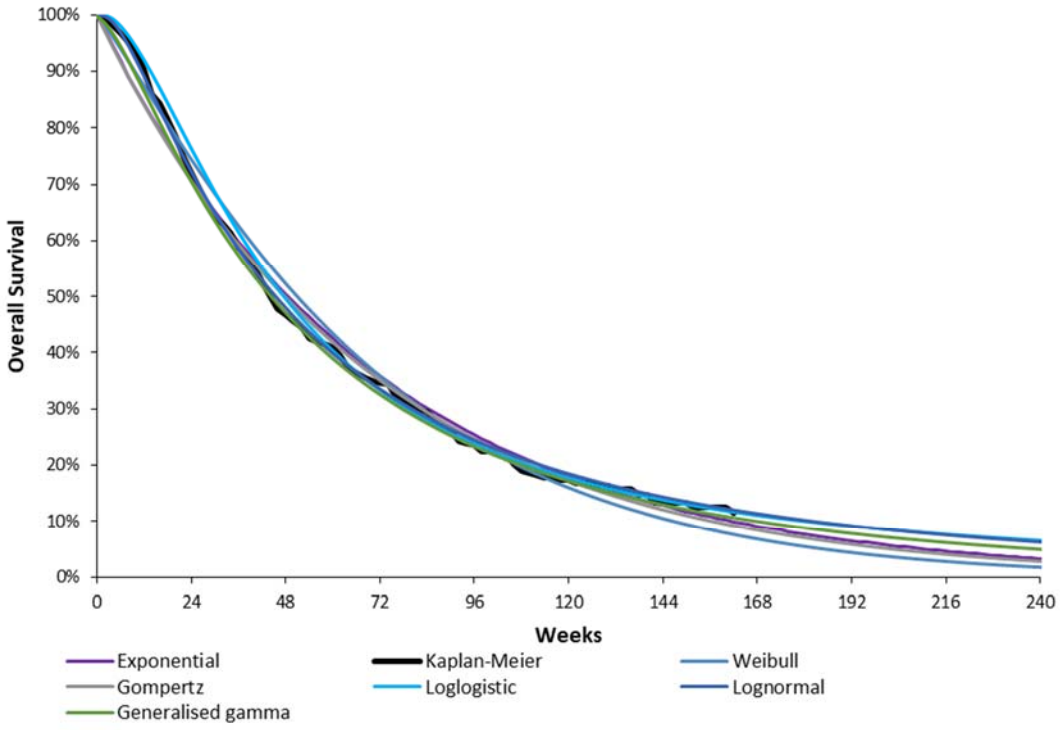


Figure 16: Extrapolation of OS Sorafenib



For scenarios run on the SARAH trial sub-populations described previously, the Weibull function was retained to model OS outcomes. Fit statistics for the SARAH trial whole population, low tumour burden/ALBI 1 subgroup and no MVI subgroup are reported in Table 74 of Appendix 13.16. Plots of each of the fitted parametric models with the observed Kaplan-Meier OS curves are presented in Figure 30 and Figure 31 (SIR-Spheres), and Figure 32 and Figure 32 (sorafenib) in Appendix 13.16. In all three scenarios, the Weibull function had a good statistical and visual fit to the observed data.

Progression-free survival

The analysis of PFS for the base-case analysis was based on supplied time-to-event data from the SARAH trial and Kaplan–Meier curves from the SIRveNIB trial.[3]

Similar to the approach previously described for OS, standard parametric survival functions were fitted to the survival data available for each of the considered populations, and log-cumulative hazard plots generated to consider the change in hazards over time, see Figure 29 in Appendix 13.16. Plots of each of the fitted parametric models with the observed Kaplan-Meier OS curves are presented in Figure 34 and Figure 35 (SIR-Spheres) and Figure 36 and Figure 37 (sorafenib) in Appendix 13.16. Similar to OS, model fit statistics for the generalised gamma, log-normal and log-logistic functions were superior to other functions, see Table 73, Appendix 13.16. These functions were however, rejected to accommodate the application of a HR for lenvatinib, and the implementation of scenarios

assuming differential effectiveness for TheraSphere. The Weibull function was therefore selected in the AG base-case analysis as this had the best statistical and visual fit to the observed data and was considered clinically plausible.

Figure 17: Extrapolation of PFS SIR-Spheres

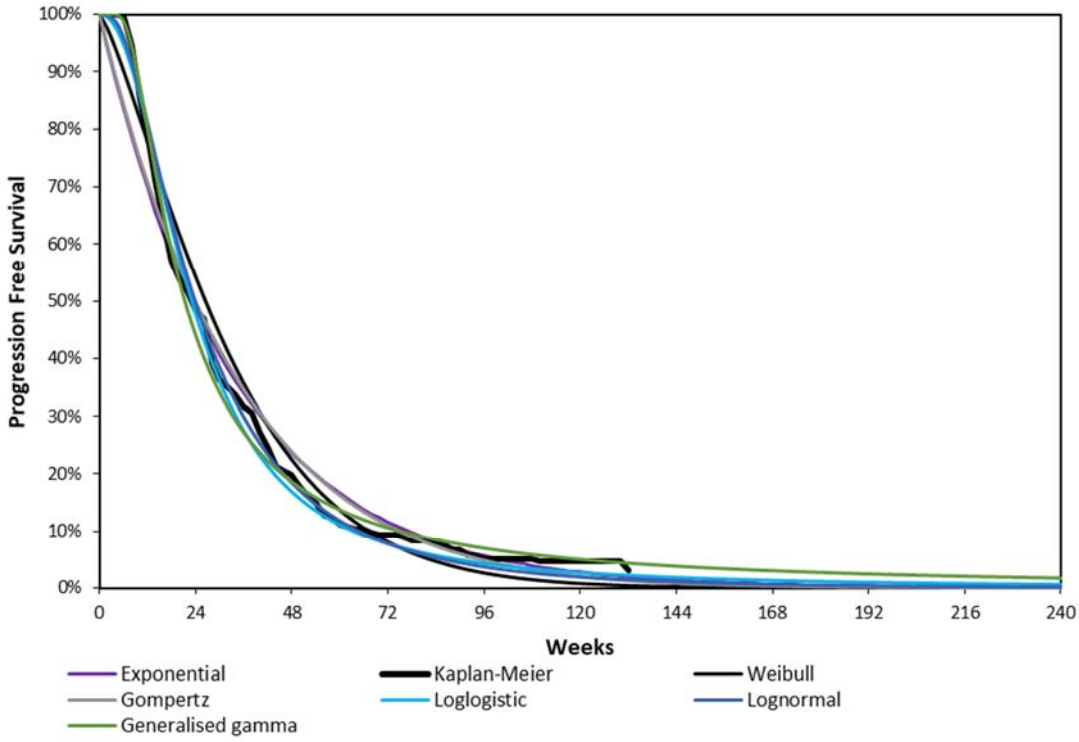
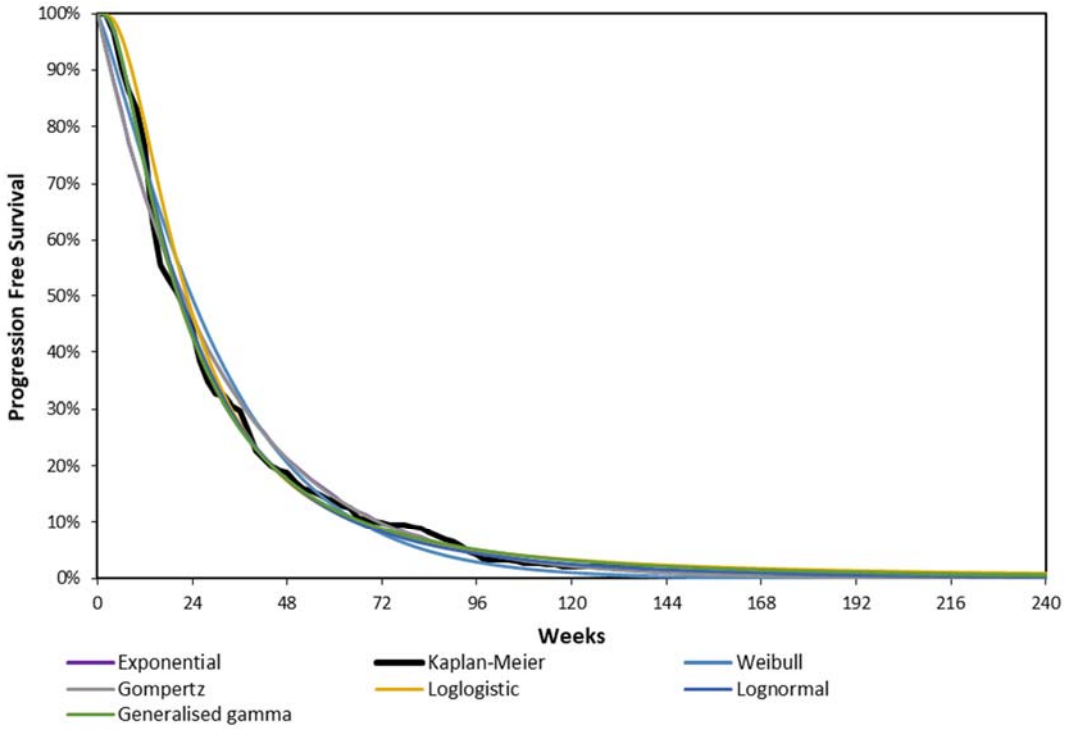


Figure 18: Extrapolation of PFS Sorafenib



Overall survival for patients downstaged to curative therapy

The base-case analysis does not allow for downstaging to curative therapies, due to uncertainties over whether this is realistic within a population of patients with advanced disease. A number of scenarios are presented in which downstaging is allowed for. The proportion of patients downstaged is based on the values reported in the SARAH trial[2] and varied depending on the efficacy subgroup used, see Table 69, in Appendix 13.16. Outcomes for patients downstaged to curative therapy were based on a US prospective cohort study[108] which recruited 267 patients with HCC, including 191 with intermediate and advanced disease. This study compared outcomes for patients who had received palliative care and those who received potentially curative therapies (liver transplantation, surgical resection, or tumour ablation). Using Cox multivariate proportional hazards, the HR for OS with potentially curative treatments vs. non-curative treatment was 0.29 (95% CI: 0.18-0.47). This HR was applied to the pooled sorafenib ITT arms of the SARAH and SIRveNIB trials in all scenarios. This was done to prevent the outcomes of downstaged patients varying depending on the patient population selected or by treatment arm; advice from clinical advisors to the AG suggested that outcomes post-curative therapy would be similar regardless of patient characteristics or treatment received to achieve downstaging. The sorafenib ITT arm was used as this was considered to best match care received in the analysed patient cohort, and is most representative of the current standard of care in UK practice.

8.2.1.2 Adverse event rates

The probability of experiencing grade 3/4 adverse events (AEs) for SIR-Spheres and sorafenib was taken directly from the per protocol population of the SARAH trial.[2] Based on clinical advice received by the AG, adverse event rates for TheraSphere and QuiremSpheres were assumed to be the same as for SIR-Spheres. Adverse event rates for lenvatinib were drawn from the REFLECT trial[23] See Table 70 in Appendix 13.16 for rates applied.

8.2.2 Health-related quality of life

8.2.2.1 Literature review and mapping of HRQoL estimates

A targeted review of published studies reporting utility estimates for patients with HCC or cirrhosis was performed to supplement data extracted from studies on SIRT and its comparators. Details of the search strategy used are described in Appendix 13.3. The objective of these searches was to identify health state utilities of patient populations which may not have been captured in studies included in the main systematic reviews. The required utilities included:

- Decompensated cirrhosis (any cause)
- Post-CTT disutility
- Post-resection disutility
- Pre- and post-transplant utilities

The identified studies recorded HRQoL using a number of tools, namely SF-36 and EORTC QLQ-C30. NICE prefers the use of generic preference-based measures (i.e. EQ-5D) for the calculation of health state utilities. Therefore, mapping algorithms typically based on multinomial regression model coefficients can be used to transform disease-specific measures of health status into an EQ-5D-based utility score. Domain scores for relevant populations were mapped onto EQ-5D using the two-part beta model as developed by Woodcock and Doble[140] for EORTC QLQ-C30 scores, and a model developed by Rowen and colleagues[141] was used to transform SF-36 outcomes.

8.2.2.2 Modelled Health State Utilities

The AG's base-case model for CTT-ineligible patients applies different health state utilities based on the type of therapy received. In the absence of any evidence suggestive of a difference in HRQoL between the three SIRT technologies, the AG has assumed patients experience the same quality of life regardless of whether they received SIR-Spheres, TheraSphere, or QuiremSpheres. Likewise the HRQoL estimates associated with the systemic therapies, namely sorafenib and lenvatinib, are assumed to be the same as one another, but marginally lower than those applied to SIRT, as observed in the SARAH trial[2] (see Table 30). An additional scenario in which health state utilities from the lenvatinib TA are applied is presented in Section 8.4.2.1.

Age-related disutilities

Age adjusted UK population norms from Szende *et al*.[142] were applied to the utility values included in the model. Age-related decrements were calculated and subtracted from the health state utility used in each cycle of the model. This allows for the trial-derived utilities applied in the model to account for age-related decline in HRQoL as the population ages over time.

SIRT health state utilities

The health state utilities associated with SIRT in the CTT-ineligible model were based on the per protocol subgroup of the SARAH trial as calculated by Sirtex in their evidence submission (See Section 6.3.2.2 for details). EORTC-QLQ-C30 summary scores were mapped to EQ-5D using the algorithm developed by Longworth and colleagues,[109] and utilities were calculated based on UK general population weights.

The per protocol utilities were considered to better reflect the HRQoL associated with SIRT than those derived from the ITT population, as 22.4% of patients randomised to SIRT did not receive SIRT in the SARAH trial. These patients may have received other systemic therapies, BSC, or were otherwise too unwell to receive SIRT, thus the ITT utility values may not have represented those of a SIRT treated population. There were no further utility decrements applied to these utilities as these are likely to have been captured in the SARAH trial results. The health state utilities applied in the model are presented in Table 30.

Systemic therapy health state utilities

Health state utilities applied to modelled patients receiving the systemic therapies sorafenib and lenvatinib were taken from the per protocol subgroup of sorafenib patients in the SARAH trial.[2] The difference in utility between SIRT and sorafenib in this subgroup was 0.011, which the AG considered to account sufficiently for the ostensibly greater burden of adverse events associated with these drugs. Utilities applied to patients who received work-up but ultimately did not receive SIRT were weighted by the proportion on systemic therapy vs BSC (61.9% and 38.1% respectively). This assumes patients not on systemic therapy had a utility equivalent to those on SIRT, which may overestimate the HRQoL of BSC patients, as a proportion were likely to have been too unwell to receive systemic therapy.

Post-transplant health state utilities

AG Scenarios 6 & 10 include the possibility for downstaging, therefore post-transplant utilities were considered for use in the model. Pre-transplant health state utilities are assumed to be equal to those experienced in pre-progression for SIRT, systemic therapies, and BSC. Post-transplant health state utilities are assumed to be equal to those experienced on SIRT, regardless of which treatment a patient

received before downstaging to transplant. However, it is likely that patients who received transplant may have a better HRQoL than the per protocol population of the SARAH trial.

Despite multiple studies showing that recipients of liver transplant enjoy increased HRQoL post-transplant in comparison with pre transplant,[109, 143-145] a lack of generalisability between these studies and the population included in the model renders the absolute utility values reported in the literature too uncertain for inclusion. Studies also show HRQoL remains lower for liver transplant recipients compared to healthy patient controls.[146-148] However, as with the pre- and post-transplant utilities, there is insufficient evidence to suggest that these studies are generalisable to the modelled population. Given the lack of evidence to definitively suggest utility values in the post-transplant HCC population are lower than the general population, the AG believes the utility values observed in the general population represents the upper bound of the utility expected in the post-transplant population.

Table 30: Health state utilities included in the AG CTT-ineligible model

Health State	**Utility**		
	SIRT	Systemic therapy	Work-up – no SIRT
Progression-free survival	0.710	0.699	0.703
Progressive disease	0.668	0.657	0.661
Post-transplant*	0.710	0.710	0.710

*AG Scenarios 6 & 10 only

8.2.3 Sources of resource utilisation and cost data

A targeted review of published studies reporting resource use and cost data for patients with HCC or cirrhosis was performed. Details of the search strategy used are described in Appendix 13.4. This review, however, identified little in the way of published literature. Resource use and cost inputs used in the AG's economic model were therefore derived primarily from targeted literature searches, previous NICE Technology Appraisals, and the estimates presented in the companies' evidence submissions for the present appraisal. Overall costs are determined by treatment costs (acquisition, procedures, and monitoring), and changes in health service utilisation driven by disease status (i.e. progression-free, progressed disease, and death), and adverse event management. The assumptions applied to each category are discussed in the following sections. Note that confidential Patient Access Scheme (PAS) discounts are available but not included here for QuiremScout, sorafenib, lenvatinib, and regorafenib. Please refer to the confidential appendix for results including all PAS discounts. A summary of the AG model cost inputs is presented in Section 8.2.3.4.

8.2.3.1 Treatment costs and resource use

Work-up costs and number of procedures

Patients allocated to receive SIRT must first undergo a work-up procedure to assess their suitability for treatment with SIRT, and to plan the procedure through angiographic evaluation and occlusion of any vessels that could carry microspheres away from the liver to the gut. While work-up is a one-off procedure, those patients who required a second SIRT procedure due to an unsuccessful or incomplete first procedure are likely to need a second work-up.

In the SARAH trial,[2] 17 of the 184 patients who received SIRT required re-treatment due to an unsuccessful or incomplete first procedure (nine received a second work-up but were not re-treated). Therefore, patients who received any of the SIRTs incurred the cost of 1.09 work-up procedures to account for re-treatment. As the model independently considered the costs and outcomes for patients who underwent work-up but ultimately did not receive SIRT, these individuals were assumed to receive 1.0 work-up procedure. The AG's base-case assumed that 18.6% of patients who underwent work-up did not go on to receive SIRT in line with the SARAH trial[2] data. However, in recognition of the uncertainty around this value, a number of alternative scenarios are presented in Section 8.4.2.

Work-up costs used in the AG base-case were based on the values BTG elicited from the Christie NHS Foundation Trust (see Appendix 13.15, Table 60). The largest expenditures were staff costs and SPECT/CT. The total cost of a single work-up procedure for SIR-Spheres and TheraSphere used in the AG model was £860.32, while the work-up cost of [redacted] for QuiremSpheres comprised the list price of QuiremScout, and the BTG-elicited value excluding the £74 cost of the Tc-99m MAA agent. This does not include the PAS discount available for QuiremScout.

SIRT treatment costs and number of procedures

Patients in the AG model received an average of 1.21 SIRT procedures. This is based on the assumption that patients requiring bilobar treatment will require two separate SIRT procedures, each separated by a few weeks (as per the SARAH protocol[149]), and that patients will be re-treated due to an incomplete or unsuccessful first treatment. The clinical advisors to the AG stated that it would be very unlikely that both lobes would be treated in the same treatment session in UK practice due to an increased risk of radioembolisation induced liver disease. SIRT patients in the SARAH study[2] had 1.28 separate SIRT treatments on average (222 treatments, 173 patients [1-2 treatments only]). This broadly reflects the results of the Sirtex resource use survey (1.2 treatments per patient). This value excludes the 11 patients who had three separate SIRT treatments, and includes only one procedure for the nine patients who received a second treatment due to disease progression, as it was unclear whether this would be permitted in UK practice.

The acquisition cost of a single SIRT treatment was taken from each company submission respectively: SIR-Spheres, £8,000; TheraSphere, £8,000; QuiremSpheres, £9,896.

The cost of the SIRT procedure applied in the AG model was taken from the NHS National Schedule of Reference Costs 2017-18 (YR57Z).[103] The average cost of 'Percutaneous, Chemoembolisation, or Radioembolisation, of Lesion of Liver' was £2,790. This cost was incurred for each separate SIRT administration for patients receiving TheraSphere and QuiremSpheres in the AG model. The Sirtex company submission stated that SIR-Spheres administration procedures use intermittent contrast medium injection to assess the distribution of the microspheres under x-ray over the course of approximately one hour. The AG therefore included an additional cost of £209 for the SIR-Spheres administration procedure (RD32Z – Contrast Fluoroscopy Procedures with duration of more than 40 minutes) for a total of £2,999.

Costs of systemic therapies

The pack costs for sorafenib (£3,576.56), lenvatinib (£1,437.00), and regorafenib (£3,744.00) were taken from the BNF.[112] The confidential patient access scheme discounts available for sorafenib, lenvatinib, and regorafenib are not included in this report. For results of the AG's economic analysis which include these discounts, please refer to Confidential Appendix.

The daily dose of sorafenib used in the AG base-case was based on the SARAH trial[2] (648.5 mg), and mean time on treatment (ToT) was calculated by applying an exponential function to the median ToT reported in the SARAH trial[2] (exponential mean 122.95 days).

The base-case daily dose of lenvatinib was 10.2 mg per day, based on the Western subgroup of the REFLECT trial[23] for lenvatinib. This value was considered by the TA Committee in TA551[32] to better represent the average weight-based dose used in UK practice. The AG considered the ToT reported in the REFLECT trial[23] for lenvatinib to be excessively long compared to SARAH,[2] and reflective of differences in the baseline characteristics of the populations recruited to these trials. To avoid inflating the relative cost of lenvatinib, the AG applied the reported HR of PFS between lenvatinib and sorafenib in REFLECT to the SARAH ToT to produce an estimate of 124.07 days on treatment.

Wastage was accounted for in the AG model using the simple assumption that if a new pack was started then in the case of treatment discontinuation, the remainder could not be used to treat other patients. However, this may be a conservative assumption, as it was reported in TA555[36] that many centres have measures in place to reduce wastage of expensive cancer treatments, such as issuing only one month of tablets at a time (approximately one pack of sorafenib). However, as it generally cannot

be predetermined when therapy will be discontinued due to adverse events, death, or non-compliance, it can be reasonably assumed some wastage will occur.

Cost of subsequent treatment

The interventions used following first-line treatment in the SARAH trial[2] were not representative of current UK practice, however, as the efficacy data used in the model is derived from these patients, the trial values are most appropriate. Therefore, the proportion of patients who received subsequent systemic therapy (98% sorafenib) following SIRT in the SARAH trial[2] (28.8%) was used to estimate the size of this population in the AG model. The AG was advised that current NICE recommendations mean that lenvatinib is rarely used in practice, as this would preclude second-line use of regorafenib. Therefore, 95% of patients continuing to subsequent systemic therapies following SIRT treatment are assumed to receive sorafenib, and 5% lenvatinib.

As a number of chemotherapeutic/systemic agents administered to patients following sorafenib in the SARAH trial[2] have now been displaced in practice by regorafenib, or are otherwise no longer in use, the AG model assumes the proportion of those who received systemic therapies after sorafenib in the trial (12.04%) would receive regorafenib in UK practice. A small proportion (3.47%; i.e. 12.04% of 28.8%) of SIRT patients also receive regorafenib following second-line sorafenib treatment. Duration of therapy and dose intensity of each of the three systemic agents modelled is assumed to be the same as first-line, while regorafenib is assumed to have the same ToT as sorafenib (122.95 days), with a mean daily dose of 160 mg (RESORCE trial).[97]

8.2.3.2 Disease management costs

There are a number of issues with the health state unit costs used in previous technology appraisals in this indication, which precluded their use in the AG base-case. The primary concern with these costs is that the original resource use surveys given to clinicians were based on the ongoing costs associated with sorafenib treatment. The resource use implications for systemic therapies may be very different with regards to monitoring and diagnostic testing to those for SIRT as a one-off procedure, therefore these values may overestimate the disease management costs associated with the PFS health state for SIRT patients. Furthermore, the committee-preferred resource use data used in TA551 was collated from two resource use surveys conducted 10 years apart, generating very different estimates which may reflect differences in practice, costs, and experience. As targeted therapies such as sorafenib were not yet in use in this first survey, it is unlikely these values are sufficiently representative of current practice.

In light of these limitations, the AG used the results of a resource use survey conducted by Sirtex, which elicited information from 11 clinicians on the frequency and type of medical staff contact,

monitoring and follow-up, hospitalisation frequency and length, and any use of personal and social services. Resource use during pre-progression, post-progression, and upon progression were reported separately. Unit costs for each resource use item were derived from NHS Reference Costs 2017/18[103] and PSSRU[102]. Differential costs were applied for systemic therapy patients during pre-progression, reflecting higher levels of ongoing diagnostic testing and additional follow-up contact.

The per-cycle post-progression costs applied in the AG model are significantly lower than those used in TA551 (£229.69 vs £1,268.16). This was driven primarily by greatly reduced use of hospital and social care-based palliative care upon progression since the original resource use survey. The health state costs used in the AG model are presented in Table 31.

Table 31: AG model health state costs

Cost item	Pre-progression post-SIRT (per cycle)	Pre-progression on systemic therapy (per cycle)	Upon progression (one off)	Progressive disease (per cycle)
Medical staff contact	£47.30	£58.18	£54.51	£102.55
Diagnostic procedures	£59.92	£61.90	£41.07	£2.83
Inpatient care	£3.13	£9.33	£0.00	£36.11
Personal and Social Services	£2.68	£2.68	£0.00	£88.20
Total	**£113.03**	**£132.10**	**£95.57**	**£229.69**

A scenario which instead uses the committee-preferred costs from the lenvatinib appraisal is presented in Section 8.4.2.

8.2.3.3 Adverse event costs

Costs associated with the management of adverse events (AEs) were derived from previous NICE TAs of HCC, [31, 32, 36] using the latest NHS Reference Cost[103] values or costs inflated to the 2018 cost year, where applicable. The AG base-case used adverse event incidence rates from the SIR-Spheres arm of the SARAH trial[2] for the three SIRT technologies, and from the sorafenib arm of this trial for sorafenib. Adverse event rates for lenvatinib were taken from the REFLECT trial.[23] For patients who received work-up but did not progress onto SIRT, the proportion of patients who received sorafenib incurred sorafenib adverse event management costs.

A full list of adverse event costs used in the AG model is presented in Appendix 13.16 Table 75: Adverse event unit costs.

8.2.3.4 Summary of AG base-case analysis inputs and assumptions

A summary of the resource use assumptions and costs applied in the AG base-case analysis is presented in Table 32.

Table 32: Summary of resource use and cost inputs in AG model

Parameter	Treatment	Model input	Reference
Proportion of work-ups leading to SIRT	SIR-Spheres	81.4%	SARAH
	TheraSphere	81.4%	SARAH
	QuiremSpheres	81.4%	SARAH
Treatment of SIRT work-up failure patients	Sorafenib	61.9%	SARAH
	BSC	38.1%	AG assumption
Mean no. work-ups (treated patients)	SIR-Spheres	1.09	SARAH
	TheraSphere	1.09	SARAH
	QuiremSpheres	1.09	SARAH
Mean no. SIRT procedures	SIR-Spheres	1.28	SARAH
	TheraSphere	1.28	SARAH
	QuiremSpheres	1.28	SARAH
Subsequent systemic therapies			
Post-SIRT	Sorafenib	27.4%	SARAH/AG assumption
	Lenvatinib	1.4%	AG assumption
	Regorafenib (third line)	3.3%	AG assumption
	BSC	71.2%	AG assumption
Post-sorafenib	Regorafenib	12.0%	AG assumption
	BSC	88.0%	AG assumption
Post-lenvatinib	BSC	100%	AG assumption
Subsequent curative therapies			
Liver transplant		£16,556.07	NHS Reference Costs 2017-18
Resection		£9,676.59	NHS Reference Costs 2017-18
Ablation		£2,344.55	NHS Reference Costs 2017-18 (YG01A/YG01B)
Treatment cost inputs			
Work-up	SIR-Spheres	£860.32	BTG elicitation (The Christie NHS Foundation Trust)
	TheraSphere	£860.32	BTG elicitation (The Christie NHS Foundation Trust)
	QuiremSpheres	[redacted]	BTG elicitation (The Christie NHS Foundation Trust); Terumo submission
Procedure	SIR-Spheres	£2,999.00	NHS Reference Costs 2017-18 (YR57Z + RD32Z)
	TheraSphere	£2,790.00	NHS Reference Costs 2017-18 (YR57Z)
	QuiremSpheres	£2,790.00	NHS Reference Costs 2017-18 (YR57Z)
Acquisition (list price)	SIR-Spheres	£8,000.00	Sirtex submission
	TheraSphere	£8,000.00	BTG submission

	QuiremSpheres	£9,896.00	Terumo submission
	Sorafenib	£3,576.56	BNF
	Lenvatinib	£1,437.00	BNF
	Regorafenib	£3,744.00	BNF
Management costs			
Adverse event costs (total)	SIR-Spheres	£477.69	NICE TA474, TA514, TA535, TA551; NHS Reference Costs 2017-18
	TheraSphere	£477.69	NICE TA474, TA514, TA535, TA551; NHS Reference Costs 2017-18
	QuiremSpheres	£477.69	NICE TA474, TA514, TA535, TA551; NHS Reference Costs 2017-18
	Sorafenib	£932.79	NICE TA474, TA514, TA535, TA551; NHS Reference Costs 2017-18
	Lenvatinib	£542.08	NICE TA474, TA514, TA535, TA551; NHS Reference Costs 2017-18
	Sorafenib/BSC (work-up/no SIRT)	£577.40	NICE TA474, TA514, TA535, TA551; NHS Reference Costs 2017-18
Health state costs (per cycle)	PFS (SIRT)	£113.03	Sirtex expert elicitation; NHS Reference Costs 2017-18, PSSRU 2018
	PFS (Systemic therapies)	£132.10	Sirtex expert elicitation; NHS Reference Costs 2017-18, PSSRU 2019
	Upon progression	£95.57	Sirtex expert elicitation; NHS Reference Costs 2017-18, PSSRU 2020
	Post-progression	£229.69	Sirtex expert elicitation; NHS Reference Costs 2017-18, PSSRU 2021
	End-of-life	£8,191.00	Georghiou and Bardsley[125]
	Post-curative therapy (scenario)	£113.03	Sirtex expert elicitation; NHS Reference Costs 2017-18.

8.3 Analytic methods

8.3.1 Base-case analysis

The AG produced fully incremental ICERs for each strategy included in the model, however, this approach generated a number of ICERs expressed in terms of dominance due to the close similarity of health outcomes predicted for the SIRT technologies.

The AG therefore considered a net benefit framework to be the most appropriate approach to present the relative cost-effectiveness of the three SIRT technologies with existing practice. This method is often preferred when there are a number of technologies under comparison, particularly when incremental costs and benefits are very similar. Technologies with identical health outcomes and marginal differences in costs are often labelled as ‘dominant/dominated’ using incremental cost-effectiveness analysis with conventional decision rules. Considering net health benefit instead permits a more informative comparison of the effect of alternative strategies.

Net monetary benefit (NMB) is calculated using a rearrangement of the ICER formula, but inherently compares the incremental health gain versus the comparator with a willingness-to-pay threshold (WTP). The NMB formula thereby assigns a value to the additional QALYs generated by an intervention, and considers the opportunity cost associated with generating these health benefits. The formula used to define NMB is $\lambda \times \Delta E - \Delta C$ where the difference in health effects (ΔE) is multiplied by the selected WTP threshold (λ) minus the difference in costs (ΔC), i.e. £30,000 in the results presented below. Using this approach, if an intervention has an incremental NMB >0, then it would be considered more cost-effective than the baseline option, in this case, the least costly option. NMB results (including PAS discounts) at a £20,000 and £30,000 threshold are also presented in the confidential appendix.

The AG model accounted for uncertainty using probabilistic and deterministic sensitivity analyses. PSA was undertaken using simple Monte Carlo sampling methods, using 20,000 samples for the AG base-case, and 5,000 samples in the primary scenario analyses. The choice of distribution to reflect uncertainty around each parameter was selected for each according to its statistical suitability. To account for uncertainty around the parametric survival models fitted to OS and PFS, outcomes were sampled via Cholesky decomposition using the variance-covariance matrices produced during survival modelling. When a hazard ratio was used to estimate PFS and OS outcomes, alternate values were drawn in each model iteration from the NMA output from WinBUGS (CODA) to model uncertainty in the predicted treatment effects.

8.3.2 Model validation

The AG adopted a number of approaches to ensure the credibility and validity of the model. These included scrutiny of the implemented model coding and formulae by two modellers, black-box testing in which the predictive validity of parameter inputs (e.g. that increasing effectiveness of the treatment lowers cost-effectiveness) was assessed, checking the accuracy of all model inputs against the original sources, and consultation with clinical experts on key assumptions (see Acknowledgements).

8.4 Results of the independent economic assessment

8.4.1 Base-case results

The deterministic and probabilistic fully incremental results of the AG's base-case analysis (excluding confidential PAS discounts for QuiremScout, sorafenib, lenvatinib, and regorafenib) are presented in

Table 33. The probabilistic results were based on 20,000 model iterations.

The AG's base-case was based on the following assumptions and data sources:

- SIR-Spheres efficacy based on a pooled survival analysis of SARAH[2] and SIRveNIB[3] data (per protocol population)
- QuiremSpheres and TheraSphere efficacy equal to SIR-Spheres
- For patients who received work-up but no SIRT, OS and PFS based on SARAH[2] Kaplan-Meier
- Sorafenib efficacy based on a pooled survival analysis of SARAH[2] and SIRveNIB[3] data (ITT population)
- Lenvatinib HR derived from AG's NMA (ITT population)
- OS and PFS extrapolated using Weibull model
- Decision-tree transition probabilities estimated using data from SARAH[2] trial
- No downstaging to curative therapy permitted
- Bilobar treatments performed in two separate procedures
- Work-up costs from Christie elicitation (as per the BTG economic analysis)
- Health state utilities from SARAH[2] per protocol subgroup, based on therapeutic class (SIRT and systemic therapy)

Based on the probabilistic version of the AG model, the three SIRT technologies are each expected to generate fewer QALYs than sorafenib or lenvatinib, but were associated with higher costs. SIRT generated 0.765 QALYs – this was 0.076 QALYs fewer than generated by sorafenib, and 0.060 fewer than by lenvatinib. TheraSphere and SIR-Spheres had very similar total costs, while QuiremSpheres was the most costly due to the additional costs associated with procurement of QuiremScout.

Figure 19 presents CEACs for the fully incremental results of the AG model. Lenvatinib has the highest likelihood of being cost-effective across any WTP threshold under £100,000. Assuming a WTP threshold of £30,000 per QALY gained, TheraSphere had an incremental NMB of -£2,154, whilst this was -£2,323 for SIR-Spheres. The NMB for QuiremSpheres versus lenvatinib was -£8,741. All three SIRT technologies were dominated by lenvatinib. Disaggregated deterministic results show that just under half of the QALY gain in both groups is accrued in the post-progression health state.

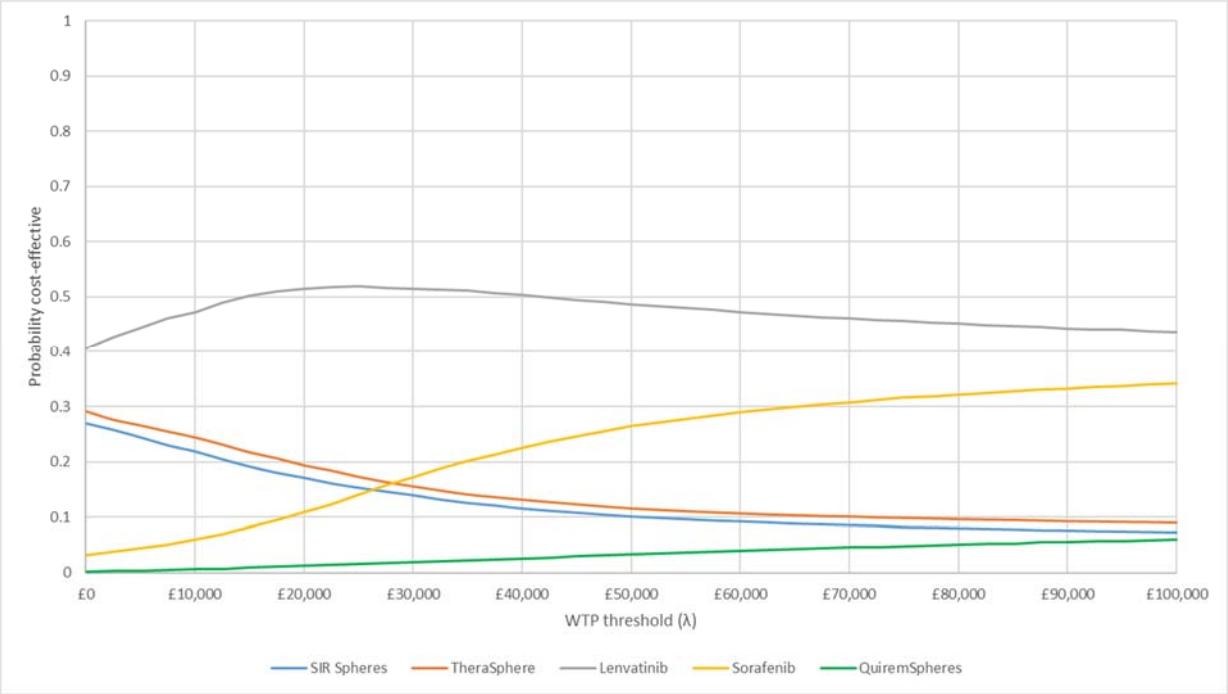
For results including the confidential PAS discounts for sorafenib, lenvatinib, regorafenib, and QuiremSpheres, the confidential appendix.

Table 33: Fully incremental results of the AG's base-case analysis

Intervention	Total			Incremental (vs baseline)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB	
AG Deterministic base-case								
TheraSphere	£29,888	1.110	0.764					
Lenvatinib	£30,005	1.183	0.805	£117	0.04	£2,911	£1,090	£2,911
SIR-Spheres	£30,107	1.110	0.764	£218	0.000	More costly	-£218	Ext. dom.
Sorafenib	£32,082	1.243	0.841	£2,194	0.076	£28,728	£97	£57,488
QuiremSpheres	£36,503	1.110	0.764	£6,614	0.000	More costly	-£6,614	Ext. dom.
AG Probabilistic base-case								
Lenvatinib	£29,658	1.202	0.825					
TheraSphere	£30,014	1.111	0.765	£356	-0.060	Dominated	-£2,154	Dominated
SIR Spheres	£30,196	1.111	0.765	£538	-0.060	Dominated	-£2,323	Dominated
Sorafenib	£32,444	1.244	0.841	£2,786	0.016	£174,320	-£2,306	£174,320
QuiremSpheres	£36,613	1.111	0.765	£6,955	-0.060	Dominated	-£8,741	Dominated

Abbreviations: Ext. dom., Extendedly dominated; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years

Figure 19: Cost-effectiveness acceptability curve for AG probabilistic base-case analysis



8.4.2 Sensitivity analyses results

8.4.2.1 Scenario analyses

Scenario 1: Efficacy data from SARAH only

The first scenario analysis explores the effect of using only data from the European SARAH trial[2] to inform efficacy estimates for SIRT and sorafenib, on the basis that this might better represent the patient population and clinical practice in the UK. Deterministic and probabilistic results are presented in Table 34. The probabilistic results are based on 5,000 model iterations. As with the AG base-case, each SIRT is associated with the same number of life-years and QALYs, however, this scenario predicts lower OS (and thus LYs/QALYs) than in the base-case, which makes SIR-Spheres marginally cheaper than lenvatinib.

Table 34: AG Scenario 1 results: Efficacy data from SARAH only

Intervention	Total			Incremental (vs baseline)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB	
Deterministic Scenario 1: Efficacy data from SARAH only								
TheraSphere	£29,395	0.976	0.671					
SIR Spheres	£29,614	0.976	0.671	£218	0.000	More costly	-£218	Ext. dom.
Lenvatinib	£29,893	1.150	0.782	£498	0.111	£4,475	£2,840	£4,475
Sorafenib	£31,951	1.209	0.817	£2,556	0.147	£17,424	£1,845	£58,080
QuiremSpheres	£36,010	0.976	0.671	£6,614	0.000	More costly	-£6,614	Ext. dom.
Probabilistic Scenario 1: Efficacy data from SARAH only								
Lenvatinib	£29,413	1.171	0.805					
TheraSphere	£29,476	0.978	0.672	£62	-0.133	Dominated	-£4,044	Dominated
SIR Spheres	£29,660	0.977	0.671	£246	-0.134	Dominated	-£4,267	Dominated
Sorafenib	£32,300	1.213	0.818	£2,887	0.014	£212,505	-£2,479	£212,505
QuiremSpheres	£36,064	0.977	0.670	£6,650	-0.134	Dominated	-£10,684	Dominated

Abbreviations: Ext. dom., Extendedly dominated; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years

Scenario 2: Low tumour burden/ALBI grade 1 subgroup (SARAH)

This scenario explores the use of the company's preferred *post-hoc* grouping of patients from the SARAH trial[2] as the source of efficacy data for SIRT and sorafenib. Further changes from the AG base-case are the use of the higher low tumour burden/ALBI 1 subgroup utilities from the SARAH trial[2], and the significantly lower proportion of patients who receive work-up but not SIRT (8.1% vs 18.6%). Note that while Sirtex used a proportion of 2.9% for work-up failures in this population, it was unclear how this figure was reached. Increasing the number of work-up failures, however, increases the cost-effectiveness of SIRT.

This scenario predicts the cost-effectiveness of an optimised decision in which only patients who have a tumour burden of ≤25% and a preserved liver function would be eligible to receive SIRT. As there is no equivalent evidence available for lenvatinib, this scenario assumes the HR between sorafenib and lenvatinib remains the same as in the base-case population.

Table 35 shows that while the systemic therapies were less costly than SIRT in this scenario, SIR-Spheres generated an additional 0.139 QALYs vs lenvatinib and 0.117 vs sorafenib in the probabilistic model. This resulted in fully incremental ICERs of £20,926 per QALY gained for TheraSphere compared with lenvatinib, and £119,562 for SIR-Spheres compared with TheraSphere. However, the two technologies were distinguished only by the additional fluoroscopy cost associated with the SIR-Spheres procedure, resulting in very similar NMB at a £30,000 threshold. This is notably the only scenario in which TheraSphere and SIR-Spheres have a positive incremental NMB versus lenvatinib at a WTP threshold of £30,000 (excluding Scenario 4). This is illustrated by the CEAC in Figure 20, which shows lenvatinib to have the highest likelihood of being cost-effective up to a WTP threshold of approximately £27,000, at which point is surpassed by TheraSphere, and SIR-Spheres at a WTP threshold of £32,000 and above.

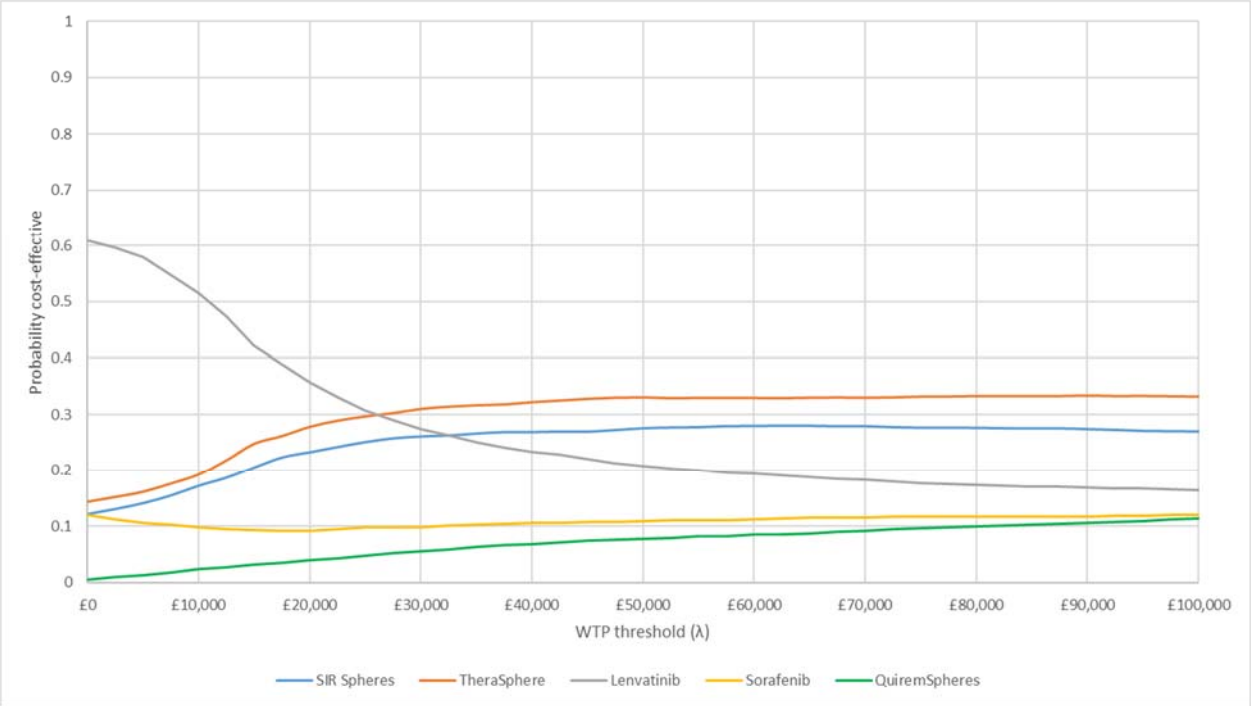
Results including the confidential PAS discounts for sorafenib, lenvatinib, regorafenib, and QuiremSpheres can be found in the confidential appendix.

Table 35: AG Scenario 2 results: Low tumour burden/ALBI grade 1 subgroup

Intervention	Total			Incremental (vs baseline)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB	
Deterministic Scenario 2: Low tumour burden/ALBI grade 1 subgroup								
Lenvatinib	£31,388	1.366	1.000					
Sorafenib	£33,388	1.420	1.037	£2,000	0.038	£53,320	-£875	Ext. dom.
TheraSphere	£34,021	1.542	1.153	£2,633	0.153	£17,175	£1,966	£17,175
SIR Spheres	£34,267	1.542	1.153	£2,879	0.153	£18,783	£1,720	Dominated
QuiremSpheres	£40,931	1.542	1.153	£9,543	0.153	£62,257	-£4,945	Dominated
Probabilistic Scenario 2: Low tumour burden/ALBI grade 1 subgroup								
Lenvatinib	£31,233	1.397	1.024					
Sorafenib	£33,834	1.436	1.048	£2,601	0.024	£109,709	-£1,890	Ext. dom.
TheraSphere	£34,086	1.552	1.161	£2,854	0.136	£20,926	£1,237	£20,926
SIR Spheres	£34,389	1.553	1.163	£3,156	0.139	£22,725	£1,010	£119,562
QuiremSpheres	£41,088	1.552	1.162	£9,855	0.138	£71,372	-£5,712	Ext. dom.

Abbreviations: Ext. dom., Extendedly dominated; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years

Figure 20: Cost-effectiveness acceptability curve for AG Scenario 2: Low tumour burden/ALBI grade 1 subgroup



Scenario 3: No macroscopic vascular invasion (SARAH)

This scenario limits the patient population to only those who had no macroscopic vascular invasion (MVI), referred to elsewhere as portal vein invasion, at baseline. These patients may be expected to benefit more from SIRT technologies due to a more favourable positioning and spread of their tumour, and were thus defined as a subgroup of interest in NICE's scope. As there is no equivalent evidence for lenvatinib, this scenario assumes the HR between sorafenib and lenvatinib remains the same as in the base-case population.

The probabilistic analysis in

Table 36 found all three SIRTs to be dominated by lenvatinib, with a significantly lower NMB than either systemic therapy. Notably, the gap in QALYs produced by SIRT vs sorafenib widened in this analysis versus the base-case, implying a reduced benefit of SIRT in this population.

Table 36: AG Scenario 3 results: No macroscopic vascular invasion

Intervention	Total			Incremental (vs baseline)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB	
Deterministic Scenario 3: No macroscopic vascular invasion (SARAH)								
TheraSphere	£29,949	1.272	0.740					
SIR Spheres	£30,167	1.326	0.740	£218	0.000	More costly	-£218	Ext. dom.
Lenvatinib	£30,399	1.078	0.865	£451	0.125	£3,594	£3,310	£3,594
Sorafenib	£32,452	1.078	0.897	£2,503	0.157	£15,923	£2,213	£64,437
QuiremSpheres	£36,563	1.078	0.740	£6,614	0.000	More costly	-£6,614	Ext. dom.
Probabilistic Scenario 3: No macroscopic vascular invasion (SARAH)								
Lenvatinib	£29,983	1.296	0.893					
TheraSphere	£30,093	1.335	0.743	£110	-0.149	Dominated	-£4,585	Dominated
SIR Spheres	£30,287	1.083	0.744	£304	-0.149	Dominated	-£4,765	Dominated
Sorafenib	£32,852	1.082	0.905	£2,868	0.012	£238,195	-£2,507	£238,195
QuiremSpheres	£36,683	1.081	0.745	£6,699	-0.148	Dominated	-£11,134	Dominated

Abbreviations: Ext. dom., Extendedly dominated; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life-years

Scenario 4: TheraSphere HR from Biederman and Van Der Gucht NMA scenario

The results presented in

Table 37 use the hazard ratio derived from the AG's NMA scenario which included the low quality retrospective studies Biederman *et al.*[19] and Van Der Gucht *et al*.[18] The patient population in Biederman *et al*. was particularly mismatched with the others included in this analysis, as it only included patients with MVI, which appeared to have a substantial impact upon the treatment effect associated with TheraSphere.

A hazard ratio of 0.46 versus SIR-Spheres was applied for both OS and PFS outcomes for TheraSphere. Based on the probabilistic analysis (5000 iterations), TheraSphere is expected to generate an additional 0.507 QALYs compared with lenvatinib, at an additional cost of £4,068, producing an ICER of £8,017 per QALY gained, and a NMB of £11,413. TheraSphere was associated with higher costs than SIR-Spheres due to the increased disease management costs associated with lower mortality, but it also produced an additional 0.566 QALYs, yielding an ICER of £6,060 per QALY gained.

Table 37: AG Scenario 4 results: TheraSphere HR from Biederman and Van Der Gucht NMA scenario

Intervention	Total			Incremental (vs baseline)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB	
Deterministic Scenario 4: TheraSphere HR from Biederman and Van Der Gucht NMA scenario								
Lenvatinib	£30,005	1.183	0.805					
SIR Spheres	£30,107	1.110	0.764	£101	-0.040	Dominated	-£1,308	Dominated
Sorafenib	£32,082	1.243	0.841	£2,077	0.036	£57,488	-£993	Ext. dom.
TheraSphere	£33,373	1.883	1.297	£3,368	0.493	£6,835	£11,413	£6,835
QuiremSpheres	£36,503	1.110	0.764	£6,497	-0.040	Dominated	-£7,705	Dominated
Probabilistic Scenario 4: TheraSphere HR from Biederman and Van Der Gucht NMA scenario								
Lenvatinib	£29,601	1.197	0.822					
SIR Spheres	£30,242	1.110	0.764	£641	-0.058	Dominated	-£2,387	Dominated
Sorafenib	£32,477	1.244	0.843	£2,876	0.021	£140,205	-£2,260	Ext. dom.
TheraSphere	£33,670	1.931	1.330	£4,068	0.507	£8,017	£11,156	£8,017
QuiremSpheres	£36,616	1.111	0.765	£7,014	-0.058	Dominated	-£8,746	Dominated

Abbreviations: Ext. dom., Extendedly dominated; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years

Further scenario analyses

Table 38 presents a number of other scenarios on the AG base-case which explore the impact of alternative assumptions, including sources of utilities, downstaging to curative therapy, resource use, and survival models.

Scenarios 6 & 10 include the possibility for downstaging; in these scenarios, the distribution of the three liver-targeted treatments were derived from the SARAH trial.[2] Patients who received TACE or radiation therapy were excluded as these would not be permitted options in this population in UK practice. Liver transplant was undergone by 1.09% of SIRT patients and 0.46% of sorafenib patients, 1.63% of SIRT patients and 0% of sorafenib patients underwent liver resection, while 3.26% of SIRT patients and 0.92% of sorafenib patients received ablation therapy.

Only the deterministic results are produced for these analyses.

Table 38: Further scenario analyses (AG Scenarios 5 - 17)

Intervention	Total			Incremental (vs baseline)				ICER (fully inc.)
	Costs	LYs	QALYs	Costs	QALYs	ICER	NMB	
Scenario 5: Utilities from lenvatinib TA511								
TheraSphere	£29,888	1.110	0.791					
Lenvatinib	£30,005	1.183	0.846	£117	0.055	£2,113	£1,546	£2,113
SIR Spheres	£30,107	1.110	0.791	£218	0.000	More costly	-£218	Ext. dom.
Sorafenib	£32,082	1.243	0.881	£2,194	0.091	£24,145	£532	£58,615
QuiremSpheres	£36,503	1.110	0.791	£6,614	0.000	More costly	-£6,614	Ext. dom.
Scenario 6: Downstaging to curative therapy possible (SARAH ITT proportions)								
TheraSphere	£28,990	1.217	0.842					
SIR Spheres	£29,208	1.217	0.842	£218	0.000	More costly	-£218	Ext. dom.
Lenvatinib	£29,817	1.212	0.826	£827	-0.016	Dominated	-£1,292	Dominated
Sorafenib	£31,850	1.271	0.862	£2,860	0.020	£142,238	-£2,256	£142,238
QuiremSpheres	£35,605	1.217	0.842	£6,614	0.000	More costly	-£6,614	Ext. dom.
Scenario 7: Bilobar disease treated in same procedure								
TheraSphere	£29,159	1.110	0.764					
SIR Spheres	£29,364	1.110	0.764	£204	0.000	More costly	-£204	Ext. dom.
Lenvatinib	£30,005	1.183	0.805	£846	0.040	£21,026	£361	£21,026
Sorafenib	£32,082	1.243	0.841	£2,923	0.076	£38,274	-£632	£57,488
QuiremSpheres	£35,646	1.110	0.764	£6,486	0.000	More costly	-£6,486	Ext. dom.
Scenario 8: Work-up costs from NHS Reference Costs (Sirtex assumption)								
Lenvatinib	£30,005	1.183	0.805					
TheraSphere	£30,170	1.110	0.764	£165	-0.040	Dominated	-£1,372	Dominated
SIR Spheres	£30,389	1.110	0.764	£383	-0.040	Dominated	-£1,590	Dominated
Sorafenib	£32,082	1.243	0.841	£2,077	0.036	£57,488	-£993	£57,488
QuiremSpheres	£36,864	1.110	0.764	£6,859	-0.040	Dominated	-£8,066	Dominated
Scenario 9: Disease management costs taken from TA551								
Lenvatinib	£48,033	1.183	0.805					
TheraSphere	£48,186	1.110	0.764	£152	-0.040	Dominated	-£1,360	Dominated
SIR Spheres	£48,404	1.110	0.764	£371	-0.040	Dominated	-£1,578	Dominated
Sorafenib	£53,682	1.243	0.841	£5,649	0.036	£156,367	-£4,565	£156,367
QuiremSpheres	£54,800	1.110	0.764	£6,767	-0.040	Dominated	-£7,974	Dominated
Scenario 10: Low tumour burden/ALBI 1 subgroup including possibility of downstaging								
Lenvatinib	£31,072	1.404	1.029					
TheraSphere	£31,255	1.752	1.316	£183	0.286	£639	£8,407	£639
SIR Spheres	£31,501	1.752	1.316	£429	0.286	£1,499	£8,160	Dominated
Sorafenib	£33,007	1.457	1.066	£1,935	0.037	£52,685	-£833	Ext. dom.

QuiremSpheres	£38,166	1.752	1.316	£7,094	0.286	£24,775	£1,496	Dominated
Scenario 11: Gompertz OS								
TheraSphere	£30,015	1.127	0.776					
Lenvatinib	£30,066	1.188	0.808	£51	0.033	£1,555	£926	£1,555
SIR Spheres	£30,234	1.127	0.776	£218	0.000	More costly	-£218	Ext. dom.
Sorafenib	£32,190	1.255	0.849	£2,174	0.073	£29,634	£27	£52,020
QuiremSpheres	£36,630	1.127	0.776	£6,614	0.000	More costly	-£6,614	Ext. dom.
Scenario 12: Exponential OS								
Lenvatinib	£30,239	1.215	0.826					
TheraSphere	£30,245	1.160	0.798	£5	-0.028	Dominated	-£860	Dominated
SIR Spheres	£30,463	1.160	0.798	£224	-0.028	Dominated	-£1,078	Dominated
Sorafenib	£32,379	1.285	0.868	£2,139	0.042	£50,493	-£868	£50,493
QuiremSpheres	£36,859	1.160	0.798	£6,620	-0.028	Dominated	-£7,474	Dominated
Scenario 13: Generalised gamma OS (lenvatinib OS equal to sorafenib)								
TheraSphere	£30,992	1.277	0.875					
Lenvatinib	£31,148	1.357	0.919	£155	0.044	£3,561	£1,154	£3,561
SIR Spheres	£31,211	1.277	0.875	£218	0.000	More costly	-£218	Ext. dom.
Sorafenib	£32,854	1.357	0.916	£1,862	0.040	£46,103	-£650	Ext. dom.
QuiremSpheres	£37,607	1.277	0.875	£6,614	0.000	More costly	-£6,614	Ext. dom.
Scenario 14: Log-normal OS (lenvatinib OS equal to sorafenib)								
TheraSphere	£30,208	1.156	0.795					
SIR Spheres	£30,426	1.156	0.795	£218	0.000	More costly	-£218	Ext. dom.
Lenvatinib	£31,480	1.408	0.952	£1,273	0.158	£8,078	£3,454	£8,078
Sorafenib	£33,187	1.408	0.949	£2,979	0.154	£19,311	£1,649	Ext. dom.
QuiremSpheres	£36,822	1.156	0.795	£6,614	0.000	More costly	-£6,614	Ext. dom.
Scenario 15: Log-logistic OS (lenvatinib OS equal to sorafenib)								
TheraSphere	£30,301	1.169	0.804					
SIR Spheres	£30,519	1.169	0.804	£218	0.000	More costly	-£218	Ext. dom.
Lenvatinib	£31,543	1.420	0.960	£1,242	0.156	£7,962	£3,439	£7,962
Sorafenib	£33,249	1.420	0.956	£2,949	0.153	£19,303	£1,634	Ext. dom.
QuiremSpheres	£36,915	1.169	0.804	£6,614	0.000	More costly	-£6,614	Ext. dom.
Scenario 16: 5% work-up/no SIRT								
Lenvatinib	£30,005	1.183	0.805					
Sorafenib	£32,082	1.243	0.841	£2,077	0.036	£57,488	-£993	£57,488
TheraSphere	£32,603	1.183	0.816	£2,597	0.011	£239,222	-£2,272	Ext. dom.
SIR Spheres	£32,858	1.183	0.816	£2,852	0.011	£262,683	-£2,526	Ext. dom.
QuiremSpheres	£39,601	1.183	0.816	£9,596	0.011	£883,746	-£9,270	Ext. dom.
Scenario 17: SIRveNIB work-up/no SIRT (28.57%)								

TheraSphere	£27,898	1.056	0.727					
SIR Spheres	£28,090	1.056	0.727	£192	0.000	More costly	-£192	Ext. dom.
Lenvatinib	£30,005	1.183	0.805	£2,107	0.078	£27,118	£224	£27,118
Sorafenib	£32,082	1.243	0.841	£4,184	0.114	£36,757	-£769	£57,488
QuiremSpheres	£34,232	1.056	0.727	£6,333	0.000	More costly	-£6,333	Dominated

Abbreviations: Ext. dom., Extendedly dominated; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALYs, quality-adjusted life years

Table 39 presents the results of the base-case and selected scenario analyses in terms of their effect upon the NMB ranking of the five technologies at list price. This shows lenvatinib to be consistently ranked first in terms of incremental NMB, except in those scenarios which use more favourable assumptions in favour of SIRT. As SIRT produces QALYs at above the WTP threshold, increasing the proportion of patients who fail work-up (Scenario 17) and do not go on to receive SIRT increases its cost-effectiveness, as overall costs are reduced and the more cost-effective QALYs produced on BSC and sorafenib are up-weighted.

Table 39: Incremental net monetary benefit rankings

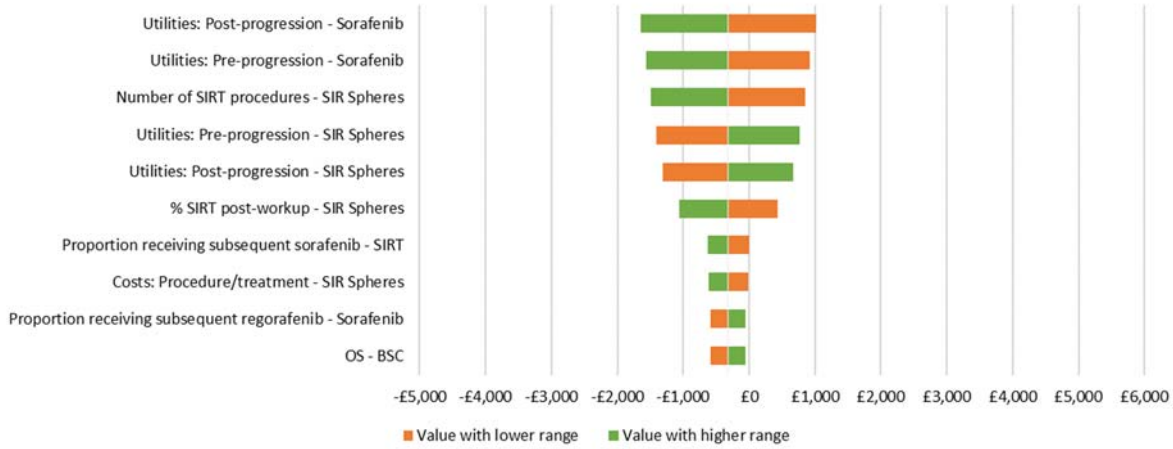
Intervention	Incremental NMB Rank (vs baseline)																	
	Base case	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14	S15	S16	S17
SIR-Spheres	4	4	2	4	4	4	2	3	4	3	2	4	4	3	4	4	4	3
TheraSphere	2	3	**1**	3	**1**	3	**1**	2	3	2	**1**	3	3	2	3	3	3	2
QuiremSpheres	5	5	5	5	5	5	5	5	5	5	3	5	5	5	5	5	5	5
Lenvatinib	**1**	**1**	3	**1**	2	**1**	3	**1**	**1**	**1**	4	**1**	**1**	**1**	**1**	**1**	**1**	**1**
Sorafenib	3	2	4	2	3	2	4	4	2	4	5	2	2	4	2	2	2	4

8.4.2.2 Deterministic sensitivity analysis

Results of the deterministic sensitivity analyses (DSA) are presented in Figure 21 to Figure 25, for the AG base-case scenario and the four scenarios presented in Section 8.4.2.1. The tornado diagrams presented the ten most influential parameters in each analysis. SIR-Spheres was compared with sorafenib, since sorafenib was considered the most relevant comparator and had direct evidence compared to SIR-Spheres.

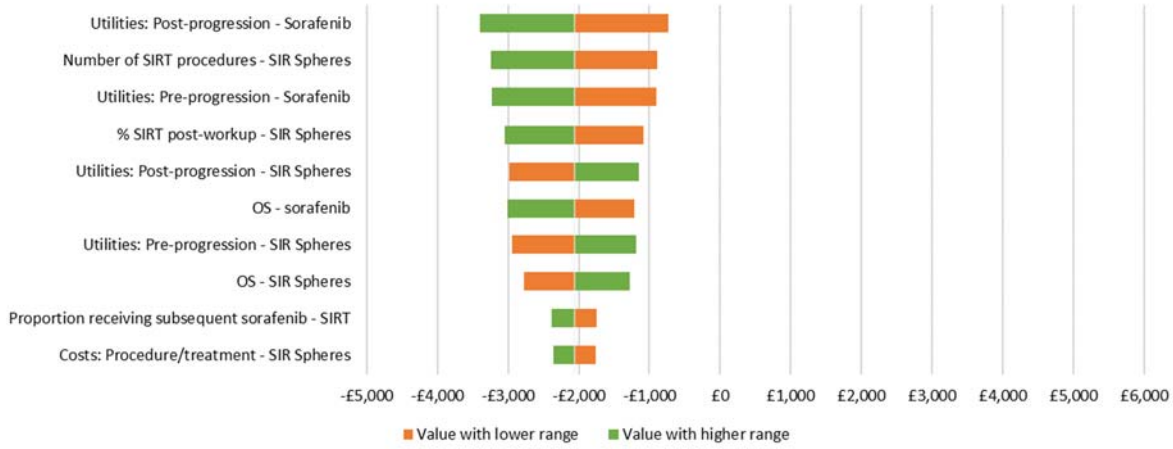
The AG base-case analysis (Figure 21) was robust to a range of parameters, with the most influential parameters providing a range of NMB between approximately -£1,600 and £1,000, with the base-case NMB as -£315. The most influential parameters were the health state utilities, the number of SIRT procedures and the proportion of patients receiving SIRT after work-up. In these scenarios, SIR-Spheres became cost-effective compared with sorafenib for some of the range of values of the parameter, i.e. SIR-Spheres had a positive incremental NMB. However, when the confidential PAS for sorafenib was applied, this was no longer the case.

Figure 21: Tornado diagram – SIR-Spheres versus sorafenib, base-case analysis (SARAH and SIRveNIB)



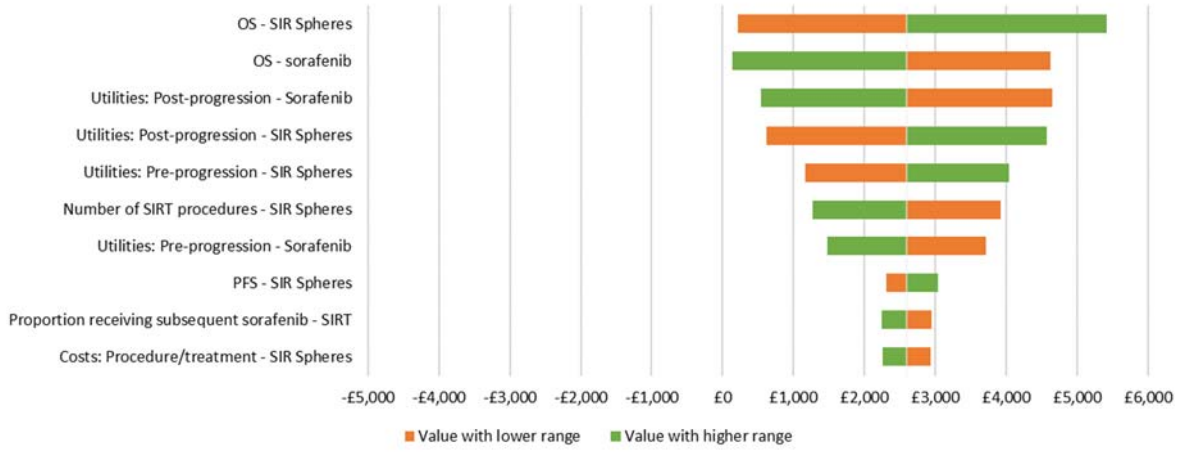
In Scenario 1, with efficacy data based on SARAH only, varying the parameters in the DSA had a larger impact on NMB than in the base-case analysis, although the variation remains small (Figure 22). Similarly to the base-case analysis, the results were most sensitive to health state utilities and SIRT procedures; however, in this analysis, OS for sorafenib and SIR-Spheres was also an influential parameter. There were no scenarios in which SIR-Spheres was estimated to be cost-effective compared with sorafenib.

Figure 22: Tornado diagram – SIR-Spheres versus sorafenib, using SARAH efficacy data (Scenario 1)



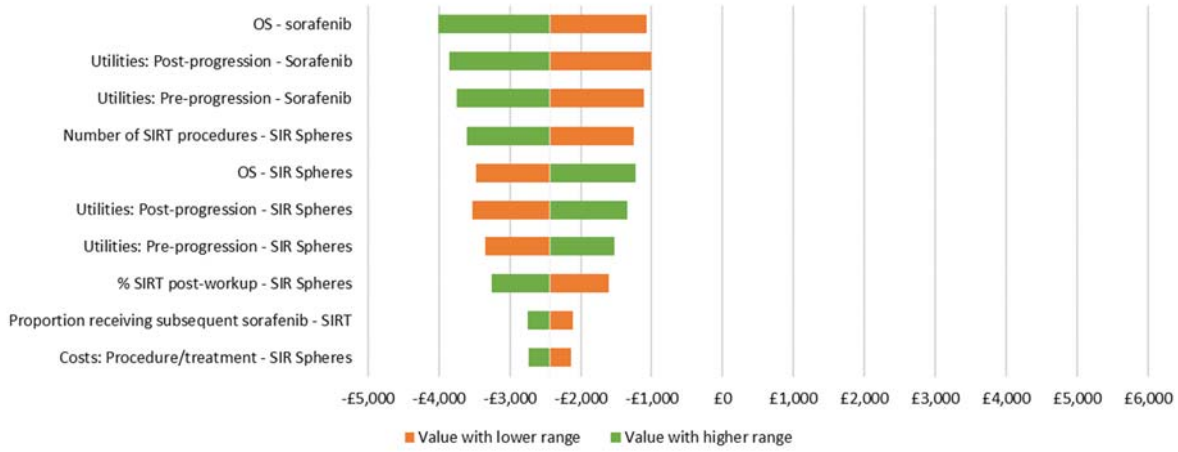
The most influential parameters in the low tumour burden/ALBI 1 subgroup was OS for both SIR-Spheres and sorafenib (Figure 23). SIR-Spheres remained cost-effective compared with sorafenib over the range of parameters; however, when the confidential PAS for sorafenib was applied, this was no longer the case.

Figure 23: Tornado diagram – SIR-Spheres versus sorafenib, low tumour burden/ALBI 1 subgroup (Scenario 2)



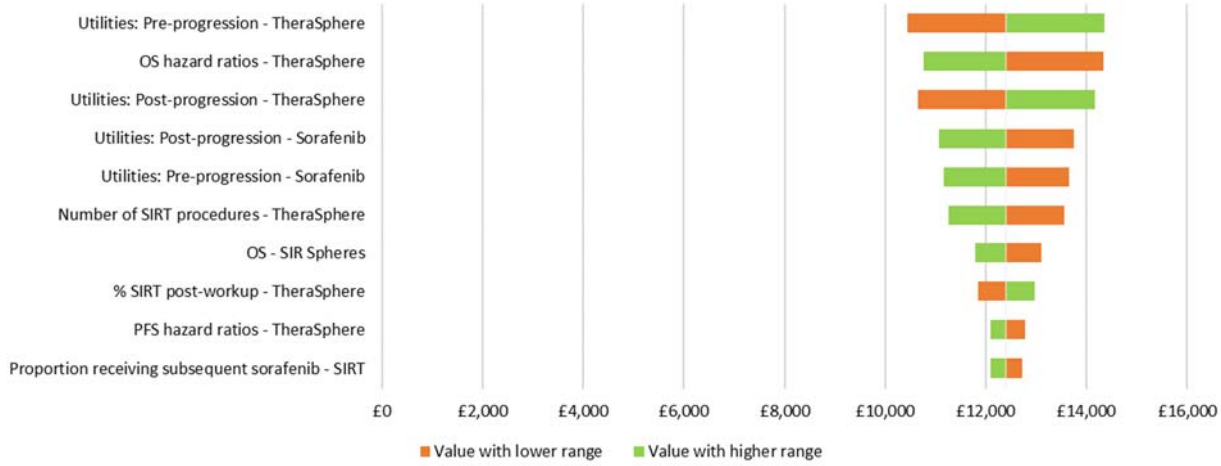
In the 'no MVI' subgroup, the most influential parameters were the health state utilities, and OS for sorafenib and SIR-Spheres (Figure 24). There were are no scenarios in which SIR-Spheres was estimated to be cost-effective compared with sorafenib.

Figure 24: Tornado diagram – SIR-Spheres versus sorafenib, no MVI subgroup (Scenario 3)



In Figure 25, TheraSphere was compared with sorafenib. In this scenario, the results of the analysis were robust to the range of parameters, and found TheraSphere to be cost-effective across all scenarios.

Figure 25: Tornado diagram – TheraSphere versus sorafenib, TheraSphere HR from Van Der Gucht and Biederman NMA (Scenario 4)



8.5 Discussion of the independent economic assessment

In light of the AG's concerns regarding the relevance of economic analyses identified in the review of cost-effectiveness studies and highlighted limitations in the economic evaluations developed by BTG and Sirtex, the AG developed a *de novo* health economic model. The AG model evaluated the three SIRT technologies and current UK practice for the treatment of advanced HCC in Child-Pugh A patients ineligible to receive (or previously failed) CTT. Results were generated as fully incremental ICERs and in terms of incremental NMB, which allows for easier comparison of 'dominated' results with small differences in cost and efficacy. The AG model used a three-state partitioned survival model approach with a decision tree which determined the proportion of patients who did not continue on to receive SIRT following the work-up procedure. The model utilises all currently available RCT evidence to generate estimates of clinical effectiveness, using data directly drawn from the SARAH[2] and SIRveNIB[3] trials, and hazard ratios generated in the AG's network meta-analysis.

Based on the AG's probabilistic base-case analysis at list price, none of the three SIRT technologies are expected to be cost-effective at any WTP threshold, being more costly and less effective than lenvatinib. When the modelled population was limited to only those with a low tumour burden and preserved liver function, the ICERs for TheraSphere and SIR-Spheres were £22,420 and £23,617 per QALY gained versus the most cost-effective systemic therapy. The most optimistic ICERs were generated in the scenario presented for the low tumour burden and preserved liver function in which downstaging to curative therapy was permitted. In this scenario the ICERs for TheraSphere and SIR-Spheres decreased to £3,569 and £4,356 respectively. However, there was no scenario in which SIRT was predicted to be cost-effective at a WTP threshold of £30,000 when confidential PAS discounts were included (see confidential appendix). In all scenarios, QuiremSpheres was not cost-effective

compared with other SIRTs due to higher work-up and acquisition costs, see below for further discussion of QuiremSpheres in relation to the limitations of the model.

AG Scenario 4 (including Biederman and van der Gucht) found TheraSphere to be cost-effective versus lenvatinib when the confidential PAS prices were used. However, the AG considers the data used to model comparative effectiveness to be of low quality and inconsistent with the wider body of evidence on the comparative effectiveness of SIR-Spheres and TheraSphere. The AG therefore does not consider this scenario to represent a realistic estimate of the relative benefits of TheraSphere.

The results of the AG's base-case analysis are robust to a wide range of assumptions, reflecting the completeness and quality of the included studies, and the substantial differences seen in costs and QALYs between the SIRT technologies and current UK practice (including confidential PAS). The AG's analyses predicted lenvatinib to rank first in terms of NMB all scenarios (excluding Scenario 4), while sorafenib was a cost-effective alternative, producing more QALYs at a higher cost. There are a number of differences between the AG model and those presented by the companies, which primarily concern the issues highlighted in the critique of these models in Section 6.3. Strengths of the AG model include: (i) all available high-quality RCT data were used to model the outcomes of the most relevant patient population to UK practice; (ii) analyses included all appropriate comparators (iii) independent modelling of the costs and outcomes of patients who receive work-up but were ineligible to receive SIRT, and (iv) preserved randomisation and greater internal consistency with regards to the use of subsequent and curative therapies.

Insurmountable limitations in the evidence base meant the AG were unable to address the question of the cost-effectiveness of SIRT in patients with early and intermediate HCC. The evidence for TheraSphere and QuiremSpheres in advanced HCC was extremely limited, and a lack of head-to-head evidence prevented a meaningful comparison of SIR-Spheres, TheraSphere, and QuiremSpheres with one another in terms of clinical effectiveness. This essentially limits this particular comparison to that of a cost-minimisation, with a full comparison of the cost-effectiveness of SIRT versus sorafenib and lenvatinib. While it is therefore not possible to discern which of the SIRT technologies offers the best value for money, the increased cost of the QuiremSpheres work-up procedure meant it was consistently positioned last by some way in terms of NMB. The structure of the AG model and a lack of supporting evidence on the comparative effectiveness of QuiremSpheres, however, meant there were no means by which the concept of 'sub-optimal SIRT', as proposed by Terumo, could realistically be explored. This includes the ostensibly greater selectivity of QuiremScout, and any quantifiable improvement in treatment effect resulting from optimisation of patient selection.

9 Assessment of factors relevant to the NHS and other parties

9.1 End-of-life considerations

In the early and intermediate HCC populations life expectancy reported in the most recent ESMO guidelines is greater than 24 months,[150] with reported expected survival of >5 years in the early population and >2.5 years in the intermediate population. There is insufficient reliable evidence to indicate whether SIRT provides an extension to life of greater than 3 months.

The NICE end of life supplementary advice [138] outlines that end-of-life criteria should be applied in the following circumstances and when both the criteria below are satisfied:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment.

Undiscounted LYG predicted in the AG's base-case analysis are presented in Table 40. These indicate that normal life expectancy for patients ineligible for CTT is less than 24 months, with expected mean survival of 14.72 months on lenvatinib and 15.49 months on sorafenib. This conclusion remains consistent irrespective of the subgroup considered or the choice of parametric model used to represent OS.

Regarding the criterion relating to >3 months life extension, the AG's base-case analysis suggests that SIRT is marginally inferior to both systemic therapies (sorafenib and lenvatinib) indicating that this criterion is not met. The subgroup with no macroscopic vascular invasion (MVI) similarly suggests that sorafenib produces marginally greater LYG than SIRT therapies. In the low tumour burden/ALBI 1 subgroup, SIRT therapies are predicted to provide an extension to life of 2.11 months compared with sorafenib and 2.80 months compared with lenvatinib. These predicted survival gains, however, exclude potential gains from downstaging. In scenarios conducted in the low tumour burden/ALBI 1 subgroup which allow for downstaging, predicted survival gains increase to 4.61 months compared with sorafenib and 5.30 months compared with lenvatinib. These predicted gains are, however, subject to significant uncertainty due to the small sample sizes and the fact that this is a *post-hoc* subgroup analysis. There are also very significant uncertainties regarding the plausibility of downstaging patients in this population.

Table 40: Undiscounted survival estimates used in the AG model

Subgroup	AG base-case (no downstaging)	AG base-case (with downstaging)	Low tumour/ALBI 1 subgroup (no downstaging)	Low tumour/ALBI 1 subgroup (with downstaging)	MVI subgroup (no downstaging)	MVI subgroup (with downstaging)
Undiscounted LYGs: lenvatinib	14.72 months	15.12 months	16.98 months	17.49 months	15.80 months	16.14 months
Undiscounted LYGs: sorafenib	15.49 months	15.89 months	17.68 months	18.17 months	16.49 months	16.82 months
Incremental undiscounted LYGs: SIRT vs lenvatinib *	-0.95 months	0.11 months	2.80 months	5.30 months	-2.49 months	-1.51 months
Incremental undiscounted LYGs: SIRT vs sorafenib *	-1.73 months	-0.65 months	2.11 months	4.61 months	-3.18 months	-2.19 months
* Each SIRT associated with the same number of LYs, due to assumed equal efficacy						

10 Discussion

10.1 Statement of principal findings

Treatment options vary for patients with unresectable HCC according to the stage of the cancer and underlying liver disease. The AG, therefore, considered three distinct unresectable HCC patient populations, defined with respect to the aim of therapy, and eligibility for comparator treatments. These three populations were as follows: patients eligible for transplant, patients ineligible for transplant but eligible for CTT, and patients ineligible for CTT. These three populations largely correspond to early, intermediate and advanced stage HCC.

There is a large body of evidence on the clinical effectiveness and safety of SIRT compared with sorafenib or transarterial chemoembolization; seven RCTs, seven prospective comparative studies, five retrospective comparative studies, and one non-comparative case series were included in the review of clinical effectiveness. However, only two studies were considered to have a low risk of bias; the SARAH[2] and SIRveNIB[3] RCTs, which both compared SIR-Spheres with sorafenib. These studies enrolled patients with locally advanced HCC not amenable to curative treatment modalities and ineligible for CTT; the evidence for the early and intermediate HCC populations was significantly more limited. Both RCTs found no significant difference in overall survival or progression-free survival between SIR-Spheres and sorafenib, despite a statistically significantly greater tumour response rate in the SIR-Spheres arm of both trials. The SARAH trial[2] reported a significant difference between groups in health-related quality of life, favouring SIR-Spheres, however the proportion of patients who completed the questionnaires was low. Adverse events, particularly grade ≥3 events, were more frequent in the sorafenib group in both trials. There are some concerns regarding the generalisability of the results of these two RCTs to the UK HCC population, particularly the SIRveNIB trial,[3] which was conducted in the Asia-Pacific region, where the aetiology and treatment of HCC differs from that in Europe.

The Sirtex Medical company submission selected a subgroup of patients from the SARAH trial[2] with ≤25% tumour burden and preserved liver function, defined as having an ALBI grade of 1, for the base-case analysis in their economic analysis. Whilst results appeared more promising in this subgroup of patients with a better prognosis, the results of this *post-hoc* subgroup analysis should be prospectively validated before being considered relevant for clinical practice.

In studies that directly compared the different SIRT technologies, patients with portal vein thrombosis appeared to have better survival outcomes with TheraSphere than with SIR-Spheres, however, this result was from a small retrospective comparative study with a high risk of bias, and therefore may not be reliable. Other studies comparing TheraSphere with SIR-Spheres that were not restricted to patients with portal vein thrombosis had conflicting results. The only study that compared

QuiremSpheres with SIR-Spheres and TheraSphere was provided by Terumo Europe as an addendum to their submission. Clinical outcomes appeared to be similar between treatment groups, however, this was a very small pilot study with several methodological limitations.

Three network meta-analysis models were produced to represent the three different populations of unresectable HCC patients described above. Both the NMA in patients eligible for transplant and in patients eligible for CTT were not conducted due to uncertainty of using SIRT for bridging to transplant and downstaging in the UK, and a lack of good quality evidence in patients eligible for CTT.

The base-case NMA was conducted in adults with unresectable HCC who have Child-Pugh A liver function and are ineligible for CTT. There were no meaningful differences in overall survival between SIR-Spheres, sorafenib, and lenvatinib in the per protocol or ITT populations. All treatments appeared to have similar efficacy. There was only one low-quality retrospective study which directly compared TheraSphere to SIR-Spheres in the base-case population. Adding this study as a sensitivity analysis had a substantial effect on the NMA results; TheraSphere showed a significant improvement in OS when compared to SIR-Spheres, sorafenib, and lenvatinib. However, these results may be biased and unreliable as they rely on only one low quality retrospective study.

The limitations in the effectiveness evidence had an important role in shaping the economic analysis, and restricted the focus of the AG's economic analysis to the population ineligible for CTT; this was the only population for which there were reliable estimates of the comparative effectiveness of SIRT with comparator technologies. The structure of the AG's model was broadly similar to the models developed by BTG and Sirtex Medical for this population and was designed around a decision tree and partitioned survival model. The decision tree was used to model the fact that some patients eligible to receive SIRT will fail the work-up procedure and will not receive SIRT treatment; in a scenario analysis the decision tree was also used to allow a proportion of patients to go on to receive curative therapies. The partitioned survival model developed was based on three health states; progression-free survival, progressive disease, and death.

The results of the AG's base-case analysis (probabilistic analysis), which assumed equal efficacy across all three SIRT technologies, suggested TheraSphere is cost saving relative to both SIR-Spheres and QuiremSpheres. However, the incremental costs between TheraSphere and SIR-Spheres are less than £300 and result from the additional cost of angiography required as part of the SIR-Spheres administration procedure. Pairwise net monetary benefit (NMB), assuming a £30,000 willingness-to-pay threshold, for SIR-Spheres compared with TheraSphere was therefore close to zero (-£182). QuiremSpheres is associated with an incremental cost of £6,955 relative to TheraSphere (exclusive of

PAS). Pairwise NMB between QuiremSpheres and TheraSphere in the AG's base-case was -£6,599, exclusive of PAS. In the analysis including the confidential PAS for QuiremScout, QuiremSpheres remained more costly than both TheraSphere and SIR-Spheres and as such, the pairwise NMB remained negative (see confidential appendix for full results).

In a fully incremental analysis, exclusive of the PAS discounts available for QuiremScout, sorafenib, lenvatinib, and regorafenib, lenvatinib was the most cost-effective therapy and dominated TheraSphere (the lowest costing SIRT treatment). Predicted NMB for lenvatinib compared with TheraSphere was -£2,154. In a pairwise comparison of sorafenib with TheraSphere, the ICER for sorafenib was £31,974 per QALY, with an estimated NMB of -£150 (implying TheraSphere is cost-effective compared to sorafenib at a WTP threshold of £30,000). In a fully incremental analysis inclusive of all confidential PAS discounts, lenvatinib remained the most cost-effective therapy across all scenarios, and dominated all three SIRTs, generating greater health benefits at lower costs. In pairwise comparisons of sorafenib with each SIRT, sorafenib also dominated all three SIRTs. Lenvatinib remained the most cost-effective option across 15 of the 17 AG scenarios when PAS discounts were included.

The results of the scenario analyses presented at list price showed that SIRT technologies were more likely to be cost effective in the low tumour burden and ALBI 1 subgroup of patients, and when downstaging was permitted. The results of analyses conducted including PAS discounts for QuiremScout, sorafenib, lenvatinib, and regorafenib, however, showed that the results of the AG's economic analysis were robust to a range of alternative parameter values and assumptions, with a negative incremental NMB predicted for all SIRTs at a £30,000 WTP threshold (see confidential appendix for details).

The AG's economic analysis suggests that while current life expectancy in patients ineligible for CTT is likely to be less than 24 months, the predicted life-extension generated by SIRT is likely to be less than 3 months.

10.2 Strengths and limitations of the assessment

The key strengths of this assessment are as follows:

- The reviews of clinical effectiveness and cost-effectiveness were based on comprehensive searches of the literature, which were supplemented by data identified in recent systematic reviews of CTT treatments.

- The review of clinical effectiveness evidence included a detailed mapping and quality assessment of all comparative evidence on SIRT treatments across a range of alternative positions in the treatment pathway.
- The AG's economic evaluation includes a fully incremental analysis of the three SIRT technologies: SIR-Spheres, TheraSphere, QuiremSpheres, and relevant systemic therapies: sorafenib and lenvatinib, in patients with CTT-ineligible HCC.
- The AG appropriately accounts for the fact that some patients eligible for SIRT treatment will fail the work-up procedure and will not go on to receive SIRT. Importantly, it recognises that patients who fail work-up are different from patients who successfully receive SIRT and tend to have inferior progression and survival outcomes.
- The AG's economic analysis includes an exploratory analysis of two potentially plausible prospective subgroups: low tumour burden/ALBI 1, and no macroscopic vascular invasion.
- The AG's economic analysis includes an exploration of the impact of downstaging in CTT-ineligible patients. The AG economic analysis also avoids double counting the outcomes of patients who are downstaged to curative therapies.

The main weaknesses of the assessment are largely a consequence of weaknesses and gaps in the clinical evidence base:

- There is very limited evidence on the comparative effectiveness of SIRT with CTT in either patients with early or intermediate stage HCC. The AG did not consider the identified clinical evidence sufficient to produce an economic analysis and therefore the presented independent economic assessment only covers part of the NICE scope. The BTG company submission included an economic analysis of downstaging in CTT-eligible patients, while Sirtex Medical presented a cost-minimisation model. The limits of the clinical evidence supporting these analyses and uncertainties regarding the equivalence of SIRT and CTT in this population, means that these analyses may be of limited relevance for decision-making.
- The AG did not have access to IPD from the SIRveNIB trial; instead, PFS and OS outcomes were replicated using a published algorithm. Although the precision of this replication is likely to be good, this process may have introduced a small loss of accuracy relative to the use of IPD directly. Further, the lack of IPD meant that the SIRveNIB trial could not be included in scenario analyses exploring the low tumour burden/ALBI 1, and no MVI subgroups.
- Lack of IPD for the REFLECT trial, comparing lenvatinib with sorafenib, meant that there were limited options for including lenvatinib in the economic analysis and the modelled HRs were based on a subgroup that did not fully align with the population eligible for SIRT.

Furthermore, the AG's base-case makes the assumption of proportional hazards between lenvatinib and sorafenib despite some evidence presented in previous technology appraisals that this assumption may not hold.

- There was limited evidence on the relative effectiveness of TheraSphere compared with other SIRT technologies or systemic therapy, with the limited studies identified all being at high risk of bias.
- There is no evidence on the comparative effectiveness of QuiremSpheres, with the exception of one small, methodologically weak pilot study provided as a late addendum by Terumo Europe.
- There is limited evidence on the long-term outcomes of patients who receive therapy with curative intent. The AG's analysis, as well as the Sirtex Medical model, present data from a historical US Cohort study; these data are now several years old and potentially reflect a broader population of patients with HCC.

10.3 Uncertainties

The main uncertainties associated with the appraisal are as follows:

- The comparative effectiveness of SIRT in patients eligible for transplant or eligible for CTT such as DEB-TACE, TACE and TAE is highly uncertain, with identified evidence limited to a small number of mainly observational studies.
- The comparative effectiveness of alternative SIRT technologies (SIR-Spheres, TheraSphere and QuiremSpheres) in all HCC populations is largely unknown. The limited evidence available suggests that TheraSphere may be superior to SIR-Spheres for advanced HCC with PVI. The identified evidence is, however, of very low quality and therefore it is unknown whether the observed effects are the result of confounding bias. There is also no evidence on the comparative effectiveness of QuiremSpheres with any therapy, other than a very small pilot study with several methodological limitations that was provided as an addendum. This is significant, as QuiremSpheres uses a different work-up procedure and different radioactive isotope and therefore it is plausible that QuiremSpheres may have differential effectiveness when compared with SIR-Spheres and TheraSphere.
- The Sirtex Medical submission puts forward a subgroup of patients with a low tumour burden and preserved liver function, as a potential subgroup who may benefit from treatment with SIR-Spheres. This subgroup was, however, not pre-specified and the randomisation procedure did not stratify for these characteristics. The subgroup analysis is also based on very few patients. The extent of any benefits in this subgroup are therefore subject to considerable

uncertainty and a confirmatory study would be required to be confident that the observed benefits are not spurious.

- The role of downstaging in a CTT-ineligible population is currently unclear. In the SARAH trial[2] a small proportion of patients were successfully downstaged to curative therapies. Advice received by the AG from clinical experts, however, suggests that downstaging in this population is likely to be very rare and it is unclear whether the SARAH trial[2] is representative of UK practice in this regard.
- In the SARAH trial patients with bilobar HCC had each lobe treated in separate SIRT administrations to avoid the risk of radioembolisation induced liver disease. The Sirtex Medical submission, however, suggests that in UK practice, patients with bilobar HCC would have both lobes treated simultaneously. The impact of sequential vs simultaneous treatment is largely unknown and it is not fully clear what practice would be adopted in the UK; advice received from the AG's clinical advisors, however, suggests that sequential treatment would be more likely to be used in the UK.
- There is currently only limited evidence on the comparative effectiveness of combination therapy (SIRT combined with a systemic therapy). The searches of trial registration databases completed as part of the clinical effectiveness review, however, identified that a large RCT, STOP-HCC,[73] is set to report shortly. This RCT compares TheraSphere plus sorafenib with sorafenib alone and will provide new evidence on this comparison.
- In the NHS, systemic therapies are only recommended for those with Child-Pugh A liver function, thus the current standard of care for those with Child-Pugh B liver function is BSC. There is a potential place for SIRT in a Child-Pugh B7 population, who were represented in in the SARAH and SIRveNIB trials. However, there is currently no direct evidence on the comparative effectiveness of SIRT with BSC in this population, and currently no means of comparing them indirectly.

11 Conclusions

The existing evidence cannot provide decision makers with clear guidance on the comparative effectiveness of treatments in early and intermediate stage HCC. All of the identified studies were at a high risk of bias and included highly heterogeneous populations, limiting the conclusions that can be drawn from these results. The results of individual studies varied considerably, with some showing that CTT was superior to SIRT and vice versa. However, the available evidence suggests that SIRT may be beneficial in this population, with moderate improvements in PFS and transplantation rates.

The very limited evidence on the effectiveness of SIRT in early and intermediate HCC patients means that the AG was not able to generate a meaningful analysis of the value of SIRT in these populations. The focus of the AG's economic assessment was therefore on the advanced HCC population who are ineligible to receive CTT. In this population, two large randomised trials (SARAH[2] and SIRveNIB[3]) have assessed the comparative effectiveness of SIR-Spheres with sorafenib. The results of these trials show that SIRT has similar effectiveness to sorafenib; notably, these studies were not designed as non-inferiority or equivalence trials. The systematic review also identified further evidence from a large RCT on the comparative effectiveness of the alternative systemic therapy lenvatinib with sorafenib as well as observational evidence on the comparative effectiveness of TheraSphere with SIR-Spheres. The results of these studies were combined in an NMA, which showed no meaningful differences in overall survival between SIR-Spheres, sorafenib, and lenvatinib. TheraSphere showed a significant improvement in OS when compared to SIR-Spheres, sorafenib and lenvatinib. However, there were only two retrospective studies that directly compared TheraSphere and SIR-Spheres, which both had a high risk of bias. Therefore, there is considerable uncertainty regarding the efficacy of TheraSphere, and the AG elected to assume equal efficacy across each SIRT technology in their base-case analysis.

The AG's economic analysis showed that SIRT technologies are very unlikely to be cost-effective up to a threshold of £30,000 per QALY. The fully incremental analysis, including confidential PAS discounts, showed that lenvatinib was the most cost-effective therapy, dominating all three SIRTs (i.e. producing more QALYs at a lower cost). Pairwise comparisons of sorafenib with each SIRT also showed that sorafenib dominated all three SIRTs. The results of deterministic sensitivity analysis and scenarios analysis, considering a variety of alternative assumptions, including the modelling of two alternative subgroups (low tumour burden/ALBI 1, and no MVI), showed the results of the AG's economic analysis were generally robust to alternative parameter values and assumptions.

The AG's economic analysis suggests that NICE's criteria[138] for life-extending therapies given at the end of life are not met for SIRT in the broad advanced population as they do not meet the required three month extension to life. In the low tumour burden/ALBI 1 subgroup, there is a possibility that

SIRT treatments may meet this threshold. However, the ICER for the most cost-effective SIRT technology in this scenario remains above £50,000 when PAS discounts are considered.

11.1 Implications for service provision

In the event that SIRT was recommended for use in the NHS, the AG does not anticipate that any substantial changes to service provision would be required, as SIRT (SIR-Spheres and TheraSphere) is already routinely administered across a number of specialist liver units.

11.2 Suggested research priorities

As discussed above, no strong conclusions should be drawn in the early and intermediate HCC populations owing to considerable uncertainty in estimates of effectiveness and high risk of bias. A priority for further research is therefore the conduct of studies in these populations. In designing any evaluations, careful consideration should be given to the recruited population and where possible studies should avoid combining these heterogeneous populations as the aims of therapy and range of treatments available varies considerably. Careful consideration should also be given to the outcomes measured. Many studies reported on time to progression, but this was rarely defined within the study report and there were concerns as to whether these data had been properly analysed. Few studies also reported on downstaging outcomes, these potentially play an important role in determining patient outcomes and is increasingly becoming a realistic option for some patients with intermediate stage HCC.

The low tumour burden and preserved liver function subgroup potentially represents a group of prospectively identifiable patients for whom SIRT may be beneficial when compared with sorafenib. However, the evidence in support of these observed benefits is weak, because the observed results are based on a *post-hoc* analysis of the SARAH trial,[2] which included only a small proportion of the total number of recruited patients. Future work considering this subgroup may therefore be useful. Of priority would be a similar analysis upon the results of the SIRveNIB trial;[3] this could not be undertaken as part of the current appraisal as IPD was unavailable. A confirmatory trial in this subgroup may also be desirable depending upon the results of any analysis of the SIRveNIB trial.[3]

There is currently only very limited evidence on the comparative effectiveness of the three SIRT technologies with one another. Future randomised prospective studies evaluating the alternative SIRT technologies would therefore be useful.

12 References

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2018;**69**:182-236.
2. Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *Lancet Oncol* 2017;**18**:1624-36.
3. Chow PK, Gandhi M, Tan SB, Khin MW, Khasbazar A, Ong J, et al. SIRveNIB: selective internal radiation therapy versus sorafenib in Asia-Pacific patients with hepatocellular carcinoma. *J Clin Oncol* 2018;**36**:1913-21.
4. Kolligs FT, Bilbao JI, Jakobs T, Inarrairaegui M, Nagel JM, Rodriguez M, et al. Pilot randomized trial of selective internal radiation therapy vs. chemoembolization in unresectable hepatocellular carcinoma. *Liver Int* 2015;**35**:1715-21.
5. Pitton MB, Kloeckner R, Ruckes C, Wirth GM, Eichhorn W, Worns MA, et al. Randomized comparison of selective internal radiotherapy (SIRT) versus drug-eluting bead transarterial chemoembolization (DEB-TACE) for the treatment of hepatocellular carcinoma. *Cardiovasc Intervent Radiol* 2015;**38**:352-60.
6. Ricke J, Bulla K, Kolligs F, Peck-Radosavljevic M, Reimer P, Sangro B, et al. Safety and toxicity of radioembolization plus sorafenib in advanced hepatocellular carcinoma: analysis of the European multicentre trial SORAMIC. *Liver Int* 2015;**35**:620-6.
7. Kirchner T, Marquardt S, Werncke T, Kirstein MM, Brunkhorst T, Wacker F, et al. Comparison of health-related quality of life after transarterial chemoembolization and transarterial radioembolization in patients with unresectable hepatocellular carcinoma. *Abdom Radiol (NY)* 2019;**44**:1554-61.
8. Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, et al. Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology* 2016;**151**:1155-63.
9. Hickey R, Mouli S, Kulik L, Desai K, Thornburg B, Ganger D, et al. Independent analysis of albumin-bilirubin grade in a 765-patient cohort treated with transarterial locoregional therapy for hepatocellular carcinoma. *J Vasc Interv Radiol* 2016;**27**:795-802.
10. El Fouly A, Ertle J, El Dorry A, Shaker MK, Dechene A, Abdella H, et al. In intermediate stage hepatocellular carcinoma: radioembolization with yttrium 90 or chemoembolization? *Liver Int* 2015;**35**:627-35.
11. Kulik L, Vouche M, Koppe S, Lewandowski RJ, Mulcahy MF, Ganger D, et al. Prospective randomized pilot study of Y90+/-sorafenib as bridge to transplantation in hepatocellular carcinoma. *J Hepatol* 2014;**61**:309-17.
12. Salem R, Gilbertsen M, Butt Z, Memon K, Vouche M, Hickey R, et al. Increased quality of life among hepatocellular carcinoma patients treated with radioembolization, compared with chemoembolization. *Clin Gastroenterol Hepatol* 2013;**11**:1358-65.
13. Memon K, Kulik L, Lewandowski RJ, Gupta R, Ryu RK, Miller FH, et al. Prospective evaluation of patients with early-/intermediate-stage hepatocellular carcinoma with disease progression following arterial locoregional therapy: candidacy for systemic treatment or clinical trials. *J Vasc Interv Radiol* 2013;**24**:1189-97.
14. Woodall CE, Scoggins CR, Ellis SF, Tatum CM, Hahl MJ, Ravindra KV, et al. Is selective internal radioembolization safe and effective for patients with inoperable hepatocellular carcinoma and venous thrombosis? *J Am Coll Surg* 2009;**208**:375-82.
15. Maccauro M, Sposito C, Chiesa C, Romito R, Spreafico C, Morosi C, et al. Trans-arterial radioembolization (TARE) with Y90 glass microspheres plus sorafenib versus tare alone for the treatment of unresectable hepatocellular carcinoma (HCC): a matched case-control study. *Eur J Nucl Med Mol Imaging* 2014;**41(Suppl. 2)**:S291.
16. Radosa CG, Radosa JC, Grosche-Schlee S, Zophel K, Plodeck V, Kuhn JP, et al. Holmium-166 radioembolization in hepatocellular carcinoma: feasibility and safety of a new treatment option in clinical practice. *Cardiovasc Intervent Radiol* 2019;**42**:405-12.

17. Bhangoo MS, Karnani DR, Hein PN, Giap H, Knowles H, Issa C, et al. Radioembolization with yttrium-90 microspheres for patients with unresectable hepatocellular carcinoma. *J Gastrointest Oncol* 2015;**6**:469-78.
18. Van Der Gucht A, Jreige M, Denys A, Blanc-Durand P, Boubaker A, Pomoni A, et al. Resin versus glass microspheres for 90Y transarterial radioembolization: comparing survival in unresectable hepatocellular carcinoma using pretreatment partition model dosimetry. *J Nucl Med* 2017;**58**:1334-40.
19. Biederman DM, Titano JJ, Tabori NE, Pierobon ES, Alshebeeb K, Schwartz M, et al. Outcomes of radioembolization in the treatment of hepatocellular carcinoma with portal vein invasion: resin versus glass microspheres. *J Vasc Interv Radiol* 2016;**27**:812-21.
20. Biederman DM, Tabori NE, Titano JJ, Pierobon ES, Fischman AM, Patel RS, et al. Outcomes of yttrium-90 therapy in the treatment of hepatocellular carcinoma (HCC) with portal vein thrombosis (PVT): resin-based vs. glassbased microspheres. *J Vasc Interv Radiol* 2015;**26**:S109-S10.
21. d'Abadie P, Hesse M, Jamar F, Lhommel R, Walrand S. 90Y TOF-PET based EUD reunifies patient survival prediction in resin and glass microspheres radioembolization of HCC tumours. *Phys Med Biol* 2018;**63**:245010.
22. Reinders MT, Hoffmann RT, Lam MG, Radosa C. *First results of homium-166 radioembolisation compared with yttrium-90 radioembolisation in HCC patients*: Terumo Europe; 2019.
23. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet* 2018;**391**:1163-73.
24. Villanueva A. Hepatocellular carcinoma. *N Engl J Med* 2019;**380**:1450-62.
25. Yang JD, Roberts LR. Epidemiology and management of hepatocellular carcinoma. *Infect Dis Clin North Am* 2010;**24**:899-+.
26. Office for National Statistics. *Cancer registration statistics, England: 2017*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [accessed 29th August 2019].
27. Ryder SD. Guidelines for the diagnosis and treatment of hepatocellular carcinoma (HCC) in adults. *Gut* 2003;**52**:iii1-iii8.
28. Park JW, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, et al. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. *Liver Int* 2015;**35**:2155-66.
29. Cancer Research UK. *Liver cancer survival*. Cancer Research UK; Available from: https://www.cancerresearchuk.org/about-cancer/liver-cancer/survival [accessed 28th August 2019].
30. Song JE, Kim DY. Conventional vs drug-eluting beads transarterial chemoembolization for hepatocellular carcinoma. *World J Hepatol* 2017;**9**:808-14.
31. National Institute for Health and Care Excellence (NICE). *Sorafenib for treating advanced hepatocellular carcinoma [TA474]*. NICE; 2017. Available from: https://www.nice.org.uk/guidance/ta474 [accessed 29th May 2019].
32. National Institute for Health and Care Excellence (NICE). *Lenvatinib for untreated advanced hepatocellular carcinoma [TA551]*. NICE; 2018. Available from: https://www.nice.org.uk/guidance/ta551 [accessed 29th May 2019].
33. National Institute for Health and Care Excellence (NICE). *Selective internal radiation therapy for primary hepatocellular carcinoma. Interventional procedures guidance [IPG460]*. 2013. Available from: https://www.nice.org.uk/guidance/ipg460 [accessed 8th May 2019].
34. Centre for Reviews and Dissemination. *CRD's guidance for undertaking reviews in health care*. York: CRD, University of York; 2009.
35. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *BMJ* 2009;**339**:b2535.
36. National Institute for Health and Care Excellence (NICE). *Regorafenib for previously treated advanced hepatocellular carcinoma [TA555]*. NICE; 2019. Available from: https://www.nice.org.uk/guidance/ta555 [accessed 29th May 2019].
37. Centre for Reviews and Dissemination. *Search strategies for DARE*. 2015. Available from: http://www.crd.york.ac.uk/crdweb/searchstrategies.asp [accessed 7th May 2019].

38. Higgins JP, Savovic J, Page MJ, Sterne JA, ROB2 Development Group. *Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)*. 2019. Available from: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2 [accessed 29th May 2019].
39. Steel J, Baum A, Carr B. Quality of life in patients diagnosed with primary hepatocellular carcinoma: hepatic arterial infusion of cisplatin versus 90-yttrium microspheres (Therasphere). *Psychooncology* 2004;**13**:73-9.
40. Moroz P, Anderson JE, Van Hazel G, Gray BN. Effect of selective internal radiation therapy and hepatic arterial chemotherapy on normal liver volume and spleen volume. *J Surg Oncol* 2001;**78**:248-52.
41. Maccauro M, Spreafico C, Chiesa C, Mira M, De Nila M, Romito R, et al. Personalized treatment planning in radioembolization of hepatocarcinoma with 90 Y glass microspheres: update of clinical outcomes in the Milan experience. *Eur J Nucl Med Mol Imaging* 2016;**43(Suppl. 1)**:S10.
42. Pellerito RE, Codegone A, Tabone M, Richetta E, Miranti A, Stasi M. Intrahepatic treatment of advanced hepatocellular carcinoma with 90Y Sirtex or 131I Lipiodol: preliminary results of a case control study. *Clin Transl Imaging* 2013;**1(Suppl. 1)**:S126-S7.
43. Bouattour M, Assenat E, Guiu B, Ilonca Alina D, Pageaux GP, Sibert A, et al. LBA-001 Efficacy, tolerability and impact on quality of life of selective internal radiation therapy (with yttrium-90 resin microspheres) or sorafenib in patients with locally advanced hepatocellular carcinoma: the SARAH trial. *Ann Oncol* 2017;**28(Suppl. 3)**:iii150–iii3.
44. Gabr A, Kallini JR, Lewandowski RJ, Salem R. Fluoroscopic radiation exposure in chemoembolization and radioembolization: results from a prospective randomized study. *J Vasc Interv Radiol* 2017;**28**:1272-3.
45. Gordon A, Lewandowski R, Hickey R, Kallini J, Gabr A, Sato K, et al. Prospective randomized phase 2 study of chemoembolization versus radioembolization in hepatocellular carcinoma: results from the PREMIERE trial. *J Vasc Interv Radiol* 2016;**27**:S61-S2.
46. Lewandowski RJ, Andreoli JM, Hickey R, Kallini JR, Gabr A, Baker T, et al. Angiogenic response following radioembolization: results from a randomized pilot study of yttrium-90 with or without sorafenib. *J Vasc Interv Radiol* 2016;**27**:1329-36.
47. Vouche M, Kulik L, Atassi R, Memon K, Hickey R, Ganger D, et al. Radiological-pathological analysis of WHO, RECIST, EASL, mRECIST and DWI: imaging analysis from a prospective randomized trial of Y90 +/- sorafenib. *Hepatology* 2013;**58**:1655-66.
48. Cho YY, Lee M, Kim HC, Chung JW, Kim YH, Gwak GY, et al. Radioembolization is a safe and effective treatment for hepatocellular carcinoma with portal vein thrombosis: a propensity score analysis. *PLoS One* 2016;**11**:e0154986.
49. de la Torre MA, Buades-Mateu J, de la Rosa PA, Lue A, Bustamante FJ, Serrano MT, et al. A comparison of survival in patients with hepatocellular carcinoma and portal vein invasion treated by radioembolization or sorafenib. *Liver Int* 2016;**36**:1206-12.
50. Gramenzi A, Golfieri R, Mosconi C, Cappelli A, Granito A, Cucchetti A, et al. Yttrium-90 radioembolization vs sorafenib for intermediate-locally advanced hepatocellular carcinoma: a cohort study with propensity score analysis. *Liver Int* 2015;**35**:1036-47.
51. Soydal C, Arslan MF, Kucuk ON, Idilman R, Bilgic S. Comparison of survival, safety, and efficacy after transarterial chemoembolization and radioembolization of Barcelona Clinic Liver Cancer stage B-C hepatocellular cancer patients. *Nucl Med Commun* 2016;**37**:646-9.
52. Salem R, Lewandowski RJ, Kulik L, Wang E, Riaz A, Ryu RK, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology* 2011;**140**:497-507.
53. Moreno-Luna LE, Yang JD, Sanchez W, Paz-Fumagalli R, Harnois DM, Mettler TA, et al. Efficacy and safety of transarterial radioembolization versus chemoembolization in patients with hepatocellular carcinoma. *Cardiovasc Intervent Radiol* 2013;**36**:714-23.
54. Akinwande O, Philips P, Scoggins C, Martin RC. Radioembolization versus chemoembolization (DEBDOX) for the treatment of unresectable hepatocellular carcinoma: a propensity matched study. *Anticancer Res* 2016;**36**:239-46.

55. Akinwande O, Martin R. Is radioembolization equivalent to chemoembolization (DEBDOX) for the treatment of HCC? A propensity matched observational study. *J Vasc Interv Radiol* 2016;**27**:S248.
56. Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, et al. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. *Cardiovasc Intervent Radiol* 2010;**33**:41-52.
57. Vogl TJ, Lammer J, Lencioni R, Malagari K, Watkinson A, Pilleul F, et al. Liver, gastrointestinal, and cardiac toxicity in intermediate hepatocellular carcinoma treated with PRECISION TACE with drug-eluting beads: results from the PRECISION V randomized trial. *AJR Am J Roentgenol* 2011;**197**:W562-70.
58. Golfieri R, Giampalma E, Renzulli M, Cioni R, Bargellini I, Bartolozzi C, et al. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. *Br J Cancer* 2014;**111**:255-64.
59. Sacco R, Bargellini I, Bertini M, Bozzi E, Romano A, Petruzzi P, et al. Conventional versus doxorubicin-eluting bead transarterial chemoembolization for hepatocellular carcinoma. *J Vasc Interv Radiol* 2011;**22**:1545-52.
60. van Malenstein H, Maleux G, Vandecaveye V, Heye S, Laleman W, van Pelt J, et al. A randomized phase II study of drug-eluting beads versus transarterial chemoembolization for unresectable hepatocellular carcinoma. *Onkologie* 2011;**34**:368-76.
61. Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002;**359**:1734-9.
62. Kawai S, Okamura J, Ogawa M, Ohashi Y, Tani M, Inoue J, et al. Prospective and randomized clinical trial for the treatment of hepatocellular carcinoma - a comparison of lipiodol-transcatheter arterial embolization with and without adriamycin (first cooperative study). *Cancer Chemother Pharmacol* 1992;**31(Suppl. 1)**:S1-6.
63. Chang JM, Tzeng WS, Pan HB, Yang CF, Lai KH. Transcatheter arterial embolization with or without cisplatin treatment of hepatocellular carcinoma. A randomized controlled study. *Cancer* 1994;**74**:2449-53.
64. Meyer T, Kirkwood A, Roughton M, Beare S, Tsochatzis E, Yu D, et al. A randomised phase II/III trial of 3-weekly cisplatin-based sequential transarterial chemoembolisation vs embolisation alone for hepatocellular carcinoma. *Br J Cancer* 2013;**108**:1252-9.
65. Yu SC, Hui JW, Hui EP, Chan SL, Lee KF, Mo F, et al. Unresectable hepatocellular carcinoma: randomized controlled trial of transarterial ethanol ablation versus transcatheter arterial chemoembolization. *Radiology* 2014;**270**:607-20.
66. Malagari K, Pomoni M, Kelekis A, Pomoni A, Dourakis S, Spyridopoulos T, et al. Prospective randomized comparison of chemoembolization with doxorubicin-eluting beads and bland embolization with BeadBlock for hepatocellular carcinoma. *Cardiovasc Intervent Radiol* 2010;**33**:541-51.
67. Brown KT, Do RK, Gonen M, Covey AM, Getrajdman GI, Sofocleous CT, et al. Randomized trial of hepatic artery embolization for hepatocellular carcinoma using doxorubicin-eluting microspheres compared with embolization with microspheres alone. *J Clin Oncol* 2016;**34**:2046-53.
68. Sangro B, Carpanese L, Cianni R, Golfieri R, Gasparini D, Ezziddin S, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. *Hepatology* 2011;**54**:868-78.
69. Cardiovascular and Interventional Radiological Society of Europe. *CIRSE registry for SIR-spheres therapy (CIRT)*. ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US); 2014. Available from: https://ClinicalTrials.gov/show/NCT02305459 [accessed 1st February 2019].
70. Vanderbilt-Ingram Cancer Center. *Yttrium Y 90 resin microspheres data collection in unresectable liver cancer: the RESIN study*. ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US); 2016. Available from: https://ClinicalTrials.gov/show/NCT02685631 [accessed 1st February 2019].

71. Taipei Veterans General Hospital. *REgistry of Selective Internal Radiation Therapy in TaiwaN (RESIN)*. ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US); 2017. Available from: https://ClinicalTrials.gov/show/NCT03292991 [accessed 1st February 2019].
72. Gebski V, Gibbs E, Gandhi M, Chatellier G, Dinut A, Pereira H, et al. VESPRO: an individual patient data prospective meta-analysis of selective internal radiation therapy versus sorafenib for advanced, locally advanced, or recurrent hepatocellular carcinoma of the SARAH and SIRveNIB trials. *JMIR Res Protoc* 2017;**6**:e17.
73. BTG International Inc. *Efficacy evaluation of therasphere in patients with inoperable liver cancer (STOP-HCC)*. ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US); 2012. Available from: https://clinicaltrials.gov/show/nct01556490 [accessed 28th January 2019].
74. UMC Utrecht. *HEPAR Primary: Holmium-166-radioembolization in hepatocellular carcinoma patients*. ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US); 2017. Available from: https://ClinicalTrials.gov/show/NCT03379844 [accessed 1st February 2019].
75. Leiden University Medical Center. *Holmium radioembolization as adjuvant treatment to RFA for early stage HCC: dose finding study (HORA EST HCC)*. ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US); 2018. Available from: https://ClinicalTrials.gov/show/NCT03437382 [accessed 1st February 2019].
76. Terumo Europe N.V. *QuiremSpheres observational study (Hope166)*. ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US); 2018. Available from: https://ClinicalTrials.gov/show/NCT03563274 [accessed 1st February 2019].
77. Kallini JR, Gabr A, Thorlund K, Balijepalli C, Ayres D, Kanters S, et al. Comparison of the adverse event profile of therasphere with sir-spheres for the treatment of unresectable hepatocellular carcinoma: a systematic review. *Cardiovasc Intervent Radiol* 2017;**40**:1033-43.
78. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc J-F, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;**359**:378-90.
79. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004;**23**:3105-24.
80. Memon K, Kulik LM, Lewandowski RJ, Wang E, Wang J, Ryu RK, et al. Comparative study of staging systems for hepatocellular carcinoma in 428 patients treated with radioembolization. *J Vasc Interv Radiol* 2014;**25**:1056-66.
81. Vilgrain V, Bouattour M, Sibert A, Lebtahi R, Ronot M, Pageaux GP, et al. SARAH: a randomised controlled trial comparing efficacy and safety of selective internal radiation therapy (with yttrium-90 microspheres) and sorafenib in patients with locally advanced hepatocellular carcinoma. *J Hepatol* 2017;**66**:S85-S6.
82. Cho MT, Kessler J, Park J, Singh G, Chen YJ, Ituarte PHG, et al. A single institute retrospective trial of concurrent chemotherapy with SIR-Sphere versus SIR-Sphere alone in patients with chemotherapy-resistant colorectal cancer liver metastases. *J Clin Oncol* 2016;**34**.
83. Dias S, Welton NJ, Sutton AJ, Ades AE. *NICE DSU Technical Support Document 2: A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials*. Sheffield: Decision Support Unit, ScHARR, University of Sheffield; 2014.
84. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012;**12**:9.
85. Kudo M. Systemic therapy for hepatocellular carcinoma: 2017 update. *Oncology* 2017;**93**:135-46.
86. Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. Good practice guidelines for decision-analytic modelling in health technology assessment. *Pharmacoeconomics* 2006;**24**:355-71.
87. Rognoni C, Ciani O, Sommariva S, Tarricone R. Real-World Data for the Evaluation of Transarterial Radioembolization versus Sorafenib in Hepatocellular Carcinoma: A Cost-Effectiveness Analysis. *Value Health* 2017;**20**:336-44.
88. Rognoni C, Ciani O, Sommariva S, Tarricone R. Treatment sequence in intermediate stage hepatocellular carcinoma: a cost-effectiveness analysis of two approaches with trans-arterial radioembolization. *Value Health* 2017;**20**:A247.

89. Rostambeigi N, Dekarske A, Austin E, Golzarian J, Cressman E. Simulation study on cost-effectiveness of radioembolization compared with trans-arterial chemoembolization for hepatocellular carcinoma. *J Vasc Interv Radiol* 2014;**25**:S104-S5.
90. Rostambeigi N, Dekarske AS, Austin EE, Golzarian J, Cressman EN. Cost effectiveness of radioembolization compared with conventional transarterial chemoembolization for treatment of hepatocellular carcinoma. *J Vasc Interv Radiol* 2014;**25**:1075-84.
91. Marqueen KE, Ang C, Mazumdar M, Buckstein M, Ferket BS. Cost-effectiveness analysis of selective internal radiation therapy with yttrium-90 resin microspheres versus sorafenib in advanced hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2018;**102**:e402.
92. Chaplin S, Taylor M, Lapon J, White J. Economic evaluation of glass yttrium-90 microspheres versus sorafenib for the treatment of advanced hepatocellular carcinoma: cost effectiveness analysis in the United Kingdom. *Cardiovasc Intervent Radiol* 2015;**38**:S279-S80.
93. Parikh ND, Singal AG, Kulik LM, Hutton D. Cost-effectiveness of sorafenib versus selective internal radiation therapy for patients with advanced hepatocellular carcinoma. *Hepatology* 2018;**68(Suppl. 1)**:532A-3A.
94. Palmer D, Ross P, Shah T, Yu D, Shergill S, Patterson K, et al. Cost effectiveness of selective internal radiation therapy (SIRT) with Y- 90 resin microspheres versus sorafenib in Barcelona Clinic Liver Cancer (BCLC) stage C hepatocellular carcinoma patients in the UK. *Ann Oncol* 2017;**28(Suppl. 5)**:239-40.
95. Rognoni C, Ciani O, Sommariva S, Tarricone R. Cost-effectiveness analysis of treatments involving radioembolization in intermediate-stage hepatocellular carcinoma. *J Comp Eff Res* 2018;**7**:209-21.
96. Llovet JM, Finn RS. Negative phase 3 study of 90Y microspheres versus sorafenib in HCC. *Lancet Oncol* 2018;**19**:e69.
97. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017;**389**:56-66.
98. SIRTEX Medical. *SIRTEX Medical company evidence submission: SIR-Spheres Y-90 resin microspheres*: SIRTEX Medical; 2019.
99. BTG. *BTG company evidence submission for TheraSphere*: BTG; 2019.
100. Terumo. *Terumo company evidence submission: Selective Internal Radiation Therapy (SIRT) with Holmium-166 microspheres (QuiremSpheres) for treating unresectable hepatocellular carcinoma and Holmium-166 Microspheres Work-up Procedure (QuiremScout)*: Terumo; 2019.
101. Fateen W, Khan F, O'Neill RJ, James MW, Ryder SD, Aithal GP. Healthcare costs of transarterial chemoembolization in the treatment of hepatocellular carcinoma. *J Hepatocell Carcinoma* 2017;**4**:123-30.
102. Curtis LA, Burns A. *Unit costs of health and social care 2018*. Canterbury: Personal Social Services Resarch Unit (PSSRU), University of Kent; 2018.
103. NHS Improvement. *National Schedule of Reference Costs 2017-2018*. 2018. Available from: https://improvement.nhs.uk/resources/reference-costs/ [accessed 27th August 2019].
104. Salem R, Gabr A, Riaz A, Mora R, Ali R, Abecassis M, et al. Institutional decision to adopt Y90 as primary treatment for hepatocellular carcinoma informed by a 1,000-patient 15-year experience. *Hepatology* 2018;**68**:1429-40.
105. National Institute for Health and Care Excellence (NICE). *Guselkumab for treating moderate to severe plaque psoriasis*. NICE; 2018. Available from: https://www.nice.org.uk/guidance/ta521 [accessed 21st August 2019].
106. National Institute for Health and Care Excellence (NICE). *Golimumab for treating non-radiographic axial spondyloarthritis*. NICE; 2018. Available from: https://www.nice.org.uk/guidance/ta497 [accessed 21st August 2019].
107. National Institute for Health and Care Excellence (NICE). *Aflibercept for treating choroidal neovascularisation*. NICE; 2017. Available from: https://www.nice.org.uk/Guidance/TA486 [accessed 21st August 2019].

108. Kanwal F, Befeler A, Chari RS, Marrero J, Kahn J, Afdhal N, et al. Potentially curative treatment in patients with hepatocellular cancer-results from the liver cancer research network. *Aliment Pharmacol Ther* 2012;**36**:1365-2036.
109. Longworth L, Yang Y, Young T, Mulhern B, Hernandez Alava M, Mukuria C, et al. Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: a systematic review, statistical modelling and survey. *Health Technol Assess* 2014;**18**:1-224.
110. CIRSE Registry for SIR-Spheres Therapy. *CIRSE Registry for SIR-Spheres Therapy (CIRT): preliminary data on patients with HCC*: Cardiovascular and Interventional Radiological Society of Europe; 2019.
111. Christie NHS Foundation Trust. *Data on file*. In; 2019.
112. Joint Formulary Committee. *British National Formulary (online)*. BMJ Group and Pharmaceutical Press; 2019. Available from: http://www.medicinescomplete.com [accessed 17th April 2019].
113. Department of Health and Social Care. *Drugs and pharmaceutical electronic market information tool (eMIT)*. 2019. Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit [accessed 20th August 2019].
114. Latimer N. *NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data*: Decision Support Unit, School of Health and Related Research, University of Sheffield; 2013.
115. Lewandowski RJ, Kulik LM, Riaz A, Senthilnathan S, Mulcahy MF, Ryu RK, et al. A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. *Am J Transplant* 2009;**9**:1920-8.
116. Yao FY, Xiao L, Bass NM, Kerlan R, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: validation of the UCSF-expanded criteria based on preoperative imaging. *Am J Transplant* 2007;**7**:2587-96.
117. NHS Blood and Transplant. *Annual report on liver transplantation*: NHS England; 2018. Available from: https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/13974/nhsbt-liver-transplantation-annual-report-2017-2018.pdf
118. NHS England. *Liver transplantation service (adults)*: NHS England; 2017.
119. Bellavance EC, Lumpkins KM, Mentha G, Marques HP, Capussotti L, Pulitano C, et al. Surgical management of early-stage hepatocellular carcinoma: resection or transplantation? *J Gastrointest Surg* 2008;**12**:1699-708.
120. Gordon-Weeks AN, Snaith A, Petrinic T, Friend PJ, Burls A, Silva MA. Systematic review of outcome of downstaging hepatocellular cancer before liver transplantation in patients outside the Milan criteria. *Br J Surg* 2011;**98**:1201-8.
121. National Institute for Health and Care Excellence (NICE). *Lenvatinib for untreated advanced hepatocellular carcinoma [TA551] - evidence*. NICE; 2018. Available from: https://www.nice.org.uk/guidance/ta551/evidence [accessed 28th August 2019].
122. Lim KC, Wang VW, Siddiqui FJ, Shi L, Chan ES, Oh HC, et al. Cost-effectiveness analysis of liver resection versus transplantation for early hepatocellular carcinoma within the Milan criteria. *Hepatology* 2015;**61**:227-37.
123. Ratcliffe J, Buxton M, Young T, Longworth L. Determining priority for liver transplantation: a comparison of cost per QALY and discrete choice experiment-generated public preferences. *Appl Health Econ Health Policy* 2005;**4**:249-55.
124. Kind P, Hardman G, Macran S. *UK population norms for EQ-5D*. York: Centre for Health Economics, University of York; 1999.
125. Georghiou T, Bardsley M. *Exploring the cost of care at the end of life*. London: Nuffield Trust; 2014.
126. Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology* 2010;**138**:52-64.
127. Bryce K, Tsochatzis EA. Downstaging for hepatocellular cancer: harm or benefit? *Transl Gastroenterol Hepatol* 2017;**2**:106.

128. Duvoux C, Roudot-Thoraval F, Decaens T, Pessione F, Badran H, Piardi T, et al. Liver transplantation for hepatocellular carcinoma: a model including alpha-fetoprotein improves the performance of Milan criteria. *Gastroenterology* 2012;**143**:986-94.
129. NHS Blood and Transplant Organ Donation and Transplantation Directorate - Liver Advisory Group. *Update on the HCC down-staging service evaluation*; 2019. Available from: https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/16186/item-71-lag-19-8-update-on-hcc-downstaging.pdf
130. Samuel D, Coilly A. Management of patients with liver diseases on the waiting list for transplantation: a major impact to the success of liver transplantation. *BMC Med* 2018;**16**:113.
131. NHS Blood and Transplant. *UK Transplant Registry data*: NHS Blood and Transplant; 2019. Available from: https://www.odt.nhs.uk/statistics-and-reports/access-data/
132. de'Angelis N, Landi F, Carra MC, Azoulay D. Managements of recurrent hepatocellular carcinoma after liver transplantation: a systematic review. *World J Gastroenterol* 2015;**21**:11185-98.
133. National Institute for Health and Care Excellence (NICE). *Midostaurin for untreated acute myeloid leukaemia [TA523]*. NICE; 2018. Available from: https://www.nice.org.uk/Guidance/TA523 [accessed 3rd September 2019].
134. National Institute for Health and Care Excellence (NICE). *Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years [TA554]*. NICE; 2018. Available from: https://www.nice.org.uk/guidance/ta554 [accessed 3rd September 2019].
135. National Institute for Health and Care Excellence (NICE). *Gemtuzumab ozogamicin for untreated acute myeloid leukaemia [TA545]*. NICE; 2018. Available from: https://www.nice.org.uk/guidance/ta545 [accessed 3rd September 2019].
136. Mazzaferro V, Sposito C, Bhoori S, Romito R, Chiesa C, Morosi C, et al. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. *Hepatology* 2013;**57**:1826-37.
137. National Institute for Health and Care Excellence (NICE). *Sorafenib for the treatment of advanced hepatocellular carcinoma [TA189]*: NICE; 2010.
138. National Institute for Health and Care Excellence (NICE). *Guide to the methods of technology appraisal 2013*. London: NICE; 2013
139. White JD, Dale M, Morgan H, Sewell B, Carolan-Rees G. *Comissioning through evaluation: Selective internal radiation therapy (SIRT)*: CEDAR Healthcare Technology Research Centre; 2017.
140. Woodcock F, Doble BA-O. Mapping the EORTC-QLQ-C30 to the EQ-5D-3L: an assessment of existing and newly developed algorithms. *Med Decis Making* 2018;**38**:954-67.
141. Rowen D, Brazier J, Roberts J. Mapping SF-36 onto the EQ-5D index: how reliable is the relationship? *Health Qual Life Outcomes* 2009;**7**:27.
142. Szende A, Janssen B, Cabase´s J, editors. *Self-reported population health: an international perspective based on EQ-5D*. Dordrecht: Springer, 2014.
143. Russell RT, Feurer ID, Wisawatapnimit P, Lillie ES, Castaldo ET, Pinson CW. Profile of health-related quality of life outcomes after liver transplantation: univariate effects and multivariate models. *HPB (Oxford)* 2008;**10**:30-7.
144. Estraviz B, Quintana JM, Valdivieso A, Bilbao A, Padierna A, de Urbina JO, et al. Factors influencing change in health-related quality of life after liver transplantation. *Clin Transplant* 2007;**21**:481-99.
145. Telles-Correia D, Barbosa A, Mega I, Mateus E, Monteiro E. When does quality of life improve after liver transplantation? A longitudinal prospective study. *Transplant Proc* 2009;**41**:904-5.
146. Tome S, Wells JT, Said A, Lucey MR. Quality of life after liver transplantation. A systematic review. *J Hepatol* 2008;**48**:567-77.
147. Younossi ZM, McCormick M, Price LL, Boparai N, Farquhar L, Henderson JM, et al. Impact of liver transplantation on health-related quality of life. *Liver Transpl* 2000;**6**:779-83.
148. Bryan S, Ratcliffe J, Neuberger JM, Burroughs AK, Gunson BK, Buxton MJ. Health-related quality of life following liver transplantation. *Qual Life Res* 1998;**7**:115-20.

149. Vilgrain V, Abdel-Rehim M, Sibert A, Ronot M, Lebtahi R, Castera L, et al. Radioembolisation with yttrium-90 microspheres versus sorafenib for treatment of advanced hepatocellular carcinoma (SARAH): study protocol for a randomised controlled trial. *Trials* 2014;**15**:474.
150. Vogel A, Cervantes A, Chau I, Daniele B, Llovet J, Meyer T, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2018;**29**:iv238-iv55.
151. Arber M, Garcia S, Veale T, Edwards M, Shaw A, Glanville JM. Performance of Ovid MEDLINE search filters to identify health state utility studies. *Int J Technol Assess Health Care* 2017;**33**:472-80.
152. Canadian Agency for Drugs and Technologies in Health (CADTH). *CADTH database search filters*. CADTH; 2016. Available from: https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters [accessed 7th March 2019].
153. Liver Advisory Group - NHS Blood and Transplant. *Update on the HCC down-staging service evaluation*. Bristol: NHS Blood and Transplant; 2018.
154. She WH, Cheung TT, Yau TC, Chan AC, Chok KS, Chu FS, et al. Survival analysis of transarterial radioembolization with yttrium-90 for hepatocellular carcinoma patients with HBV infection. *Hepatobiliary Surg Nutr* 2014;**3**:185-93.
155. Kooby DA, Egnatashvili V, Srinivasan S, Chamsuddin A, Delman KA, Kauh J, et al. Comparison of yttrium-90 radioembolization and transcatheter arterial chemoembolization for the treatment of unresectable hepatocellular carcinoma. *J Vasc Interv Radiol* 2010;**21**:224-30.
156. Kwok PC, Leung KC, Cheung MT, Lam TW, Szeto LT, Chou SQ, et al. Survival benefit of radioembolization for inoperable hepatocellular carcinoma using yttrium-90 microspheres. *J Gastroenterol Hepatol* 2014;**29**:1897-904.
157. Song JE, Jung KS, Kim DY, Song K, Won JY, Lee HW, et al. Transarterial radioembolization versus concurrent chemoradiation therapy for locally advanced hepatocellular carcinoma: a propensity score matching analysis. *Int J Radiat Oncol Biol Phys* 2017;**99**:396-406.
158. Oladeru OT, Miccio JA, Yang J, Xue Y, Ryu S, Stessin AM. Conformal external beam radiation or selective internal radiation therapy - a comparison of treatment outcomes for hepatocellular carcinoma. *J Gastrointest Oncol* 2016;**7**:433-40.
159. Ruhl R, Seidensticker M, Peters N, Mohnike K, Bornschein J, Schutte K, et al. Hepatocellular carcinoma and liver cirrhosis: assessment of the liver function after yttrium-90 radioembolization with resin microspheres or after CT-guided high-dose-rate brachytherapy. *Dig Dis* 2009;**27**:189-99.
160. D'Avola D, Inarrairaegui M, Bilbao JI, Martinez-Cuesta A, Alegre F, Herrero JI, et al. A retrospective comparative analysis of the effect of Y90-radioembolization on the survival of patients with unresectable hepatocellular carcinoma. *Hepatogastroenterology* 2009;**56**:1683-8.
161. Carr BI, Kondragunta V, Buch SC, Branch RA. Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma: a two-cohort study. *Cancer* 2010;**116**:1305-14.
162. Kallini JR, Gabr A, Ali R, Abouchaleh N, Riaz A, Baker T, et al. Pretransplant intra-arterial liver-directed therapy does not increase the risk of hepatic arterial complications in liver transplantation: a single-center 10-year experience. *Cardiovasc Intervent Radiol* 2018;**41**:231-8.
163. Gabr A, Abouchaleh N, Ali R, Vouche M, Atassi R, Memon K, et al. Comparative study of post-transplant outcomes in hepatocellular carcinoma patients treated with chemoembolization or radioembolization. *Eur J Radiol* 2017;**93**:100-6.
164. Riaz A, Ryu RK, Kulik LM, Mulcahy MF, Lewandowski RJ, Minocha J, et al. Alpha-fetoprotein response after locoregional therapy for hepatocellular carcinoma: oncologic marker of radiologic response, progression, and survival. *J Clin Oncol* 2009;**27**:5734-42.
165. Biederman DM, Titano JJ, Korff RA, Fischman AM, Patel RS, Nowakowski FS, et al. Radiation segmentectomy versus selective chemoembolization in the treatment of early-stage hepatocellular carcinoma. *J Vasc Interv Radiol* 2018;**29**:30-7.
166. Ahmad J, Rhee J, Carr BI. The effects of hepatic artery chemotherapy on viral hepatitis in patients with hepatocellular carcinoma. *Dig Dis Sci* 2005;**50**:331-5.

167. Padia SA, Johnson GE, Horton KJ, Ingraham CR, Kogut MJ, Kwan S, et al. Segmental yttrium-90 radioembolization versus segmental chemoembolization for localized hepatocellular carcinoma: results of a single-center, retrospective, propensity score-matched study. *J Vasc Interv Radiol* 2017;**28**:777-85.
168. Padia SA, Johnson GE, Horton KJ, Kwan S, Vaidya S, Ingraham CR, et al. Segmental yttrium-90 radioembolization versus chemoembolization for localized hepatocellular carcinoma. *J Clin Oncol* 2016;**34**:4084.
169. Newell PH, Wu Y, Hoen H, Uppal R, Thiesing JT, Sasadeusz K, et al. Multimodal treatment of unresectable hepatocellular carcinoma to achieve complete response results in improved survival. *HPB (Oxford)* 2015;**17**:454-60.
170. Taussig MD, Koran ME, Mouli SK, Ahmad A, Geevarghese S, Baker JC, et al. Neutrophil to lymphocyte ratio predicts disease progression following intra-arterial therapy of hepatocellular carcinoma. *HPB (Oxford)* 2017;**19**:458-64.
171. McDevitt JL, Alian A, Kapoor B, Bennett S, Gill A, Levitin A, et al. Single-center comparison of overall survival and toxicities in patients with infiltrative hepatocellular carcinoma treated with yttrium-90 radioembolization or drug-eluting embolic transarterial chemoembolization. *J Vasc Interv Radiol* 2017;**28**:1371-7.
172. Akinwande O, Kim D, Edwards J, Brown R, Philips P, Scoggins C, et al. Is radioembolization (90Y) better than doxorubicin drug eluting beads (DEBDOX) for hepatocellular carcinoma with portal vein thrombosis? A retrospective analysis. *Surg Oncol* 2015;**24**:270-5.
173. Philips P, Edwards J, Russell B, Scoggins CR, Martin RC. A comparative analysis of transarterial therapy for unresectable hepatocellular carcinoma with portal vein thrombosis: radioembolization 90Y versus doxorubicin drug eluting beads (DEB-DOX). *Ann Surg Oncol* 2015;**22**:S109.
174. Biederman DM, Titano JJ, Bishay VL, Durrani RJ, Dayan E, Tabori N, et al. Radiation segmentectomy versus TACE combined with microwave ablation for unresectable solitary hepatocellular carcinoma up to 3 cm: a propensity score matching study. *Radiology* 2017;**283**:895-905.
175. Biederman D, Titano J, Bishay V, Durrani R, Dayan E, Schwartz M, et al. Radiation segmentectomy vs. microwave ablation for unresectable solitary hepatocellular carcinoma <3 cm: a propensity score matching study. *J Vasc Interv Radiol* 2016;**27**:S5-S6.
176. Padia SA, Chewning RH, Kogut MJ, Ingraham CR, Johnson GE, Bhattacharya R, et al. Outcomes of locoregional tumor therapy for patients with hepatocellular carcinoma and transjugular intrahepatic portosystemic shunts. *Cardiovasc Intervent Radiol* 2015;**38**:913-21.
177. Radunz S, Saner FH, Treckmann J, Rekowski J, Theysohn JM, Muller S, et al. Hepatic artery and biliary complications in liver transplant recipients with radioembolization bridging treatment for hepatocellular carcinoma. *Clin Transplant* 2017;**31**:e13096.
178. Ali R, Gabr A, Abouchaleh N, Al Asadi A, Mora RA, Kulik L, et al. Survival analysis of advanced HCC treated with radioembolization: comparing impact of clinical performance status versus vascular invasion/metastases. *Cardiovasc Intervent Radiol* 2018;**41**:260-9.
179. National Institute for Health and Care Excellence (NICE). *SIR-Spheres for treating inoperable hepatocellular carcinoma. Medtech innovation briefing [MIB63]*. 2016. Available from: https://www.nice.org.uk/advice/mib63 [accessed 8th May 2019].

13 Appendices

13.1 Search strategies for clinical and cost-effectiveness

The search strategies below were used to identify studies for the systematic reviews of the clinical effectiveness and cost-effectiveness of SIRT.

Database search strategies

MEDLINE ALL

(includes: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE)

via Ovid http://ovidsp.ovid.com/

1946 to January 25th, 2019

Searched on: 28th January 2019

Records retrieved: 1790

1 Carcinoma, Hepatocellular/ (77414)

2 Liver Neoplasms/ (137452)

3 ((liver or hepato$ or hepatic$) adj3 (carcinoma$ or cancer$ or neoplas$ or tumour$ or tumor$ or malign$)).ti,ab. (131703)

4 hepatocarcinoma$.ti,ab. (3749)

5 hepatoma$.ti,ab. (27351)

6 or/1-5 (207214)

7 (Therasphere$ or Thera-sphere$).ti,ab. (66)

8 (SIR-Sphere$ or SIRSphere$).ti,ab. (100)

9 (QuiremSphere$ or Quirem-Sphere$).ti,ab. (0)

10 or/7-9 (142)

11 6 and 10 (127)

12 Microspheres/ (27127)

13 (microsphere$ or sphere$).ti,ab. (67569)

14 (microbead$ or bead$).ti,ab. (49738)

15 or/12-14 (123972)

16 Yttrium Radioisotopes/ (2861)

17 Yttrium/ (2899)

18 Yttrium Isotopes/ (708)

19 (Yttrium$ or 90Yttrium$ or Y90 or Y-90 or 90Y or 90-Y).ti,ab. (8538)

20 Holmium/ (806)

21 (Holmium$ or 166Holmium$ or Ho-166 or Ho166 or 166Ho or 166-Ho).ti,ab. (2939)

22 Radiopharmaceuticals/ (47137)

23 or/16-22 (60317)

24 15 and 23 (1616)

25 ((radioactiv$ or radio-activ$ or radionuclide$ or radio-nuclide$ or radioisotope$ or radio-isotope$ or radiolabel$ or radio-label$ or radiopharmaceutic$ or radio-pharmaceutic$) adj2 (sphere$ or microsphere$ or bead$ or microbead$)).ti,ab. (4140)

26 (radiomicrosphere$ or radio-microsphere$).ti,ab. (31)

27 or/24-26 (5660)

28 6 and 27 (1020)

29 Brachytherapy/ (18640)

30 (brachytherap$ or brachy-therap$ or microbrachytherap$).ti,ab. (16214)

31 Embolization, Therapeutic/ (29974)

32 or/29-31 (53284)

33 32 and (23 or 25 or 26) (1603)

34 6 and 33 (815)

35 (radioemboli$ or radio-emboli$ or radioembolotherap$ or radio-embolotherap$).ti,ab. (1365)

36 TARE.ti,ab. (158)

37 (internal$ adj3 (radiation$ or radiotherap$ or radio therap$ or radionuclide$ or radio-nuclide$ or radioisotope$ or radio-isotope$)).ti,ab. (2182)

38 ((intra-arterial$ or intraarterial$) adj3 (radiation$ or radiotherap$ or radio therap$ or radionuclide$ or radio-nuclide$ or radioisotope$ or radio-isotope$)).ti,ab. (276)

39 ((intra-arterial$ or intraarterial$) adj2 (brachytherap$ or brachy-therap$)).ti,ab. (19)

40 SIRT.ti,ab. (1120)

41 (SIR adj2 (therap$ or treatment$)).ti,ab. (80)

42 (radiation adj2 (segmentectom$ or lobectom$)).ti,ab. (32)

43 or/35-42 (4675)

44 6 and 43 (1675)

45 11 or 28 or 34 or 44 (1978)

46 exp animals/ not humans/ (4541052)

47 45 not 46 (1915)

48 limit 47 to yr="2000 -Current" (1790)

Key:

/ = indexing term (MeSH heading)

exp = exploded indexing term (MeSH heading)

$ = truncation

ti,ab = terms in either title or abstract fields

adj3 = terms within three words of each other (any order)

EMBASE

via Ovid http://ovidsp.ovid.com/

1974 to 2019 January 25

Searched on: 28th January 2019

Records retrieved: 3440

1 liver cell carcinoma/ (137127)

2 liver cancer/ (28908)

3 ((liver or hepato$ or hepatic$) adj3 (carcinoma$ or cancer$ or neoplas$ or tumour$ or tumor$ or malign$)).ti,ab. (185054)

4 hepatocarcinoma$.ti,ab. (4972)

5 hepatoma$.ti,ab. (30720)

6 or/1-5 (242887)

7 (Therasphere$ or thera-sphere$).ti,ab,dv. (320)

8 (SIR-Sphere$ or SIRSphere$).ti,ab,dv. (479)

9 (QuiremSphere$ or Quirem-Sphere$).ti,ab,dv. (2)

10 brachytherapy device/ (555)

11 or/7-10 (1167)

12 6 and 11 (487)

13 microsphere/ (28744)

14 (microsphere$ or sphere$).ti,ab. (73618)

15 (microbead$ or bead$).ti,ab. (71652)

16 or/13-15 (148521)

17 yttrium/ (4631)

18 yttrium 90/ (7567)

19 (Yttrium$ or 90Yttrium$ or Y90 or Y-90 or 90Y or 90-Y).ti,ab. (11105)

20 holmium/ (1495)

21 (Holmium$ or 166Holmium$ or Ho-166 or Ho166 or 166Ho or 166-Ho).ti,ab. (4761)

22 radiopharmaceutical agent/ (26611)

23 or/17-22 (46979)

24 16 and 23 (2924)

25 radioactive microsphere/ (937)

26 ((radioactiv$ or radio-activ$ or radionuclide$ or radio-nuclide$ or radioisotope$ or radio-isotope$ or radiolabel$ or radio-label$ or radiopharmaceutic$ or radio-pharmaceutic$) adj2 (sphere$ or microsphere$ or bead$ or microbead$)).ti,ab. (4430)

27 (radiomicrosphere$ or radio-microsphere$).ti,ab. (39)

28 or/24-27 (7517)

29 6 and 28 (1922)

30 brachytherapy/ (34809)

31 (brachytherap$ or brachy-therap$ or microbrachytherap$).ti,ab. (27633)

32 artificial embolization/ (6954)

33 or/30-32 (44694)

34 33 and (23 or 25 or 26 or 27) (869)

35 6 and 34 (221)

36 radioembolization/ (1554)

37 selective internal radiation.dq. (258)

38 intra arterial brachytherapy.dq. (1)

39 transarterial radioembolization.dq. (72)

40 (radioemboli$ or radio-emboli$ or radioembolotherap$ or radio-embolotherap$).ti,ab. (2887)

41 TARE.ti,ab. (416)

42 (internal$ adj3 (radiation$ or radiotherap$ or radio-therap$ or radionuclide$ or radio-nuclide$ or radioisotope$ or radio-isotope$)).ti,ab. (3166)

43 ((intra-arterial$ or intraarterial$) adj3 (radiation$ or radiotherap$ or radio-therap$ or radionuclide$ or radio-nuclide$ or radioisotope$ or radio-isotope$)).ti,ab. (363)

44 ((intra-arterial$ or intraarterial$) adj2 (brachytherap$ or brachy-therap$)).ti,ab. (18)

45 SIRT.ti,ab. (2238)

46 (SIR adj2 (therap$ or treatment$)).ti,ab. (185)

47 (radiation adj2 (segmentectom$ or lobectom$)).ti,ab. (77)

48 or/36-47 (8358)

49 6 and 48 (3229)

50 12 or 29 or 35 or 49 (3651)

51 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (5653185)

52 50 not 51 (3560)

53 limit 52 to yr="2000 -Current" (3440)

Key:

/ = indexing term (Emtree heading)

exp = exploded indexing term (Emtree heading)

$ = truncation

ti,ab = terms in either title or abstract fields

dv = terms in the device trade name field

dq = terms in the candidate term word field

adj3 = terms within three words of each other (any order)

Cumulative Index to Nursing & Allied Health (CINAHL Plus)

via EBSCO https://www.ebscohost.com/

Inception to 28th January 2019

Searched on: 28th January 2019

Records retrieved: 724

S1 (MH "Carcinoma, Hepatocellular") 7,801

S2 (MH "Liver Neoplasms") 12,189

S3 TI ((liver or hepato* or hepatic*) N3 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*)) OR AB ((liver or hepato* or hepatic*) N3 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*)) 14,708

S4 TI hepatocarcinoma* OR AB hepatocarcinoma* 173

S5 TI hepatoma* OR AB hepatoma* 649

S6 S1 OR S2 OR S3 OR S4 OR S5 20,300

S7 TI (Therasphere* or Thera-sphere*) OR AB (Therasphere* or Thera-sphere*) 19

S8 TI (SIR-Sphere* or SIRSphere*) OR AB (SIR-Sphere* or SIRSphere*) 33

S9 TI (QuiremSphere* or Quirem-Sphere*) OR AB (QuiremSphere* or Quirem-Sphere*) 0

S10 S7 OR S8 OR S9 46

S11 S6 AND S10 42

S12 TI (microsphere* or sphere*) OR AB (microsphere* or sphere*) 3,575

S13 TI (microbead* or bead*) OR AB (microbead* or bead*) 2,272

S14 S12 OR S13 5,795

S15 (MH "Radioisotopes") 3,321

S16 TI (Yttrium* or 90Yttrium* or Y90 or Y-90 or 90Y or 90-Y) OR AB (Yttrium* or 90Yttrium* or Y90 or Y-90 or 90Y or 90-Y) 1,061

S17 TI (Holmium* or 166Holmium* or Ho-166 or Ho166 or 166Ho or 166-Ho) OR AB (Holmium* or 166Holmium* or Ho-166 or Ho166 or 166Ho or 166-Ho) 281

S18 (MH "Radiopharmaceuticals") 6,050

S19 S15 OR S16 OR S17 OR S18 9,807

S20 S14 AND S19 356

S21 TI ((radioactiv* or radio-activ* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope* or radiolabel* or radio-label* or radiopharmaceutic* or radio-pharmaceutic*) N2 (sphere* or microsphere* or bead* or microbead*)) OR AB ((radioactiv* or radio-activ* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope* or radiolabel* or radio-label* or radiopharmaceutic* or radio-pharmaceutic*) N2 (sphere* or microsphere* or bead* or microbead*)) 104

S22 TI (radiomicrosphere* or radio-microsphere*) OR AB (radiomicrosphere* or radio-microsphere*) 1

S23 S20 OR S21 OR S22 440

S24 S6 AND S23 261

S25 (MH "Brachytherapy") 3,045

S26 TI (brachytherap* or brachy-therap* or microbrachytherap*) OR AB (brachytherap* or brachy-therap* or microbrachytherap*) 2,956

S27 (MH "Embolization, Therapeutic") 5,975

S28 S25 OR S26 OR S27 10,145

S29 S19 OR S21 OR S22 9,890

S30 S28 AND S29 603

S31 S6 AND S30 309

S32 (MH "Radioembolization") 29

S33 TI ((radioemboli* or radio-emboli* or radioembolotherap* or radio-embolotherap*) OR AB ((radioemboli* or radio-emboli* or radioembolotherap* or radio-embolotherap*) 654

S34 TI TARE OR AB TARE 49

S35 TI (internal* N3 (radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*)) OR AB (internal* N3 (radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*)) 327

S36 TI ((intra-arterial* or intraarterial*) N3 (radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*)) OR AB ((intra-arterial* or intraarterial*) N3 (radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*)) 45

S37 TI ((intra-arterial* or intraarterial*) N2 (brachytherap* or brachy-therap*)) OR AB ((intra-arterial* or intraarterial*) N2 (brachytherap* or brachy-therap*)) 5

S38 TI SIRT OR AB SIRT 187

S39 TI (SIR N2 (therap* or treatment*)) OR AB (SIR N2 (therap* or treatment*)) 37

S40 TI (radiation N2 (segmentectom* or lobectom*)) OR AB (radiation N2 (segmentectom* or lobectom*)) 15

S41 S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 1,140

S42 S6 AND S41 639

S43 S11 OR S24 OR S31 OR S42 727

S44 TI (animal or animals or rat or rats or mouse or mice or rodent or rodents or porcine or murine or sheep or lamb or lambs or ewe or ewes or pig or pigs or piglet or piglets or sow or sows or minipig or minipigs or rabbit or rabbits or kitten or kittens or dog or dogs or puppy or puppies or monkey or monkeys or horse or horses or foal or foals or equine or calf or calves or cattle or heifer or heifers or hamster or hamsters or chicken or chickens or livestock or alpaca* or llama*) 87,260

S45 S43 NOT S44 724

S46 S43 NOT S44

Limiters - Published Date: 20000101-20191231 724

Key:

MH = indexing term (CINAHL heading)

* = truncation

TI = terms in the title

AB = terms in the abstract

N3 = terms within three words of each other (any order)

Science Citation Index

via Web of Science, Clarivate Analytics https://clarivate.com/

1900 – 25th January 2019

Searched on: 28th January 2019

Records retrieved: 2242

38 2,242 #35 NOT #36

Indexes=SCI-EXPANDED Timespan=2000-2019

37 2,347 #35 NOT #36

36 2,811,336 TI=(animal or animals or rat or rats or mouse or mice or rodent or rodents or porcine or murine or sheep or lamb or lambs or ewe or ewes or pig or pigs or piglet or piglets or sow or sows or minipig or minipigs or rabbit or rabbits or kitten or kittens or dog or dogs or puppy or puppies or monkey or monkeys or horse or horses or foal or foals or equine or calf or calves or cattle or heifer or heifers or hamster or hamsters or chicken or chickens or livestock or alpaca* or llama*)

35 2,419 #34 OR #24 OR #20 OR #9

34 2,106 #33 AND #4

33 7,874 #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25

32 48 TS=(radiation NEAR/2 (segmentectom* or lobectom*))

31 205 TS=(SIR NEAR/2 (therap* or treatment*))

30 1,676 TS=SIRT

29 20 TS=((intra-arterial* or intraarterial*) NEAR/2 (brachytherap* or brachy-therap*))

28 289 TS=((intra-arterial* or intraarterial*) NEAR/3 (radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*))

27 3,822 TS=(internal* NEAR/3 (radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*))

26 883 TS=TARE

25 2,096 TS=(radioemboli* or radio-emboli* or radioembolotherap* or radio-embolotherap*)

24 263 #23 AND #4

23 533 #22 AND #21

22 47,345 #18 OR #17 OR #15

21 24,888 TS=(brachytherap* or brachy-therap*or microbrachytherap*)

20 1,517 #19 AND #4

19 4,871 #18 OR #17 OR #16

18 19 TS=(radiomicrosphere* or radio-microsphere*)

17 2,262 TS=((radioactiv* or radio-activ* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope* or radiolabel* or radio-label* or radiopharmaceutic* or radio-pharmaceutic*) NEAR/2 (sphere* or microsphere* or bead* or microbead*))

16 2,721 #15 AND #12

15 45,198 #14 OR #13

14 7,124 TS=(Holmium* or 166Holmium* or Ho-166 or Ho166 or 166Ho or 166-Ho)

13 38,768 TS=(Yttrium* or 90Yttrium* or Y90 or Y-90 or 90Y or 90-Y)

12 310,417#11 OR #10

11 81,252 TS=(microbead* or bead*)

10 235,358TS=(microsphere* or sphere*)

9 216 #8 AND #4

8 283 #7 OR #6 OR #5

7 0 TS=(QuiremSphere* or Quirem-Sphere*)

6 172 TS=(SIR-Sphere* or SIRSphere*)

5 145 TS=(Therasphere* or Thera-sphere*)

4 199,180#3 OR #2 OR #1

3 31,512 TS=(hepatoma*)

2 3,551 TS=(hepatocarcinoma*)

1 173,805TS=((liver or hepato* or hepatic*) NEAR/3 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*))

Key:

TS = topic tag; searches in title, abstract, author keywords and keywords plus fields

TI = search in title field

* = truncation

NEAR/2 = terms within two words of each other (any order)

Cochrane Central Register of Controlled Trials (CENTRAL)

via Wiley http://onlinelibrary.wiley.com/

Issue 1 of 12, January 2019

Searched on: 28th January 2019

Records retrieved: 144

The strategy below was used to search both CENTRAL and CDSR.

#1 MeSH descriptor: [Carcinoma, Hepatocellular] this term only 1483

#2 MeSH descriptor: [Liver Neoplasms] this term only 2218

#3 ((liver or hepato* or hepatic*) near/3 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*)):ti,ab,kw 6211

#4 hepatocarcinoma*:ti,ab,kw 57

#5 hepatoma*:ti,ab,kw 119

#6 [OR #1-#5] 6287

#7 (Therasphere* or Thera next sphere*):ti,ab,kw 9

#8 (SIRSphere* or SIR next Sphere*):ti,ab,kw 43

#9 (QuiremSphere* or Quirem next Sphere*):ti,ab,kw 0

#10 [OR #7-#9] 52

#11 #6 AND #10 42

#12 MeSH descriptor: [Microspheres] this term only 216

#13 (microsphere* or sphere*):ti,ab,kw 1202

#14 (microbead* or bead*):ti,ab,kw 948

#15 [OR #12-#14] 2109

#16 MeSH descriptor: [Yttrium Radioisotopes] this term only 78

#17 MeSH descriptor: [Yttrium] this term only 123

#18 MeSH descriptor: [Yttrium Isotopes] this term only 8

#19 (Yttrium* or 90Yttrium* or "Y90" or "Y-90" or "90Y" or "90-Y"):ti,ab,kw 1147

#20 MeSH descriptor: [Holmium] this term only 27

#21 (Holmium* or 166Holmium* or "Ho-166" or "Ho166" or "166Ho" or "166-Ho"):ti,ab,kw 334

#22 MeSH descriptor: [Radiopharmaceuticals] this term only 1425

#23 [OR #16-#22] 2844

#24 #15 AND #23 117

#25 ((radioactiv* or (radio next activ*) or radionuclide* or (radio next nuclide*) or radioisotope* or (radio next isotope*) or radiolabel* or (radio next label*) or radiopharmaceutic* or (radio next pharmaceutic*)) near/2 (sphere* or microsphere* or bead* or microbead*)):ti,ab,kw 15

#26 (radiomicrosphere* or (radio next microsphere*)):ti,ab,kw 0

#27 #24 OR #25 OR #26 123

#28 #6 AND #27 94

#29 MeSH descriptor: [Brachytherapy] this term only 653

#30 (brachytherap* or brachy next therap* or microbrachytherap*):ti,ab,kw 1583

#31 MeSH descriptor: [Embolization, Therapeutic] this term only 340

#32 [OR #29-#31] 1919

#33 #32 AND (#23 OR #25 OR #26) 46

#34 #6 AND #33 21

#35 (radioemboli* or (radio next emboli*) or radioembolotherap* or (radio next embolotherap*)):ti,ab,kw 95

#36 TARE:ti,ab,kw 105

#37 (internal* near/3 (radiation* or radiotherap* or (radio next therap*) or radionuclide* or (radio next nuclide*) or radioisotope* or (radio next isotope*))):ti,ab,kw 116

#38 ((intraarterial* or (intra next arterial)) near/3 (radiation* or radiotherap* or (radio next therap*) or radionuclide* or (radio next nuclide*) or radioisotope* or (radio next isotope*))):ti,ab,kw 17

#39 ((intraarterial* or (intra next arterial*)) near/2 (brachytherap* or (brachy next therap*))):ti,ab,kw 2

#40 SIRT:ti,ab,kw 99

#41 (SIR near/2 (therap* or treatment*)):ti,ab,kw 10

#42 (radiation near/2 (segmentectom* or lobectom*)):ti,ab,kw 1

#43 [OR #35-#42] 336

#44 #6 AND #43 133

#45 #11 OR #28 OR #34 OR #44 150

#46 #11 OR #28 OR #34 OR #44 with Cochrane Library publication date Between Jan 2000 and Jan 2019, in Cochrane Reviews, Cochrane Protocols 3

#47 #11 OR #28 OR #34 OR #44 with Publication Year from 2000 to 2019, in Trials 144

Key:

MeSH descriptor = indexing term (MeSH heading)

* = truncation

ti,ab,kw = terms in either title or abstract or keyword fields

near/3 = terms within three words of each other (any order)

next = terms are next to each other

Cochrane Database of Systematic Reviews (CDSR)

via Wiley http://onlinelibrary.wiley.com/

Issue 1 of 12, January 2019

Searched on: 28th January 2019

Records retrieved: 3

See above under CENTRAL for search strategy used.

Database of Abstracts of Reviews of Effects (DARE)

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2015

Searched on: 28th January 2019

Records retrieved: 13

The strategy below was used to search all three of the CRD databases - DARE, the HTA database and NHS EED.

1 MeSH DESCRIPTOR Carcinoma, Hepatocellular 385

2 MeSH DESCRIPTOR Liver Neoplasms 567

3 ((liver or hepato* or hepatic*) NEAR3 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*)) 850

4 ((carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*) NEAR3 (liver or hepato* or hepatic*)) 587

5 (hepatocarcinoma*) 8

6 (hepatoma*) 7

7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 891

8 (Therasphere* or Thera-sphere*) 2

9 (SIR-Sphere* or SIRSphere*) 5

10 (QuiremSphere* or Quirem-Sphere*) 0

11 #8 OR #9 OR #10 5

12 #7 AND #11 4

13 MeSH DESCRIPTOR Microspheres 16

14 (microsphere* or sphere*) 44

15 (micro-sphere* or sphere*) 16

16 (microbead* or bead*) 34

17 #13 OR #14 OR #15 OR #16 74

18 MeSH DESCRIPTOR Yttrium Radioisotopes 16

19 MeSH DESCRIPTOR Yttrium 1

20 MeSH DESCRIPTOR Yttrium Isotopes 0

21 (Yttrium* or 90Yttrium* or Y90 or Y-90 or 90Y or 90-Y) 43

22 MeSH DESCRIPTOR Holmium9

23 (Holmium* or 166Holmium* or Ho-166 or Ho166 or 166Ho or 166-Ho) 43

24 MeSH DESCRIPTOR Radiopharmaceuticals 276

25 #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 350

26 #17 AND #25 10

27 ((radioactiv* or radio-activ* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope* or radiolabel* or radio-label* or radiopharmaceutic* or radio-pharmaceutic*) NEAR2 (sphere* or microsphere* or bead* or microbead*)) 5

28 ((sphere* or microsphere* or bead* or microbead*) NEAR2 (radioactiv* or radio-activ* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope* or radiolabel* or radio-label* or radiopharmaceutic* or radio-pharmaceutic*)) 3

29 (radiomicrosphere* or radio-microsphere*) 0

30 #26 OR #27 OR #28 OR #29 11

31 #7 AND #30 11

32 MeSH DESCRIPTOR Brachytherapy 133

33 (brachytherap* or brachy-therap* or microbrachytherap*) 205

34 MeSH DESCRIPTOR Embolization, Therapeutic 145

35 #32 OR #33 OR #34 348

36 #25 OR #27 OR #28 351

37 #35 AND #36 13

38 #7 AND #37 9

39 (radioemboli* or radio-emboli* or radioembolotherap* or radio-embolotherap*) 17

40 (TARE) 2

41 (internal* NEAR3 (radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*)) 15

42 ((radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*) NEAR3 internal*) 2

43 ((intra-arterial* or intraarterial*) NEAR3 (radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*)) 0

44 ((radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*) NEAR3 (intra-arterial* or intraarterial*)) 2

45 ((intra-arterial* or intraarterial*) NEAR2 (brachytherap* or brachy-therap*)) 0

46 ((brachytherap* or brachy-therap*) NEAR2 (intra-arterial* or intraarterial*)) 0

47 (SIRT) 9

48 (SIR NEAR2 (therap* or treatment*)) 0

49 ((therap* or treatment*) NEAR2 SIR) 1

50 (radiation NEAR2 (segmentectom* or lobectom*)) 0

51 ((segmentectom* or lobectom*) NEAR2 radiation) 0

52 #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 34

53 #7 AND #52 25

54 #12 OR #31 OR #38 OR #53 29

Key:

MeSH DESCRIPTOR = indexing term (MeSH heading)

* = truncation

NEAR3 = terms within three words of each other (order specified)

Health Technology Assessment (HTA) database

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2018

Searched on: 28th January 2019

Records retrieved: 14

See above under DARE for search strategy used.

NHS Economic Evaluations Database (NHS EED)

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2015

Searched on: 28th January 2019

Records retrieved: 2

See above under DARE for search strategy used.

EconLit

via Ovid http://ovidsp.ovid.com/

1886 to January 17, 2019

Searched on: 28th January 2019

Records retrieved: 0

1 ((liver or hepato$ or hepatic$) adj3 (carcinoma$ or cancer$ or neoplas$ or tumour$ or tumor$ or malign$)).ti,ab. (17)

2 hepatocarcinoma$.ti,ab. (0)

3 hepatoma$.ti,ab. (0)

4 or/1-3 (17)

5 (Therasphere$ or Thera-sphere$).ti,ab. (0)

6 (SIR-Sphere$ or SIRSphere$).ti,ab. (0)

7 (QuiremSphere$ or Quirem-Sphere$).ti,ab. (0)

8 5 or 6 or 7 (0)

9 4 and 8 (0)

10 (microsphere$ or sphere$).ti,ab. (2659)

11 (microbead$ or bead$).ti,ab. (12)

12 10 or 11 (2671)

13 (Yttrium$ or 90Yttrium$ or Y90 or Y-90 or 90Y or 90-Y).ti,ab. (3)

14 (Holmium$ or 166Holmium$ or Ho-166 or Ho166 or 166Ho or 166-Ho).ti,ab. (1)

15 13 or 14 (4)

16 12 and 15 (0)

17 ((radioactiv$ or radio-activ$ or radionuclide$ or radio-nuclide$ or radioisotope$ or radio-isotope$ or radiolabel$ or radio-label$ or radiopharmaceutic$ or radio-pharmaceutic$) adj2 (sphere$ or microsphere$ or bead$ or microbead$)).ti,ab. (0)

18 (radiomicrosphere$ or radio-microsphere$).ti,ab. (0)

19 16 or 17 or 18 (0)

20 4 and 19 (0)

21 (brachytherap$ or brachy-therap$ or microbrachytherap$).ti,ab. (6)

22 21 and (15 or 17 or 18) (0)

23 4 and 22 (0)

24 (radioemboli$ or radio-emboli$ or radioembolotherap$ or radio-embolotherap$).ti,ab. (0)

25 TARE.ti,ab. (2)

26 (internal$ adj3 (radiation$ or radiotherap$ or radio therap$ or radionuclide$ or radio-nuclide$ or radioisotope$ or radio-isotope$)).ti,ab. (1)

27 ((intra-arterial$ or intraarterial$) adj3 (radiation$ or radiotherap$ or radio therap$ or radionuclide$ or radio-nuclide$ or radioisotope$ or radio-isotope$)).ti,ab. (0)

28 ((intra-arterial$ or intraarterial$) adj2 (brachytherap$ or brachy-therap$)).ti,ab. (0)

29 SIRT.ti,ab. (1)

30 (SIR adj2 (therap$ or treatment$)).ti,ab. (0)

31 (radiation adj2 (segmentectom$ or lobectom$)).ti,ab. (0)

32 or/24-31 (4)

33 4 and 32 (0)

34 9 or 20 or 23 or 33 (0)

Key:

$ = truncation

ti,ab = terms in either title or abstract fields

adj3 = terms within three words of each other (any order)

On-going, unpublished or grey literature search strategies

ClinicalTrials.gov

https://clinicaltrials.gov/

Searched on: 1st February 2019

Records retrieved: 157

Advanced search screen used. 10 separate searches were used retrieving 681 records in total which were imported into EndNote x9 and deduplicated.

1. 93 Studies found for: (Therasphere OR Thera-sphere OR SIR-Sphere OR SIRSphere OR QuiremSphere OR Quirem-Sphere) | (hepatocellular OR liver OR hepatic) AND (carcinoma OR cancer OR neoplasm OR tumour OR tumor OR malignancy)

2. 73 Studies found for: (Therasphere OR Thera-sphere OR SIR-Sphere OR SIRSphere OR QuiremSphere OR Quirem-Sphere) | (hepatocarcinoma OR hepatoma)

3. 103 Studies found for: (Microsphere OR sphere OR microbead OR bead) AND (Yttrium OR 90Yttrium OR Y90 OR Y-90 OR 90Y OR 90-Y OR Holmium OR 166Holmium OR Ho-166 OR Ho166 OR 166Ho OR 166-Ho) | (hepatocellular OR liver OR hepatic) AND (carcinoma OR cancer OR neoplasm OR tumour OR tumor OR malignancy)

4. 77 Studies found for: (Microsphere OR sphere OR microbead OR bead) AND (Yttrium OR 90Yttrium OR Y90 OR Y-90 OR 90Y OR 90-Y OR Holmium OR 166Holmium OR Ho-166 OR Ho166 OR 166Ho OR 166-Ho) | (hepatocarcinoma OR hepatoma)

5. 38 studies found for: (brachytherapy OR brachy-therapy OR microbrachytherapy) AND (Yttrium OR 90Yttrium OR Y90 OR Y-90 OR 90Y OR 90-Y OR Holmium OR 166Holmium OR Ho-166 OR Ho166 OR 166Ho OR 166-Ho) | (hepatocellular OR liver OR hepatic) AND (carcinoma OR cancer OR neoplasm OR tumour OR tumor OR malignancy)

6. 26 Studies found for: (brachytherapy OR brachy-therapy OR microbrachytherapy) AND (Yttrium OR 90Yttrium OR Y90 OR Y-90 OR 90Y OR 90-Y OR Holmium OR 166Holmium OR Ho-166 OR Ho166 OR 166Ho OR 166-Ho) | (hepatocarcinoma OR hepatoma)

7. 123 Studies found for: (radioembolisation OR radioembolization OR radio-embolisation OR radio-embolization OR TARE OR SIRT OR SIR) | (hepatocellular OR liver OR hepatic) AND (carcinoma OR cancer OR neoplasm OR tumour OR tumor OR malignancy)

8. 94 Studies found for: (radioembolisation OR radioembolization OR radio-embolisation OR radio-embolization OR TARE OR SIRT OR SIR) | (hepatocarcinoma OR hepatoma)

9. 32 Studies found for: selective AND internal AND (radiation OR radiotherapy OR radio-therapy) | (hepatocellular OR liver OR hepatic) AND (carcinoma OR cancer OR neoplasm OR tumour OR tumor OR malignancy)

10. 22 Studies found for: selective AND internal AND (radiation OR radiotherapy OR radio-therapy) | (hepatocarcinoma OR hepatoma)

WHO International Clinical Trials Registry Platform

http://www.who.int/ictrp/search/en/

Searched on: 1st February 2019

Records retrieved: 68

Advanced search screen used. 10 separate searches were used retrieving 103 records in total which were imported into EndNote x9 and deduplicated.

1. Condition: hepatocellular carcinoma OR liver cancer AND Intervention: Therasphere OR Thera-sphere OR SIR-Sphere OR SIRSphere OR QuiremSphere OR Quirem-Sphere 11 hits

2. Condition: hepatocarcinoma OR hepatoma AND Intervention: Therasphere OR Thera-sphere OR SIR-Sphere OR SIRSphere OR QuiremSphere OR Quirem-Sphere 4 hits

3. Condition: hepatocellular carcinoma OR liver cancer AND Intervention: Microsphere OR sphere OR Yttrium OR 90Yttrium OR Y90 OR Y-90 OR 90Y OR 90-Y OR Holmium OR 166Holmium OR Ho-166 OR Ho166 OR 166Ho OR 166-Ho 45 records 37 trials

4. Condition: hepatocarcinoma OR hepatoma AND Intervention: Microsphere OR sphere OR Yttrium OR 90Yttrium OR Y90 OR Y-90 OR 90Y OR 90-Y OR Holmium OR 166Holmium OR Ho-166 OR Ho166 OR 166Ho OR 166-Ho 6 hits

5. Condition: hepatocellular carcinoma OR liver cancer AND Intervention: brachytherapy OR brachy-therapy OR microbrachytherapy 21 hits

6. Condition: hepatocarcinoma OR hepatoma AND Intervention: brachytherapy OR brachy-therapy OR microbrachytherapy 6 hits

7. Condition: hepatocellular carcinoma OR liver cancer AND Intervention: radioembolisation OR radioembolization OR radio-embolisation OR radio-embolization OR TARE OR SIRT OR SIR 23 records for 15 trials

8. Condition: hepatocarcinoma OR hepatoma AND Intervention: radioembolisation OR radioembolization OR radio-embolisation OR radio-embolization OR TARE OR SIRT OR SIR 2 hits

9. Condition: hepatocellular carcinoma OR liver cancer AND Intervention: selective internal radiation OR selective internal radiotherapy OR selective internal radio-therapy 1 hit

10. Condition: hepatocarcinoma OR hepatoma AND Intervention: selective internal radiation OR selective internal radiotherapy OR selective internal radio-therapy 0 hit

EU Clinical Trials Register

https://www.clinicaltrialsregister.eu/ctr-search/search

Searched on: 1st February 2019

Records retrieved: 62

1. 3 result(s) found for: hepatocellular carcinoma AND (Therasphere OR Thera-sphere OR SIR-Sphere OR SIRSphere OR QuiremSphere OR Quirem-Sphere)

2. 3 result(s) found for: liver cancer AND (Therasphere OR Thera-sphere OR SIR-Sphere OR SIRSphere OR QuiremSphere OR Quirem-Sphere

3. 5 result(s) found for: hepatocellular carcinoma AND (Microsphere OR sphere OR Yttrium OR 90Yttrium OR Y90 OR Y-90 OR 90Y OR 90-Y OR Holmium OR 166Holmium OR Ho-166 OR Ho166 OR 166Ho OR 166-Ho)

4. 12 result(s) found for: liver cancer AND (Microsphere OR sphere OR Yttrium OR 90Yttrium OR Y90 OR Y-90 OR 90Y OR 90-Y OR Holmium OR 166Holmium OR Ho-166 OR Ho166 OR 166Ho OR 166-Ho)

5. 1 result(s) found for: hepatocellular carcinoma AND (brachytherapy OR brachy-therapy OR microbrachytherapy)

6. 7 result(s) found for: liver cancer AND (brachytherapy OR brachy-therapy OR microbrachytherapy)

7. 10 result(s) found for: hepatocellular carcinoma AND (radioembolisation OR radioembolization OR radio-embolisation OR radio-embolization OR TARE OR SIRT OR SIR)

8. 19 result(s) found for: liver cancer AND (radioembolisation OR radioembolization OR radio-embolisation OR radio-embolization OR TARE OR SIRT OR SIR).

9. 1 result(s) found for: hepatocellular carcinoma AND selective internal radiation

10. 1 result(s) found for: liver cancer AND selective internal radiation

PROSPERO

http://www.crd.york.ac.uk/PROSPERO/

Searched on: 1st February 2019

Records retrieved: 23

#1 MeSH DESCRIPTOR Carcinoma, Hepatocellular 107

#2 MeSH DESCRIPTOR Liver Neoplasms 158

#3 (liver or hepato* or hepatic*) adj3 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*) 342

#4 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*) ADJ3 (liver or hepato* or hepatic*) 206

#5 hepatocarcinoma* 8

#6 hepatoma* 11

#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 411

#8 Therasphere* or Thera-sphere* 1

#9 SIR-Sphere* or SIRSphere* 1

#10 QuiremSphere* or Quirem-Sphere* 0

#11 #8 OR #9 OR #10 1

#12 #11 AND #7 1

#13 MeSH DESCRIPTOR Microspheres 4

#14 microsphere* or sphere* 87

#15 microbead* or bead* 33

#16 #13 OR #14 OR #15 118

#17 MeSH DESCRIPTOR Yttrium Radioisotopes 4

#18 MeSH DESCRIPTOR Yttrium 3

#19 MeSH DESCRIPTOR Yttrium Isotopes 0

#20 Yttrium* or 90Yttrium* or Y90 or Y-90 or 90Y or 90-Y 13

#21 MeSH DESCRIPTOR Holmium1

#22 Holmium* or 166Holmium* or Ho-166 or Ho166 or 166Ho or 166-Ho 11

#23 MeSH DESCRIPTOR Radiopharmaceuticals 10

#24 #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 32

#25 #24 AND #16 6

#26 (radioactiv* or radio-activ* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope* or radiolabel* or radio-label* or radiopharmaceutic* or radio-pharmaceutic*) adj2 (sphere* or microsphere* or bead* or microbead*) 0

#27 (sphere* or microsphere* or bead* or microbead*) adj2 (radioactiv* or radio-activ* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope* or radiolabel* or radio-label* or radiopharmaceutic* or radio-pharmaceutic*) 0

#28 radiomicrosphere* or radio-microsphere* 0

#29 #26 OR #27 OR #28 0

#30 #25 OR #29 6

#31 #30 AND #7 6

#32 MeSH DESCRIPTOR Brachytherapy 14

#33 brachytherap* or brachy-therap* or microbrachytherap* 76

#34 MeSH DESCRIPTOR Embolization, Therapeutic 27

#35 #32 OR #33 OR #34 104

#36 #24 OR #26 OR #27 OR #28 32

#37 #35 AND #36 0

#38 #37 AND #7 0

#39 radioemboli* or radio-emboli* or radioembolotherap* or radio-embolotherap* 14

#40 TARE 10

#41 internal* adj3 (radiation* or radiotherap* or radio therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*) 10

#42 (radiation* or radiotherap* or radio therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*) adj3 internal* 3

#43 (intra-arterial* or intraarterial*) adj3 (radiation* or radiotherap* or radio therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*) 1

#44 (radiation* or radiotherap* or radio therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*) adj3 (intra-arterial* or intraarterial*) 3

#45 (intra-arterial* or intraarterial*) adj2 (brachytherap* or brachy-therap*) 0

#46 (brachytherap* or brachy-therap*) adj2 (intra-arterial* or intraarterial*) 0

#47 SIRT 5

#48 SIR adj2 (therap* or treatment*)0

#49 (therap* or treatment*) adj2 SIR0

#50 radiation adj2 (segmentectom* or lobectom*) 0

#51 (segmentectom* or lobectom*) adj2 radiation 0

#52 #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 35

#53 #52 AND #7 23

#54 #53 OR #38 OR #31 OR #12 23

Key:

MeSH DESCRIPTOR = indexing term (MeSH heading)

* = truncation

adj3 = terms within 3 words of each other (order specified)

NICE website

https://www.nice.org.uk/

Searched on: 8th May 2019

Records retrieved: 6

Search terms entered into main search box of the website:

1. 5 results for Therasphere OR Thera-sphere OR SIR-Sphere OR SIRSphere OR QuiremSphere OR Quirem-Sphere

2. 10 results for SIRT OR "SIR therapy" OR "SIR treatment" – browsed for any relevant to HCC – 3 results found

3. 5 results for radioembolisation OR radioembolization OR radioembolotherapy OR TARE - browsed for any relevant to HCC – 2 results found

4. 60 results found for hepatocellular carcinoma – browsed for any relevant to SIRT – 4 results found

Browsed the NICE Guidance for liver cancers section of the website https://www.nice.org.uk/guidance/conditions-and-diseases/cancer/liver-cancers - 3 results found relevant to SIRT

The above search results were deduplicated leaving 6 results in total retrieved from searches of this website.

NHS Evidence

https://www.evidence.nhs.uk/

Searched on: 8th May 2019

Records retrieved: 18

The following search strings were entered into the search box with the inbuilt guidance filters box checked to limit results to guidelines.

1. Therasphere OR "Thera sphere" OR "Thera-sphere" OR "SIR Sphere" OR "SIR-Sphere" OR SIRSphere OR QuiremSphere OR "Quirem Sphere" OR "Quirem-Sphere"

2 results

2. "hepatocellular carcinoma" AND (SIRT OR "SIR therapy" OR "SIR treatment")

9 results

3. "hepatocellular carcinoma" AND (radioembolisation OR radioembolization OR radioembolotherapy OR TARE)

13 results

4. "hepatocellular carcinoma" AND (microsphere OR yttrium or holmium)

12 results

5. "hepatocellular carcinoma" AND (brachytherapy OR microbrachytherapy)

4 results

The above search results were imported into EndNote x9 and deduplicated leaving 18 results in total.

Conference Proceedings Citation Index: Science
via Web of Science, Clarivate Analytics https://clarivate.com/
1990 – 25th January 2019
Searched on: 28th January 2019
Records retrieved: 377

38 377 #35 not #36 Timespan=2000-2019
37 391 #35 NOT #36

36 257,731 TI=(animal or animals or rat or rats or mouse or mice or rodent or rodents or porcine or murine or sheep or lamb or lambs or ewe or ewes or pig or pigs or piglet or piglets or sow or sows or minipig or minipigs or rabbit or rabbits or kitten or kittens or dog or dogs or puppy or puppies or monkey or monkeys or horse or horses or foal or foals or equine or calf or calves or cattle or heifer or heifers or hamster or hamsters or chicken or chickens or livestock or alpaca* or llama*)

35 398 #34 OR #24 OR #20 OR #9

34 316 #33 AND #4

33 1,585 #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25

32 4 TS=(radiation NEAR/2 (segmentectom* or lobectom*))

31 24 TS=(SIR NEAR/2 (therap* or treatment*))

30 333 TS=SIRT

29 4 TS=((intra-arterial* or intraarterial*) NEAR/2 (brachytherap* or brachy-therap*))

28 52 TS=((intra-arterial* or intraarterial*) NEAR/3 (radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*))

27 755 TS=(internal* NEAR/3 (radiation* or radiotherap* or radio-therap* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope*))

26 180 TS=TARE

25 357 TS=(radioemboli* or radio-emboli* or radioembolotherap* or radio-embolotherap*)

24 11 #23 AND #4

23 48 #22 AND #21

22 8,066 #18 OR #17 OR #15

21 6,589 TS=(brachytherap* or brachy-therap*or microbrachytherap*)

20 193 #19 AND #4

19 606 #18 OR #17 OR #16

18 2 TS=(radiomicrosphere* or radio-microsphere*)

17 153 TS=((radioactiv* or radio-activ* or radionuclide* or radio-nuclide* or radioisotope* or radio-isotope* or radiolabel* or radio-label* or radiopharmaceutic* or radio-pharmaceutic*) NEAR/2 (sphere* or microsphere* or bead* or microbead*))

16 468 #15 AND #12

15 7,929 #14 OR #13

14 1,346 TS=(Holmium* or 166Holmium* or Ho-166 or Ho166 or 166Ho or 166-Ho)

13 6,670 TS=(Yttrium* or 90Yttrium* or Y90 or Y-90 or 90Y or 90-Y)

12 44,967 #11 OR #10

11 10,567 TS=(microbead* or bead*)

10 34,955 TS=(microsphere* or sphere*)

9 34 #8 AND #4

8 56 #7 OR #6 OR #5

7 0 TS=(QuiremSphere* or Quirem-Sphere*)

6 29 TS=(SIR-Sphere* or SIRSphere*)

5 30 TS=(Therasphere* or Thera-sphere*)

4 22,436 #3 OR #2 OR #1

3 1,675 TS=(hepatoma*)

2 305 TS=(hepatocarcinoma*)

1 20,826 TS=((liver or hepato* or hepatic*) NEAR/3 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*))

Key:

TS = topic tag; searches terms in title, abstract, author keywords and keywords plus fields

TI = search in title field

* = truncation

NEAR/3 = terms within 3 words of each other (any order)

ProQuest Dissertations & Theses A&I

via ProQuest https://www.proquest.com/

Searched on: 28th January 2019

Records retrieved: 25

Six separate searches were run in this database giving 38 hits in total which were then imported into EndNote x9 for deduplication.

1. (TI,AB,IF(Therasphere* OR Thera-sphere*) OR TI,AB,IF(SIR-Sphere* OR SIRSphere*) OR TI,AB,IF(QuiremSphere* OR Quirem-Sphere*)) AND (TI,AB,IF((liver OR hepato* OR hepatic*) NEAR/3 (carcinoma* OR cancer* OR neoplas* OR tumour* OR tumor* OR malign*)) OR TI,AB,IF(hepatocarcinoma*) OR TI,AB,IF(hepatoma*))

0 hits

2. (TI,AB,IF((liver OR hepato* OR hepatic*) NEAR/3 (carcinoma* OR cancer* OR neoplas* OR tumour* OR tumor* OR malign*)) OR TI,AB,IF(hepatocarcinoma*) OR TI,AB,IF(hepatoma*)) AND (((TI,AB,IF(microsphere* OR sphere*) OR TI,AB,IF(microbead* OR bead*)) AND (TI,AB,IF(Yttrium* OR 90Yttrium* OR Y90 OR Y-90 OR 90Y OR 90-Y) OR TI,AB,IF(Holmium* OR 166Holmium* OR Ho-166 OR Ho166 OR 166Ho OR 166-Ho))) OR TI,AB,IF((radioactiv* OR radio-activ* OR radionuclide* OR radio-nuclide* OR radioisotope* OR radio-isotope* OR

radiolabel* OR radio-label* OR radiopharmaceutic* OR radio-pharmaceutic*) NEAR/2 (sphere* OR microsphere* OR bead* OR microbead*)) OR TI,AB,IF(radiomicrosphere* OR radio-microsphere*)) date limit 2000-2019

15 hits

3. (TI,AB,IF(brachytherap* OR brachy-therap*or microbrachytherap*) AND ((TI,AB,IF(Yttrium* OR 90Yttrium* OR Y90 OR Y-90 OR 90Y OR 90-Y) OR TI,AB,IF(Holmium* OR 166Holmium* OR Ho-166 OR Ho166 OR 166Ho OR 166-Ho)) OR TI,AB,IF((radioactiv* OR radio-activ* OR radionuclide* OR radio-nuclide* OR radioisotope* OR radio-isotope* OR radiolabel* OR radio-label* OR radiopharmaceutic* OR radio-pharmaceutic*) NEAR/2 (sphere* OR microsphere* OR bead* OR microbead*)) OR TI,AB,IF(radiomicrosphere* OR radio-microsphere*))) AND (TI,AB,IF((liver OR hepato* OR hepatic*) NEAR/3 (carcinoma* OR cancer* OR neoplas* OR tumour* OR tumor* OR malign*)) OR TI,AB,IF(hepatocarcinoma*) OR TI,AB,IF(hepatoma*)) date limit 2000-2019

1 hit

4. (TI,AB,IF(radioemboli* OR radio-emboli* OR radioembolotherap* OR radio-embolotherap*) OR TI,AB,IF(TARE)) AND (TI,AB,IF((liver OR hepato* OR hepatic*) NEAR/3 (carcinoma* OR cancer* OR neoplas* OR tumour* OR tumor* OR malign*)) OR TI,AB,IF(hepatocarcinoma*) OR TI,AB,IF(hepatoma*)) date limit 2000-2019

0 hits

5. (TI,AB,IF(internal* NEAR/3 (radiation* OR radiotherap* OR radio-therap* OR radionuclide* OR radio-nuclide* OR radioisotope* OR radio-isotope*)) OR TI,AB,IF((intra-arterial* OR intraarterial*) NEAR/3 (radiation* OR radiotherap* OR radio-therap* OR radionuclide* OR radio-nuclide* OR radioisotope* OR radio-isotope*))) AND (TI,AB,IF((liver OR hepato* OR hepatic*) NEAR/3 (carcinoma* OR cancer* OR neoplas* OR tumour* OR tumor* OR malign*)) OR TI,AB,IF(hepatocarcinoma*) OR TI,AB,IF(hepatoma*)) date limit 2000-2019

12 hits

6. (TI,AB,IF((intra-arterial* OR intraarterial*) NEAR/2 (brachytherap* OR brachy-therap*)) OR TI,AB,IF(SIRT) OR TI,AB,IF(SIR NEAR/2 (therap* OR treatment*)) OR TI,AB,IF(radiation NEAR/2 (segmentectom* OR lobectom*))) AND (TI,AB,IF((liver OR hepato* OR hepatic*) NEAR/3 (carcinoma* OR cancer* OR neoplas* OR tumour* OR tumor* OR malign*)) OR TI,AB,IF(hepatocarcinoma*) OR TI,AB,IF(hepatoma*)) date limit 2000-2019

10 hits

Key:

TI,AB,IF = terms in title or abstract or keywords field.

* = truncation

NEAR/3 = terms within 3 words of each other (any order)

13.2 Search strategies for comparator therapies

MEDLINE ALL

(includes: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE)

via Ovid http://ovidsp.ovid.com/

1946 to May 03, 2019

Searched on: 7th May 2019

Records retrieved: 449

Lines 25-104 below are to limit the search to systematic reviews or meta-analyses, taken from a previous search strategy for finding reviews in MEDLINE developed by the Centre for Reviews and Dissemination.[37] The strategy has been updated to include new MeSH headings and terminology relating to systematic reviews and network meta-analysis.

1 Carcinoma, Hepatocellular/ (78688)

2 Liver Neoplasms/ (139353)

3 ((liver or hepato$ or hepatic$) adj3 (carcinoma$ or cancer$ or neoplas$ or tumour$ or tumor$ or malign$)).ti,ab. (133795)

4 hepatocarcinoma$.ti,ab. (3798)

5 hepatoma$.ti,ab. (27491)

6 or/1-5 (209848)

7 Chemoembolization, Therapeutic/ (5314)

8 (chemo-emboli$ or chemoemboli$).ti,ab. (7127)

9 (chemoembolotherap$ or chemo-embolotherap$).ti,ab. (4)

10 TACE.ti,ab. (4674)

11 cTACE.ti,ab. (87)

12 (DEBTACE or DEB-TACE).ti,ab. (157)

13 (eluting adj2 bead$).ti,ab. (500)

14 DC bead$.ti,ab. (95)

15 or/7-14 (9758)

16 6 and 15 (7632)

17 Embolization, Therapeutic/ (30350)

18 (embolization$ or embolisation$ or embolize$ or embolise$ or embolizing$ or embolising$ or embolotherap$).ti,ab. (46678)

19 TAE.ti,ab. (2173)

20 or/17-19 (56670)
21 6 and 20 (6182)
22 ((locoregional or loco-regional) adj2 (therap$ or intervention$ or treatment$)).ti,ab. (2545)
23 6 and 22 (914)
24 16 or 21 or 23 (12277)
25 "systematic review"/ (105413)
26 systematic$ review$.ti,ab. (145034)
27 meta-analysis as topic/ (16900)
28 network meta-analysis/ (771)
29 meta-analytic$.ti,ab. (6484)
30 meta-analysis.ti,ab,pt. (150374)
31 metanalysis.ti,ab. (186)
32 metaanalysis.ti,ab. (1505)
33 meta analysis.ti,ab. (125205)
34 meta-synthesis.ti,ab. (731)
35 metasynthesis.ti,ab. (277)
36 meta synthesis.ti,ab. (731)
37 meta-regression.ti,ab. (6437)
38 metaregression.ti,ab. (577)
39 meta regression.ti,ab. (6437)
40 (synthes$ adj3 literature).ti,ab. (2958)
41 (synthes$ adj3 evidence).ti,ab. (8954)
42 integrative review.ti,ab. (2486)
43 data synthesis.ti,ab. (10362)
44 (research synthesis or narrative synthesis).ti,ab. (2491)
45 (systematic study or systematic studies).ti,ab. (11184)
46 (systematic comparison$ or systematic overview$).ti,ab. (3075)
47 evidence based review.ti,ab. (1870)
48 comprehensive review.ti,ab. (13081)
49 critical review.ti,ab. (14731)
50 quantitative review.ti,ab. (638)
51 structured review.ti,ab. (759)
52 realist review.ti,ab. (252)
53 realist synthesis.ti,ab. (173)
54 ((mixed or multiple or indirect) adj treatment$ comparison$).ti,ab. (672)
55 or/25-54 (310742)

56 review.pt. (2507320)
57 medline.ab. (102777)
58 pubmed.ab. (94743)
59 cochrane.ab. (69813)
60 embase.ab. (75244)
61 cinahl.ab. (23088)
62 psyc?lit.ab. (913)
63 psyc?info.ab. (28630)
64 (literature adj3 search$).ab. (52835)
65 (database$ adj3 search$).ab. (52049)
66 (bibliographic adj3 search$).ab. (2270)
67 (electronic adj3 search$).ab. (19250)
68 (electronic adj3 database$).ab. (25028)
69 (computeri?ed adj3 search$).ab. (3402)
70 (internet adj3 search$).ab. (2953)
71 included studies.ab. (19694)
72 (inclusion adj3 studies).ab. (14219)
73 inclusion criteria.ab. (74336)
74 selection criteria.ab. (28289)
75 predefined criteria.ab. (1803)
76 predetermined criteria.ab. (1001)
77 (assess$ adj3 (quality or validity)).ab. (71198)
78 (select$ adj3 (study or studies)).ab. (60541)
79 (data adj3 extract$).ab. (55029)
80 extracted data.ab. (12670)
81 (data adj2 abstracted).ab. (4907)
82 (data adj3 abstraction).ab. (1520)
83 published intervention$.ab. (160)
84 ((study or studies) adj2 evaluat$).ab. (169641)
85 (intervention$ adj2 evaluat$).ab. (10195)
86 confidence interval$.ab. (373846)
87 heterogeneity.ab. (149380)
88 pooled.ab. (79714)
89 pooling.ab. (11224)
90 odds ratio$.ab. (244194)
91 (Jadad or coding).ab. (169547)

92 or/57-91 (1312289)

93 56 and 92 (226468)

94 review.ti. (419930)

95 94 and 92 (121453)

96 (review$ adj4 (papers or trials or studies or evidence or intervention$ or evaluation$)).ti,ab. (169610)

97 55 or 93 or 95 or 96 (514084)

98 letter.pt. (1024828)

99 editorial.pt. (488807)

100 comment.pt. (769090)

101 98 or 99 or 100 (1719142)

102 97 not 101 (502003)

103 exp animals/ not humans/ (4576104)

104 102 not 103 (489196)

105 24 and 104 (587)

106 limit 105 to yr="2010 -Current" (449)

Key:

/ = indexing term (MeSH heading)

exp = exploded indexing term (MeSH heading)

$ = truncation

? = optional wildcard – stands for zero or one character

ti,ab = terms in either title or abstract fields

adj3 = terms within three words of each other (any order)

pt. = publication type

EMBASE

via Ovid http://ovidsp.ovid.com/

1974 to 2019 May 03

Searched on: 7th May 2019

Records retrieved: 826

Lines 26-122 below are to limit the search to systematic reviews or meta-analyses, taken from a previous search strategy for finding reviews in EMBASE developed by the Centre for Reviews and Dissemination.[37] The strategy has been updated to include terminology relating to network meta-analysis.

1 liver cell carcinoma/ (139370)

2 liver cancer/ (29412)

3 ((liver or hepato$ or hepatic$) adj3 (carcinoma$ or cancer$ or neoplas$ or tumour$ or tumor$ or malign$)).ti,ab. (188432)

4 hepatocarcinoma$.ti,ab. (5049)

5 hepatoma$.ti,ab. (30865)

6 or/1-5 (246579)

7 chemoembolization/ (14765)

8 (chemo-emboli$ or chemoemboli$).ti,ab. (12156)

9 (chemoembolotherap$ or chemo-embolotherap$).ti,ab. (6)

10 TACE.ti,ab. (9522)

11 cTACE.ti,ab. (242)

12 (DEBTACE or DEB-TACE).ti,ab. (563)

13 (eluting adj2 bead$).ti,ab,dq. (1254)

14 DC bead$.ti,ab. (291)

15 or/7-14 (20050)

16 6 and 15 (14882)

17 artificial embolization/ (7551)

18 (embolization$ or embolisation$ or embolize$ or embolise$ or embolizing$ or embolising$ or embolotherap$).ti,ab. (68834)

19 arterial embolization/ (2817)

20 TAE.ti,ab. (3247)

21 or/17-20 (72488)

22 6 and 21 (6603)

23 ((locoregional or loco-regional) adj2 (therap$ or intervention$ or treatment$)).ti,ab,dq. (4421)

24 6 and 23 (1805)

25 16 or 22 or 24 (19749)

26 systematic$ review$.ti,ab. (179774)

27 systematic$ literature review$.ti,ab. (13292)

28 "systematic review"/ (201979)

29 "systematic review (topic)"/ (23396)

30 meta analysis/ (161490)

31 "meta analysis (topic)"/ (39538)

32 network meta-analysis/ (1756)

33 meta-analytic$.ti,ab. (7595)

34 meta-analysis.ti,ab. (162787)
35 metanalysis.ti,ab. (506)
36 metaanalysis.ti,ab. (7350)
37 meta analysis.ti,ab. (162787)
38 meta-synthesis.ti,ab. (789)
39 metasynthesis.ti,ab. (328)
40 meta synthesis.ti,ab. (789)
41 meta-regression.ti,ab. (7989)
42 metaregression.ti,ab. (948)
43 meta regression.ti,ab. (7989)
44 ((mixed or multiple or indirect) adj treatment$ comparison$).ti,ab. (1407)
45 (synthes$ adj3 literature).ti,ab. (3468)
46 (synthes$ adj3 evidence).ti,ab. (9985)
47 (synthes$ adj2 qualitative).ti,ab. (2510)
48 integrative review.ti,ab. (2400)
49 data synthesis.ti,ab. (12440)
50 (research synthesis or narrative synthesis).ti,ab. (2765)
51 (systematic study or systematic studies).ti,ab. (11923)
52 (systematic comparison$ or systematic overview$).ti,ab. (3381)
53 (systematic adj2 search$).ti,ab. (27836)
54 systematic$ literature research$.ti,ab. (306)
55 (review adj3 scientific literature).ti,ab. (1709)
56 (literature review adj2 side effect$).ti,ab. (17)
57 (literature review adj2 adverse effect$).ti,ab. (3)
58 (literature review adj2 adverse event$).ti,ab. (15)
59 (evidence-based adj2 review).ti,ab. (3512)
60 comprehensive review.ti,ab. (15039)
61 critical review.ti,ab. (15755)
62 critical analysis.ti,ab. (7854)
63 quantitative review.ti,ab. (732)
64 structured review.ti,ab. (1026)
65 realist review.ti,ab. (267)
66 realist synthesis.ti,ab. (168)
67 (pooled adj2 analysis).ti,ab. (18168)
68 (pooled data adj6 (studies or trials)).ti,ab. (2772)
69 (medline and (inclusion adj3 criteria)).ti,ab. (23061)

70 (search adj (strateg$ or term$)).ti,ab. (34448)
71 or/26-70 (501726)
72 medline.ab. (127052)
73 pubmed.ab. (120450)
74 cochrane.ab. (90230)
75 embase.ab. (95039)
76 cinahl.ab. (26915)
77 psyc?lit.ab. (992)
78 psyc?info.ab. (26334)
79 lilacs.ab. (7057)
80 (literature adj3 search$).ab. (67451)
81 (database$ adj3 search$).ab. (65231)
82 (bibliographic adj3 search$).ab. (2672)
83 (electronic adj3 search$).ab. (23469)
84 (electronic adj3 database$).ab. (33807)
85 (computeri?ed adj3 search$).ab. (4093)
86 (internet adj3 search$).ab. (3981)
87 included studies.ab. (24875)
88 (inclusion adj3 studies).ab. (17595)
89 inclusion criteria.ab. (128601)
90 selection criteria.ab. (33810)
91 predefined criteria.ab. (2418)
92 predetermined criteria.ab. (1252)
93 (assess$ adj3 (quality or validity)).ab. (94916)
94 (select$ adj3 (study or studies)).ab. (79681)
95 (data adj3 extract$).ab. (75259)
96 extracted data.ab. (16453)
97 (data adj2 abstracted).ab. (8082)
98 (data adj3 abstraction).ab. (2225)
99 published intervention$.ab. (204)
100 ((study or studies) adj2 evaluat$).ab. (242677)
101 (intervention$ adj2 evaluat$).ab. (14361)
102 confidence interval$.ab. (448335)
103 heterogeneity.ab. (190795)
104 pooled.ab. (111807)
105 pooling.ab. (14826)

106 odds ratio$.ab. (306423)

107 (Jadad or coding).ab. (200705)

108 evidence-based.ti,ab. (130860)

109 or/72-108 (1828351)

110 review.pt. (2433403)

111 109 and 110 (227600)

112 review.ti. (477956)

113 109 and 112 (151152)

114 (review$ adj10 (papers or trials or trial data or studies or evidence or intervention$ or evaluation$ or outcome$ or findings)).ti,ab. (501852)

115 (retriev$ adj10 (papers or trials or studies or evidence or intervention$ or evaluation$ or outcome$ or findings)).ti,ab. (26856)

116 71 or 111 or 113 or 114 or 115 (945210)

117 letter.pt. (1060080)

118 editorial.pt. (598624)

119 117 or 118 (1658704)

120 116 not 119 (927165)

121 (animal/ or nonhuman/) not exp human/ (5382670)

122 120 not 121 (894026)

123 25 and 122 (1410)

124 limit 123 to yr="2010 -Current" (1141)

125 limit 124 to conference abstracts (315)

126 124 not 125 (826)

Key:

/ = indexing term (Emtree heading)

exp = exploded indexing term (Emtree heading)

$ = truncation

? = optional wildcard – stands for zero or one character

ti,ab = terms in either title or abstract fields

dq = terms in the candidate term word field

adj3 = terms within three words of each other (any order)

pt. = publication type

Cochrane Database of Systematic Reviews (CDSR)

via Wiley http://onlinelibrary.wiley.com/

Issue 5 of 12, May 2019

Searched on: 7th May 2019

Records retrieved: 19

#1 MeSH descriptor: [Carcinoma, Hepatocellular] this term only 1552

#2 MeSH descriptor: [Liver Neoplasms] this term only 2259

#3 ((liver or hepato* or hepatic*) near/3 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*)):ti,ab,kw 8211

#4 hepatocarcinoma*:ti,ab,kw 74

#5 hepatoma*:ti,ab,kw 141

#6 [OR #1-#5] 8301

#7 MeSH descriptor: [Chemoembolization, Therapeutic] this term only 289

#8 (chemo next emboli* or chemoemboli*):ti,ab,kw1252

#9 (chemoembolotherap* or chemo next embolotherap*):ti,ab,kw 0

#10 TACE:ti,ab,kw 991

#11 cTACE:ti,ab,kw 35

#12 (DEBTACE or DEB next TACE):ti,ab,kw 46

#13 (eluting near/2 bead*):ti,ab,kw 100

#14 DC next bead*:ti,ab,kw 32

#15 [OR #7-#14] 1478

#16 #6 and #15 1332

#17 MeSH descriptor: [Embolization, Therapeutic] this term only 345

#18 (embolization* or embolisation* or embolize* or embolise* or embolizing* or embolising* or embolotherap*):ti,ab,kw 2276

#19 TAE:ti,ab,kw 3688

#20 [OR #17-#19] 5858

#21 #6 and #20 521

#22 ((locoregional or loco next regional) near/2 (therap* or intervention* or treatment*)):ti,ab,kw 426

#23 #6 and #22 122

#24 #16 or #21 or #23 1641

#25 #16 or #21 or #23 with Cochrane Library publication date Between Jan 2010 and May 2019, in Cochrane Reviews, Cochrane Protocols 19

Key:

MeSH descriptor = indexing term (MeSH heading)

* = truncation

ti,ab,kw = terms in either title or abstract or keyword fields

near/3 = terms within three words of each other (any order)

next = terms are next to each other

Database of Abstracts of Reviews of Effects (DARE)

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2015

Searched on: 7th May 2019

Records retrieved: 78

1 MeSH DESCRIPTOR Carcinoma, Hepatocellular IN DARE,HTA 316

2 MeSH DESCRIPTOR Liver neoplasms IN DARE,HTA 459

3 (((liver or hepato* or hepatic*) NEAR3 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*))) IN DARE, HTA 627

4 ((carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*) NEAR3 (liver or hepato* or hepatic*)) IN DARE, HTA 457

5 (hepatocarcinoma*) IN DARE, HTA 3

6 (hepatoma*) IN DARE, HTA 3

7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 652

8 MeSH DESCRIPTOR Chemoembolization, Therapeutic IN DARE,HTA 74

9 ((chemo-emboli* or chemoemboli*)) IN DARE, HTA 98

10 (chemoembolotherap* or chemo-embolotherap*) IN DARE, HTA 0

11 (TACE) IN DARE, HTA 23

12 (cTACE) IN DARE, HTA 0

13 (DEBTACE or DEB-TACE) IN DARE, HTA 2

14 (eluting NEAR2 bead*) IN DARE, HTA 10

15 (bead* NEAR2 eluting) IN DARE, HTA 0

16 (DC bead*) IN DARE, HTA 3

17 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 101

18 #7 AND #17 98

19 MeSH DESCRIPTOR Embolization, Therapeutic IN DARE,HTA 106

20 ((emboli* or embolotherap*)) IN DARE, HTA 759

21 (TAE) IN DARE, HTA 12

22 #19 OR #20 OR #21 767

23 #7 AND #22 39

24 ((locoregional or loco-regional) NEAR2 (therap* or intervention* or treatment*)) IN DARE, HTA 17

25 ((therap* or intervention* or treatment*) NEAR2 (locoregional or loco-regional)) IN DARE, HTA 6

26 #24 OR #25 19

27 #7 AND #26 7

28 #18 OR #23 OR #27 119

29 (#28) IN DARE, HTA FROM 2010 TO 2019 96

30 (#29) IN DARE 78

31 (#29) IN HTA 18

Key:

MeSH DESCRIPTOR = indexing term (MeSH heading)

* = truncation

NEAR3 = terms within three words of each other (order specified)

Health Technology Assessment (HTA) database

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2018

Searched on: 7th May 2019

Records retrieved: 18

See above under DARE for search strategy used.

PROSPERO

http://www.crd.york.ac.uk/PROSPERO/

Searched on: 7th May 2019

Records retrieved: 63

#1 MeSH DESCRIPTOR Carcinoma, Hepatocellular 119

#2 MeSH DESCRIPTOR Liver Neoplasms 172

#3 (liver or hepato* or hepatic*) adj3 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*) 378

#4 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*) adj3 (liver or hepato* or hepatic*) 224

#5 hepatocarcinoma* 9

#6 hepatoma* 12

#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 452

#8 MeSH DESCRIPTOR Liver Neoplasms EXPLODE ALL TREES 183

#9 MeSH DESCRIPTOR Chemoembolization, Therapeutic 14

#10 chemo-emboli* or chemoemboli* 47

#11 chemoembolotherap* or chemo-embolotherap* 0

#12 TACE 41

#13 cTACE 1

#14 DEBTACE or DEB-TACE 6

#15 eluting adj2 bead* 7

#16 bead* adj2 eluting 0

#17 DC bead* 0

#18 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 59

#19 #18 AND #7 54

#20 #18 NOT #19 5

#21 MeSH DESCRIPTOR Chemoembolization, Therapeutic EXPLODE ALL TREES 14

#22 MeSH DESCRIPTOR Embolization, Therapeutic 29

#23 embolization* or embolisation* or embolize* or embolise* or embolizing* or embolising* or embolotherap* 173

#24 TAE 64

#25 #22 OR #23 OR #24 238

#26 #25 AND #7 34

#27 (locoregional or loco-regional) adj2 (therap* or intervention* or treatment*) 20

#28 #27 AND #7 6

#29 #28 OR #26 OR #19 63

Key:

MeSH DESCRIPTOR = indexing term (MeSH heading)

* = truncation

adj3 = terms within 3 words of each other (order specified)

13.3 Search strategies for quality of life studies

The aim of the search was to identify published studies reporting utility estimates for patients with HCC or cirrhosis. A search strategy was developed in MEDLINE (Ovid), consisting of terms for HCC or cirrhosis combined with a study design search filter to restrict retrieval to health state utility studies.[151] Specific named instruments used to measure HRQoL in HCC patients were also included in the strategy. No language or date restrictions were applied to the searches. The MEDLINE strategy was translated to run appropriately on the other databases searched.

The following databases were searched in February 2019: MEDLINE ALL (Ovid), Cost-Effectiveness Analysis (CEA) Registry, EMBASE (Ovid), Health Technology Assessment (HTA) database (CRD Databases), NHS Economic Evaluation Database (NHS EED) (CRD Databases) and the ScHARRHUD database.

Search results were imported into EndNote x9 and deduplicated.

MEDLINE ALL

via Ovid http://ovidsp.ovid.com/
1946 to February 25th, 2019
Searched on: 26th February 2019
Records retrieved: 1837

A study design search filter developed by Arber et al. designed to restrict retrieval to health state utility studies was included in the strategy.[151] The sensitivity maximizing version of the filter was used – see lines 13-35 below.

1 Carcinoma, Hepatocellular/ (77760)
2 Liver Neoplasms/ (137948)
3 ((liver or hepato$ or hepatic$) adj3 (carcinoma$ or cancer$ or neoplas$ or tumour$ or tumor$ or malign$)).ti,ab. (132386)
4 hepatocarcinoma$.ti,ab. (3764)
5 hepatoma$.ti,ab. (27397)
6 or/1-5 (208036)
7 exp Liver Cirrhosis/ (84653)
8 (cirrhos$ or cirrhot$).ti,ab. (93295)
9 ((liver or hepatic$) adj3 fibros$).ti,ab. (22118)
10 (biliary adj3 (cirrhos$ or cirrhot$ or cholangitis)).ti,ab. (9992)

11 or/7-10 (132914)

12 6 or 11 (311502)

13 quality-adjusted life years/ (10727)

14 (quality adjusted or adjusted life year$).ti,ab,kf. (14531)

15 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kf. (9350)

16 (illness state$1 or health state$1).ti,ab,kf. (5828)

17 (hui or hui1 or hui2 or hui3).ti,ab,kf. (1350)

18 (multiattribute$ or multi attribute$).ti,ab,kf. (814)

19 (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kf. (13429)

20 utilities.ti,ab,kf. (6374)

21 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kf. (9564)

22 (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kf. (3329)

23 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kf. (20320)

24 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. (1743)

25 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf. (10526)

26 quality of life/ and ec.fs. (9271)

27 quality of life/ and (health adj3 status).ti,ab,kf. (8092)

28 (quality of life or qol).ti,ab,kf. and Cost-Benefit Analysis/ (11091)

29 ((qol or hrqol or quality of life).ti,kf. or *quality of life/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab. (32288)

30 Cost-Benefit Analysis/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kf. (2980)

31 *quality of life/ and (quality of life or qol).ti. (48595)

32 quality of life/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kf. (23881)

33 quality of life/ and health-related quality of life.ti,ab,kf. (27802)

34 models,economic/ (9191)

35 or/13-34 (146623)

36 12 and 35 (1437)

37 (utility adj3 (score$1 or scoring or valu$ or measur$ or evaluat$ or scale$1 or instrument$1 or weight or weights or weighting or information or data or unit or units or health$ or life or estimat$ or

elicit$ or disease$ or mean or cost$ or expenditure$1 or gain or gains or loss or losses or lost or analysis or index$ or indices or overall or reported or calculat$ or range$ or increment$ or state or states or status)).ti,ab,kf. (29854)

38 disutili$.ti,ab,kf. (405)

39 (short form$ or shortform$).ti,ab,kf. (29550)

40 (sf12 or sf 12 or sf twelve or sftwelve).ti,ab,kf. (4154)

41 or/37-40 (61362)

42 12 and 41 (709)

43 36 or 42 (1801)

44 "European Organization for Research and Treatment of Cancer Quality of Life".ti,ab. (830)

45 "European Organisation for Research and Treatment of Cancer Quality of Life".ti,ab. (336)

46 EORTC quality of life.ti,ab. (412)

47 (EORTC QLQ$ or EORTCQLQ$).ti,ab. (3173)

48 (QLQ-C30$ or QLQC30$ or QLQ-C-30$ or QLQC-30$).ti,ab. (3609)

49 (FACT-Hep or FACTHep).ti,ab. (35)

50 FACT-hepatobiliary.ti,ab. (10)

51 Functional Assessment of Cancer Therapy Hepatobiliary.ti,ab. (45)

52 (FHSI-8 or FHSI8).ti,ab. (6)

53 (FACT-G or FACTG).ti,ab. (554)

54 FACT-General.ti,ab. (69)

55 Functional Assessment of Cancer Therapy General.ti,ab. (452)

56 (QLQ-LC$ or QLQLC$).ti,ab. (114)

57 (QLQ-HCC18$ or QLQHCC18$ or QLQ-HCC-18$ or QLQHCC-18$).ti,ab. (11)

58 (QLQ-PAN$ or QLQPAN$).ti,ab. (40)

59 (Gastrointestinal Quality of Life adj (index$ or indices)).ti,ab. (387)

60 GIQLI$.ti,ab. (329)

61 or/44-60 (5833)

62 12 and 61 (132)

63 43 or 62 (1837)

Key:

/ = indexing term (MeSH heading)
exp = exploded indexing term (MeSH heading)
$ = truncation
$1 = limited truncation – restricts to one character only after word
ti,ab = terms in either title or abstract fields
ec.fs. = floating economics subheading search
kf = author keywords field

adj3 = terms within three words of each other (any order)

Cost Effectivieness Analysis (CEA) Registry

http://healtheconomics.tuftsmedicalcenter.org/cear2n/search/search.aspx

Searched on: 26th February 2019

Records retrieved: 124

The CEA Registry was searched using the basic search interface using a set of simple searches for the population. Duplicates were removed before exporting records.

1. hepatocellular carcinoma – 86
2. hepatocellular cancer – 1
3. hepatocellular neoplasm – 0
4. hepatocellular tumor – 0
5. hepatocellular tumour – 0
6. hepatocellular malignancy – 0
7. hepatocarcinoma – 0
8. hepatoma - 1
9. liver cancer – 12
10. liver carcinoma – 0
11. liver neoplasm – 6
12. liver tumor – 2
13. liver tumour – 1
14. liver malignancy – 0
15. liver cirrhosis – 21
16. liver fibrosis – 15

EMBASE

via Ovid http://ovidsp.ovid.com/

1974 to 2019 February 25

Searched on: 26th February 2019

Records retrieved: 2415

1 liver cell carcinoma/ (136695)

2 liver cancer/ (28869)

3 ((liver or hepato$ or hepatic$) adj3 (carcinoma$ or cancer$ or neoplas$ or tumour$ or tumor$ or malign$)).ti,ab. (184856)

4 hepatocarcinoma$.ti,ab. (4990)

5 hepatoma$.ti,ab. (30679)

6 or/1-5 (242352)

7 exp liver cirrhosis/ (141130)

8 (cirrhos$ or cirrhot$).ti,ab. (135400)

9 ((liver or hepatic$) adj3 fibros$).ti,ab. (36133)

10 (biliary adj3 (cirrhos$ or cirrhot$ or cholangitis)).ti,ab. (13554)

11 or/7-10 (194904)

12 6 or 11 (388577)

13 quality adjusted life year/ (23009)

14 (quality adjusted or adjusted life year$).ti,ab,kw. (21303)

15 (qaly$ or qald$ or qale$ or qtime$).ti,ab,kw. (17652)

16 (illness state$1 or health state$1).ti,ab,kw. (10032)

17 (hui or hui1 or hui2 or hui3).ti,ab,kw. (2027)

18 (multiattribute$ or multi attribute$).ti,ab,kw. (1040)

19 (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw. (21358)

20 utilities.ti,ab,kw. (10356)

21 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kw. (17622)

22 (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw. (5144)

23 short form 36/ (24680)

24 (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw. (34476)

25 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw. (2512)

26 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kw. (22209)

27 "quality of life"/ and pe.fs. (8003)

28 "quality of life"/ and de.fs. (300)

29 "quality of life"/ and (health adj3 status).ti,ab,kw. (14248)

30 (quality of life or qol).ti,ab,kw. and "cost benefit analysis"/ (5014)

31 ((qol or hrqol or quality of life).ti,kw. or *"quality of life"/) and ((qol or hrqol$ or quality of life) adj2 (increas$ or decrease$ or improv$ or declin$ or reduc$ or high$ or low$ or effect or effects or worse or score or scores or change$1 or impact$1 or impacted or deteriorat$)).ab. (49462)

32 "cost benefit analysis"/ and (cost-effectiveness ratio$ and (perspective$ or life expectanc$)).ti,ab,kw. (726)

33 *"quality of life"/ and (quality of life or qol).ti. (74391)

34 "quality of life"/ and ((quality of life or qol) adj3 (improv$ or chang$)).ti,ab,kw. (65833)

35 "quality of life"/ and health-related quality of life.ti,ab,kw. (50090)

36 economic model/ (1547)

37 (utility adj3 (score$1 or scoring or valu$ or measur$ or evaluat$ or scale$1 or instrument$1 or weight or weights or weighting or information or data or unit or units or health$ or life or estimat$ or elicit$ or disease$ or mean or cost$ or expenditure$1 or gain or gains or loss or losses or lost or analysis or index$ or indices or overall or reported or calculat$ or range$ or increment$ or state or states or status)).ti,ab,kw. (45473)

38 disutili$.ti,ab,kw. (802)

39 (short form$ or shortform$).ti,ab,kw. (39683)

40 short form 12/ (5132)

41 (sf12 or sf 12 or sf twelve or sftwelve).ti,ab,kw. (7154)

42 or/13-41 (294270)

43 12 and 42 (3994)

44 "European Organization for Research and Treatment of Cancer Quality of Life".ti,ab. (1083)

45 "European Organisation for Research and Treatment of Cancer Quality of Life".ti,ab. (445)

46 EORTC quality of life.ti,ab. (678)

47 (EORTC QLQ$ or EORTCQLQ$).ti,ab. (6855)

48 (QLQ-C30$ or QLQC30$ or QLQ-C-30$ or QLQC-30$).ti,ab. (7303)

49 (FACT-Hep or FACTHep).ti,ab. (88)

50 FACT-hepatobiliary.ti,ab. (21)

51 Functional Assessment of Cancer Therapy Hepatobiliary.ti,ab. (58)

52 (FHSI-8 or FHSI8).ti,ab. (14)

53 (FACT-G or FACTG).ti,ab. (1231)

54 FACT-General.ti,ab. (112)

55 Functional Assessment of Cancer Therapy General.ti,ab. (678)

56 (QLQ-LC$ or QLQLC$).ti,ab. (254)

57 (QLQ-HCC18$ or QLQHCC18$ or QLQ-HCC-18$ or QLQHCC-18$).ti,ab. (21)

58 (QLQ-PAN$ or QLQPAN$).ti,ab. (77)

59 (Gastrointestinal Quality of Life adj (index$ or indices)).ti,ab. (526)

60 GIQLI$.ti,ab. (550)

61 or/44-60 (11272)

62 12 and 61 (236)

63 43 or 62 (4054)

64 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (5661185)

65 63 not 64 (3979)

66 limit 65 to conference abstracts (1564)

67 65 not 66 (2415)

Key:

/ = indexing term (Emtree heading)
exp = exploded indexing term (Emtree heading)
$ = truncation
$1 = limited truncation – restricts to one character only after word
ti,ab = terms in either title or abstract fields
pe.fs = floating pharmacoeconomics subheading search
de.fs = floating device economics subheading search
kw = terms in the author keywords field
adj3 = terms within three words of each other (any order)

Health Technology Assessment (HTA) database

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2018

Searched on: 26th February 2019

Records retrieved: 188

1 MeSH DESCRIPTOR Carcinoma, Hepatocellular IN NHSEED,HTA 97

2 MeSH DESCRIPTOR Liver Neoplasms IN NHSEED,HTA 174

3 ((liver or hepato* or hepatic*) NEAR3 (carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*)) IN NHSEED, HTA 343

4 ((carcinoma* or cancer* or neoplas* or tumour* or tumor* or malign*) NEAR3 (liver or hepato* or hepatic*)) IN NHSEED, HTA 202

5 (hepatocarcinoma*) IN NHSEED, HTA 8

6 (hepatoma*) IN NHSEED, HTA 5

7 #1 OR #2 OR #3 OR #4 OR #5 OR #6 365

8 MeSH DESCRIPTOR Liver Cirrhosis EXPLODE ALL TREES IN NHSEED,HTA 129

9 (cirrhos* or cirrhot*) IN NHSEED, HTA 340

10 ((liver or hepatic*) NEAR3 fibros*) IN NHSEED, HTA 43

11 (fibros* NEAR3 (liver or hepatic*)) IN NHSEED, HTA 11

12 (biliary NEAR3 (cirrhos* or cirrhot* or cholangitis)) IN NHSEED, HTA 14

13 ((cirrhos* or cirrhot* or cholangitis) NEAR3 biliary) IN NHSEED, HTA 8

14 #8 OR #9 OR #10 OR #11 OR #12 OR #13 350

15 #7 OR #14 540

16 (#15) IN NHSEED 352

17 (#15) IN HTA 188

Key:
MeSH DESCRIPTOR = indexing term (MeSH heading)
* = truncation
NEAR3 = terms within three words of each other (order specified)

NHS Economic Evaluations Database (NHS EED)
via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2015

Searched on: 26th February 2019

Records retrieved: 352

See above under HTA database for search strategy used.

ScHARRHUD

https://www.scharrhud.org/

Searched on: 26th February 2019

Records retrieved: 11

1. liver OR hepato* OR hepatic*

2. cirrhos* OR cirrhot*

3. biliary AND cholangitis

4. (#1 OR #2 OR #3)

Key:
* = truncation

13.4 Search strategies for resource use and cost evidence

The aim of the search was to identify published studies relating to costs or resource use in patients with HCC. A search strategy was developed in MEDLINE (Ovid), comprising of a set of terms for HCC combined with terms relating to costs or resource use. The terms included for costs were based on a search strategy developed by the Canadian Agency for Drugs and Technologies in Health (CADTH).[152]Retrieval was restricted to studies published from 2010 onwards in any language. The MEDLINE strategy was translated to run appropriately on the other databases searched.

The following databases were searched on 7th March 2019: MEDLINE ALL (Ovid), and EMBASE (Ovid). The previous results obtained for the health utilities search from the Health Technology Assessment (HTA) database and the NHS Economic Evaluation Database (NHS EED) were added to the results from MEDLINE and EMBASE.

Search results were imported into EndNote x9 and deduplicated.

MEDLINE ALL

via Ovid http://ovidsp.ovid.com/
1946 to March 06, 2019
Searched on: 7th March 2019
Records retrieved: 2153

Lines 7-19 below are based upon a search strategy developed by Canadian Agency for Drugs and Technologies in Health (CADTH) to identify studies about costs/economics.[152]

1 Carcinoma, Hepatocellular/ (77885)
2 Liver Neoplasms/ (138136)
3 ((liver or hepato$ or hepatic$) adj3 (carcinoma$ or cancer$ or neoplas$ or tumour$ or tumor$ or malign$)).ti,ab. (132179)
4 hepatocarcinoma$.ti,ab. (3767)
5 hepatoma$.ti,ab. (27406)
6 or/1-5 (207882)
7 economics/ (27006)
8 exp "costs and cost analysis"/ (222429)
9 economics, dental/ (1901)
10 exp "economics, hospital"/ (23378)
11 economics, medical/ (9002)

12 economics, nursing/ (3986)

13 economics, pharmaceutical/ (2843)

14 exp "Fees and Charges"/ (29616)

15 exp Budgets/ (13465)

16 budget*.ti,ab,kf. (27124)

17 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. (209622)

18 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 (258034)

19 or/7-18 (523885)

20 6 and 19 (1325)

21 Health Resources/ (12010)

22 Healthcare Financing/ (695)

23 (resource$ adj2 ("use" or utilis$ or utiliz$ or consum$ or usage)).ti,ab. (25314)

24 ((healthcare or health-care) adj2 ("use" or utilis$ or utiliz$ or consum$ or usage)).ti,ab. (25383)

25 21 or 22 or 23 or 24 (56988)

26 6 and 25 (134)

27 Length of Stay/ (80203)

28 (cost$ adj2 (illness$ or disease$ or sickness$)).ti,ab. (4600)

29 (burden$ adj2 (disease$ or illness$ or sickness$)).ti,ab. (22257)

30 ((length or hospital$ or duration) adj2 stay$).ti,ab. (120889)

31 ((extended or prolonged) adj stay$).ti,ab. (1013)

32 ((hospitali?ation$ or hospitali?ed) adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab. (6753)

33 economic consequenc$.ti,ab. (3229)

34 or/27-33 (190256)

35 6 and 34 (2349)

36 20 or 26 or 35 (3467)

37 exp animals/ not humans/ (4553712)

38 36 not 37 (3454)

39 limit 38 to yr="2010 -Current" (2153)

Key:

/ = indexing term (MeSH heading)
exp = exploded indexing term (MeSH heading)
$ = truncation
? = optional wild card – stands for zero or one character within a word
ti,ab = terms in either title or abstract fields
ab. /freq=2 = frequency operator – term must appear at least twice in the abstract for the record to be retrieved
kf = author keywords field
adj3 = terms within three words of each other (any order)

EMBASE

via Ovid http://ovidsp.ovid.com/
1974 to 2019 March 06
Searched on: 7th March 2019
Records retrieved: 3913

Lines 7-14 below are based upon a search strategy developed by Canadian Agency for Drugs and Technologies in Health (CADTH) to identify studies about costs/economics.[153]

1 liver cell carcinoma/ (136950)
2 liver cancer/ (28936)
3 ((liver or hepato$ or hepatic$) adj3 (carcinoma$ or cancer$ or neoplas$ or tumour$ or tumor$ or malign$)).ti,ab. (185215)
4 hepatocarcinoma$.ti,ab. (5000)
5 hepatoma$.ti,ab. (30696)
6 or/1-5 (242760)
7 Economics/ (231508)
8 Cost/ (56142)
9 exp Health Economics/ (783424)
10 Budget/ (26815)
11 budget*.ti,ab,kw. (35333)

12 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kw. (253689)

13 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 (357407)

14 or/7-13 (1153032)

15 6 and 14 (4962)

16 health care utilization/ (63300)

17 health care financing/ (12931)

18 (resource$ adj2 ("use" or utilis$ or utiliz$ or consum$ or usage)).ti,ab. (39541)

19 ((healthcare or health-care) adj2 ("use" or utilis$ or utiliz$ or consum$ or usage)).ti,ab. (36926)

20 16 or 17 or 18 or 19 (122638)

21 6 and 20 (501)

22 disease burden/ (8049)

23 Length of Stay/ (159340)

24 (cost$ adj2 (illness$ or disease$ or sickness$)).ti,ab. (6874)

25 (burden$ adj2 (disease$ or illness$ or sickness$)).ti,ab. (33648)

26 ((length or hospital$ or duration) adj2 stay$).ti,ab. (204289)

27 ((extended or prolonged) adj stay$).ti,ab. (1581)

28 ((hospitali?ation$ or hospitali?ed) adj3 (economic$ or cost or costs or costly or costing or price or prices or pricing)).ti,ab. (11727)

29 economic consequenc$.ti,ab. (4245)

30 or/22-29 (313622)

31 6 and 30 (3966)

32 15 or 21 or 31 (8470)

33 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (5667672)

34 32 not 33 (8389)

35 limit 34 to yr="2010 -Current" (6403)

36 limit 35 to conference abstracts (2490)

37 35 not 36 (3913)

Key:

/ = indexing term (Emtree heading)

exp = exploded indexing term (Emtree heading)

$ = truncation

? = optional wild card – stands for zero or one character within a word

ti,ab = terms in either title or abstract fields

ab. /freq=2 = frequency operator – term must appear at least twice in the abstract for a record to be retrieved

kw = terms in the author keywords field

adj3 = terms within three words of each other (any order)

Health Technology Assessment (HTA) database

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2018

Searched on: 26th February 2019

Records retrieved: 188

To view the search strategy see under HRQoL search strategies in Appendix 13.3.

NHS Economic Evaluations Database (NHS EED)
via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2015

Searched on: 26th February 2019

Records retrieved: 352

To view the search strategy see under HRQoL search strategies in Appendix 13.3.

13.5 Risk of bias assessment results

Risk of bias assessment results for RCTs

Trial	Risk of bias arising from the randomisation process	Risk of bias due to deviations from the intended interventions	Missing outcome data (primary outcome)	Risk of bias in measurement of the outcome	Risk of bias in selection of the reported result	Overall judgement of risk of bias
Vilgrain, 2017[2, 43] SARAH	Low	Low	Low	Low	Low	Low
Chow, 2018[3] SIRveNIB	Low	Low	Low	Low	Low	Low
Kolligs, 2015[4] SIR-TACE	High	Low	High	High	Low	High
Pitton, 2015[5]	Some concerns	Low	Low	Low	Low	Some concerns
Ricke, 2015[6] SORAMIC	Some concerns	High	Low	Low	Low	High
Salem, 2016[8, 44, 45] PREMIERE	High	Some concerns	Low	Low	Low	High
Kulik, 2014[11, 46, 47]	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns

Risk of bias assessment results for prospective comparative studies

Trial	Inclusion criteria clearly defined	Allocation to treatment groups adequately described/appropriate	Groups similar at baseline	Clearly described and consistently delivered intervention	Clearly described and consistently delivered comparator	Outcome assessors blinded	Missing outcome data balanced across groups	Free from suggestion of selective reporting	Overall judgement of risk of bias
Kirchner, 2019[7]	No	No	No	Yes	No	No	Yes	Yes	High
El Fouly, 2015[10]	Yes	No	No	Yes	Yes	No	Yes	Yes	High
Salem, 2013[12]	Yes	No	No	Yes	Yes	No	Yes	Yes	High
Memon, 2013[13]	Yes	No	Yes	Yes	Yes	No	Yes	Unclear	High
Hickey, 2016[9]	Yes	No	No	Yes	Yes	No	Yes	Yes	High
Maccauro, 2014[15]	No	No	Unclear	No	No	Unclear	Unclear	Unclear	High
Woodall, 2009[14]	Yes	No	No	Yes	Yes	No	Yes	Yes	High

Risk of bias assessment results for retrospective comparative studies

Trial	Inclusion criteria clearly defined	Representative sample from relevant population	Groups similar at baseline	Clearly described and consistently delivered intervention	Clearly described and consistently delivered comparator	Outcome assessors blinded	Missing outcome data balanced across groups	Free from suggestion of selective reporting	Overall judgement of risk of bias
Biederman, 2015[20]	No	Unclear	Unclear	No	No	Unclear	Unclear	Unclear	High
Biederman, 2016[19]	Yes	Yes	No	Yes	Yes	Unclear	Unclear	Unclear	High
Van Der Gucht, 2017[18]	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	High
Bhangoo, 2015[17]	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Unclear
d'Abadie, 2018[21]	No	Unclear	No	No	No	Unclear	Unclear	Yes	High

Risk of bias assessment results for non-comparative studies

Trial	Inclusion criteria clearly defined	Representative sample from relevant population	Clearly described and consistently delivered intervention	Outcome measures pre-specified, reliable and consistently assessed	Outcome assessors blinded	Attrition low and accounted for in analysis	Incomplete outcome data minimal/dealt with in analysis	Overall judgement of risk of bias
Radosa, 2019[16]	Yes	Unclear	Yes	No	No	N/A (retrospective database of treated patients)	Yes	High

13.6 Study details and results for all studies included in systematic review of clinical effectiveness (n=20)

Study name and location	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
Vilgrain, 2017[2, 43] SARAH France	Multicentre open-label RCT Funding: Sirtex Medical Inc	Locally advanced HCC (BCLC C), or new HCC not eligible for surgery/ablation after previously cured HCC, or HCC with two unsuccessful rounds of transarterial chemoembolization. Life expectancy >3 months, ECOG PS 0 or 1, Child-Pugh class A or B score ≤7	SIR-Spheres (n=237)	Sorafenib (400 mg twice daily orally, administered until the occurrence of radiological progression, unacceptable AEs or death) (n=222)	**Overall survival:** SIR-Spheres: median 8.0 months (95% CI: 6.7-9.9). 196/237 (83%) patients died. 1-year OS: 39.5% (95% CI: 33.3-45.9). Sorafenib: median 9.9 months (95% CI: 8.7-11.4). 177/222 (80%) patients died. 1-year OS: 42.1% (95% CI: 35.6-48.7). Comparison between groups: ITT population HR: 1.15 (95% CI: 0.94-1.41, p=0.18). Per protocol population HR: 0.99 (95% CI: 0.79-1.24). **Progression-free survival:** SIR-Spheres: median 4.1 months (95% CI: 3.8-4.6). 218/237 (92%) had progression events. Sorafenib: median 3.7 months (95% CI: 3.3-5.4). 205/222 (92%) had progression events. Comparison between groups: ITT population HR: 1.03 (95% CI: 0.85-1.25, p=0.76). **Complete or partial response rate:** SIR-Spheres: 36/190 (19%) evaluable patients. Sorafenib: 23/198 (12%) evaluable patients. **Health-related quality of life:** The global health status subscore was significantly better in the SIRT group than in the sorafenib group (group effect p=0.0048; time effect p<0.0001) and the between group difference tended to increase with time	Low

Study name and location	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					(group-time interaction p=0.0447) for both the intention-to-treat and per protocol populations. **Adverse events:** SIR-Spheres: 173/226 (77%) patients reported at least one AE. 19 treatment-related deaths (6 did not receive SIRT and subsequently received sorafenib). Sorafenib: 203/216 (94%) patients reported at least one AE. 12 treatment-related deaths. 139/216 (64%) patients discontinued sorafenib due to drug-related toxicity; 108 of whom permanently discontinued. **Time on treatment/number of treatments:** SIR-Spheres: 53/237 (22%) did not receive SIRT. Of 184 patients who received SIRT, 115 (63%) received a single administration, 58 patients received 2 treatments, 11 patients received 3 treatments. Sorafenib: median dose intensity 800 mg/day (IQR 585-800). Median cumulative time of sorafenib intake 2.8 months (IQR 1.0-5.8). 82/216 (38%) required a dose reduction. Permanent discontinuation occurred in 132 (61%) patients; 49 (37%) patients discontinued sorafenib before tumour progression.	
Chow, 2018[3] SIRveNIB Asia-Pacific region	Multicentre open-label RCT Funding: Sirtex Medical	Locally advanced HCC (BCLC B or C without extrahepatic disease) with or without PVT, not amenable to curative treatment modalities	SIR-Spheres (n=182)	Sorafenib (400 mg twice daily orally, administered until the occurrence of treatment failure, complete response,	**Overall survival:** SIR-Spheres: median 8.8 months (95% CI: 7.5-10.8). Sorafenib: median 10.0 months (95% CI: 8.6-13.8). Comparison between groups: ITT population HR: 1.12 (95% CI: 0.9-1.4, p=0.36). Per protocol population HR: 0.86 (95% CI: 0.7-1.1, p=0.27). **Progression-free survival:**	Low

Study name and location	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
				initiation of other HCC therapies, unacceptable AEs, patient request to stop treatment or death) (n=178)	SIR-Spheres: median 5.8 months (95% CI: 3.7-6.3). Sorafenib: median 5.1 months (95% CI: 3.9-5.6). Comparison between groups: ITT population HR: 0.89 (95% CI: 0.7-1.1, p=0.31). **Complete or partial response rate:** SIR-Spheres: 16.5%. Sorafenib: 1.7%. **Health-related quality of life:** There were no statistically significant differences in the EQ-5D index between the RE and sorafenib groups throughout the study in either the ITT or treated populations. **Adverse events:** SIR-Spheres: 78/130 (60.0%) patients reported at least one AE. 36/130 (27.7%) reported at least one AE grade ≥3. 27/130 (20.8%) reported at least one serious AE. Sorafenib: 137/162 (84.6%) patients reported at least one AE. 82/130 (50.6%) reported at least one AE grade ≥3. 57/162 (35.2%) reported at least one serious AE. **Time on treatment/number of treatments:** SIR-Spheres: 52/182 (28.6%) did not receive SIRT. All 130 patients who received SIRT received a single administration. Sorafenib: 16/178 (9%) did not receive sorafenib. Median treatment duration was 13.8 weeks and mean daily dose was 644.5 mg.	

Study name and location	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
Kolligs, 2015[4] SIR-TACE Germany and Spain	Multicentre open-label RCT Funding: Sirtex Medical	Unresectable HCC with preserved liver function (Child-Pugh ≤B7; total bilirubin ≤2 mg/dl), an ECOG performance status ≤2, and absence of any form of vascular invasion or extrahepatic spread	SIR-Spheres (n=13)	TACE (n=15)	**Overall survival:** Not reported **Progression-free survival:** SIR-Spheres: median 3.6 months (95% CI: 2.3-6.2). TACE: median 3.7 months (95% CI: 1.6-11.0). **Complete or partial response rate:** SIR-Spheres: 4/13 (30.8%). TACE: 2/15 (13.3%). **Health-related quality of life:** HRQoL data were analyzed for 18 patients (8 SIRT and 10 TACE). Higher scores reflect higher functioning and fewer symptoms. At baseline, median scores were lower for patients receiving SIRT than TACE, particularly for sub-scales of physical functioning (82.0 vs 96.0; P = 0.04) by Kruskal–Wallis test. This manifested in the lower scores with SIRT throughout the first 12 weeks after treatment, although the differences between the treatment groups by week 12 were not statistically significant for either FACT-Hep total or its subscales. **Adverse events:** SIR-Spheres: 12/13 (92.3%) patients reported at least one AE. 3/13 reported at least one AE grade ≥3. 7/13 reported at least one serious AE requiring hospitalisation.	High

Study name and location	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					TACE: 10/15 (66.7%) patients reported at least one AE. 2/15 reported at least one AE grade ≥3. 5/15 reported at least one serious AE requiring hospitalisation. **Time on treatment/number of treatments:** SIR-Spheres: 7/13 (53.8%) received whole-liver SIRT, 5 (38.5%) received lobar and 1 (7.7%) received segmental treatment. All patients received one course of treatment. TACE: On average, patients received 3.4 (SD 2.9; median 2.0) separate sessions during the study. 3 patients received one course of TACE, 5 patients received 2 courses, 3 patients received 4 courses, 3 patients received 5 courses and one patient received 11 courses.	
Pitton, 2015[5] Germany	Single centre open-label RCT Funding: Johannes Gutenberg University Mainz	Unresectable N0, M0 HCC (BCLC stage B)	SIR-Spheres (n=12)	DEB-TACE (n=12)	**Overall survival:** SIR-Spheres: median 592 days (Q1: 192, Q3: -). Mean 437 days (SE: 72). Cause of death was predominantly liver failure (n=4) with only one death due to tumour progression. DEB-TACE: median 788 days (Q1: 178, Q3: 950). Mean 583 days (SE: 119). Cause of death was predominantly tumour progression (n=4) with only one death due to liver failure. **Progression-free survival:** SIR-Spheres: median 180 days (Q1: 120, Q3: 414). Mean 266 days (SE: 55) DEB-TACE: median 216 days (Q1: 88, Q3: 355). Mean 237 days (SE: 49) **Complete or partial response rate:** Not reported	Some concerns

Study name and location	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					Health-related quality of life: Not reported **Adverse events:** Not reported **Time on treatment/number of treatments:** SIR-Spheres: Patients received either one (n=4) or two treatment sessions (n=8). Eight patients had a bilobar approach. DEB-TACE: The mean number of treatment sessions was 3.8 ± 2.6 (range 1-10). Embolisation was unilobar in five and bilobar in seven patients.	
Ricke, 2015[6] SORAMIC Germany	Multicentre open-label RCT Funding: Sirtex Medical and Bayer Healthcare	Unresectable intermediate or advanced HCC (BCLC stage B or C) with preserved liver function (Child-Pugh ≤B7) and ECOG <2, who were poor candidates for TACE (including those failing TACE)	SIR-Spheres + sorafenib (n=20)	Sorafenib alone (n=20)	**Overall survival:** Not reported **Progression-free survival:** Not reported **Complete or partial response rate:** Not reported **Health-related quality of life:** Not reported **Adverse events:** SIR-Spheres + sorafenib: There were 196 adverse events reported, 43/196 (21.9%) were grade 3 or worse. Sorafenib alone: There were 222 adverse events reported, 47/222 (21.2%) were grade 3 or worse.	High

Study name and location	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					Time on treatment/number of treatments: SIR-Spheres + sorafenib: SIRT was administered as a sequential lobar treatment in 10/20 patients, whilst 10 patients received unilobar treatment. Patients received a median daily sorafenib dose of 614 mg (range 45-793 mg) over a median of 8.5 months. Sorafenib alone: Patients received a median daily sorafenib dose of 557 mg (range 284-792 mg) over a median of 9.6 months.	
Salem, 2016[8, 44, 45] PREMIERE USA	Single centre open-label RCT Funding: NIH grant (in part)	BCLC stage A/B unablatable/unresectable HCC with no vascular invasion. Child-Pugh A/B	TheraSphere (n=24)	TACE (n=21)	**Overall survival:** TheraSphere: median 18.6 months (95% CI: 7.4-32.5). TACE: median 17.7 months (95% CI: 8.3-NC). **Time to progression:** TheraSphere: not reached (>26 months). TACE: 6.8 months. **Complete or partial response rate:** TheraSphere: 20/23 (87%) achieved EASL response, 12/23 (52%) achieved WHO response. TACE: 14/19 (74%) achieved EASL response, 12/19 (63%) achieved WHO response. **Health-related quality of life:** Not reported **Adverse events:** Not reported	High

Study name and location	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					Time on treatment/number of treatments: TheraSphere: Selective SIRT treatment was performed in 17/24 patients; 7 were lobar treatments. TACE: Selective chemoembolization was performed in 16/19 patients; 3 were lobar treatments.	
Kulik, 2014[11, 46, 47] USA	Single centre open-label RCT pilot study Funding: Bayer/Onyx and a Northwestern University departmental pilot grant program	HCC, Child-Pugh ≤B8 and potential candidates for OLT	TheraSphere (n=10)	TheraSphere + sorafenib (n=10)	**Overall survival:** TheraSphere: 3 patients died. TheraSphere + sorafenib: 2 patients died. **Progression-free survival:** Not reported **Complete or partial response rate:** Not reported **Health-related quality of life:** Not reported **Adverse events:** The most commonly reported adverse events were fatigue (9/10 TheraSphere patients and 4/10 TheraSphere + sorafenib patients), pain (5/10 TheraSphere patients and 0 TheraSphere + sorafenib patients) and nausea (7/10 TheraSphere patients and 2 TheraSphere + sorafenib patients). **Time on treatment/number of treatments:** TheraSphere: 2/10 patients had more than one SIRT treatment; one patient had two SIRT treatments and one patient had three SIRT treatments plus one TACE.	Some concerns

Study name and location	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					TheraSphere + sorafenib: 3/10 patients had more than one SIRT treatment; one patient had 3 SIRT treatments, one patient had a second SIRT treatment plus TACE and one patient had a second SIRT treatment plus radiofrequency ablation.	
Kirchner, 2019[7] Germany	Prospective single centre comparative study Funding: None	All patients undergoing initial TACE or TARE due to HCC between November 2014 and March 2016 agreed to participate (n=94). Twenty-seven patients failed to answer the questionnaire, therefore, quality of life after 67 interventions was analysed	TheraSphere (n=21)	cTACE (n=33) DEB-TACE (n=13)	**Overall survival:** Not reported **Progression-free survival:** Not reported **Complete or partial response rate (RECIST):** TheraSphere: 0/19 (0%) evaluable patients. TACE: 1/44 (2.3%) evaluable patients. **Complete or partial response rate (WHO):** TheraSphere: 1/19 (5.3%) evaluable patients. TACE: 3/44 (6.8%) evaluable patients. **Health-related quality of life:** Before the intervention the mean global health status/QoL in SIRT group (50.8%) was significantly lower compared to TACE group (62.5%, p = 0.029). After treatment, the mean absolute decrease in global health status/QoL was higher in the TACE group (-10.5%) compared to the SIRT group (-4.8%), which was not statistically significant (p=0.396). The absolute increase in fatigue after initial treatment was significantly higher with TACE (+19.1%) compared to SIRT (+7.9%, p=0.021).	High

Study name and location	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					The SIRT group showed the highest changes in financial difficulties (14.3% increase), role functioning (12.7 % decrease) and dyspnea (11.1% increase), C30 role functioning (12.7% decrease), social functioning (10.3% decrease), QLQ-HCC18 nutrition (10.2% increase). The TACE group showed the highest changes in QOL-C30 physical functioning (14.1% decrease), role functioning (21.7% decrease), emotional functioning (10.2% decrease), social functioning (17.4% decrease) and fatigue (19.1% increase). It also showed an 11.6% increase in pain, QLQ-HCC18 fatigue (11.6% increase), body image (11.2% increase) and sex life (11.6% increase). Relative pre-/post change in global health status was -16.8% in TACE group and -9.4% in SIRT group. **Adverse events:** Not reported **Time on treatment/number of treatments:** Not reported	
El Fouly, 2015[10] Germany, Egypt	Prospective multi-centre comparative study Funding: Not reported	Intermediate stage (BCLC B) HCC and good liver function (Child-Pugh B<7)	TheraSphere (n=44)	TACE (n=42)	**Overall survival:** TheraSphere: median 16.4 months (95% CI: 7.9-25.3). 1-year OS: 59%, 2-year OS: 40%, 3-year OS: 31%. TACE: median 18 months (95% CI: 12.1-25.5). 1-year OS: 64%, 2-year OS: 36%, 3-year OS: 11%. **Time to progression:** TheraSphere: median 13.3 months (95% CI: 3.4-23.1). TACE: median 6.8 months (95% CI: 3.9-8.8).	High

Study name and location	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					Complete or partial response rate: TheraSphere: 7% complete response, 68% partial response. TACE: 5% complete response, 45% partial response. **Health-related quality of life:** Not reported **Adverse events:** The most commonly reported adverse event was unspecific abdominal pain, which was found in 83% TACE patients (versus 5% SIRT patients). **Time on treatment/number of treatments:** TheraSphere: total number of sessions=63, with a mean average of 1.4 sessions per patient (median=1). TACE: total number of sessions=93, with a mean average of 2.2 sessions per patient (median=2).	
Salem, 2013[12] USA	Prospective comparative study Funding: Dimitrovich Family Foundation and National Institutes of Health (in part)	Treatment naïve HCC patients with ECOG performance status 0-2	TheraSphere (n=29)	TACE (n=27)	**Overall survival:** Not reported **Progression-free survival:** Not reported **Complete or partial response rate:** Not reported **Health-related quality of life:** Overall, most of the FACT-Hep scales showed a reduction in score in the TACE group, with stability or increase in the SIRT group between baseline and 4 week assessments.	High

Study name and location	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					Despite more advanced disease at baseline (regression analysis incorporating BCLC stage), SIRT patients showed significantly better quality of life relative to TACE in social well-being (p=0.019), functional well-being (p=0.031) and embolotherapy-specific score (p=0.018). Strong trends favouring SIRT were noted in overall quality of life (p=0.055), the Trial Outcome Index (p=0.05), and FACT-Hep (p=0.071). Differences in physical wellbeing, hepatobiliary cancer subscale and FACT Hepatobiliary-Pancreatic Symptom Index were less pronounced. The only subscale which appeared to favour TACE was emotional wellbeing (p=0.656). In terms of specific variables, two weeks after treatment, SIRT patients reported greater closeness to friends (p=0.035), and TACE patients reported a greater feeling of sadness (p=0.034). At 4 weeks, TACE patients complained of being bothered by treatment side effects (p=0.029) and nervousness (p=0.047). SIRT patients experienced greater satisfaction with coping with illness (p=0.019) and good appetite (p=0.045). **Adverse events:** Not reported **Time on treatment/number of treatments:** Not reported	
Memon, 2013[13] USA	Prospective follow-up to a retrospective comparative study Funding: National	HCC that progressed after intra-arterial locoregional therapies: TACE and SIRT	TheraSphere (n=42)	TACE (n=54)	**Overall survival:** Not reported **Time to progression:** TheraSphere: median 13.3 months (range: 9.3-25.0). TACE: median 8.4 months (range: 7.3-10.6).	High

<table>
<tr><th>Study name and location</th><th>Study design and funding source</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Main results</th><th>Risk of bias</th></tr>
<tr><td></td><td>Institutes of Health (in part)</td><td></td><td></td><td></td><td>Complete or partial response rate:
Not reported

Health-related quality of life:
Not reported

Adverse events:
Not reported

Time on treatment/number of treatments:
Not reported</td><td></td></tr>
<tr><td>Hickey, 2016[9]

USA</td><td>Prospective single centre comparative study

Funding: Not reported</td><td>Unresectable HCC and bilirubin ≤3.0 mg/dL</td><td>TheraSphere (n=428)</td><td>TACE (n=337)</td><td>Overall survival:
Survival outcomes (months) were stratified by Child-Pugh (C-P) class and BCLC stage:
<table>
<tr><td></td><td>TheraSphere</td><td>TACE</td></tr>
<tr><td>BCLC A and C-P A</td><td>21.4 (95% CI: 9.8-33.1)</td><td rowspan="2">Not evaluable (most patients still alive at study termination)</td></tr>
<tr><td>BCLC A and C-P B</td><td>27.6 (95% CI: 11.6-43.6)</td></tr>
<tr><td>BCLC B and C-P A</td><td>18.3 (95% CI: 12.3-24.3)</td><td>19.2 (95% CI: 16.0-22.4)</td></tr>
<tr><td>BCLC B and C-P B</td><td>12.2 (95% CI: 8.1-16.3)</td><td>17.4 (95% CI: 8.8-26.0)</td></tr>
<tr><td>BCLC C and C-P A</td><td>9.5 (95% CI: 7.0-11.9)</td><td>8.6 (95% CI: 5.1-12.0)</td></tr>
<tr><td>BCLC C and C-P B</td><td>5.6 (95% CI: 4.1-7.1)</td><td>3.5 (95% CI: 2.6-4.4)</td></tr>
</table>
Progression-free survival:
Not reported</td><td>High</td></tr>
</table>

Study name and location	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					Complete or partial response rate: Not reported **Health-related quality of life:** Not reported **Adverse events:** Not reported **Time on treatment/number of treatments:** Not reported	
Maccauro, 2014[15] Location: Not reported	Prospective matched case-control study Funding: Not reported	Unresectable HCC, Child-Pugh A. 80% patients in both groups were BCLC stage C because of PVT	TheraSphere + sorafenib (n=15)	TheraSphere alone (n=30)	**Overall survival:** TheraSphere + sorafenib: median 10 months. TheraSphere alone: median 10 months. **Progression-free survival:** TheraSphere + sorafenib: median 6 months. TheraSphere alone: median 7 months. **Complete or partial response rate:** TheraSphere + sorafenib: 45.5% mRECIST, 10% EASL. TheraSphere alone: 42.8% mRECIST, 40% EASL. **Health-related quality of life:** Not reported **Adverse events:** Not reported	High

Study name and location	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					Time on treatment/number of treatments: TheraSphere + sorafenib: Patients started sorafenib at a median time of 2 months prior to SIRT; median time on sorfenib = 9 months and median dose = 600 mg/day.	
Woodall, 2009[14] USA	Prospective comparative study Funding: MDS Nordion (maker of TheraSphere)	Unresectable HCC, including patients with and those without PVT	TheraSphere in patients without PVT (n=20) TheraSphere in patients with PVT (n=15)	Best supportive care/no treatment (n=17)	**Overall survival:** TheraSphere: HCC patients without PVT: median 13.9 months; HCC patients with PVT: median 3.2 months. Best supportive care/no treatment: median 5.2 months. **Progression-free survival:** Not reported **Complete or partial response rate:** Not reported **Health-related quality of life:** Not reported **Adverse events:** TheraSphere: Adverse events were reported by 25% of patients without PVT and 33% of patients with PVT. **Time on treatment/number of treatments:** TheraSphere: median 2 treatments per patient (range 1-3).	High
Biederman, 2015[20] Location: Not reported	Retrospective comparative study Funding: Not reported	BCLC stage C HCC with portal vein thrombosis	TheraSphere (n=72)	SIR-Spheres (n=25)	**Overall survival:** TheraSphere: median 15 months (95% CI: 8.6-19.5). SIR-Spheres: median 4.1 months (95% CI: 2.7-6.6).	High

Study name and location	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					Time to progression: Median 9.1 months (95% CI: 5.4-11.7) – not reported for separate treatment groups. **Complete or partial response rate:** 4/40 (10%) evaluable patients had complete response, 16/40 (40%) evaluable patients had partial response – not reported for separate treatment groups. **Health-related quality of life:** Not reported **Adverse events:** Clinical toxicities included grade 1/2: fatigue=30%, abdominal pain=28%, nausea=17%, ascites=7% - not reported for separate treatment groups. Laboratory toxicities included grade 1/2: bilirubin=37%, AST=64%, ALT=46% and grade 3/4: bilirubin=17%, AST=15%, ALT=2% - not reported for separate treatment groups. **Time on treatment/number of treatments:** A total of 101 treatments (across both treatment arms) were administered.	
Biederman, 2016[19] USA	Retrospective comparative study Funding: Not reported	Unresectable HCC with associated main or lobar portal vein thrombosis	SIR-Spheres (n=21)	TheraSphere (n=69)	**Overall survival:** SIR-Spheres: median 3.7 months (95% CI: 2.3-6.0). TheraSphere: median 9.5 months (95% CI: 7.6-15.0). Comparison between groups: HR: 0.39 (95% CI: 0.23-0.67, p<0.001). **Time to progression:** SIR-Spheres: median 2.8 months (95% CI: 1.9-4.3).	High

Study name and location	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					TheraSphere: median 5.9 months (95% CI: 4.2-9.1). **Complete or partial response rate:** SIR-Spheres: 0/15 (0%) evaluable patients had complete response, 2/15 (13.3%) had partial response, 4/15 (26.7%) had stable disease, 9/15 (60%) had progressive disease. TheraSphere: 5/57 (8.8%) evaluable patients had complete response, 18/57 (31.6%) had partial response, 8/57 (14%) had stable disease, 26/57 (45.6%) had progressive disease. **Health-related quality of life:** Not reported **Adverse events:** Grade 3/4 bilirubin: 39% SIR-Spheres versus 14% TheraSphere group Grade 3/4 AST: 44% SIR-Spheres versus 9% TheraSphere group Grade 3/4 ALT: 0% SIR-Spheres versus 4% TheraSphere group Grade 3/4 Alk-Phos: 0% SIR-Spheres versus 7% TheraSphere group Grade 3/4 Albumin: 0% SIR-Spheres versus 2% TheraSphere group Abdominal pain (32.9%) and fatigue (18.3%) were the most common clinical toxicities experienced; clinical toxicities were not significantly different between treatment groups. Reported in supplementary data file (online): Pain: 41.2% SIR-Spheres versus 30.8% TheraSphere group Fatigue: 17.6% SIR-Spheres versus 18.5% TheraSphere group Nausea: 17.6% SIR-Spheres versus 3.1% TheraSphere group Anorexia: 0% SIR-Spheres versus 9.2% TheraSphere group	

Study name and location	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					Time on treatment/number of treatments: A total of 100 treatments (across both treatment arms) were administered, with 10 (11.1%) patients undergoing staged treatment.	
Van Der Gucht, 2017[18] Switzerland	Retrospective comparative study Funding: Not reported	Unresectable HCC, ECOG PS <2 and life expectancy >3 months	SIR-Spheres (n=41)	TheraSphere (n=36)	**Overall survival:** SIR-Spheres: median 7.7 months (95% CI: 7.2-8.2). OS at 6 months=63%, 1 year=22%, 2 years=11%. TheraSphere: median 7.0 months (95% CI: 1.6-12.4). OS at 6 months=57%, 1 year=29%, 2 years=14%. **Progression-free survival:** SIR-Spheres: median 6.1 months (95% CI: 4.7-7.4). PFS at 6 months=52%, 1 year=7%, 2 years=0%. TheraSphere: median 5.0 months (95% CI: 0.9-9.2). PFS at 6 months=47%, 1 year=18%, 2 years=6%. **Complete or partial response rate:** Not reported **Health-related quality of life:** Not reported **Adverse events:** Not reported **Time on treatment/number of treatments:** Not reported	High
Bhangoo, 2015[17] USA	Retrospective comparative study	Unresectable HCC patients who had either failed or had disease not amenable to alternative	TheraSphere (n=11)	SIR-Spheres (n=6)	**Overall survival:** TheraSphere: median 8.4 months (95% CI: 1.3-21.1). SIR-Spheres: median 7.8 months (95% CI: 2.3-12.5).	Unclear

Study name and location	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
	Funding: Not reported	locoregional therapies. ECOG PS <2, serum total bilirubin <2 mg/dL			OS results presented for 15 out of the full 17 patient cohort, as 2 patients still alive. **Progression-free survival:** Not reported **Complete or partial response rate:** 0/17 patients had complete response, 4/17 (24%) had partial response, 4/17 (24%) had stable disease, 6/17 (35%) had progressive disease and 3/17 (18%) had no data – not reported for separate treatment groups. **Health-related quality of life:** Not reported **Adverse events:** Grade 3/4 bilirubin: 18% TheraSphere versus 0% SIR-Spheres group Grade 3/4 Albumin: 11% TheraSphere versus 0% SIR-Spheres group Grade 3/4 Alk-Phos: 0% TheraSphere versus 17% SIR-Spheres group Fatigue: 45% TheraSphere versus 67% SIR-Spheres group Abdominal pain: 27% TheraSphere versus 33% SIR-Spheres group Nausea/vomiting: 55% TheraSphere versus 67% SIR-Spheres group Anorexia/weight loss: 9% TheraSphere versus 33% SIR-Spheres group Diarrhoea: 0% TheraSphere versus 17% SIR-Spheres group Gastric ulcer: 0% TheraSphere versus 17% SIR-Spheres group **Time on treatment/number of treatments:** 65% patients received one treatment and 35% received two treatments (across both treatment arms).	
d'Abadie, 2018[21] USA	Retrospective comparative study	HCC imaged by ^{90}Y TOF-PET	TheraSphere (n=33 procedures)	SIR-Spheres (n=25 procedures)	**Overall survival:** Not reported (Kaplan-Meier curves for different equivalent uniform doses (EUDs) presented in publication).	High

Study name and location	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
	Funding: Not reported				**Progression-free survival:** Not reported **Complete or partial response rate:** Not reported **Health-related quality of life:** Not reported **Adverse events:** Not reported **Time on treatment/number of treatments:** Not reported	
Radosa, 2019[16] Germany	Single centre retrospective case series Funding: None	HCC	QuiremSpheres (n=9)	Not applicable	**Overall survival:** Not reported **Progression-free survival:** Not reported **Complete or partial response rate:** 60 days: 0 complete response, 5/9 (56%) partial response, 3/9 (33%) stable disease, 1/9 (11%) progressive disease. 6 months: 1/9 (11%) complete response, 4/9 (45%) partial response, 3/9 (33%) stable disease, 1/9 (11%) progressive disease. **Health-related quality of life:** Not reported **Adverse events:** Presence of REILD at 60 days: 0	High

Study name and location	Study design and funding source	Population	Intervention	Comparator	Main results	Risk of bias
					Median MELD-score (range) 1 day before SIRT: 8 (7-13) Median MELD-score (range) 1 day after SIRT: 8 (6-11) Median MELD-score (range) 60 days after SIRT: 8 (6-14) There were 16 reportable adverse events in the 9 patients, but no grade 3-4 adverse events. Most common adverse events were nausea (n=3), fatigue (n=3), vomiting (n=3), abdominal pain (n=2) and ascites (n=2). **Time on treatment/number of treatments:** Not reported	

13.7 Lower priority studies not included in the systematic review of clinical effectiveness or considered for the network meta-analyses (n=28)

Study	Intervention	Comparator	Reason for not including in systematic review
Moroz, 2001[40]	SIR-Spheres + hepatic arterial chemotherapy	Hepatic arterial chemotherapy	Clinical advice that hepatic arterial chemotherapy is not applicable to current UK practice
Pellerito, 2013[42]	SIR-Spheres	131 I-Lipiodol	Clinical advice that 131 I-Lipiodol is not applicable to current UK practice
Steel, 2004[39]	TheraSphere	Hepatic arterial infusion of cisplatin	Clinical advice that hepatic arterial infusion of cisplatin is not applicable to current UK practice
Maccauro, 2016[41]	Standard dose TheraSphere	Personalised treatment planning TheraSphere	Clinical advice standard dose TheraSphere is not applicable to current UK practice
She, 2014[154]	SIR-Spheres	TACE	Group imbalances make comparison meaningless (patients were allocated to SIRT if they were not eligible for TACE, e.g. had previously failed on TACE)
Kooby, 2010[155]	SIR-Spheres	TACE	Study included a more advanced population than in other studies in the NMA of patients eligible for conventional transarterial therapies and there was a baseline imbalance between groups in relation to portal vein invasion.
Kwok, 2014[156]	SIR-Spheres	No SIR-Spheres	All patients included in the study opted for SIRT, but 16 were ineligible (primarily due to lung shunt), the study compares those who received it with those who did not
Song, 2017[157]	SIR-Spheres	Concurrent chemoradiation therapy	Clinical advice that concurrent chemoradiation therapy is not applicable to current UK practice
Oladeru, 2016[158]	SIR-Spheres	External beam radiotherapy	Clinical advice that external beam radiotherapy is not applicable to current UK practice
Ruhl, 2009[159]	SIR-Spheres	High-dose-rate brachytherapy	Clinical advice that high-dose-rate brachytherapy is not applicable to current UK practice
D'Avola, 2009[160]	SIR-Spheres	No SIRT (combination of conventional or experimental therapies or no therapy)	Comparator was a combination of conventional or experimental therapies or no therapy; conventional therapy patients were not reported separately, therefore the trial was not informative for the NMA
Carr, 2010[161]	TheraSphere	TACE	All patients had ECOG >2 therefore were a more advanced population than in other studies in the NMA of patients eligible for conventional transarterial therapies
Kallini, 2018[162]	TheraSphere	TACE	No OS or PFS outcomes reported therefore not informative for the NMA
Gabr, 2017[163]	TheraSphere	TACE	Population of patients who had received a transplant therefore not comparable population to other studies in the NMA of patients eligible for conventional transarterial therapies
Riaz, 2009[164]	TheraSphere	TACE	Group imbalances make comparison meaningless
Biederman, 2018[165]	TheraSphere	TACE	Patients within Milan criteria therefore not comparable population to other studies in the NMA of patients eligible for conventional transarterial therapies

Lewandowski, 2009[115]	TheraSphere	TACE	No hazard ratios or Kaplan-Meier curves presented therefore not informative for the NMA. Also patients received SIRT or TACE for downstaging therefore not comparable population to other studies in the NMA of patients eligible for conventional transarterial therapies
Ahmad, 2005[166]	TheraSphere	TACE	No OS or PFS outcomes reported therefore not informative for the NMA
Padia, 2017[167, 168]	TheraSphere	TACE or DEB-TACE	Mixed population of BCLC A, B and C (70% within Milan criteria) therefore not informative for the NMA of patients eligible for conventional transarterial therapies
Newell, 2015[169]	TheraSphere	TACE or DEB-TACE	Mixed population of BCLC B and C patients therefore not informative for the NMA of patients eligible for conventional transarterial therapies.
Taussig, 2017[170]	TheraSphere	TACE or DEB-TACE	No OS or PFS outcomes reported therefore not informative for the NMA
McDevitt, 2017[171]	TheraSphere	DEB-TACE	Mixed population of BCLC B and C patients therefore not informative for the NMA of patients eligible for conventional transarterial therapies. Patients without main PVI could receive DEB-TACE, those with PVI received SIRT therefore group imbalances.
Akinwande, 2015[172, 173]	TheraSphere	DEB-TACE	Unclear population, but all patients had PVT, therefore, not informative for the NMA of patients eligible for conventional transarterial therapies
Biederman, 2017[174, 175]	TheraSphere	TACE combined with microwave ablation	Clinical advice that TACE combined with microwave ablation is not widely practiced in the UK
Padia, 2015[176]	TheraSphere	Ablation, chemoembolisation or BSC	Comparator was a combination of ablation, chemoembolisation and best supportive care; chemoembolisation patients were not reported separately, therefore the trial was not informative for the NMA of patients eligible for conventional transarterial therapies
Radunz, 2017[177]	TheraSphere	TACE, radiofrequency ablation or no bridging therapy	Patients were eligible for transplant and received SIRT or TACE for bridging therefore not comparable population to other studies in the NMA of patients eligible for conventional transarterial therapies
Salem, 2018[104]	TheraSphere	N/A	Non-comparative study
Ali, 2018[178]	TheraSphere	N/A	Non-comparative study

13.8 Risk of bias assessment results for retrospective comparative studies used in the network meta-analysis

Trial	Inclusion criteria clearly defined	Representative sample from relevant population	Groups similar at baseline	Clearly described and consistently delivered intervention	Clearly described and consistently delivered comparator	Outcome assessors blinded	Missing outcome data balanced across groups	Free from suggestion of selective reporting	Overall judgement of risk of bias
Biederman, 2015[20]	No	Unclear	Unclear	No	No	Unclear	Unclear	Unclear	High
Biederman, 2016[19]	Yes	Yes	No	Yes	Yes	Unclear	Unclear	Unclear	High
Van Der Gucht, 2017[18]	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	High
Bhangoo, 2015[17]	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Unclear
d'Abadie, 2018[21]	No	Unclear	No	No	No	Unclear	Unclear	Yes	High
Gramenzi, 2015[50]	Yes	Yes	No	Yes	Yes	Unclear	Unclear	Yes	High
De la Torre, 2016[49]	Yes	Yes	No	Yes	Yes	Unclear	Unclear	Yes	High
Cho, 2016[48]	Yes	Yes	No	Yes	Yes	Unclear	Yes	Yes	High

13.9 Risk of bias assessment results for RCTs of comparative therapies used in the network meta-analysis

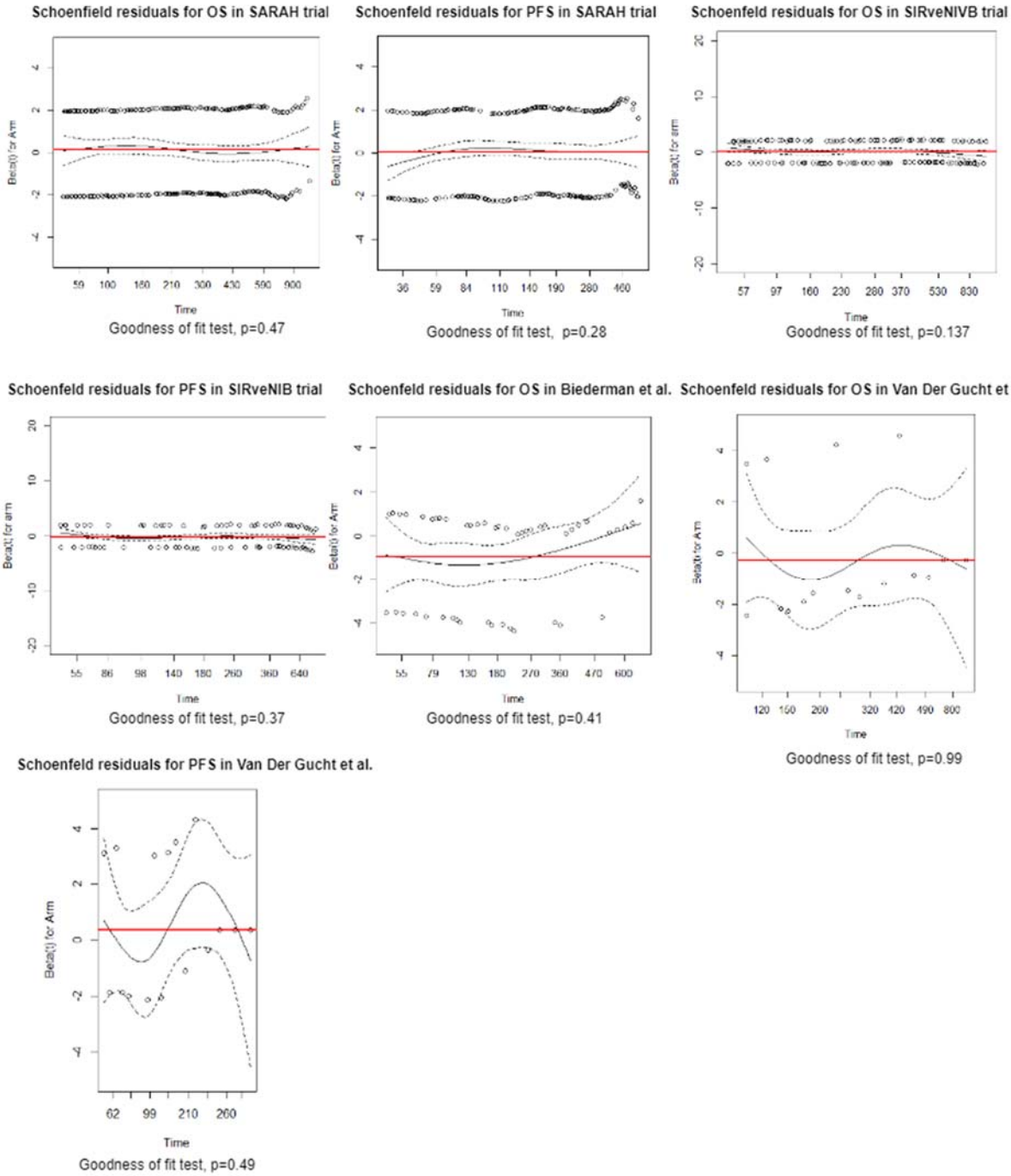
Trial	Risk of bias arising from the randomisation process	Risk of bias due to deviation from the intended interventions	Missing outcome data (primary outcomes)	Risk of bias in measurement of the outcomes	Risk of bias in selection of the reported result	Overall judgement of risk of bias
Yu (2014)[65]	Some concerns	Low	Low	Low	Low	Some concerns
Chang (1994)[63]	Some concerns	Some concerns	Low	Low	Low	Some concerns
Meyer (2013)[64]	Some concerns	Low	Low	Low	Low	Some concerns
Malagari (2010)[66]	Some concerns	Some concerns	Low	Low	Low	Some concerns
Sacco (2011)[59]	High	Low	Low	Low	Low	High

13.10 Study details and results for studies of comparators included in the network meta-analysis

Study name and location	Study design and funding source	Population	Intervention	Comparator	Main results
Yu, 2014[65] China	Parallel group RCT Funding: Not reported	Patients with unresectable HCC with Child Pugh A or B and ECOG <2	TAE (n=45)	TACE (n=45)	**Overall survival:** TAE: median 24.3 months (95% CI: 12.8-32.7) TACE: median 20.1 months (95% CI: 9.3-31.2) **Progression-free survival:** TAE: median 6.5 months (95% CI: 7.8-9.2) TACE: median 4.4 months (95% CI: 1.6-7.2) **Time to progression:** TAE: median 8.4 months (95% CI: 5.3-11.4) TACE: median 4.4 months (95% CI: 1.7-7.1)
Malagari, 2010[66] Greece	RCT Funding: Not reported	Patients with HCC unsuitable for curative therapy and at high risk for surgery	DEB-TACE (n=48)	TAE (n=47)	**Overall survival:** DEB-TACE: 100% were alive at 6 months and 85.3% at 12 months TAE: 100% were alive at 6 months and 86% at 12 months **Progression-free survival**: Not reported **Time to progression:** DEB-TACE: 42.4 ± 9.5 weeks TAE: 36.2 ± 9.0 weeks
Sacco, 2011[59] Italy	Single centre RCT Funding: Not reported	Patients with unresectable HCC with Child-Pugh class A or B, ECOG 0-1 and unsuitable for ablative treatments	TACE (n=34)	DEB-TACE (n=33)	**Overall survival:** TACE: 83.6% were alive at 24 months DEB-TACE: 86.8% were alive at 24 months **Progression-free survival:** TACE: 80.1% were disease progression-free DEB-TACE: 82.5% were disease progression-free

					Time to progression: TACE: mean 24.2 months DEB-TACE: mean 15.6 months
Meyer, 2013[64] UK	Phase II/III RCT Funding: NIHR, Experimental Cancer Medicine Centre Network	Patients with unresectable HCC with Child-Pugh class A or B and ECOG 0-2	TAE (n=42)	TACE (n=44)	**Overall survival:** Hazard ratio of 0.91, 95% C.I: 0.51-1.62 TAE: median 17.3 months TACE: median 16.3 months **Progression-free survival:** Hazard ratio of 0.87, 95% CI: 0.52-1.45 TAE: median 7.2 months TACE: median 7.5 months **Time to progression:** Not reported
Chang, 1994[63] China	Single centre RCT Funding: Not reported	Patients with inoperable HCC and Child-Pugh class A or B	TACE (n=22)	TAE (n=24)	**Overall survival:** TACE: 52.5% were alive at 1 year and 26.2% were alive at 2 years TAE: 72.5% were alive at 1 year and 39.5% were alive at 2 years **Progression-free survival:** Not reported **Time to progression:** Not reported

13.11 Schoenfield residual plots for the studies included in the network meta-analysis for adults with unresectable HCC who are ineligible for CTT



13.12 Hazard ratio estimates for each treatment comparison for all patients in the NMA ITT population

Table 41: Hazard ratio estimates (95% CrI) for OS for each treatment comparison for all patients in the NMA ITT population

Sorafenib	0.88 (0.78-0.99)	0.96 (0.71-1.27)
1.14 (1.01 to 1.28)	**SIR-Spheres**	1.1 (0.80-1.48)
1.06 (0.79 to 1.40)	0.93 (0.67 to 1.25)	**Lenvatinib**

Significant differences in the relative effects between a pair of agents are given in bold.

Table 42: Hazard ratio estimates (95% CrI) for PFS for each treatment comparison for all patients in the NMA ITT population

Sorafenib	1.04 (0.89-1.20)	1.61 (0.45-4.15)
0.97 (0.84 to 1.12)	**SIR-Spheres**	1.56 (0.43-4.07)
0.86 (0.24 to 2.22)	0.89 (0.25 to 2.31)	**Lenvatinib**

Significant differences in the relative effects between a pair of agents are given in bold

13.13 Random effects network meta-analysis results

Table 43: Random effects network meta-analysis OS results of base-case NMA including Beiderman *et al*. in the ITT and per protocol populations: Adults with unresectable HCC who are ineligible for CTT

Intervention	Comparator	Hazard ratio (95% CrI) – ITT	Hazard ratio (95% CrI) – Per protocol
SIR-Spheres	Sorafenib	0.94 (0.68-1.26)	1.13 (0.86-1.46)
SIR-Spheres	Lenvatinib	0.92 (0.52-1.51)	1.11 (0.66-1.74)
TheraSphere	SIR-Spheres	0.46 (0.19-0.94)	0.42 (0.19-0.82)
TheraSphere	Sorafenib	0.42 (0.18-0.83)	0.48 (0.20-0.97)
TheraSphere	Lenvatinib	0.41 (0.15-0.89)	0.46 (0.17-1.02)
Lenvatinib	Sorafenib	1.07 (0.67-1.63)	1.07 (0.70-1.58)
SD		0.11 (0.004-0.352)	0.13 (0.005-0.378)
DIC		0.9	2.1
pD		3.4	3.4

Table 44: Random effects OS and PFS outcomes for all patients in the NMA ITT population: Adults with unresectable HCC who are ineligible for CTT

Intervention	Comparator	OS Hazard ratio (95% CrI) – random effects	PFS Hazard ratio (95% CrI) – random effects
SIR-Spheres	Sorafenib	0.97 (0.73-1.26)	1.15 (0.89-1.45)
SIR-Spheres	Lenvatinib	1.58 (0.40-4.21)	1.12 (0.68-1.73)
Lenvatinib	Sorafenib	0.87 (0.23-2.33)	1.07 (0.70-1.57)
SD		0.11 (0.004-0.352)	0.12 (0.005-0.367)
DIC		-1.69	2.18
pD		2.4	2.5

Table 45: Random effects NMA of all adults with unresectable HCC who are ineligible for CTT including studies Biederman *et al.* and Van Der Gucht *et al.*

Intervention	Comparator	OS Hazard ratio (95% CrI)
SIR-Spheres	Sorafenib	1.15 (0.89-1.45)
SIR-Spheres	Lenvatinib	1.11 (0.68-1.73)
TheraSphere	SIR-Spheres	0.50 (0.26-0.89)
TheraSphere	Sorafenib	0.58 (0.29-1.06)
TheraSphere	Lenvatinib	0.56 (0.24-1.13)
Lenvatinib	Sorafenib	1.07 (0.70-1.57)

CrI: credible interval

Table 46: Results of random effects base-case NMA excluding the SIRveNIB study

Intervention	Comparator	OS Hazard ratio, ITT pop (95% CrI)	OS Hazard ratio, per protocol (95% CrI)
SIR-Spheres	Sorafenib	1.16 (0.71-1.78)	1.03 (0.63-1.61)
SIR-Spheres	Lenvatinib	1.13 (0.55-2.09)	1.02 (0.49-1.88)
Lenvatinib	Sorafenib	1.08 (0.65-1.71)	1.08 (0.65-1.71)
SD		0.15 (0.006-0.426)	0.15 (0.006-0.426)
DIC		0.92	1.1
pD		2.0	2.0

13.14 Quality assessment of idenified economic evidence

Table 47: Quality assessment of economic studies: modified Philips checklist[86]

	Study	
Structure	Rostambeigi 2014	Rognoni 2017
1. Is there a clear statement of the decision problem?	Yes	Yes
2. Is the perspective and scope of the model stated clearly?	No	Yes
3. Are the model inputs consistent with the stated perspective?	NA	Yes
4. Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	NA	Yes
5. Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	No	Yes
6. Is there a clear definition and justification for the alternative options under evaluation?	Yes	Yes
7. Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	No	Yes
8. Are the time horizon of the model, the duration of treatment and the duration of treatment effect described and appropriately justified?	No	Yes
9. Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	No	Yes
10. Is the cycle length defined and justified in terms of the natural history of disease?	No	Yes
Data		
11. Are the data identification methods transparent and appropriate given the objectives of the model?	Yes	Yes
12. Has the quality of the data been assessed appropriately?	No	NA
13. Is the data modelling methodology based on justifiable statistical and epidemiological techniques?	Partial	Yes
14. Is the choice of baseline data described and justified?	NA	Yes
15. Are transition probabilities calculated appropriately?	NA	Yes
16. Has a half-cycle correction been applied to both costs and outcomes?	NA	No
17. If relative treatment effects have been derived from trial data, have they been synthesised using appropriate techniques?	No	NA
18. Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	Partial	Partial
19. Have alternative assumptions been explored through sensitivity analysis?	Partial	Yes
20. Have assumptions regarding the continuing effect of treatment once treatment is complete been documented and justified?	No	NA
Costs and discounting		
21. Are the costs incorporated into the model described and justified?	Yes	Yes
22. Has the source for all costs been described?	Yes	Yes
23. Have discount rates been described and justified given the target decision-maker?	NA	Yes

24. Were currency, price date, and price adjustments/currency conversion information stated	No	Yes
HRQoL		
25. Are the utilities incorporated into the model appropriate?	NA	Yes
26. Is the source for the utility weights referenced?	NA	Yes
Validation		
27. Has heterogeneity been dealt with by running the model separately for different subgroups?	Yes	NA
28. Have the results of the model been compared with those of previous models and any differences in results explained?	No	Partial

13.15 Model parameters from submitted economic models

13.15.1 Sirtex model parameters – CTT-eligible model

Table 48: Summary of TACE treatment costs, Sirtex CTT-eligible model (adapted from Table 99 of Sirtex CS)

Input	Inflated value	Source
Scenario 1: CTT cost from literature		
Proportion of CTT with DEB-TACE	25%	Fateen *et al.* (2017)[101]
TACE cost	£9,801.00	Fateen *et al.* (2017)
DEB-TACE cost	£5,727.03	Fateen *et al.* (2017)
CTT cost (literature)	**£8,792.59**	Calculated
Scenario 2: CTT resource use from literature, with NHS Reference Costs		
Drug-eluding beads (DEBs)	£594.30	Fateen *et al.* (2017)
TACE length of stay	2.37	Fateen *et al.* (2017)
DEB-TACE length of stay	2.81	Fateen *et al.* (2017)
Mean number of TACE procedures	3.03	Fateen *et al.* (2017)
Mean number of DEB-TACE procedures	1.43	Fateen *et al.* (2017)
Proportion of CTT with DEB-TACE	25%	Fateen *et al.* (2017)
TACE cost	£12,620.41	Calculated
DEB-TACE cost	£7,911.80	Calculated
CTT cost (Reference costs)	**£11,454.91**	Calculated
Scenario 3: CTT resource use from survey, literature with NHS Reference Costs		
Drug-eluding beads (DEBs)	£594.30	Fateen *et al.* (2017)
TACE length of stay	2.37	Fateen *et al.* (2017)
DEB-TACE length of stay	2.81	Fateen *et al.* (2017)
Mean number of TACE procedures	2.5	Sirtex resource use survey
Mean number of DEB-TACE procedures	2.83	Sirtex resource use survey
Proportion of CTT with DEB-TACE	63%	Sirtex resource use survey
TACE cost	£10,412.88	Calculated
DEB-TACE cost	£15,676.06	Calculated
CTT cost	**£13,702.37**	Calculated

Table 49: Summary of cost of SIRT, Sirtex CTT-eligible model (adapted from Table 100 in Sirtex CS)

	SIR-Spheres		**TheraSphere**	
	Value	**Source**	**Value**	**Source**
Outpatient costs for code YR57Z	£1,123.15	National Schedule of Reference Costs 2017/18	£1,123.15	National Schedule of Reference Costs 2017/18
Inpatient cost / day for YR57Z	£1,757.45		£1,757.45	
SIRT	£8,000.00	Sirtex	£8,000.00	Sirtex
Survey results				
Number of work-ups	1.05	Survey	1.05	Assumed same as SIR-Spheres
Length of stay for work-up	0.69		0.69	
Number of procedures	1.20		1.20	
Length of stay for procedure	1.19		1.19	
Cost of work-up	£1,175.56	-	£1,175.56	-
Cost of procedure	£2,500.13	-	£2,500.13	-
Total cost	***£13,239.33***	-	***£13,239.33***	-
Survey results with outpatient procedures				
Number of work-ups	1.05	Survey	1.05	Assumed same as SIR-Spheres
Length of stay for work-up	outpatient		outpatient	
Number of procedures	1.20		1.20	
Length of stay for procedure	outpatient		outpatient	
Cost of work-up	£1,175.56	-	£1,175.56	-
Cost of procedure	£1,342.67	-	£1,342.67	-
Total cost	***£12,081.87***	-	***£12,081.87***	-
The Christie NHS Foundation Trust results				
Number of work-ups	[redacted]	The Christie NHS Foundation Trust data	[redacted]	The Christie NHS Foundation Trust data
Length of stay for work-up	[redacted]		[redacted]	
Number of procedures	[redacted]		[redacted]	
Length of stay for procedure	[redacted]		[redacted]	
Cost of work-up	[redacted]	-	[redacted]	-
Cost of procedure	[redacted]	-	[redacted]	-
Total cost	[redacted]	-	[redacted]	-
Sangro 2011, Salem 2018 for # procedures, rest survey				
Number of work-ups	1.05	Survey	1.05	Survey
Length of stay for work-up	0.69	Survey	0.69	Survey

Number of procedures	1.08	ENRY reigster [68]	1.58	PREMIERE[104]
Length of stay for procedure	1.19	Survey	1.19	Survey
Cost of work-up	£1,175.56	-	£1,175.56	-
Cost of procedure	£2,252.24	-	£3,298.08	-
Total cost	***£12,043.19***	-	***£17,089.64***	-

Table 50: Adverse event rates, Sirtex CTT-eligible model (Table 40 in Sirtex CS)

AE	TACE (n=19)	TheraSphere (n=24)	Unit costs	Source for unit cost
Abdominal pain	0%	4%	£42.19	NICE TA474 sorafenib TA
Elevated aspartate aminotransferase	11%	0%	£634.50	NICE TA551 lenvatinib TA
Hypoalbuminemia	0%	4%	£634.50	Assumed average of elevated aspartate aminotransferase and blood bilirubin
Increased blood bilirubin	5%	8%	£916.47	NICE TA551 lenvatinib TA
Leukopenia	0%	4%	£215.00	NICE TA509 pertuzumab
Neutropenia	11%	0%	£2,097.50	NHS Reference Costs 2017/18 (WJ11Z)
Total costs	**£346.34**	**£108.99**		

13.15.2 Sirtex model parameters – CTT-ineligible model

Table 51: Summary of the base-case utility values, Sirtex CTT-ineligible model (Table 17 in Sirtex CS)

Comparator	Utility value: mean (standard error)	Reference
Pre-progression SIR-Spheres	0.762 (0.078)	*Post-hoc* analyses of the SARAH trial for the low tumour burden + ALBI grade 1 subgroup.
Pre-progression sorafenib	0.746 (0.076)	
Post-progression SIR-Spheres	0.738 (0.075)	
Post-progression sorafenib	0.722 (0.074)	
After subsequent treatment with curative intent	0.762 (0.078)	Assumed same as the pre-progression utilities with SIR-Spheres

Table 52: Assumptions and costs of the SIRT procedure, Sirtex CTT-ineligible model (Table 21 in Sirtex CS)

Cost item	Value	Source
Outpatient costs for code YR57Z	£1,123.15	National Schedule of Reference Costs 2017/18
Inpatient cost / day for YR57Z	£1,757.45	
SIR-Spheres	£8,000.00	Sirtex
Number of work-ups per patient	1.05	Resource use survey
Length of stay for work-up, days	0.69	
Number of treatments per patient	1.20	
Length of stay for treatment, days	1.19	
Cost of a single work-up	*£1,175.56*	*Subtotal*
Cost of a single treatment	*£2,500.13*	*Subtotal*
Total cost	**£13,239.33**	**-**

Table 53: Proportions of treatments with curative intent observed in SARAH trial, Sirtex CTT-ineligible model (Table 22 in Sirtex CS)

	After SIRT	After sorafenib
% of liver resection among treatments with curative intent	33.3%	0.0%
% of liver transplantation among treatments with curative intent	16.7%	33.3%
% of ablation among treatments with curative intent	58.3%	66.7%

Table 54: Health state costs, Sirtex CTT-ineligible model (Table 25 in Sirtex CS)

	Pre-progression post SIRT (per month)	Pre-progression on sorafenib / lenvatinib (per month)	At progression (one off)	Progressive disease (per month)
Medical staff contact	£102.84	£126.49	£118.50	£222.96
Diagnostic procedures	£130.26	£134.58	£89.28	£6.15
Inpatient care	£6.80	£20.29	-	£78.50
Personal and Social Services	£5.83	£5.83	-	£191.76
Total	**£245.74**	**£287.19**	**£207.79**	**£499.37**

Table 55: Adverse event costs, Sirtex CTT-ineligible model (Table 26 in Sirtex CS)

	Inflated cost	Reported costs	Costing year	Source
Abdominal pain	£42.19	£40.15	2014 / 15	NICE TA474 sorafenib TA
Alopecia	£18.59	£17.69	2014 / 15	NICE TA474 sorafenib TA
Anaemia	£1,319.84	£1,283.67	2015 / 16	NICE TA514 regorafenib TA
Anorexia	£657.86	£639.83	2016 / 17	NICE TA535 lenvatinib and sorafenib
Ascites	£1,713.98	£1,667.00	2015 / 16	NICE TA514 regorafenib TA
Aspartate aminotransferase increased	£634.50	£617.11	2016 / 17	NICE TA551 lenvatinib TA
Asthenia	£677.68	£659.11	2016 / 17	NICE TA551 lenvatinib TA
Blood bilirubin increased	£916.47	£891.35	2016 / 17	NICE TA551 lenvatinib TA
Cardiac failure, congestive	£1,979.71	£1,979.71	2017 / 18	National Schedule of Reference Costs 2017/18: Weighted average HRG codes EB03A, EB03E
Diarrhoea	£605.13	£588.54	2016 / 17	NICE TA551 lenvatinib TA
Fatigue	£677.68	£659.11	2016 / 17	NICE TA551 lenvatinib TA
Gamma-glutamyl transferase increased	£634.50	£617.11	2016 / 17	NICE TA551 lenvatinib TA
Haematological biological abnormalities	£1,319.84	£1,283.67	2015 / 16	NICE TA514 regorafenib TA
Haemorrhage	£0.00	£0.00	2014 / 15	NICE TA474 sorafenib TA
Hand foot skin reaction	£897.98	£873.37	2015 / 16	NICE TA514 regorafenib TA
Hypertension	£888.12	£863.78	2016 / 17	NICE TA551 lenvatinib TA
Hypophosphataemia	£1,297.52	£1,261.96	2015 / 16	NICE TA514 regorafenib TA
Liver dysfunction	£1,713.98	£1,667.00	2015 / 16	NICE TA514 regorafenib TA
Nausea/vomiting	£82.18	£78.20	2014 / 15	NICE TA474 sorafenib TA
Other increase liver function	£634.50	N/A	N/A	NICE TA551 lenvatinib TA
Palmar-plantar erthrodysaesthesia syndrome	£443.80	£431.64	2016 / 17	NICE TA551 lenvatinib TA
Platelet count decreased	£634.50	£617.11	2016 / 17	NICE TA551 lenvatinib TA
Proteinuria	£812.04	£789.78	2016 / 17	NICE TA551 lenvatinib TA
Rash/desquamation	£71.09	£67.65	2014 / 15	NICE TA474 sorafenib TA
Weight decreased	£665.35	£647.11	2016 / 17	NICE TA551 lenvatinib TA

13.15.3 BTG model parameters – CTT-eligible model

Table 56: Summary of per-cycle transition probabilities, BTG CTT-eligible model

Parameter	Per-cycle transition probability	Source
"Watch and wait" to pre-transplant	SIRT = 10.8% CTT = 5.8%	Lewandowski *et al*. (2009)
"Watch and wait" to pharmacological management	SIRT = 7.8% CTT = 12.8%	Calculation
"Watch and wait" to "Watch and wait"	81.4%	Lewandowski *et al*. (2009)
Pre-transplant to pharmacological management	2.2%	National Audit for Liver Transplant
Pre-transplant to post-transplant	13.9%	NHS Annual Report on Liver Transplantation 2017/18
Pre-transplant to pre-transplant	84.0%	Calculation

Table 57: Summary of per-cycle mortality parameters, BTG CTT-eligible model (Table 6-2 in BTG CS)

Health state	Mortality rate (per cycle)	Source
Watch and wait	3.88%	Assumed the same as pre-transplant
Pre-transplant	3.88%	NHS England. Schedule 2 – The Services. A. Service Specifications. 170003/S. Liver Transplantation service (Adults).
Pharmacological management	7.74%	Derived from the median overall survival for BSC from the NICE sorafenib submission [TA474]
Post-transplant 1	1.39%	Bellavance *et al.* (2008)
Post-transplant 2	1.39%	Bellavance *et al.* (2008)
Post-transplant 3	1.39%	Bellavance *et al.* (2008)
No HCC (post-transplant)	0.29%	NHS. Survival rates following transplantation.
Note: one cycle is equal to four weeks		

Table 58: Adverse event rates, BTG CTT-eligible model (adapted from Table 6-5 in BTG CS)

Adverse event	TheraSphere	SIR-Spheres	Quirem Spheres	TACE	DEB-TACE	TAE
Aspartate aminotransferase increase	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Proteinuria	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Blood bilirubin increase	0.0%	0.0%	0.0%	0.0%	0.0%	16.0%
Diarrhoea	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Fatigue	1.9%	2.3%	2.3%	0.0%	0.0%	8.0%

Gamma-glutamyl transferase increase	0.0%	0.0%	0.0%	0.0%	0.0%	26.0%
Hypertension	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Weight decrease	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Platelet count decrease	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Palmar-plantar erythrodysesthesia syndrome	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Ascites	6.1%	2.3%	2.3%	0.0%	0.0%	0.0%
Cholecystitis	1.9%	5.0%	5.0%	0.0%	1.1%	0.0%
Hepatic encephalopathy	2.8%	8.0%	8.0%	0.0%	0.0%	0.0%
Post-procedural pain	1.9%	1.2%	1.2%	18.2%	0.0%	21.0%

Table 59: Utility values, BTG CTT-eligible model

Health State	**Source utility**	**Applied utility***	**Source**
Watch & wait	0.75	0.534	TA535 (pre-progression)
Pre-transplant	0.75	0.534	TA535 (pre-progression)
Post-transplant 1	0.69	0.474	Lim *et al*. (2014)
Post-transplant 2	0.69	0.473	Lim *et al*. (2014)
Post-transplant 3	0.69	0.473	Lim *et al*. (2014)
No HCC post-transplant	0.75	0.534	TA535 (pre-progression)
Pharmacological management	0.72	0.499	TA535 (calculated as an average of pre-progression and post-progression utilities)
*Based on the age in the first cycle of the model			

Table 60: Micro-costing of SIRT work-up assessment procedure, BTG CTT-eligible model (Table H1 in BTG CS)

Work-up factors - costs included in the BTG analysis	**Cost**
Band 6 technician @ 30 minutes (unit cost per hour £15.96)	£7.98
Band 7 clinical scientist @ 30 minutes (unit cost per hour £19.06)	£9.53
MAA body spect*	£353
Lung shunt calculation – Band 7 clinical scientist @ 10 minutes (unit cost per hour £19.06)	£3.18
Volumetary - Band 7 clinical scientist @ 1 hour (unit cost per hour £19.06)	£19.06
Volumetary Band radiologist @ 1 hour (unit cost per hour £75.16)	£75.16
Total cost	**£467.91**
Additional costs provided by BTG following the CS	
Two radiologist @ 2 hours (unit cost per hour £75.16)	£150.3

Two band 6 nurse @ 3 hours (unit cost per hour £23.82)	£142.92
One band 6 radiographer @ 3 hours (unit cost per hour £23.82)	£71.46
One band 4 coordinator @ 1 hour (unit cost per hour £16.30)	£16.30
Blood work	£11.35
Total cost	**£860.32**
*There is not currently an NHS tariff for an MAA body spect. However, it is thought that a sum of the RN codes (from the National Tariff Payment System) for the following is suitable for the total cost of an MAA body spect: A whole body spect for one area (RN04A - £147 minus the agent cost £26 = £121); a whole body spect for two areas (£180 minus the agent cost £22 = £158); MAA consumable agent (£74).	

Table 61: Unit costs of adverse events BTG CTT-eligible model (adapted from Table N1 in BTG CS)

Item	Unit cost	Source
Aspartate aminotransferase increase	£615.76	NHS reference costs 2017/18. Hospitalisation. Average non-elective short stay
Proteinuria	£657.76	NHS reference costs 2017/18. Average non-elective short stay (for hospitalisation) at £615.76 Plus a nurse visit (GP practice) £42 (PSSRU 2018 - cost per hour including qualifications)
Blood bilirubin increase	£886.56	NHS reference costs 2017/18. Average non-elective short stay (for hospitalisation) at £615.76. Plus CT scan at £103.95. Weighted average of RD10Z - RD28Z. Adults only. NHS reference costs 2017/18. Plus £166.85: Outpatient consultant led, non-admitted face-to-face attendance, follow up (medical oncology). Code WF01A. NHS reference costs 2017/18.
Diarrhoea	£561.30	NHS reference costs 2017/18 – FD10K. Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 6-10 – non-elective short-stay
Fatigue	£657.76	NHS reference costs 2017/18. Average non-elective short stay (for hospitalisation) at £615.76 Plus a nurse visit (GP practice) £42 (PSSRU 2018 - cost per hour including qualifications)
Gamma-glutamyl transferase increase	£615.76	NHS reference costs 2017/18. Average non-elective short stay
Hypertension	£856.61	NHS reference costs 2017/18. Average non-elective short stay (for hospitalisation) at £615.76 Plus 2 GP appointments (9.22 minutes) at £37 each (PSSRU 2018 - cost per hour including qualifications) Plus £166.85: Outpatient consultant led, non-admitted face-to-face attendance, follow up (medical oncology). Code WF01A. NHS reference costs 2017/18.
Weight decrease	£646.76	Hospitalisation: NHS reference costs 2017/18 average cost of non-elective short-stay (£615.76) Plus Dietician PSSRU 2018 - dieticians band 4 cost per working hour(£31)
Platelet count decrease	£615.76	NHS reference costs 2017/18. Hospitalisation. Average non-elective short stay
Palmar-plantar erythrodysesthesia syndrome	£413.03	NHS reference costs 2017/18 – JD07J Skin Disorders without Interventions, with CC score 2-5 – non-elective short stay.

Ascites	£615.76	NHS reference costs 2017/18. Hospitalisation. Average non-elective short stay
Cholecystitis	£507.81	Weighted average of GA07C-E. Intermediate, Hepatobiliary or Pancreatic Procedures, with CC Score 0 -3+
Hepatic encephalopathy	£615.76	NHS reference costs 2017/18. Hospitalisation. Average non-elective short stay
Post-procedural pain	£615.76	NHS reference costs 2017/18. Hospitalisation. Average non-elective short stay

Table 62: Summary of unit costs, BTG CTT-eligible model (adapted from Table N1 in BTG BTG CS)

Item	Unit cost	Source
Treatment and aftercare costs		
TheraSphere	£8,000	Clinician informed
QuiremSpheres	£8,000	Assumed the same as TheraSphere
SIR-Spheres	£8,000	NICE MIB[179]
Sorafenib	£3,576.56	NICE BNF[112]
Best supportive care	£0.00	Assumed
Doxorubicin (loaded on to DEB-TACE)	£109	Clinician informed
Drug-eluting beads (DEB-TACE)	£550	
Lipiodol (TACE)	£250	
Bland beads (TAE)	£40	
Ciclosporin immunosuppressants	£68.28	NICE BNF
Admissions and procedure costs		
Hospitalisation (general)	£1,928	NHS reference costs 2017/18. Weighted average of HRG GC12C-GC12K
Outpatient attendance	£167	NHS Reference Costs 2017-18. Consultant-led: first attendance non-admitted face to face. Code 105 hepatobiliary and pancreatic surgery
Embolisation procedure	£2,790	NHS reference costs 2017-18. HRG code YR57Z
SIRT work-up	£467.91	Christie Hospital
Liver transplant procedure	£17,340	NHS Reference costs 2017-18. HRG code GA15A
Liver resection procedure	£4,994	NHS Reference costs 2017-18. Weighted average of HRG code GA06
Physician costs		
Oncologist	£166.85	NHS reference costs 2017/2018. Code WF01A. Non-Admitted Face-to-Face Attendance, Follow-up. Medical oncology
Hepatologist	£262.40	NHS reference costs 2017/18. WF01A Consultant-led, Non-Admitted Face-to-Face Attendance, Follow-up (hepatology)
Macmillan nurse	£42	PSSRU, Unit Costs of Health and Social Care 2018. Nurse (GP practice). Cost per hour, including qualifications
Gastroenterologist	£146.29	NHS reference costs 2016/17. WF01A Consultant-led, Non-Admitted Face-to-Face Attendance, Follow-up (gastroenterology)

Item	Unit cost	Source
Radiologist	£152.27	NHS reference costs 2016/17. WF01A Consultant-led, Non-Admitted Face-to-Face Attendance, Follow-up (interventional radiology)
Clinical nurse specialist	£42	PSSRU, Unit Costs of Health and Social Care 2018. Nurse (GP practice). Cost per hour, including qualifications.
Palliative care physician/care	£42	
GP	£37	PSSRU, Unit Costs of Health and Social Care 2018. Cost per 9.22 minute session, including qualifications.
Laboratory tests		
Full blood count	£2.32	NHS reference costs 2017/18. Weighted average of DAPS03, DAPS05 and DAPS08 (integrated blood services, haematology and phlebotomy).
Liver function tests	£20.07	NHS reference costs 2017/18. Weighted average of DAPS01 and DAPS02
Alpha fetoprotein test	£20.07	
INR	£2.32	NHS reference costs 2017/18. Weighted average of DAPS03, DAPS05 and DAPS08 (integrated blood services, haematology and phlebotomy)
Biochemistry	£1.11	NHS reference costs 2017/18. DAPS04 (clinical biochemistry)
Endoscopy	£499.51	NHS reference costs 2017/18. FE50A (Wireless Capsule Endoscopy, 19 years and over). Outpatient procedures.
CT scan	£103.95	NHS reference costs 2017/18. Weighted average of RD10Z - RD28Z. Adults only
MRI scan	£145.56	NHS reference costs 2017/18. Weighted average of all magnetic resonance imaging currency codes (adult only, excluding cardiac magnetic resonance imaging) (RD01A, RD02A, RD03Z, RD04Z, RD05Z, RD06Z, RD07Z).
Ultrasound scan	£52.06	NHS Reference costs 2017/18. HRG codes RD40Z and RD41Z. Ultrasound scan with duration <20 mins, weighted average of cost with/without contrast.

Table 63: Health state costs, BTG CTT-eligible model (Table 6-10 in BTG CS)

Item	Cost per cycle
Total watch and wait	£539.16
Total pre-transplant	£577.42
Total post-transplant 0-1	£971.71
Total post-transplant 1-2	£1049.22
Total post-transplant 2-3	£516.42
No HCC post-transplant	£502.49
Resection	£345.07
No HCC other	£306.50
Pharmacological management	£1308.57
Note, one cycle is equal to four weeks	

13.15.4 BTG model parameters – CTT-ineligible model

Table 64: Utility values, BTG CTT-ineligible model (Table 6-7 in BTG CS)

	Absolute utility	Source	Utility decrement
Progression-free	0.75	Lenvatinib NICE submission [32]	0.26
Progressed	0.68	Lenvatinib NICE submission [32]	0.32

Table 65: Drug acquisition costs, BTG CTT-ineligible model (Table N1 in BTG CS)

Item	Unit Cost	Source
Treatment and aftercare costs		
TheraSphere	£8,000.00	Clinician informed
QuiremSpheres	£8,000.00	Assumed the same as TheraSphere
SIR-Spheres	£8,000.00	NICE MIB[179]
Sorafenib	£3,576.56	NICE BNF[112]
Lenvatinib	£1,437.00	
Regorafenib	£3,744.00	
Best supportive care	£0.00	Assumed

Table 66: Health state costs and one off progression costs, BTG CTT-ineligible model (economic model in BTG CS)

Item		Unit Cost	Cost per cycle progression-free	Cost per cycle progressed
Physician visits	Oncologist	£166.85	£115.51	£58.53
	Hepatologist	£262.40	£41.18	£121.11
	Macmillan nurse	£42.00	£19.38	£38.77
	Gastroenterologist	£146.29	£10.80	£0.00
	Radiologist	£152.27	£11.24	£0.00
	Clinical nurse specialist	£42.00	£19.38	£9.69
	Palliative care physician/care	£42.00	£5.04	£29.08
Laboratory tests	Full blood count	£2.32	£1.61	£1.07
	Liver function tests	£20.07	£6.21	£4.63
	Alpha fetoprotein test	£20.07	£11.53	£7.04
	INR	£2.32	£0.72	£0.00
	Biochemistry	£1.11	£0.51	£0.26
	Endoscopy	£499.51	£38.04	£0.00
Radiological tests	CT scan	£103.95	£23.12	£27.32
	MRI scan	£145.56	£12.42	£18.81
Hospitalisation	Hospitalisation	£1,928.00	£130.99	£341.70
Hospital follow-ups	Hepatologist	£262.40	£60.55	£262.40
	GP	£37.00	£51.23	£37.00
	Clinical nurse specialist	£42.00	£67.85	£42.00
Total cycle costs			**£627.31**	**£999.40**

Table 67: One-off progression costs, BTG CTT-ineligible model (adapted from Table 6-13 in BTG CS)

Resource item	Mean cost
Physician visits	£0.00
Laboratory tests	£82.86
Radiological tests	£12.46
Hospitalisation	£0.00
Hospital follow-ups	£0.00
Total	**£95.32**

Table 68: Treatment-related adverse event costs, CTT-ineligible model (Table 6-12 in BTG CS)

Treatment	Total adverse event cost
TheraSphere	£88.65
SIR-Spheres	£111.33
QuiremSpheres	£111.33
cTACE	£112.07
DEB-TACE	£5.59
TAE	£483.88
Sorafenib	£384.15
Lenvatinib	£502.93
Regorafenib	£559.69

13.16 Model parameters and plots independent economic assessment

Table 69: Proportion of patients down staged to curative therapy

Population	After SIR-Spheres	After sorafenib
Base-case (whole population)		
Liver transplant	1.09%	0.46%
Resection	1.63%	0.00%
Ablation	3.26%	0.92%
Low tumour burden and ALBI grade 1		
Liver transplant	2.25%	0.70%
Resection	4.50%	0.00%
Ablation	7.87%	1.40%

Table 70: Adverse event rates

Grade 3/4 adverse events (significant/≥5%)	SIR Spheres	TheraSphere	QuiremSpheres	Sorafenib	Lenvatinib
Abdominal pain	3.0%	3.0%	3.0%	6.0%	0.0%
Alopecia	0.0%	0.0%	0.0%	0.0%	0.0%
Anaemia	0.0%	0.0%	0.0%	0.0%	0.0%
Anorexia	3.0%	3.0%	3.0%	5.0%	0.0%
Ascites	0.0%	0.0%	0.0%	0.0%	0.0%
Aspartate aminotransferase increase	0.0%	0.0%	0.0%	0.0%	5.0%
Blood bilirubin increase	4.0%	4.0%	4.0%	4.0%	6.5%
Cardiac failure, congestive	1.0%	1.0%	1.0%	5.0%	0.0%
Diarrhoea	1.0%	1.0%	1.0%	14.0%	4.2%
Fatigue	9.0%	9.0%	9.0%	19.0%	3.8%
Gamma-glutamyltransferase increase	0.0%	0.0%	0.0%	0.0%	5.5%
Haematological biological abnormalities	10.0%	10.0%	10.0%	13.0%	0.0%
Haemorrhage	0.0%	0.0%	0.0%	0.0%	0.0%
Hypophosphataemia	0.0%	0.0%	0.0%	0.0%	0.0%
Hand-foot skin reaction	0.0%	0.0%	0.0%	6.0%	2.9%
Hypertension	0.0%	0.0%	0.0%	2.0%	23.3%
Liver dysfunction	8.0%	8.0%	8.0%	13.0%	0.0%
Nausea/vomiting	0.0%	0.0%	0.0%	0.0%	0.0%
Other increased liver values	9.0%	9.0%	9.0%	7.0%	0.0%
Platelet count decreased	0.0%	0.0%	0.0%	0.0%	5.5%
Proteinuria	1.0%	1.0%	1.0%	4.0%	5.7%

Rash/desquamation	0.0%	0.0%	0.0%	0.0%	0.0%
Weight loss	0.0%	0.0%	0.0%	3.0%	7.6%
Cholecystitis	0.0%	0.0%	0.0%	0.0%	0.0%
Hepatic encephalopathy	0.0%	0.0%	0.0%	0.0%	0.0%

Figure 26: Kaplan-Meier plot of overall survival, for SIR-Spheres and sorafenib, from pooled SARAH and SIRveNIB dataset

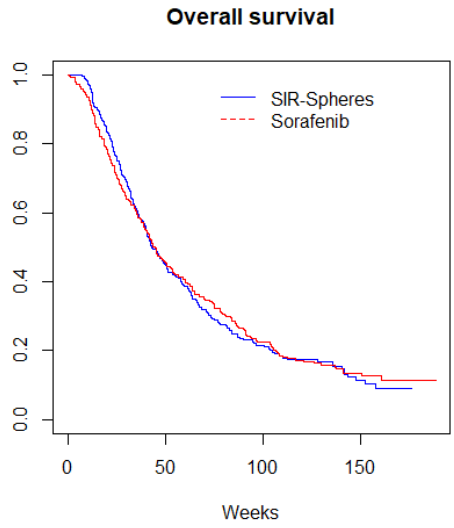


Figure 27: Kaplan-Meier plot of overall survival, for SIR-Spheres and sorafenib, from pooled SARAH and SIRveNIB dataset

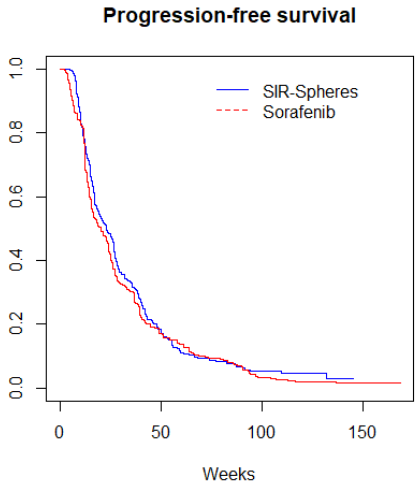


Table 71: Summary of observed survival estimates for SIR-Spheres and sorafenib, SARAH and SIRveNIB pooled dataset

	SIR-Spheres	**Sorafenib**
Overall survival		
Median (weeks)	42.86 (95% CI 39.86 – 51.14)	44.38 (95% CI 40.68 – 50.82)
Interquartile range	26.43 – 84.00	21.99 – 90.96
Progression-free survival		
Median (weeks)	22.99 (95% CI 19.00 – 26.77)	20.52 (95% CI 16.29 – 23.73)
Interquartile range	12.76 – 41.14	12.09 – 39.49

Figure 28: Log-cumulative hazard plot of overall survival, for SIR-Spheres and sorafenib, from pooled SARAH and SIRveNIB dataset

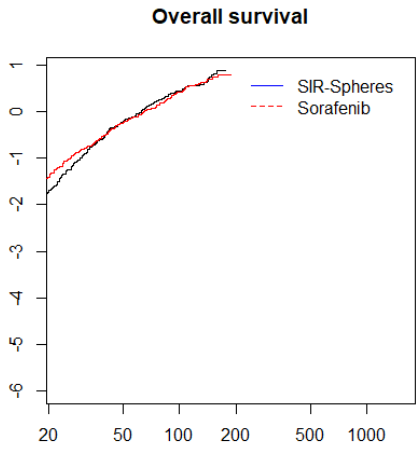


Figure 29: Log-cumulative hazard plot of progression-free survival, for SIR-Spheres and sorafenib, from pooled SARAH and SIRveNIB dataset

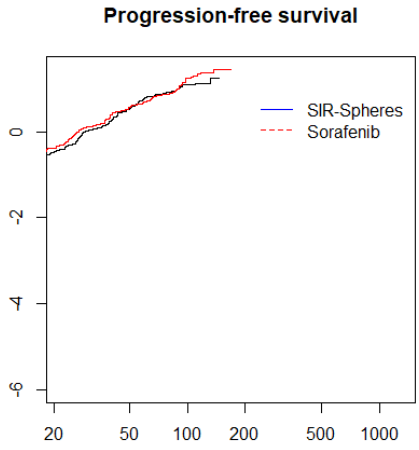


Table 72: AIC and BIC - Overall survival for SIR-Spheres and sorafenib, from pooled SARAH and SIRveNIB dataset (survival analysis conducted by AG)

	SIR-Spheres		**Sorafenib**	
	AIC	**BIC**	**AIC**	**BIC**
Generalised gamma	2343.50	2354.54	3146.87	3158.84
Weibull	2394.10	2401.46	3168.12	3176.10
Exponential	2412.02	2415.70	3173.08	3177.08
Log-logistic	2357.55	2364.91	3144.28	3152.26
Log-normal	2350.14	2357.50	3146.02	3154.00
Gompertz	2412.72	2420.08	3175.06	3183.04

Table 73: AIC and BIC - Progression-free survival for SIR-Spheres and sorafenib, from pooled SARAH and SIRveNIB dataset

	SIR-Spheres		Sorafenib	
	AIC	**BIC**	**AIC**	**BIC**
Generalised gamma	2225.88	2236.91	3120.26	3132.24
Weibull	2312.97	2320.33	3182.16	3190.15
Exponential	2337.34	2341.02	3195.35	3199.34
Log-logistic	2254.74	2262.10	3129.63	3137.61
Log-normal	2245.68	2253.04	3120.23	3128.21
Gompertz	2338.53	2345.89	3197.35	3205.33

Table 74: Fit statistics for the survival analyses of SARAH data (conducted by Sirtex)

	PFS		OS	
	AIC	**BIC**	**AIC**	**BIC**
Per protocol population (SARAH only)				
Log-normal	1881.7	1897.4	2181.2	2196.8
Exponential	1977.8	1985.6	2233.6	2241.4
Weibull	1953.4	1969	2213.8	2229.4
Generalised gamma	1874.7	1898.1	2183.9	2207.3
Gompertz	1976.3	1991.9	2231.3	2246.9
Log-logistic	1895.1	1910.8	2190	2205.6
Low tumour burden and ALBI 1 subgroup				
Log-normal	386.3	395.4	427.6	436.7
Exponential	394.4	398.9	442.6	447.1
Weibull	393.8	402.9	429.6	438.7
Generalised gamma	389.3	403	431.3	445
Gompertz	397.4	406.5	435.2	444.3
Log-logistic	389.4	398.5	428.4	437.5
No macrovascular invasion subgroup				
Log-normal	783.4	795.3	846.2	858.1
Exponential	815.5	821.4	872.6	878.6
Weibull	805.6	817.6	855	866.9
Generalised gamma	786.2	804.1	848.8	866.7
Gompertz	817.1	829	866.8	878.8
Log-logistic	789.5	801.5	848.7	860.6

Figure 30: Extrapolation of OS Low tumour burden and ALBI 1 subgroup: SIR-Spheres

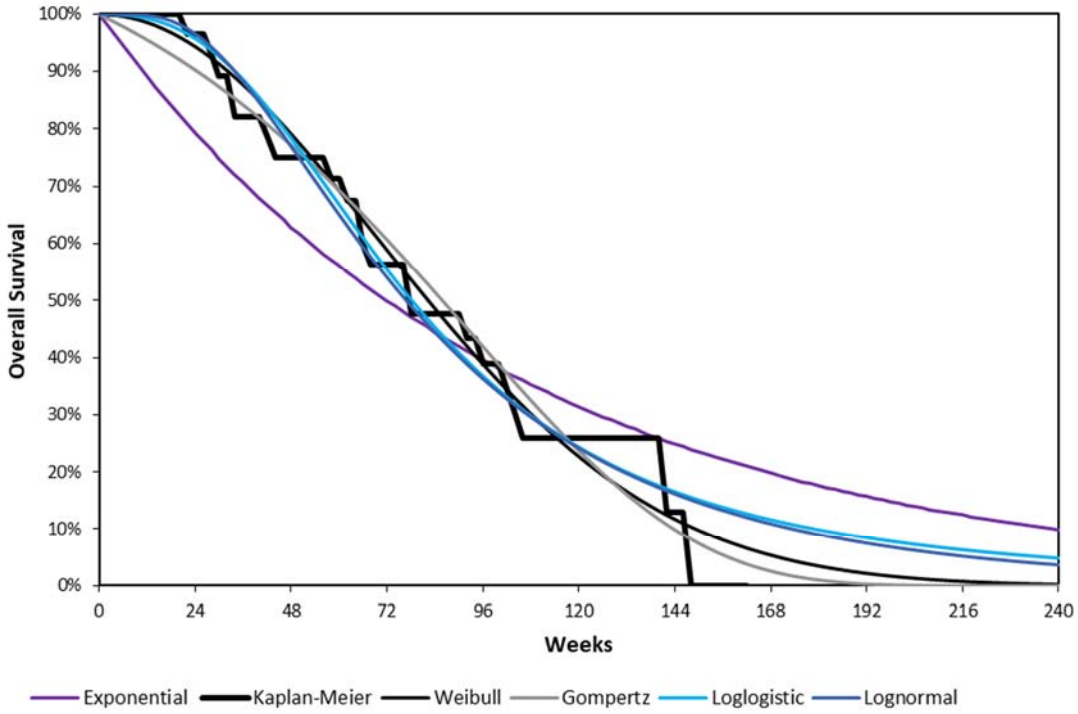


Figure 31: Extrapolation of OS No MVI subgroup: SIR-Spheres

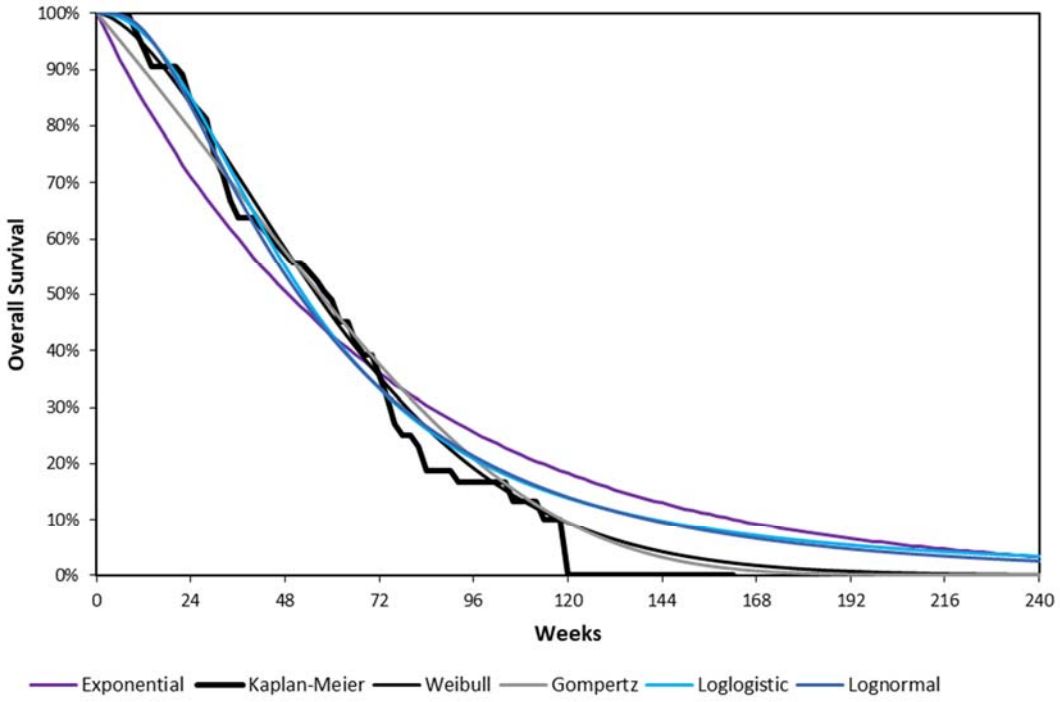


Figure 32: Extrapolation of OS Low tumour burden and ALBI 1 subgroup: Sorafenib

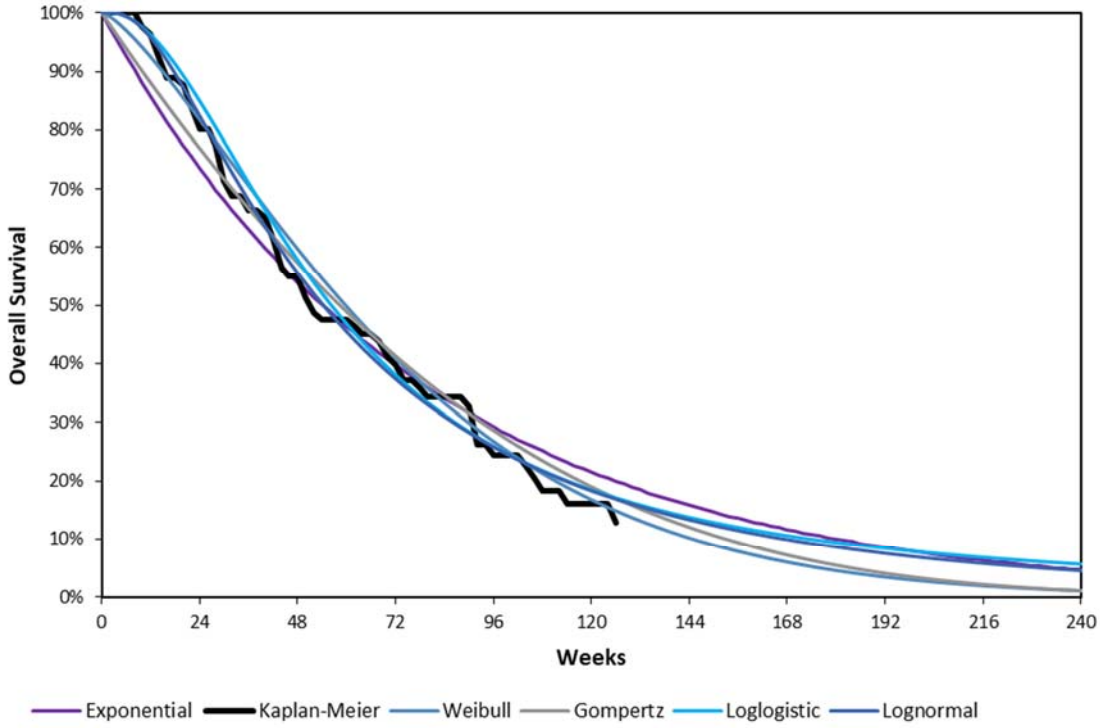


Figure 33: Extrapolation of OS No MVI subgroup: Sorafenib

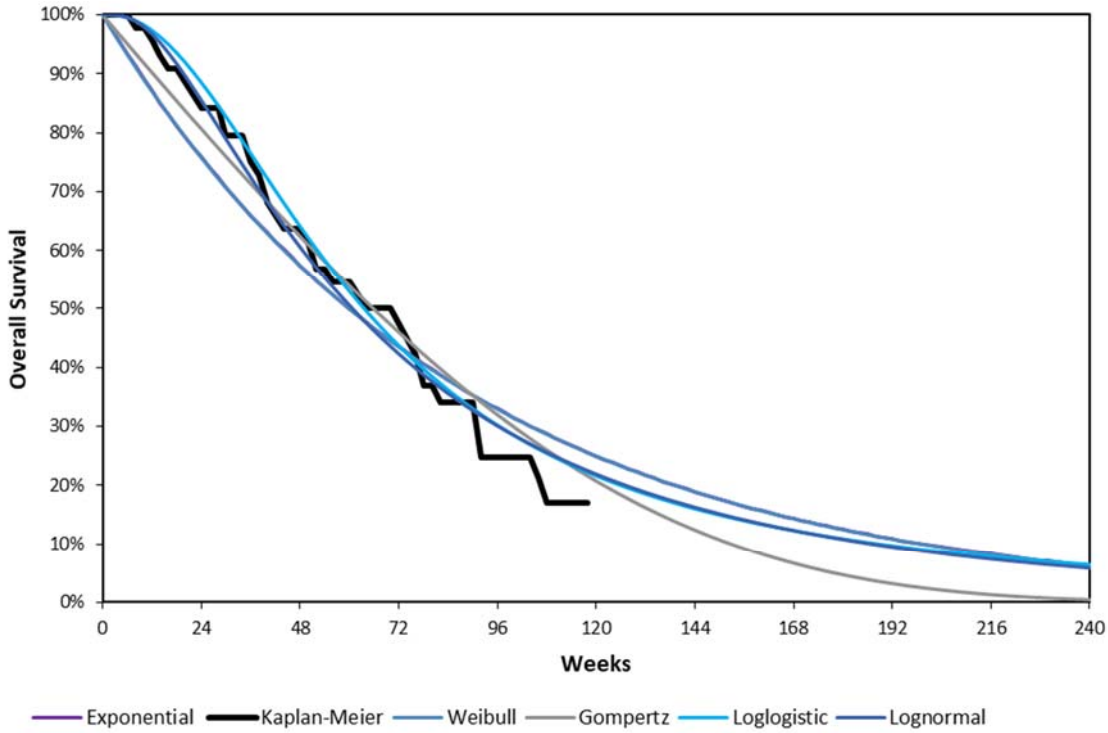


Figure 34: Extrapolation of PFS Low tumour burden and ALBI 1 subgroup: SIR-Spheres

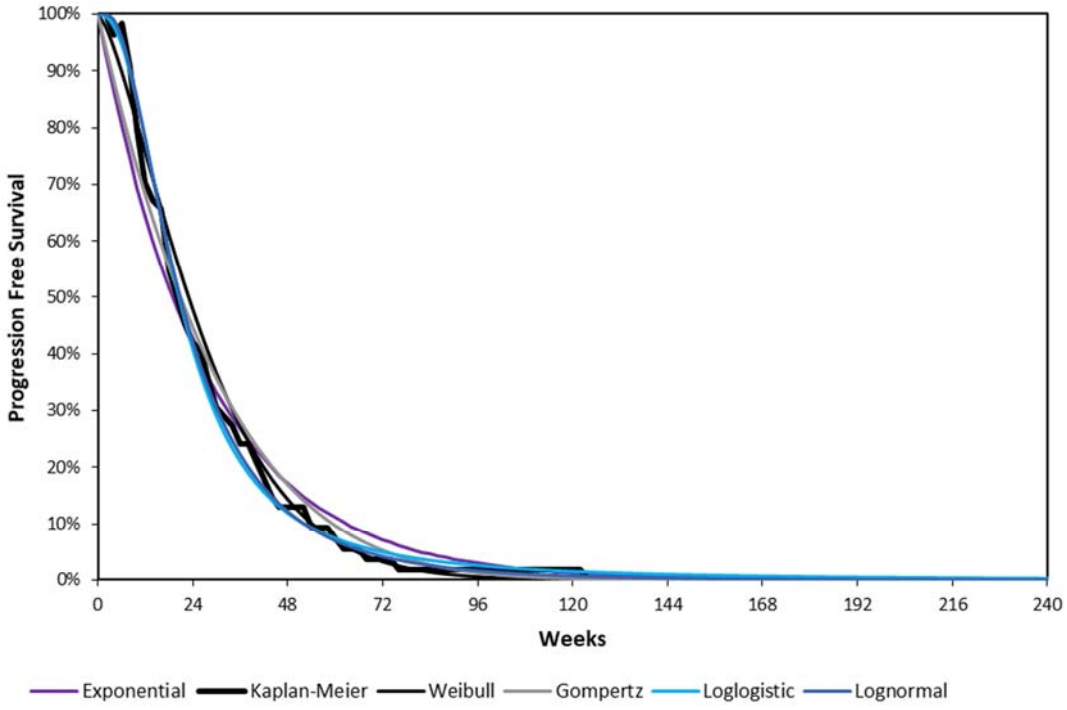


Figure 35: Extrapolation of PFS No MVI subgroup: SIR-Spheres

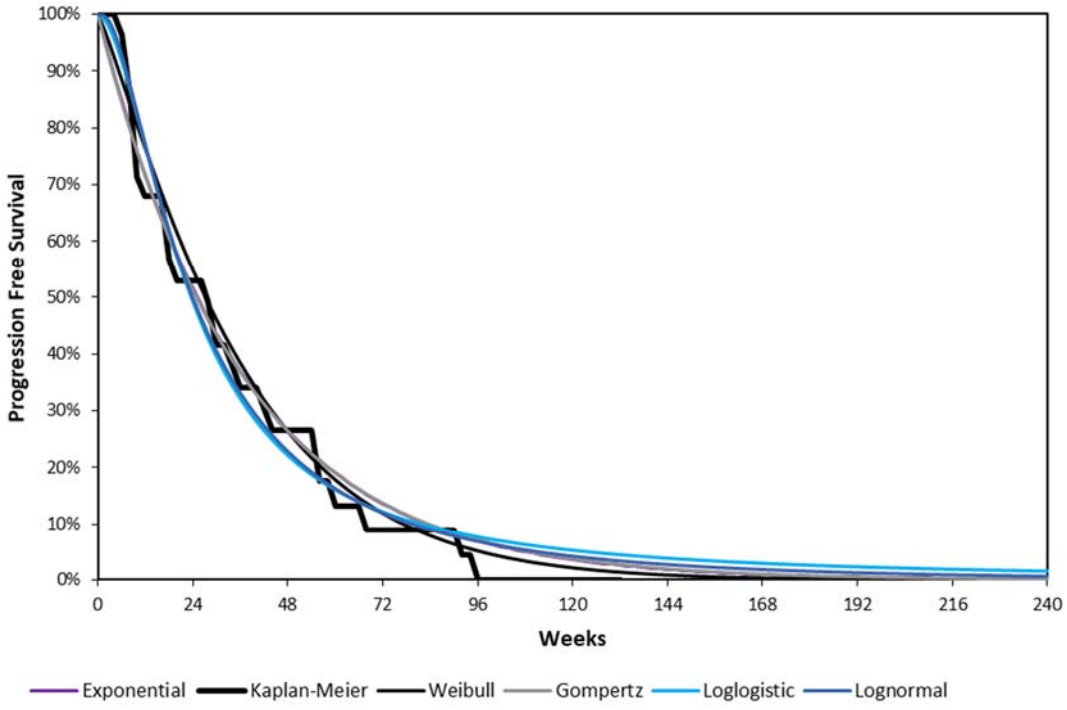


Figure 36: Extrapolation of PFS Low tumour burden and ALBI 1 subgroup: Sorafenib

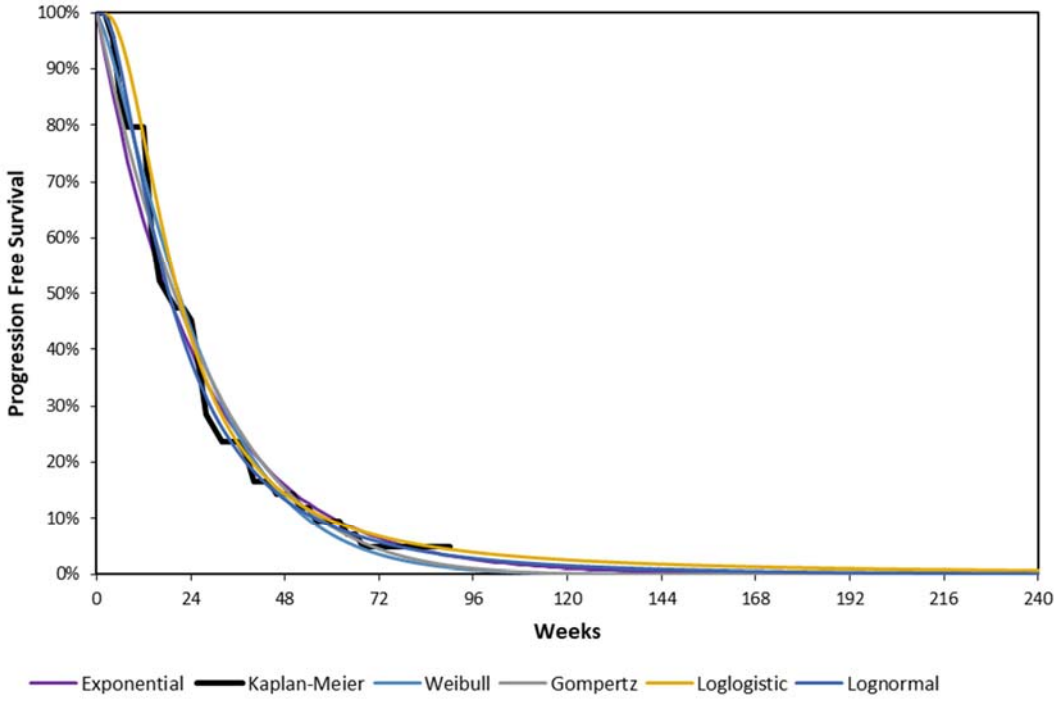


Figure 37: Extrapolation of PFS No MVI subgroup: Sorafenib

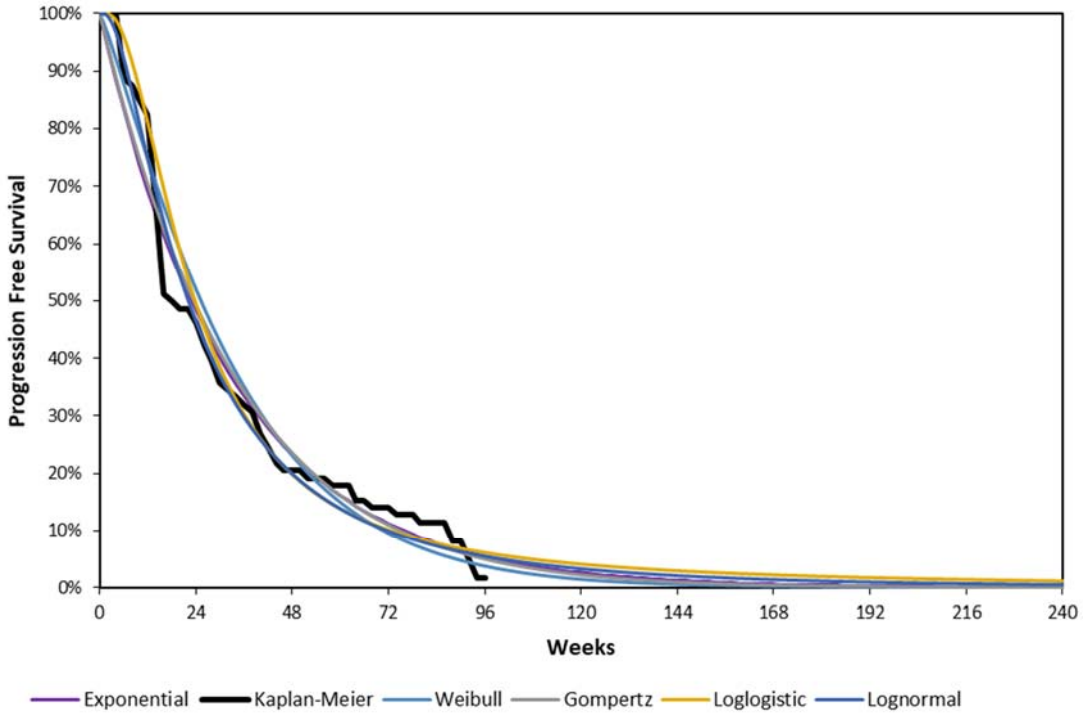


Table 75: Adverse event unit costs

Adverse Event	Unit cost per episode	Source
Abdominal pain	£42.19	Sirtex submission (inflated from TA474)
Alopecia	£18.59	Sirtex submission (inflated from TA474)
Anaemia	£615.76	NHS Reference costs (hospitalisation) (TA535)
Anorexia	£657.86	Sirtex submission (inflated from TA535)
Ascites	£615.76	NHS Reference costs (hospitalisation) (TA535)
Aspartate aminotransferase increase	£634.50	Sirtex submission (inflated from TA551)
Blood bilirubin increase	£916.47	Sirtex submission (inflated from TA535)
Cardiac failure, congestive	£1,979.71	National Schedule of Reference Costs 2017/18
Diarrhoea	£605.13	Sirtex submission (inflated from TA551)
Fatigue	£677.68	Sirtex submission (inflated from TA551)
Gamma-glutamyltransferase increase	£634.50	Sirtex submission (inflated from TA551)
Haematological biological abnormalities	£1,713.98	Assumed same as anaemia (TA514)
Haemorrhage	£0.00	Sirtex submission (TA474)
Hypophosphataemia	£1,297.52	Sirtex submission (inflated from TA551)
Palmar-plantar erthrodysaesthesia syndrome	£897.98	Sirtex submission (inflated from TA535)
Hypertension	£888.12	Sirtex submission (inflated from TA551)
Liver dysfunction	£1,207.13	Sirtex submission (inflated from TA535)
Nausea/vomiting	£82.18	NHS Reference costs (hospitalisation) (TA535)
Other increased liver values	£634.50	Sirtex submission (inflated from TA551)
Platelet count decreased	£634.50	Sirtex submission (inflated from TA551)
Proteinuria	£812.04	Sirtex submission (inflated from TA551)
Rash/desquamation	£71.09	Sirtex submission (inflated from TA474)
Weight loss	£665.35	Sirtex submission (inflated from TA551)

Multiple Technology Appraisal (MTA) Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276]
Response to AG report

Contents

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Executive summary

Overview

Hepatocellular carcinoma (HCC) is a challenging heterogenous cancer. The aim of treatment in HCC is to increase survival while maintaining quality of life. Guidelines emphasise that treatment for HCC should be individualised to each patient to ensure optimal outcomes (1). Careful selection of candidates for each treatment option and the expert application of these treatments is essential. BTG believes that TheraSphere is a treatment option for both curative and palliative intent.

NICE and the Assessment Group (AG) have divided the HCC population into two populations: conventional transarterial therapy (CTT)-eligible and CTT-ineligible which broadly reflect potentially resectable/curative intent and unresectable/palliative intent. However, these delineations are arbitrary, since the clinician may initiate treatment according to the categories above, with no certainty as to how the patient will actually respond.

Comparative assessment of clinical and cost-effectiveness for treatments in HCC is challenging because of the heterogeneous nature of the disease. The NICE scope for this MTA defined patient populations using the commonly used HCC patient staging/classification system (Barcelona Clinic Liver Cancer [BCLC]). However, BCLC is not aligned with treatment goals (curative or palliative) and has not been considered in earlier NICE Technology Appraisals for systemic chemotherapy for HCC, which makes assessment extremely difficult.

Early stage disease

In early stage disease, treatment can potentially be curative (surgical liver resection, liver transplantation and local destructive methods). SIRT are alternative treatments in this patient group to provide complete tumour destruction in well-selected candidates or as a treatment for downstaging unresectable disease to potentially curative therapy.

For patients with early stage disease (stage 0/A) the AG did not complete a network meta-analysis (NMA) or an economic model, making decision making very difficult. BTG appreciate the difficulty in developing a model for this group, however, believe that SIRT is potentially suitable as curative intent for early stage disease patients (as radiation segmentectomy, radiation lobectomy and downstaging for transplant, resection or ablation) as per guidelines. BTG believe that non-comparative evidence, which the AG did not consider, provides support for the use of TheraSphere in these specific patient groups, but acknowledge that more evidence is required before robust recommendations can be made. We suggest consideration of the Cancer Drugs Fund for this population, enabling a choice of therapy while further data is collected.

Intermediate stage disease

CTT is the standard of care in patients with intermediate (stage B) disease. Patients with intermediate disease fall into the CTT-eligible/potentially resectable/curative intent population and indeed some patients will undergo curative treatment post-downstaging with CTT. However, in many cases this will not be possible or successful and treatment is life-extending rather than curative.

For patients with intermediate stage disease (stage B) the AG did not complete an NMA or an economic model, again making decision making very difficult. It is extremely important to help the committee make an informed decision about the use of SIRT in this key population.

We believe that the AG rationale for not carrying out an NMA in this population is flawed. The AG suggested that the network was disconnected, however, advice from experts suggests that this is not the case. Furthermore, methods exist to combine randomised and non-randomised evidence in an NMA and BTG suggests that the AG could have explored these methods. In the absence of an AG model, we suggest that the Committee consider the BTG economic model developed for patients with earlier stage disease (early/intermediate) to help to make a decision in this important patient population. The original base case presented in the BTG submission was an incremental cost-effectiveness ratio (ICER) of £24,647 per quality adjusted life year (QALY) gained. After correcting errors and taking into account AG input, the aggregated updates to the model produced an ICER for TheraSphere of £23,479 per QALY gained.

Clinical opinion suggests that patients with intermediate stage disease (stage B) are the most appropriate candidates for SIRT. Clinicians have advised BTG that there is a specific group of intermediate patients, in whom there are currently limited options, that will gain the most benefit from SIRT. These patients are eligible for CTT but are unable to receive CTT due to size of their lesion (≥7 cm) or because they have undergone and failed CTT. Currently, the alternative treatment options for this group include systemic therapy, which unlike SIRT, does not have the potential for curative intent. There are also the well documented toxicities associated with systemic therapy, which ultimately may lead to discontinuation of therapy.

Improved outcomes have been demonstrated with SIRT delivered via personalised dosimetry (PDA). A recent phase II, multicentre, randomised study, the DosiSphere study, was presented at European Conference on Interventional Oncology (ECIO) in 2019 (2) and revealed improved outcomes in patients with intermediate and advanced disease. Patients had at least one tumour ≥7 cm and were randomised to TheraSphere either following standard dosimetry (SDA), where they received <205 Gy to the tumour or PDA, where they received >205 Gy to the tumour. Response rates by blinded central review were 78.6% in the PDA arm and 42.9% in the SDA arm, indicating superior efficacy with PDA and impressive outcomes with TheraSphere.

This data is in line with a poster recently presented at ESMO (3), of a post-hoc sub-analysis of the SARAH data, which revealed improved outcomes with tumour doses >100 Gy. A recent expert recommendation consensus paper (Salem 2019 (4)) reflects on the benefits of PDA and stated that '*As new prospective trials are designed, incorporation of a refined and personalized dosimetry model will be essential for improved outcomes*'.

Advanced stage disease

For patients with advanced disease (stage C) treatment is palliative. Guidelines recommend that systemic chemotherapy as standard of care, with SIRT as an alternative treatment for those patients unable to take systemic treatment. CTT are not recommended for these patients.

The AG did complete an NMA and a model in the advanced patient population, which aids decision making somewhat. However, BTG believe that there are several important flaws in the AG approach. The AG did not include TheraSphere in the base case NMA, because the evidence was non-randomised. Methods exist to combine randomised and non-randomised evidence in an NMA and BTG suggests that the AG could have explored these methods further.

The AG included TheraSphere as scenario analyses to the base case NMA and BTG also produced an NMA including TheraSphere in this population. The scenario analyses and the BTG NMA indicate that TheraSphere and SIR-Spheres do not have a common relative effect, this together with non-comparative evidence, not considered by the AG, suggest that TheraSphere and SIR-Spheres are not equal in efficacy.

The AG model and the BTG model are broadly common in structure. BTG believes that the economic model produced by the AG has a number of flaws, including equivalence of all SIRTs, an incorrect method of modelling state occupancy and misleading pooling of sorafenib OS data. The AG pointed out a number of calculation and input errors in the BTG model: correcting these errors reduced the ICER from £66,641 to £30,591 per QALY gained. The key driver of costs is the proportion of the cohort on systemic therapy at any given time point (pre-and post-progression). Clinical opinion and standard protocols suggest that patients receive systemic therapy on progression rather than directly after SIRT; if this assumption is modelled then the ICER falls still further to £6,077.

Two subgroups are of particular interest: patients with PVT and patients unable to tolerate sorafenib.

Patients with PVT have a particularly poor prognosis. BTG believes that these patients derive particular benefit from TheraSphere, especially if delivered via PDA. A study by Garin et al in HCC patients with PVT (n=41) revealed a significant improvement in OS with PDA (>205 Gy) versus SDA (<205 Gy): 18.2 months versus 4.3 months, p<0.005 (5). Further work by Garin et al (6) in a mixed intermediate/advanced disease population showed significantly improved OS in patients receiving PDA versus SDA: median OS of 15.7 months versus 4.35 months, p=0.0004 in the PVT population. Given the limited options and poor prognosis for this patient group and positive evidence using PDA to deliver TheraSphere, BTG suggests that TheraSphere is an alternative treatment in these patients.

Patients not eligible for systemic therapies or unable to tolerate systemic treatment toxicities are another important subgroup. In the SARAH study (7), 64% (139/216) of patients discontinued sorafenib for drug-related toxicity; of whom 108 (78%) permanently discontinued treatment. Quality of life, an important issue in patients with advanced cancer, was also significantly poorer in the sorafenib arm than with SIRT. Given the limited options (best supportive care) for these patients, BTG suggests that TheraSphere provides an alternative treatment option for this patient group.

Incremental life years gained (undiscounted) results when all pooled alterations are included show an increased survival of over 3 months (5.5 months when compared with sorafenib and 6.5 months when compared with SIR-Spheres) suggesting that TheraSphere would meet the End of Life criteria of improving OS when compared with other palliative treatments. This is echoed by clinical advice gained during the consultation process undertaken by BTG in responding to the AG report.

Providing treatment choice

In conclusion:

1. Early stage patients: TheraSphere is a treatment option in specific patient groups. Although comparative and economic evidence is lacking, BTG believe that TheraSphere should be

available for these patients. We suggest consideration of the Cancer Drugs Fund for this population, enabling a choice of therapy while further data is collected.

2. Intermediate stage patients (curative intent): Clinical opinion suggests these patients are most likely to benefit from treatment with TheraSphere. Using data from the AG NMA scenario including TheraSphere and the BTG model (the AG did not produce a model for this patient group) the ICER for TheraSphere is £23,479 per QALY gained. BTG believe that patients who are eligible, but unsuitable for, CTT e.g. those who have failed CTT or have large tumours, will benefit most from SIRT. This patient group have no alternative treatment options, prior to systemic therapy.
3. Advanced stage patients: Treatment is palliative at this stage, TheraSphere is a cost-effective treatment option and may be of particular interest in treating those patients with PVT or those unable to take systemic treatment with an alternative treatment choice. BTG also believes that End of Life criteria could apply.

1. Introduction

BTG have presented evidence to assess the clinical and cost-effectiveness of SIRT technologies for treating people with unresectable hepatocellular carcinoma (HCC), in populations of people who are conventional transarterial therapy (CTT) -eligible and CTT-ineligible. In line with clinical practice, we have used the synonyms of these definitions as outlined in Table 1 in our response:

Table 1: Patient group definitions used in this document

Appraisal scope	**Assessment group**	**BTG**
Potentially resectable	CTT eligible	Curative intent
Unresectable	CTT ineligible	Palliative intent

It is important to remember that these delineations are arbitrary, since the clinician may initiate treatment according to the categories above, with no certainty as to how the patient will actually respond.

Although we understand the need to divide the population up in this way, the artificial division makes assessment of the intermediate patient group where the standard of care is CTT, particularly complex. These patients fall into the CTT-eligible/potentially resectable/curative intent population and indeed some patients will undergo curative treatment post-downstaging with CTT. however, in many cases this will not be possible or successful and treatment is life-extending rather than curative. A sub-group of intermediate patients eligible for CTT but not suitable (due to size of lesion or failed CTT) and not yet candidates for systemic therapy (no PVT or metastasis) are key candidates for SIRT. A third group of intermediate patients will not be treated with curative intent and will fall into the CTT-ineligible/unresectable/palliative population. In this document we have included the intermediate patients in both curative and palliative intent in an attempt to reflect clinical practice.

Assessment of clinical and cost-effectiveness for treatments in HCC is challenging because of the heterogeneous nature of the disease. The NICE scope for this MTA defined patient populations using the commonly used HCC patient staging/classification system (Barcelona Clinic Liver Cancer [BCLC]). However, BCLC is not aligned with treatment goals (curative or palliative) and has not been considered in earlier NICE Technology Appraisals for systemic chemotherapy for HCC, which makes assessment extremely difficult. Both the AG and BTG have worked hard to assess the clinical and cost-effectiveness of SIRT, despite these challenges.

The aim of treatment in HCC is to increase survival while maintaining quality of life. Guidelines emphasise that treatment for HCC should be individualised to each patient to ensure optimal outcomes (1). Careful selection of candidates for each treatment option and the expert application of these treatments is essential. In order to achieve individualised treatment, alternative treatment options must be available. BTG believe that TheraSphere is a treatment option for both curative and palliative intent.

We present our initial comments on the technical content of the Assessment Report and the AG model.

2. Response to AG assessment of TheraSphere in the curative intent patient group

2.1 Clinical evidence

2.1.1 International guidelines

In patients with early stage disease treatment can potentially be curative. The European Society for Medical Oncology (ESMO) guidelines which were updated and published in 2018 (1) recommend surgical liver resection, liver transplantation and local destructive methods (radiofrequency ablation or microwave ablation) and CTT for early stage disease. The ESMO guidelines suggest that SIRT are alternative treatments in this patient group (BTG submission, Table 3-1, page 21) to provide complete tumour destruction in well-selected candidates or as a treatment for downstaging unresectable disease to potentially curative therapy, such as liver resection or transplantation or as a bridge to transplantation.

The AG considered some of these patients in Network 1: People with unresectable HCC who are eligible for transplant (AG report section 5.2.1).

As per ESMO guidelines, BTG believe that SIRT is also potentially suitable as curative intent for early stage disease patients:

- with small HCC tumours (≤5 cm) which are not amenable to ablation or are otherwise unresectable due to location and/or proximity to critical structures. In such cases TheraSphere® is administered super-selectively using radiation segmentectomy to apply high dose radiation to ≤2 liver segments.
- who cannot undergo resection due insufficient remaining normal tissue (radiation lobectomy). Lobar treatment with TheraSphere results in hypertrophy of the contralateral untreated lobe such that resection of the diseased lobe becomes an option. This response occurs while the tumours in the diseased lobe are being irradiated and atrophied. Other agents used to effect hypertrophy (e.g. portal vein embolisation) do so without treating the diseased lobe, whereas radiation lobectomy with TheraSphere® does both.
- who would become candidates for potentially curative treatment (resection or ablation) if disease was downstaged.

For patients with intermediate stage disease (stage B) the ESMO guidelines recommend CTT as standard of care, with SIRT, transplantation, resection or systemic treatment as alternative treatments depending on the individual's prognosis. Treatment aims to downstage disease so that potentially curative approaches can be carried out, however, in many cases this will not be possible or successful and treatment is life-extending rather than curative.

A proportion of patients with intermediate disease, although eligible for CTT, will not be suitable for treatment with CTT either because they are refractory to treatment (have failed CTT twice) or are have large tumours >7cm. Clinicians consulted as part of the consultation process undertaken by BTG in responding to the AG report felt that this group was the most likely to benefit from SIRT. Alternative treatment options include systemic therapy, which unlike SIRT, does not have the potential for curative intent.

Recent data on using personalised dosimetry (PDA) to deliver TheraSphere indicates that outcomes are significantly improved with this method of delivery which has not been included in previous RCTs. PDA delivers a higher more targeted dose to the tumour whilst limiting radiation to the rest of the liver and the lungs. A recent phase II, multicentre, randomised study (Dosisphere) was presented at ECIO 2019. Patients had at least one tumour ≥7cm and were randomised to TheraSphere either following Standard dosimetry (SDA) or PDA. Response rates were 78.6% and 42.9% in the PDA and SDA arms respectively, by blinded central review, indicating superior efficacy with PDA (2).

Additional evidence for SIRT delivered using PDA, comes from a poster presented at ESMO (3), of a post-hoc sub-analysis of the SARAH data. The study included 39% intermediate patients and 56% advanced patients, with the remainder having early disease. Mean OS was 23 months with PDA >100 Gy SIR-Spheres versus 18.2 months with sorafenib. Furthermore, patients undergoing PDA with SIRT were significantly more likely to undergo treatment for curative intent (12.5% versus 1.6% with SDA SIRT versus1.4% with sorafenib).

Indeed, a recent expert recommendation consensus paper (Salem 2019 (4)) reflects on the benefits of PDA and stated that '*As new prospective trials are designed, incorporation of a refined and personalized dosimetry model will be essential for improved outcomes'*.

The AG considered intermediate patients suitable for CTT in Network 2: People with unresectable HCC who are eligible for CTT (AG report section 5.2.2).

2.1.2 AG description/ interpretation of relevant studies

The clinical evidence for TheraSphere, and the other SIRTS, is predominantly from comparative studies rather than randomised controlled studies (RCT). This makes the interpretation of evidence challenging.

The AG carried out a systematic literature review (SLR) and identified 27 studies across all HCC populations (AG report Figure 1, page 41 and Table 3, page 42).

The AG identified several additional studies which were not identified in the BTG submission (Kirchner, 2019; Salem, 2013; Memon, 2013; Hickey, 2016; d'Abadie, 2018). The AG did not include many of the comparative studies included in the BTG submission, their reasons given were plausible

However, non-comparative trials included in the BTG submission were not identified or included in the AG report. The study design mentions inclusion of non-comparative studies (page 36) but on page 39 of the report the AG state that there were 176 comparative studies and the decision was made to focus on these. We believe that given the paucity of data, non-comparative studies may provide additional evidence in early stage disease and direct the AG to Table 4-2 (page 28) and Table 4.3 (page 29) which provide an overview of the TheraSphere studies providing evidence for overall survival (OS) and progression free survival (PFS) respectively.

Four non-comparative studies provide evidence for OS with TheraSphere in early stage disease used as radiation segmentectomy (Table 4-9, page 51), three studies provide evidence for radiation lobectomy and (Table 4-11, page 55) and six studies for downstaging (Table 4-10, page 53). We accept that these studies do not provide high quality evidence, but they do support the use of TheraSphere in these patient populations.

2.1.3 AG evidence synthesis

The AG considered the creation of two evidence networks of relevance to this patient population:

- Network 1 (AG report section 5.2.1) for individuals with early/ intermediate stage unresectable HCC who are eligible for transplant
- Network 2 (AG report section 5.2.2) for individuals with unresectable HCC who are eligible for CTT

Ultimately, the AG did not create networks and so no relative efficacy estimates were available for either patient population. Whilst we accept that Network 1 would be based on a small amount of information, and hence of limited use, we would like to raise serious concerns about the lack of results for Network 2.

The evidence network presented in Figure 2 of the AG report (page 75) contains five interventions and is based on information from six RCTs and one study labelled as 'retrospective'. Based on a detailed reading of the submission, we see no justification for the following statement:

"…*there is no common comparator in the evidence base for both OS and PFS outcomes in this population, therefore it forms a disconnected network*" (AG report page 74)

Even if the retrospective study is removed, the evidence network in Figure 2 is **not disconnected**. Furthermore, the need for a common comparator is not a pre-requisite of an NMA, and NICE have previously received, and used in their decision making NMAs that do not include common comparators. Examples include psoriasis (ID1060) (8), cardiology (TA314) (9) oncology (TA384) (10) and rheumatoid (ID994).

Other reasons given by the AG for the non-generation of relative efficacy estimates in this population include:

"*Implementing an NMA in this population would produce very uncertain results as it relies on a single small trial by Pitton et al. to connect SIR-Spheres in the network."* (AG report page 74)

And

"*it would not provide reliable evidence on TheraSphere comparisons with CTT as there is only one small, retrospective, low-quality study connecting TheraSphere in the network*." (AG report page. 74)

Neither of these are justifiable reasons not to undertake an NMA since:

- Uncertainty in the results would be represented via wide credible intervals around any central estimate where small studies such as Pitton et al. are needed to connect the network
- Techniques exist for combining randomised and non-randomised evidence in an NMA (11-13)

There is a paucity of high-quality randomised studies in this appraisal, therefore, it is important that all available data is considered for use in any evidence synthesis including non-randomised and non-comparative data.

BTG would like to raise particular concern around the AG failing to use alternative techniques, which may have provided a more robust method for comparison. In order to provide the committee with suitable evidence on which to base their decisions for this patient group, we

request that the AG revisit the decision not to undertake this NMA and undertake the analysis using appropriate techniques to include both randomised and non-randomised evidence.

2.1.4 Summary

The AG considered patients with early stage disease in Network 1: People with unresectable HCC who are eligible for transplant. BTG believe that SIRT is also potentially suitable as curative intent for early stage disease patients (as radiation segmentectomy, radiation lobectomy and downstaging for resection or ablation). We accept that the AG did not carry out an NMA in this patient population, due to a lack of data, which is a sensible approach. However, BTG believe that non-comparative evidence, which the AG did not consider, provides support for the use of TheraSphere in specific early stage patient groups. Guidelines emphasise that treatment for HCC should be individualised to each patient to ensure optimal outcomes and BTG would like TheraSphere to be included in this patient population for those people likely to benefit from treatment. We suggest consideration of the Cancer Drugs Fund for this population, enabling a choice of therapy while further data is collected.

The AG considered patients with intermediate disease in Network 2. People with unresectable HCC who are eligible for CTT. This network would have compared SIRT with CTT. BTG believe that the AG's rationale for not carrying out an NMA for Network 2 is flawed and request that the AG revisit their decision and undertake the analysis using appropriate techniques to include both randomised and non-randomised evidence.

In patients with intermediate disease, guidelines (1) consider CTT as first-line treatment, with SIRT as an alternative option. In line with this guidelines, clinical opinion suggests that the patients likely to benefit most from SIRT are patients with intermediate disease in whom CTT is unsuitable (two failed TACE or tumours $\geq$7 cm). At present, there are no alternative treatment options in this patient group before progression to palliative systemic therapy.

2.2 Critique of AG economic modelling

The AG model only considers SIRT in the CTT-ineligible population, limiting the use of SIRT to people unable to receive CTT (the advanced/palliative population). Their model includes curative therapy as a scenario as part of the same model (AG report Figure 14 page 175).

The AG state when introducing their model that the evidence base is very limited (AG report page 172). We agree that developing any economic model in this therapy area is challenging, however, we believe the AG model is based on a number of fundamental conceptual errors:

1) That a single framework can be used to capture the costs and benefits of treatments in individuals who receive curative or palliative therapy
2) The patient population and comparators covered by the modelling is misaligned with the scope of the appraisal
3) That the clinical efficacy (PFS and OS) is assumed to be identical for all forms of SIRT (SIR-Spheres, TheraSphere, QuiremSpheres)
4) A mixed approach is used to capture state occupancy for each treatment; some are modelled independently and others via relative effects
5) The source data for SIRT PFS and OS is stated as pooled from two trials (AG report Table 29 page 175) but it is unclear how these data are derived

We expand our thoughts on numbers three to five in the section of this response relating to TheraSphere in the palliative intent group. Our detailed thoughts on numbers one and two are outlined below in Sections 2.2.1 and 2.2.2.

2.2.1 The use of a single framework for both curative and palliative intent is not appropriate given fundamental differences in the patient pathways for each group

The final appraisal scope issued by NICE for the assessment of SIRT for treating HCC gave all consultees a clear steer that they viewed this population as being made up of two mutually exclusive sub-populations: To use our preferred notation, these groups can be referred to as curative intent and palliative intent. The scope listed distinct comparators to SIRT in each of these groups.

The AG developed a single model to facilitate their economic analysis of SIRT in both of these distinct patient groups, based on a common conceptual framework. The AG used the conventional "three state" model used in many evaluations of late stage oncology products. The states were defined as 'alive and pre-progressed', 'alive and progressed' and 'dead'. However, this approach is unsuitable since people classified as meeting the criteria for palliative or curative intent therapy have distinct treatment pathways.

The primary purpose of treatment in people diagnosed with early and some intermediate HCC is tumour downstaging or organ stabilisation to facilitate access to one of several curative interventions including organ transplant, tumour resection or ablation. If an individual is indicated for an organ transplant, there is a period of time on a waiting list while a donor is found and also a period of convalescence post-transplant, while the body becomes accustomed to the new organ. Long term survival and relapse rates may also differ between these three curative options.

The AG model framework has the functionality for people to receive curative therapy, though this functionality is not used in the base case. However, there are no specific health states in the model to enable accurate modelling of the patient pathway outlined in the previous paragraph. Lifetime costs and benefits for these individuals are quantified using the same three-state framework as those who are receiving systemic therapy – with the states defined by progression status. Further limitations to this approach include:

- The baseline prognosis against which a hazard ratio (HR) is applied is derived in patients who meet the criteria for palliative and not curative intent (data from the SARAH trial – patients with unresectable, advanced (BCLC-C) stage HCC (7)).
- The HR used to generate survival benefit is derived from one US study which compared outcomes for patients who had received palliative care and those who received potentially curative therapies (such as liver transplant or resection). The HR used was for patients with late stage HCC.
- The model assumed differential OS following receipt of curative therapies depending on the initial treatment received. However, when critiquing Sirtex's model, the AG state they received expert advice stating that outcomes would be the same post-curative therapy, regardless of previous therapy received, therefore OS post-curative therapy should not differ depending on the initial treatment received (AG report, page 137).

This framework has no relevance to a group of people who have potentially had their tumour or entire liver removed in a curative intervention. A model of this group should distinguish between

those who have active HCC and those who do not, and the failure of the AG model to do this is a fundamental flaw.

Therefore, we believe that the committee should not use the AG model for the basis of decision making in this patient population. The only model that attempts to model the patient pathway in this patient group is the BTG model (Sirtex submitted a simple cost-minimisation model). As such, the BTG model is the only model which can give committee meaningful cost-effectiveness estimates in this group.

2.2.2 The patient population and comparators covered by the modelling are misaligned with the scope of the appraisal

Despite the scope of appraisal setting out three distinct sub-populations: early, intermediate and advanced HCC (AG report, page 170), only one of these populations (advanced) was addressed by the AG model in the base case. This decision was explained by a lack of data in the other two populations.

Our thoughts on the validity of choosing not to complete the 'intermediate' network (Network 2) are noted above. In the scenario analysis to the AG model which considered the curative intent group the comparators were SIRT, lenvatinib and sorafenib, which makes little clinical sense.

Therefore, the AG have not provided the committee with any economic evidence for the cost-effectiveness of SIRT compared cTACE, DEB-TACE and TAE in any patient population. As this is an MTA, common convention would be to generate fully incremental analyses containing both interventions and comparators. In the curative intent population, this would mean comparing all SIRTS and all TACE options as well as best supportive care since it is possible that none of the SIRTs or the TACEs represent good value for money. The AG have not given the committee any economic evidence on which to base such decisions. This is particularly important because SIRT is recommended as an alternative treatment to CTT (cTACE, DEB-TACE and TAE) in patients with intermediate stage disease in the ESMO guidelines. This is echoed by clinical advice sought by BTG as part of their consultation process around the AG report, which suggested that '*SIRT is best used in intermediate stage patients that have either failed TACE or who have lesions ≥7 cm'*.

Whilst we agree that more robust evidence is required to make confident decisions, we would urge the committee not to disregard the company models in this sub-population. Only the BTG model can be used as the basis for decision making in this patient group.

2.3 Responses to AG critique of BTG modelling

We readily acknowledge that the BTG model has several limitations, primarily as a consequence of sub-optimal data. However, we feel strongly that a distinct model framework is needed to model patients with early and intermediate disease. We believe that the BTG model will be of considerable value to the committee in making their decision.

We feel that our underlying conceptual model is an accurate reflection of the UK patient pathway for individuals with HCC classified as eligible for curative intent. We consulted widely with UK and international clinicians on the model structure and believe that it is both robust and realistic.

We have addressed the AG's key concerns within the BTG curative intent model below. We have also re-run our model based on the expressed preferences of the AG in order to provide committee with the best available estimates of cost-effectiveness in this patient population.

Please note the following: for all amendments and scenario analyses a work-up cost of £860.32 is used; all results presented are discounted and a minor calculation error in utilities has been corrected.

2.3.1 The assumption that all downstaged patients go onto the transplant wait list, with no resections

The BTG model included the assumption that resections would not be carried out on downstaged patients and all patients would join the wait list for a liver transplant instead. This assumption was made for simplicity, on the basis of clinical advice which suggested that few resections are carried out in favour of transplants (BTG submission, Section 6.1.1.3.1, page 118). The AG commented (AG report, page 149) that our assumption is inconsistent with the clinical advice that they received, and that they believe a split between transplants and resections to be more appropriate.

Included in the BTG original submission was a scenario analysis where 50% of downstaged patients transition to resection (BTG submission Appendix P, Table P5 and P6). The impact of this amendment was a change in the ICER for TheraSphere from £25,062 to £31,851 per QALY gained. When interpreting these results, please note that there is an assumption in the model of a 75% “success rate” for liver resections as a curative treatment for HCC, with a further 5% per cycle recurrence rate for those individuals who have an initially successful resection. The fully incremental results of this analysis are reported in Appendix A.

2.3.2 Modelling of pharmacological management

The AG questioned (AG report, page 150) the appropriateness of the assumed split between pre-progressed and post-progressed patients in the pharmacological management state, set at 50:50 in the base case. It was suggested by the AG that 33:67 was a more realistic split; this was applied in a scenario analysis. In isolation, the impact of this amendment on the model was a nominal change in the ICER for TheraSphere from £25,062 to £25,739 per QALY gained. The fully incremental results of this analysis are reported in Appendix A.

2.3.3 The omission of SIRT work-up failures from the model

The title of this appraisal is SIRT for treating HCC, we believe that the assumption that the appraisal covers individuals who are eligible for treatment with SIRT is implicit in this title. In practice, this means that patients have been identified as potential candidates for treatment based on clinical criteria and clinician experience and have undergone, and successfully completed, a work-up programme for this treatment option.

The AG noted that work-up failures were not included in the BTG model (AG report, page 150). We agree that it is appropriate to include the costs of these failed work-ups in the model, as they are attributable to the introduction of SIRT to the treatment pathway. We do not consider it a reasonable suggestion, however, that the efficacy estimates of TheraSphere should incorporate the inferior outcomes of individuals who are deemed ineligible for SIRT during the work-up phase. These patients would be expected to go on to receive an alternative treatment option and thus do not enter the TheraSphere arm in the model. BTG views the question of which treatments are cost-effective in this sub-population as a separate decision problem to that being evaluated during this appraisal.

We accept that we did not inflate the cost of work-up in our original submission and an amendment has been made to the BTG model.

Firstly, the number of units of work-up received by each patient in the model was amended from 1 to 1.05, in light of the newly available evidence from the Sirtex clinician survey (AG report, Table 49). Then, adopting the 81.4% "pass rate" from the SARAH trial data as used in the AG model (AG report, Table 32), it was estimated that for every patient who goes on to receive SIRT following the work-up there are 0.229 patients who do not. These hypothetical patients are not included in the model but the cost of the additional work-ups (1 per person) is accounted for.

The impact of this change to the model, in isolation, was a nominal change in TheraSphere's total per patient lifetime costs from £57,731 to £58,017 and a corresponding nominal change in ICER from £25,062 to £25,454 per QALY gained. The fully incremental results of this analysis are reported in Appendix A.

2.3.4 Age-adjustment of utilities

The AG believe the estimation of age-adjusted utilities is incorrect in the BTG models. However, we believe that we have used a standard method. However, we have adopted the alternative AG method in a scenario analysis. We also noted a minor error where the age at each cycle was calculated on the basis of a monthly cycle, rather than 4 weeks. This was corrected at this stage and all the new results are presented from the corrected model.

The isolated impact of this amendment was substantial: the ICER of TheraSphere changed from £25,062 to £17,665 per QALY gained. The fully incremental results of this analysis are reported in Appendix A.

2.3.5 Transplant wait list

As raised by the AG in their critique of the BTG model, median time spent on the transplant wait list was estimated from a cohort of people not specific to HCC. The AG obtained data on wait list times that are specific to HCC patients, which we agree is far preferable for use in the model. Transition probabilities in the model were amended based on the median waiting time given by the AG (AG report, page 152).

In isolation, this amendment resulted in a change in the ICER for TheraSphere from £25,062 to £24,078 per QALY gained. The fully incremental results of this analysis are reported in Appendix A.

2.3.6 Summary

The AG's criticisms of BTG's model do not highlight any critical structural weaknesses. Therefore, in the absence of a model developed by the AG for early and intermediate disease, we recommend that the BTG model is used to guide decision making around SIRT as a curative intent therapy. It is undeniable that confidence in the model results is limited by poor quality data. However, we maintain that the structure is a fair representation of the treatment pathway for the patients it is intended to model and is predicated on clinically valid assumptions. The minor criticisms raised by the AG have been addressed wherever possible, and updated results are summarised in Table 2 below.

The original base case presented in the BTG submission was an ICER of £24,647 per QALY gained. After correcting errors and taking into account the AG's input, the aggregated updates to the model produced an ICER for TheraSphere of £23,479 per QALY gained. This is not a substantial change from the original results and further strengthens the argument that TheraSphere has the potential to be a cost-effective treatment for this sub-population, in a variety of scenarios.

Table 2: Summary table of results from BTG curative intent model when parameterised using AG preferred data or methods

Scenario	**ICER (cost per QALY)**
Original base case	£24,647
Original base case with updated work-up cost (£860.32) and calculation error corrected*	£25,062
50% of downstaged patients receive resection	£31,851
33:67 split in progression status of patients in pharmacological management	£25,739
Inflated work-up costs	£25,454
Age-adjusted utilities calculated according to AG method	£17,665
Reduced transplant wait list time according to AG data	£24,078
All of the above changes aggregated	£23,479

*This correction was maintained for all other amendments

3. Response to AG assessment of TheraSphere in the palliative intent patient group

3.1 Clinical evidence

3.1.1 International guidelines

For patients with advanced disease (stage C) and some patients with intermediate disease (stage B) treatment is palliative. For these patients systemic treatment: sorafenib (first-line), lenvatinib (first-line) and regorafenib (second-line) are the standard of care. SIRT is recommended as an alternative treatment for those patients unable to take systemic treatment due to severe systemic side effects or contra-indications. CTT are not recommended for these patients. Patients with PVT are considered to have advanced disease and are particularly challenging to treat.

The AG considered these patients in Network 3: Adults with unresectable HCC who are ineligible for CTT.

The AG states that *The most likely position for SIRT in the HCC treatment pathway is for patients with intermediate (BCLC stage B) or advanced (BCLC stage C) stage HCC as a non-curative option, as the use of SIRT is not precluded by reduced liver function as strictly as CTTs*. (AG report, page 31).

This positioning is supported by clinical evidence using PDA to deliver TheraSphere, which indicates that outcomes are significantly improved with this method of delivery. A study by Garin et al in HCC patients with PVT (n=41) revealed a significant improvement in OS with PDA (>205 Gy) versus SDA (<205 Gy): 18.2 months versus 4.3 months, p<0.005 (5). Further work by Garin et al (6) in a mixed intermediate/advanced disease population showed significantly improved OS in patients receiving PDA versus SDA: median OS of 15.7 months versus 4.35 months, p=0.0004 in the PVT population.

3.1.2 AG description/ interpretation of relevant studies

The AG carried out a systematic literature review (SLR) and identified 27 studies across all HCC populations (AG report Figure 1, page 41 and Table 3, page 42). The AG identified several additional studies which were not identified in the BTG submission (Maccauro, 2014 (14) and d'Abadie, 2018 (15)).

However, non-comparative trials included in the BTG submission were not identified or included in the AG report. The study design mentions inclusion of non-comparative studies (page 36) but on page 39 of the report the AG state that there were 176 comparative studies and the decision was made to focus on these. We believe that given the paucity of data, non-comparative studies may provide additional evidence and direct the AG to Table 4-2 (page 28) and Table 4.3 (page 29) which provide an overview of the TheraSphere studies providing evidence for OS and PFS respectively.

3.1.3 AG evidence synthesis

Network 3 – individuals with unresectable HCC who are ineligible for CTT (AG report, section 5.3) is relevant here. The full network presented in Figure 3 (AG report P.82) contains four treatments and is designed around three randomised studies and five 'retrospective' studies. The AG removed three of the five retrospective studies comparing sorafenib to SIR-Spheres *"due to*

already having identified high quality RCTs [for this comparison]" (AG report page 83) to generate the final network for this patient group (AG report Figure 4 page 84). The final two retrospective studies, Biederman and Van Der Gucht, which link TheraSphere with the network via SIR-Spheres were excluded from the base case due to poor quality and concerns around face validity but were included as a sensitivity analysis.

However, as mentioned previously, methods exist to combine randomised and non-randomised evidence in an NMA, meaning that the five studies excluded from the base case should not have been excluded. In particular, removal of these studies meant that the AG were forced to assume that all three SIRTs have a common relative treatment effect compared to sorafenib in the economic modelling, since only results for SIR-Spheres are generated. This is a limitation of the AG NMA.

The impact of these decisions can be seen by comparing the outputs for OS from the base case analysis (AG report Tables 11 and 13, page 96 and page 99) and sensitivity analyses (AG report Tables 14 and 16, page102 and page106). For convenience, these results are reproduced in Table 3. Bold values correspond to statistically significant differences.

Scenario 1a in the Table below reflects inclusion of the two retrospective studies, Biederman and Van Der Gucht (Scenario 4 in the AG report, pages 198-199) and scenario 1b reflects the inclusion of Biederman alone (Scenario 1 in the AG report, pages 99-100). These two scenarios allow TheraSphere be included in the NMA.

Table 3: Results from AG Network 3 (base case and sensitivity analyses) reproduced from tables 11,13,14,16 in AG report. All values mean and 95% credible intervals and derived using fixed effects models.

Intervention	Comparator	Base case (PP)	Base case (ITT)	Scenario 1[a]	Scenario 1[b]
SIR-Spheres	Sorafenib	0.94 (0.78-1.14)	1.13 (0.96-1.32)	0.94 (0.77-1.13)	**1.14 (1.01-1.28)**
SIR-Spheres	Lenvatinib	0.91 (0.63-1.26)	1.09 (0.77-1.48)	0.91 (0.63-1.26)	1.10 (0.80-1.48)
Lenvatinib	Sorafenib	1.06 (0.79-1.40)	1.06 (0.79-1.40)	1.06 (0.79-1.40)	1.06 (0.79-1.40)
TheraSphere	SIR-Spheres	N/A	N/A	**0.44 (0.20-0.84)**	**0.46 (0.28-0.72)**
TheraSphere	Sorafenib	N/A	N/A	**0.41 (0.20-0.77)**	**0.53 (0.31-0.84)**
TheraSphere	Lenvatinib	N/A	N/A	**0.40 (0.18-0.78)**	**0.51 (0.28-0.86)**

PP: Per Protocol; ITT: Intention To treat; N/A: Not Applicable; a) Inclusion of Biederman et al. into PP base case; b) inclusion of Biederman et al. and Van Der Gucht et al. into the ITT base case.

To assist the committee in interpreting and contextualising these values, we have reproduced the relevant results from the BTG meta-analysis in Table 4 below. We have reproduced our base case values as well as the meta-regression outputs for individuals categorised as BCLC-C or with PVT as these align more closely with the patient definition underpinning AG Network 3. Bold values again correspond to statistically significant differences.

Table 4: Results from the BTG network meta-analysis. All values mean and 95% credible intervals and derived using fixed effects models (original information in BTG submission, Table K3, Appendix K)

Intervention	Comparator	Base case	BCLC-C	PVT
TheraSphere	SIR-Spheres	**0.62 (0.40-0.99)**	**0.58 (0.36-0.95)**	**0.59 (0.36-0.93)**
TheraSphere	Sorafenib	0.70 (0.44-1.12)	0.63 (0.39-1.04)	0.62 (0.36-1.01)
TheraSphere	No treatment	**0.55 (0.35-0.87)**	**0.50 (0.31-0.82)**	**0.48 (0.29-0.79)**

We agree that Biederman and Van der Gucht are of low quality, however, we believe that the AG's concerns about the unrealistic OS benefit with TheraSphere can be allayed by evidence from other studies. The AG were particularly concerned about the OS in Biederman (AG report, page 99) which showed a much stronger treatment effect on OS with TheraSphere compared to SIR-Spheres (9.5 months with TheraSphere vs. 3.7 months with SIR-Spheres). Biederman was in patients with PVT therefore we have reviewed OS with TheraSphere and SIR-Spheres in studies with similar patient populations.

Looking first at the OS of 9.5 months with TheraSphere

- Four non-comparative studies reported OS in patients with PVT (Abouchaleh *et al.* 2018 (16): Kokabi *et al.* 2015 (17); Kulik *et al.* 2008 (18) and Pracht *et al.* 2013 (19)) and reported OS of 4.6 months to 14.3 months.
- Five studies reported OS in patients with PVT as sub-group analyses (Woodall *et al.* 2009 (20), Ali *et al.* 2017 (21), Garin *et al.* 2017 (6), Mazzaferro *et al.* 2013 (22), Salem *et al,* 2010 (23)) and reported OS of 3.2 months to 13 months.

These studies provide supporting evidence, with the caveat that studies were small and populations heterogenous (BTG submission, page 43, 44, Table 4.7 and Table 4.8).

Turning to the OS of 3.7 months with SIR-Spheres, evidence is more variable.

- In SIRveNIB (Chow *et al,* 2018 (24)), which was used in Network 3, subgroup data for patients with advanced disease (PVT) was provided in a data supplement – OS was 5.3 months in those patients receiving SIR-Spheres, suggesting that the OS of 3.7 months with sorafenib in Biederman is not unrealistic.
- In SARAH, also used in Network 3, median OS with SIR-Spheres was 8 months (overall mixed intermediate and advanced population). A proportion of patients in SARAH had PVT which we can use as a proxy for advanced disease. Unfortunately, the published paper does not include OS for subgroups, but a Forest Plot indicates that patients with PVT (complete occlusion in the main portal vein) show greater benefit with sorafenib than with SIR-Spheres, suggesting that OS for this group is shorter than 8 months.

The differences in baseline PVT, patient populations and treatment post-SIRT make the SIR-Spheres and TheraSphere data extremely difficult to compare. However, allowing for potential methodological limitations in the studies on which both analyses are based, themes around the relative efficacy of all products emerge:

- It is likely that TheraSphere and SIR-Spheres are **not equivalent** in terms of impact on OS, with all five NMAs demonstrating statistically different outcomes for both treatments
- TheraSphere may offer greater benefits than sorafenib, with results from two of the five NMAs being statistically significant, and those from two others marginally non-significant

Of note, the relative efficacy values for TheraSphere from the BTG NMA are, in general, smaller than those from the AG analysis, suggesting that were the AG values used in the BTG economic model, the ICER would be lower than in the BTG base case.

3.1.4 Summary

In patients in whom treatment is viewed as palliative rather than potentially curative, we ask that the committee consider inclusion of TheraSphere into the base case NMA for Network 3. Data from Scenario 1 and 4 (inclusion of Biederman and Van Der Gucht) of the AG NMA and the NMA

developed by BTG all show a difference between TheraSphere and SIR-Spheres. We accept that Biederman and Van Der Gucht which link TheraSphere to SIR-Spheres in the network are not high quality RCT, however, a body of evidence suggests that TheraSphere and SIR-Spheres are not equivalent in terms of their impact on OS.

3.2 Critique of AG economic modelling

Of the list of key concerns with the AG model (see Section 2.2 above), three relate primarily to the cost-effectiveness modelling in the palliative intent patient group. Our rationale for raising these concerns with committee are outlined below.

3.2.1 Equivalency of efficacy across all SIRTs

The AG model assumes that all SIRTs are equivalent in terms of OS and PFS, such equivalence is maintained in the economic model via the use of HRs of one being forced for TheraSphere PFS and OS versus SIR-Spheres in both the deterministic and probabilistic analyses (Model worksheet Parameters cells N13 and N19). The approach used by the AG to generate model outputs for QuiremSphere seems curious since there is no model engine relating to this comparator, with results being assumed to be the same as for SIR-Spheres (see cells L42:L45 on the Results worksheet).

As discussed above, there is a plausible argument, even accounting for the limitations of the studies included in the analyses, that this assumption of equivalence is not certain. We would like to remind the committee that in the NMAs undertaken by the AG and BTG, there was a consistent, statistically significant difference between the HRs for SIR-Spheres and TheraSphere when comparative evidence for TheraSphere was included.

This potential difference in efficacy is supported by differences between the two SIRTs. Although TheraSphere and SIR-Spheres both use Y^{90} as the active isotope, differences in physical composition (glass versus resin) mean that TheraSphere has a higher specific activity than SIR-Spheres (AG report, page 32 Table 2) of 2,500 Bq/sphere versus 50 Bq/sphere. TheraSphere are smaller than SIR-Spheres, which means that TheraSphere delivers a higher dose of radiation with relatively fewer, smaller microspheres than SIR-Spheres, limiting macrovascular damage and maximising radiation dose (BTG submission, page 17).

3.2.2 The use of a mixed approach to modelling state occupancy is conceptually flawed

The AG explicitly state that PFS and OS for SIR-Spheres and sorafenib are modelled independently (AG report, page 172 Table 29), with the HRs from the AG NMA for lenvatinib compared to sorafenib being used to generate an estimate for that comparison. As stated above, there is an explicit HR of one used to capture the benefits of TheraSphere over SIR-Spheres and there is no formal model engine for QuiremSpheres.

This approach is both highly unusual, and conceptually flawed – especially when undertaking the PSA. In such an analysis, PFS and OS for both SIR-Spheres and sorafenib are assumed to vary independently of each other when sampling for state occupancy (i.e. no relationship between the two treatments) but at the same time a formal relationship between the survival estimates for sorafenib and lenvatinib is explicitly assumed (via the use of a HR). We believe this may be the source of the programming error in the lenvatinib engine where it is possible, for some iterations of the PSA, for there to be more patients in the PFS state than in the OS state (and hence negative numbers of patients in the PD state).

This approach also means a likely key driver of cost-effectiveness (the relative treatment effects for SIRTs versus sorafenib) are not included in the deterministic sensitivity analysis (AG report section 8.4.2.2). Such a fundamental omission calls into question the usefulness of the Tornado plots from a decision-making perspective.

What is more puzzling about this choice of modelling approach is that the AG generated relative treatment effects for sorafenib, lenvatinib and SIR-Spheres in their NMA and the data on which these estimates are based map almost entirely onto the data used in the independent modelling. This means that it was entirely possible to construct the model in way that allows for a meaningful interpretation of base case results and any sensitivity analyses (probabilistic and deterministic). In particular, it is possible in the AG model to pick one intervention (e.g. sorafenib) and include relative effects for all other interventions for that product.

Further inconsistencies in the justification for the mixed modelling approach can be found in the description of the parametric survival analyses used to extrapolate the pooled data described for PFS and PFS. The TAG correctly state that accelerated failure time (AFT) models were consistently the best statistical fit to the data, and Figures 15 and 16 of the AG report (page 178-179) show there is no substantive difference in long term predictions for any of the trialled distributions. Nonetheless, the rationale given for choosing to use Weibull functions was "*To accommodate the use of HRs*" in their base case analysis (AG report P. 178). This makes the non-use of such HRs, especially when they are available even more puzzling.

As discussed earlier, the justification for assumption of equivalence of efficacy "*a lack of randomised evidence on the relative effectiveness of each SIRT*" (AG report page 176) is misleading. We would like to make committee aware that the functionality to parameterise the model in this way is already included in the framework and we strongly request that committee use a model based on this form of parameterisation in their decision making.

To aid the committee, we have used the AG model to generate ICERs using the relevant outputs from the AG NMA and the BTG NMA. These are presented in Table 5 and Table 6 below. In both situations, the ICER generated for TheraSphere is lower than the cost-effectiveness threshold stated in the NICE methods guide (25).

Table 5: AG model results from Biederman and Van Der Gucht NMA scenario (taken from AG report)

Intervention	**Total costs**	**Total QALYs**	**ICER (fully incremental)**
Lenvatinib	£30,005	0.805	
SIR-Spheres	£30,107	0.764	Dominated
Sorafenib	£32,082	0.841	Ext. Dom
TheraSphere	£33,373	1.297	£6,835
QuiremSpheres	£36,503	0.764	Dominated

*Table 6: AG model results using BTG NMA OS HRs (results taken from model)**

Intervention	**Total costs**	**Total QALYs**	**ICER (fully incremental)**
Lenvatinib	£27,894	0.577	
TheraSphere	£29,266	0.679	£13,441
SIR-Spheres	£29,484	0.679	Dominated
Sorafenib	£32,082	0.841	£17,422
QuiremSpheres	£35,880	0.679	Ext. Dom

* We are aware these figures may be slightly different to the true results due to some AIC data being removed from the AG model

3.2.3 The AG method for pooling of PFS and OS data from SARAH and SIRveNIB is potentially misleading

The use of pooled data on which to base a formal parametric survival analysis is an established and acceptable approach, however, we would like to make clear that when such an approach is used, the method for pooling the data should be transparently reported. Beyond stating that the source Kaplan-Meier data were taken from a published study (24) and from data provided by Sirtex as part of their submission no additional information is provided by the AG in their dossier. A close review of the model is not helpful as the relevant information is a series of hard coded numbers (Worksheet 'Data tables' cells L199:L280 and cells L302:M372).

As such, it is unclear how the following elements were incorporated into the analyses:

- The transformation of the Kaplan-Meier information back into individual or quasi-individual patient level data
- The number of individuals contributing data to the pooled curve at each time point. This is important as dropout and censoring will be occurring at different rates in each study, meaning that it is highly unlikely that the ratio of individuals in the study at time T=0 is constant for all time points
- The aggregation of uncertainty around each of the pooled Kaplan-Meier time points

Without such information, it is not clear that data have been correctly synthesised, which in turn has potential implications on the choice, and parameterisation of, statistical function used to generate long term state occupancy estimates, and hence the ICERs. We therefore request that the AG make this information available to committee and to all stakeholders.

3.3 Response to AG critique of BTG modelling

The AG group expressed criticism of various elements of the BTG palliative intent model. Our responses to these concerns are outlined below, as with our responses to concerns about the BTG curative intent model and where necessary, we have re-run the BTG model containing AG preferred assumptions or data.

3.3.1 Calculation errors

The error relating to the per-cycle mortality and progression has been corrected in our version of the model, which changed the TheraSphere ICER from £66,641 to £75,913 per QALY gained. The AG also mentioned an error in relation to the estimation of the comparator time to progression (TTP). Unfortunately, the AG did not detail the error and therefore we do not know if we can agree on it being an error and have no mechanism to correct it.

Whilst running additional analyses we also noted a minor error in relation to the age-adjusted utility calculations where the age at each cycle was calculated on the basis of a monthly cycle, rather than 4 weeks. This was corrected at this stage. The impact of this change was negligible, with the ICER remaining at £75,913 per QALY gained.

The results presented from this point forward are from the BTG model with these two errors corrected, and the updated work-up cost BTG presented in their initial responses to clarification questions, of £860.32.

3.3.2 Inclusion of regorafenib as a comparator

The assessment group suggested that the inclusion of regorafenib as a comparator in this model is inappropriate since it is recommended only as a second-line therapy following sorafenib. We agree with the AG and have removed regorafenib as a comparator in a scenario. This reduces the TheraSphere ICER from £75,913 to £66,854 per QALY gained. The fully incremental results of this analysis are reported in Appendix B.

3.3.3 Work-up without SIRT procedure

The AG stated that people who received work-up but did not continue on to the SIRT procedure should have been included in the analysis. This was based on evidence in the SARAH and SIRvenNIB trials where 18.6% and 28.6% of patients received work-up but not SIRT. Firstly, these figures are both from SIR-Spheres data, rather than TheraSphere data. We should be wary in assuming that both SIRTs have the same proportion of people who do not continue to have the SIRT procedure. Secondly, as previously described in relation to BTG's curative intent model, as it is the cost-effectiveness of SIRT which is being assessed, those who are ineligible for SIRT are a different decision problem.

However, taking into consideration that the cost of work-ups to the NHS of those people who do not go on to have SIRT, further analysis has been conducted as described in Section 2.3.3. The data from the SARAH trial (a failure rate of 18.6%) was used since SARAH was carried out in a European population, rather than data from SIRvenNIB which was carried out in an Asian population. With an initial work-up cost of £860.32, this increases the ICER from £75,913 to £77,328 per QALY gained. The fully incremental results of this analysis are reported in Appendix B.

3.3.4 Limited exploration of uncertainty surrounding survival functions

As highlighted by the AG, a number of parametric functions were fitted to the available data for OS in our model. The distribution selected was that which was most clinically plausible, whilst also taking statistical fit into consideration (the AIC and BIC values). We believe that it is not necessary to explore the impact of alternative parametric functions on cost-effectiveness as scenario analyses. Exploring alternative parametric functions would mean that we would, for example, be generating ICERs for parametric functions which we know are either poor fits to the data or generate implausible long-term clinical predictions.

The methods used by BTG to select the parametric functions used in our model, including tables of AIC and BIC estimates are provided in our submission (BTG submission, Section 6.1.2.3.1 and Section 6.1.2.3.2 and Appendix I, Table I1 and I2).

3.3.5 Omission of downstaging

As noted in this response, and also in our original submission, there are two mutually exclusive patient populations. The appraisal scope defines them as potentially resectable and unresectable whereas BTG, in line with clinical practice, refers to them as curative intent or palliative intent populations (or TAE-eligible and TAE-ineligible).

In line with this clear clinical distinction between the two groups, the BTG partitioned-survival model did not include the possibility that palliative intent patients may be downstaged to receive curative therapy. The AG themselves state it would be very rare in UK practice in this patient population, where TheraSphere is used with palliative intent and not curative intent. They further criticise Sirtex's submission and point out that no previous TAs which assessed systemic cancer

treatments for advanced HCC have modelled the possibility of curative therapies (AG report, page 137). We believe that it would not be a good representation of clinical practice to include downstaging in the palliative intent model and that it would be of little use for decision making in this particular patient population.

Modelling for the curative intent population was carried out by BTG; as discussed earlier BTG were the only organisation (including the AG) to model this patient population.

3.3.6 Systemic therapy dosing

The AG suggest that dosing of systemic therapy is potentially overestimated in the model. Therefore, the mean dose of sorafenib, regorafenib and lenvatinib were updated in order to match the cycle costs in the AG model. This reduces the ICER from £75,913 to £68,223 per QALY gained.

However, if the number of tablets a day were rounded up to incorporate wastage (e.g. an average of 3.2 tablets for sorafenib rounded up to 4), this leads to same overall dose as recommended in the BNF, leading to no difference in cycle costs.

3.3.7 Subsequent therapy costs

The AG suggested that it is not typical clinical practice for a proportion of people to receive systemic therapies directly after receiving SIRT, before disease progression. "*The AG considers the modelling of subsequent therapy in this way to be inconsistent with likely NHS practice and the supporting trial evidence, and that typically initiation of systemic therapy following SIRT would occur following disease progression*" (AG report, page 165).

In the UK, TheraSphere is currently commissioned by NHS England (Specialist Commissioning) in a salvage setting in colorectal cancer metastases for a limited number of patients and is not in commonly used within the NHS in HCC. When used in HCC it is typically provided on a compassionate basis given the current lack of NHS funding for this indication. In their original model, BTG assumed that systemic treatment was maintained until disease progression, at which point patients would switch to best-supportive care (BSC) (with no treatment costs).

Clinicians consulted as part of the consultation process undertaken by BTG in responding to the AG report clarified subsequent treatment patterns. They suggested that patients would receive systemic therapy on progression, rather than directly after SIRT. Disease progression would be unlikely to be identified before around 6-9 months post-SIRT.

In light of the AG's thoughts and new information from clinicians using SIRT in the UK, the following scenario analyses were carried out using the BTG model, matching the proportions of subsequent systemic therapy that were utilised in the AG model (as referenced below).

Scenario 1a: Subsequent therapy at the point of progression

- Post-SIRT: systemic therapy after SIRT at progression, where 27.4% of patients then receive sorafenib, 1.4% receive lenvatinib, and the remaining BSC (AG report, Table 32)
- Sorafenib: 12% move on to regorafenib at progression and the remaining to BSC (AG report, Table 32)
- Lenvatinib: 100% to BSC at progression (AG report, Table 32)
- In this scenario regorafenib remains in the model, and 100% move to BSC at progression

With these changes, the TheraSphere ICER decreases from £75,913 to £14,569 per QALY gained.

Scenario 1b: Subsequent therapy at the point of progression, removing regorafenib as a comparator

Removing regorafenib as a comparator leads TheraSphere to become dominant against all comparators.

Scenario 2: Subsequent therapy pre-progression – when regorafenib remains as a comparator

The AG acknowledge that a proportion of patients within the SARAH trial received systemic therapy (post SIRT) prior to progression (AG report, Section 6.3.4.3, page 166), though it is unknown when this treatment was started.

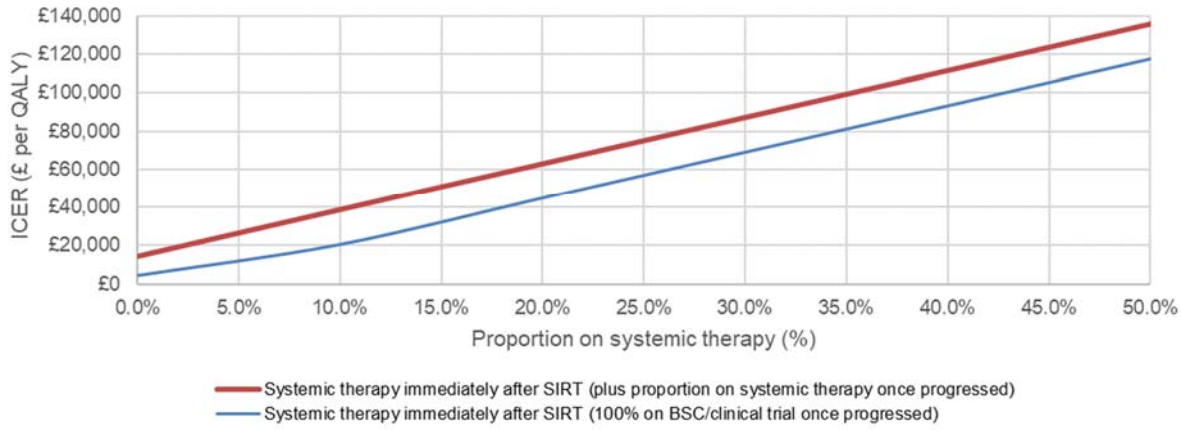
With the possibility that a proportion of patients would receive subsequent systemic therapy before progression, we ran a further scenario:

- 21% of patients (stated by the AG as the proportion of patients who received sorafenib before progression from the SARAH trial (AG report, page 166)) receive subsequent systemic therapy after receiving SIRT (with the assumption of an immediate start). We have assumed that 95% of these patients receive sorafenib and 5% receive lenvatinib (matching the AG model (AG report, page 187).
- Patients in the systemic therapy arms stay on systemic therapy until they progress.
- SIRT patients - 100% move on to BSC once progressed.
- In the sorafenib arm, 12% move on to regorafenib at progression and the remaining to BSC (AG report, Table 32).
- Lenvatinib: 100% to BSC at progression (AG report, Table 32).

With these changes, the TheraSphere ICER changes from £75,913 to £47,348 per QALY gained. The fully incremental results of this analysis are reported in Appendix B.

We have also created the graph below to illustrate the effect on the TheraSphere ICER of varying the proportion on systemic therapy pre-progression after SIRT. The red line represents a scenario where all post-progressed patients move on to BSC, and the blue line a scenario where the proportions from scenario 1a remain in the model for post-progressed patients.

Figure 1: The effect on the TheraSphere ICER when changing the proportion of patients who receive subsequent systemic therapy after SIRT whilst pre-progressed



Scenario 3: Subsequent therapy pre-progression and post-progression – when regorafenib remains as a comparator

A third scenario was run which was a combination of Scenario 1a and Scenario 2 (with some patients receiving subsequent systemic therapy immediately after SIRT during pre-progression, and some patients receiving it once progressed (the respective proportions matching Scenario 1a and 3). With these changes, the TheraSphere ICER is £65,334.

3.3.8 Duration on systemic therapy

The AG comment that the duration patients are on systemic therapy is less than PFS, and "*using PFS as an indicator of treatment discontinuation may produce overestimates of ToT and consequently total drug acquisition costs for sorafenib, lenvatinib and regorafenib*". However, we believe that the AG's approach of using the mean duration to calculate a one-off cost for the systemic therapies in pre-progression is flawed and based on the following assumptions:

- Time on treatment is independent of time in state
- All drug costs are incurred in the first cycle – hence discounting is ignored
- All patients in the cohort are assumed to incur the average drug costs

This approach, particularly the first bullet point, leads to situations where time on treatment is longer than time in pre-progression in some probabilistic simulations. Therefore, we have not changed this in the BTG model.

3.3.9 Survival analysis

The AG considers there to be weaknesses to BTG's approach of calculating time to progression (TTP), and that the TTP value for TheraSphere lacks face validity (AG report, page 164). BTG consider the method to calculate PFS/TTP to be appropriate based on the level of evidence available. It is noted that some sources may have been missed when calculating median PFS.

The PFS HR used by the AG in their model was taken from the AG NMA base case and assumes that all SIRTS are equal in efficacy. BTG disagree with this approach and do not believe that these HRs are suitable for use in economic modelling.

However, the OS HR have been adjusted in the BTG model to match the AG scenario HR (as shown in Table 3 above, Scenario 1b – reported in Table 16 in the AG report) reduces the TheraSphere ICER to £59,321 per QALY gained when regorafenib is removed as a comparator. Further details of the results can be found in Appendix B.

3.3.10 Application of age-adjusted utilities

The AG believe the estimation of age-adjusted utilities is incorrect. However, BTG believe we have used a standard method. In light of the AG comments, we have used the alternative AG method in the additional analyses. We also noted a minor error where the age at each cycle was calculated on the basis of a monthly cycle, rather than 4 weeks, which has been corrected. The use of the AG preferred approach to generating age adjusted utility values reduces the TheraSphere ICER to £55,726 per QALY gained. Further details of the results can be found in Appendix B.

3.3.11 Summary

The original results from the BTG submission, with the updated work-up cost of £860.32, produced an ICER for TheraSphere of £66,641. After correcting errors and taking into account the AG's input, the aggregated updates to the model produced an ICER for TheraSphere of £30,591 per QALY gained (see summary Table 7 below). Clinical opinion and standard protocols suggest that patients receive systemic therapy on progression rather than directly after SIRT, if this assumption is modelled then the ICER falls still further to £6,077 per QALY gained. This strengthens the argument for the committee, that TheraSphere has the potential to be used to treat HCC with palliative intent.

As the proportion of patients on subsequent systemic therapy is a key driver of the ICER, we have also created the graph below to demonstrate the effect on the aggregated TheraSphere ICER when varying the proportion on systemic therapy during pre-progression after SIRT. The blue line illustrates a scenario where all post-progressed patients move on to BSC or clinical trial. The red line illustrates a scenario where the proportions from scenario 1 (in Section 3.3.7) remain in the model for post-progressed patients. With a proportion of patients receiving systemic therapy on progression, up to 11% of patients can receive subsequent systemic therapy after SIRT before the ICER rises above £20,000, and over 37% can receive subsequent systemic therapy after SIRT before the ICER rises above £50,000, the End of Life threshold.

Figure 2: The effect on the aggregated TheraSphere ICER when changing the proportion of patients who receive subsequent systemic therapy after SIRT whilst pre-progressed

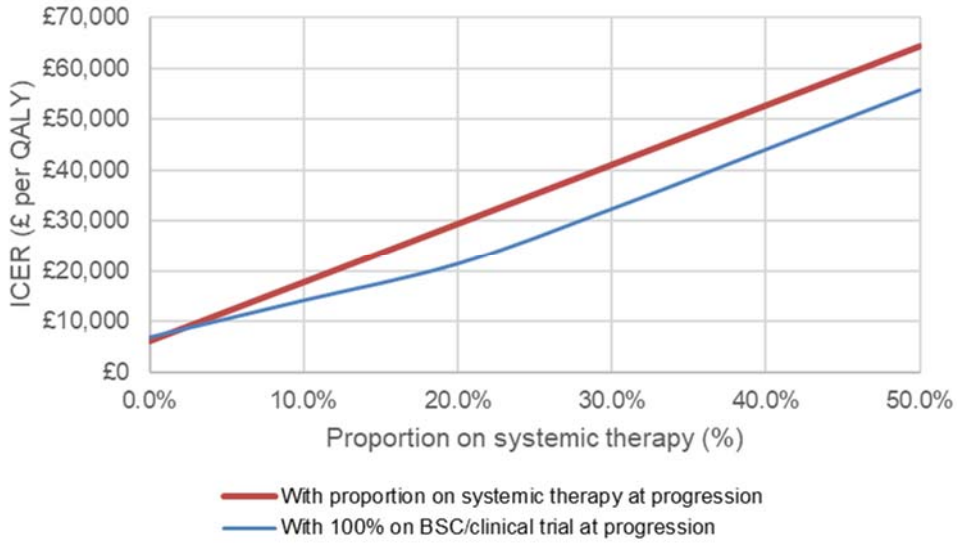


Table 7: Summary table of results

Scenario	ICER (cost per QALY)
Original BTG base case	£66,641
Original BTG base case with errors identified by the AG corrected*	£75,913
Regorafenib excluded as a comparator	£66,852
Work-up failure costs included	£77,328
Systemic therapy dosing updated	£68,223
Systemic therapy post-SIRT and post-progression updated Scenario 1a: Subsequent therapy at the point of progression Scenario 1b: Subsequent therapy at the point of progression (no regorafenib) Scenario 2: Subsequent therapy pre-progression Scenario 3: Subsequent therapy pre-progression and post-progression	 £14,569 Dominant £47,348 £65,334
HR updated with regorafenib removed	£59,321
Age-adjusted utilites updated	£55,726
All the above changes aggregated (using scenario 3 for systemic therapy)	**£30,591**
All the above changes aggregated (using scenario 1a for systemic therapy)	**£6,077**

* This correction was maintained for all other scenarios

Further to updated cost-effectiveness results, the incremental life years gained (undiscounted) results when all pooled alterations are included show an increased survival of over 3 months (5.5 months when compared with sorafenib and 6.5 months when compared with SIR-Spheres). Unlike the figures presented by the AG, these figures suggest that TheraSphere would meet the End of Life criteria of improving OS when compared with other palliative treatments.

BTG suggest that TheraSphere should be made available as a treatment option for patients requiring palliative treatment. We believe that there are two particular subgroups who may gain the most benefit from treatment with TheraSphere: patients with PVT and patients unable to tolerate sorafenib.

Patients with PVT have a particularly poor prognosis. BTG believe that these patients derive particular benefit from TheraSphere, particularly if delivered via PDA. A study by Garin et al in HCC patients with PVT (n=41) revealed a significant improvement in OS with PDA (>205 Gy) versus SDA (<205 Gy): 18.2 months versus 4.3 months, p<0.005 (5). Further work by Garin et al (6) in a mixed intermediate/advanced disease population showed significantly improved OS in patients receiving PDA versus SDA: median OS of 15.7 months versus 4.35 months, p=0.0004 in the PVT sub-population. Given the limited options and poor prognosis for this patient group and positive evidence using PDA to deliver TheraSphere, BTG suggests that TheraSphere is an alternative treatment in these patients.

Patients not eligible for systemic therapies or unable to tolerate systemic treatment toxicities are another important subgroup. In the SARAH study (7), 64% (139/216) of patients discontinued sorafenib for drug-related toxicity; of whom 108 (78%) permanently discontinued treatment. Quality of life, an important issue in patients with advanced cancer, was also significantly poorer in the sorafenib arm than with SIRT. Given the limited options for these patients, BTG suggests that TheraSphere provides an alternative treatment option for this patient group

In the original submission we pointed out that the prognosis of HCC is poor, with median OS for patients with advanced HCC of <1 year (26, 27) (BTG submission, page 142). Lastly, this treatment group is indicated for a fairly small patient group. If 51% of patients are typically classified as having intermediate or advanced stage HCC (28), and 4,925 are diagnosed with the disease per year (29), approximately 2,511 patients would be indicated to receive TheraSphere.

This is echoed by clinical advice gained during the consultation process undertaken by BTG in responding to the AG report. The updated results and clinical advice suggest that TheraSphere has the potential to meet the End of Life criteria in the palliative population and we hope that the committee will consider this.

3 Factual errors

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The BTG submission presents twelve additional ongoing or planned studies of TheraSphere

The additional studies presented by BTG are all completed. STOP-HCC (NCT01556490) is an ongoing phase III RCT comparing TheraSphere plus sorafenib vs. sorafenib alone in 500 patients which was detailed in Appendix D of the BTG submission.

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There was only one low-quality retrospective study which directly compared TheraSphere to SIR-Spheres in the base-case population.

There are two studies (although both are low quality) and are listed in Scenario 4 (Biederman and Van der Gucht)

References

1. A. Vogel, A. Cervantes, I. Chau, B. Daniele, J. Llovet, T. Meyer, et al. Hepatocellular Carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29:iv238-iv55.
2. E. Garin, L. Tselikas, Guiu B. Major impact of personalized dosimetry on the targeted tumor response using 90Y loaded glass microspheres SIRT in HCC : preliminary results of a prospective multicentric randomized study. Presented at European Conference on Interventional Oncology, Amsterdam, April 2019. 2019.
3. N. Hawkins, P. Ross, D. Palmer, G. Chatellier, H. Pereira, Vilgrain V. Overall survival of patients with hepatocellular carcinoma receiving sorafenib versus selective internal radiation therapy with predicted dosimetry in the SARAH trial (poster). European Society for Medical Oncology 2019; Barcelona.; 2019.
4. Salem R, Padia SA, Lam M, Bell J, Chiesa C, Fowers K, et al. Clinical and dosimetric considerations for Y90: recommendations from an international multidisciplinary working group. European journal of nuclear medicine and molecular imaging. 2019;46(8):1695-704.
5. Garin E, Rolland Y, Edeline J, Icard N, Lenoir L, Laffont S, et al. Personalized dosimetry with intensification using 90Y-loaded glass microsphere radioembolization induces prolonged overall survival in hepatocellular carcinoma patients with portal vein thrombosis. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2015;56(3):339-46.
6. Garin E, Rolland Y, Pracht M, Le Sourd S, Laffont S, Mesbah H, et al. High impact of macroaggregated albumin-based tumour dose on response and overall survival in hepatocellular carcinoma patients treated with (90) Y-loaded glass microsphere radioembolization. Liver international : official journal of the International Association for the Study of the Liver. 2017;37(1):101-10.
7. Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. The Lancet Oncology. 2017;18(12):1624-36.
8. National Institute for Health and Care Excellence. Tildrakizumab for treating chronic plaque psoriasis after systemic therapy [ID1060]. 2019.
9. National Institute for Health and Care Excellence. Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure (TA314). 2014.
10. National Institute for Health and Care Excellence. Nivolumab for treating advanced (unresectable or metastatic) melanoma TA384. 2016.
11. Cochrane Training. Combining randomised and non-randomised evidence in network meta-analysis (NMA): Cochrane Training,; 2016 [cited 2019. Available from: https://training.cochrane.org/resource/combining-randomised-and-non-randomised-evidence-network-meta-analysis-nma.
12. Efthimiou O, Mavridis D, Debray TP, Samara M, Belger M, Siontis GC, et al. Combining randomized and non-randomized evidence in network meta-analysis. Statistics in medicine. 2017;36(8):1210-26.
13. Mueller M, D'Addario M, Egger M, Cevallos M, Dekkers O, Mugglin C, et al. Methods to systematically review and meta-analyse observational studies: a systematic scoping review of recommendations. BMC Medical Research Methodology. 2018;18(1):44.
14. M. Maccauro, C. Sposito, C. Chiesa, Romito R, C. Spreafico, Morosi C ea. Trans-arterial radioembolization (TARE) with Y90 glass microspheres plus sorafenib versus tare alone for the treatment of unresectable hepatocellular carcinoma (HCC) : A matched case-control study. European journal of nuclear medicine and molecular imaging. 2014:41(Suppl. 2):S291.

15. d'Abadie P, Hesse M, Jamar F, Lhommel R, Walrand S. (90)Y TOF-PET based EUD reunifies patient survival prediction in resin and glass microspheres radioembolization of HCC tumours. Physics in medicine and biology. 2018;63(24):245010.
16. Abouchaleh N, Gabr A, Ali R, Al Asadi A, Mora RA, Kallini JR, et al. (90)Y Radioembolization for Locally Advanced Hepatocellular Carcinoma with Portal Vein Thrombosis: Long-Term Outcomes in a 185-Patient Cohort. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2018;59(7):1042-8.
17. Kokabi N, Camacho JC, Xing M, El-Rayes BF, Spivey JR, Knechtle SJ, et al. Open-label prospective study of the safety and efficacy of glass-based yttrium 90 radioembolization for infiltrative hepatocellular carcinoma with portal vein thrombosis. Cancer. 2015;121(13):2164-74.
18. Kulik LM, Carr BI, Mulcahy MF, Lewandowski RJ, Atassi B, Ryu RK, et al. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. Hepatology (Baltimore, Md). 2008;47(1):71-81.
19. Pracht M, Edeline J, Lenoir L, Latournerie M, Mesbah H, Audrain O, et al. Lobar hepatocellular carcinoma with ipsilateral portal vein tumor thrombosis treated with yttrium-90 glass microsphere radioembolization: preliminary results. International journal of hepatology. 2013;2013:827649.
20. Woodall CE, Scoggins CR, Ellis SF, Tatum CM, Hahl MJ, Ravindra KV, et al. Is selective internal radioembolization safe and effective for patients with inoperable hepatocellular carcinoma and venous thrombosis? Journal of the American College of Surgeons. 2009;208(3):375-82.
21. Ali R, Riaz A, Gabr A, Abouchaleh N, Mora R, Al Asadi A, et al. Clinical outcomes of Y90 radioembolization for recurrent hepatocellular carcinoma following curative resection. European journal of nuclear medicine and molecular imaging. 2017;44(13):2195-202.
22. Mazzaferro V, Sposito C, Bhoori S, Romito R, Chiesa C, Morosi C, et al. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. Hepatology (Baltimore, Md). 2013;57(5):1826-37.
23. Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology. 2010;138(1):52-64.
24. Chow PKH, Gandhi M, Tan SB, Khin MW, Khasbazar A, Ong J, et al. SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018;36(19):1913-21.
25. National Institute for Health and Care Excellence. The Guidelines Manual: Process and Methods. 2012.
26. El-Serag HB. Epidemiology of hepatocellular carcinoma in USA. Hepatology research : the official journal of the Japan Society of Hepatology. 2007;37 Suppl 2:S88-94.
27. Nordenstedt H, White DL, El-Serag HB. The changing pattern of epidemiology in hepatocellular carcinoma. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver. 2010;42 Suppl 3:S206-14.
28. BTG (Internal). Understanding patient pathways in HCC for Europe (EU5) United Kingdom (internal). 2015.
29. Statistics. OfN. Cancer registration statistics, England: 2016. London; 2018.

Appendix A – BTG curative intent (CTT ineligible) model additional analyses

50% of downstaged patients receive resection

Table 8: Raw model outputs (unranked)

Intervention	QALYs (Disc)	Costs (Disc)
TheraSphere	1.537	£49,490
QuiremSpheres	1.537	£49,513
SIR-Spheres	1.537	£49,513
cTACE	1.084	£39,115
DEB-TACE	1.084	£35,062
Bland embolisation	1.084	£39,097

Table 9: Results ranked by incremental cost model outputs

Intervention	Δ Costs	Δ QALYs	ICER
DEB-TACE	£0	0.000	Referent
Bland embolisation	£4,035	-0.001	Dominated
cTACE	£4,053	0.000	Dominated
TheraSphere	£14,428	0.453	£31,851
QuiremSpheres	£14,451	0.453	£31,851
SIR-Spheres	£14,451	0.453	£31,851

33:67 split in progression status of patients in pharmacological management

Table 10: Raw model outputs (unranked)

Intervention	QALYs (Disc)	Costs (Disc)
TheraSphere	2.127	£56,744
QuiremSpheres	2.127	£56,766
SIR-Spheres	2.127	£56,766
cTACE	1.397	£42,007
DEB-TACE	1.397	£37,954
Bland embolisation	1.396	£41,989

Table 11: Results ranked by incremental cost model outputs

Intervention	Δ Costs	Δ QALYs	ICER
DEB-TACE	£0	0.000	Referent
Bland embolisation	£4,035	-0.001	Dominated
cTACE	£4,053	0.000	Dominated
TheraSphere	£18,789	0.730	£25,739
QuiremSpheres	£18,812	0.730	£25,739
SIR-Spheres	£18,812	0.730	£25,739

Inflated work-up costs

Table 12: Raw model outputs (unranked)

Intervention	QALYs (Disc)	Costs (Disc)
TheraSphere	2.127	£58,017
QuiremSpheres	2.127	£58,040
SIR-Spheres	2.127	£58,040
cTACE	1.397	£43,488
DEB-TACE	1.397	£39,435
Bland embolisation	1.396	£43,470

Table 13: Results ranked by incremental cost model outputs

Intervention	Δ Costs	Δ QALYs	ICER
DEB-TACE	£0	0.000	Referent
Bland embolisation	£4,035	-0.001	Dominated
cTACE	£4,053	0.000	Dominated
TheraSphere	£18,582	0.730	£25,454
QuiremSpheres	£18,604	0.730	£25,454
SIR-Spheres	£18,604	0.730	£25,454

Age-adjusted utilities calculated according to AG method

Table 14: Raw model outputs (unranked)

Intervention	QALYs (Disc)	Costs (Disc)
TheraSphere	3.021	£57,731
QuiremSpheres	3.021	£57,753
SIR-Spheres	3.021	£57,753
cTACE	1.986	£43,488
DEB-TACE	1.986	£39,435
Bland embolisation	1.985	£43,470

Table 15: Results ranked by incremental cost model outputs

Intervention	Δ Costs	Δ QALYs	ICER
DEB-TACE	£0	0.000	Referent
Bland embolisation	£4,035	-0.001	Dominated
cTACE	£4,053	0.000	Dominated
TheraSphere	£18,295	1.036	£17,665
QuiremSpheres	£18,318	1.036	£17,665
SIR-Spheres	£18,318	1.036	£17,665

Reduced transplant wait list time according to AG data

Table 16: Raw model outputs (unranked)

Intervention	QALYs (Disc)	Costs (Disc)
TheraSphere	2.317	£60,755
QuiremSpheres	2.317	£60,778
SIR-Spheres	2.317	£60,778
cTACE	1.498	£45,105
DEB-TACE	1.498	£41,052
Bland embolisation	1.498	£45,087

Table 17: Results ranked by incremental cost model outputs

Intervention	Δ Costs	Δ QALYs	ICER
DEB-TACE	£0	0.000	Referent
Bland embolisation	£4,035	-0.001	Dominated
cTACE	£4,053	0.000	Dominated
TheraSphere	£19,703	0.818	£24,078
QuiremSpheres	£19,726	0.818	£24,078
SIR-Spheres	£19,726	0.818	£24,078

All changes aggregated

Table 18: Raw model outputs (unranked)

Intervention	QALYs (Disc)	Costs (Disc)
TheraSphere	2.240	£49,826
QuiremSpheres	2.239	£49,848
SIR-Spheres	2.239	£49,848
cTACE	1.571	£38,194
DEB-TACE	1.572	£34,141
Bland embolisation	1.571	£38,176

Table 19: Results ranked by incremental cost model outputs

Intervention	Δ Costs	Δ QALYs	ICER
DEB-TACE	£0	0.000	Referent
Bland embolisation	£4,035	-0.001	Dominated
cTACE	£4,053	0.000	Dominated
TheraSphere	£15,684	0.668	£23,479
QuiremSpheres	£15,707	0.668	£23,479
SIR-Spheres	£15,707	0.668	£23,479

Appendix B – BTG palliative intent (CTT ineligible) model additional analyses

Work-up costs inflated

Table 20: Raw model outputs (unranked)

Intervention	QALYs (Disc)	Costs (Disc)
TheraSphere	0.695	£50,663
QuiremSpheres	0.467	£37,802
SIR-Spheres	0.467	£37,802
Sorafenib	0.497	£37,152
Lenvatinib	0.527	£60,496
Regorafenib	0.492	£34,993

Table 21: Results ranked by incremental cost model outputs

Intervention	Δ Costs	Δ QALYs	ICER
Regorafenib	£0	0.000	Referent
Sorafenib	£2,159	0.005	Ext dominated
SIR-Spheres	£2,809	-0.025	Dominated
QuiremSpheres	£2,809	-0.025	Dominated
TheraSphere	£15,670	0.203	£77,328
Lenvatinib	£25,502	0.035	Dominated

Dose of systemic therapies updated

Table 22: Raw model outputs (unranked)

Intervention	QALYs (Disc)	Costs (Disc)
TheraSphere	0.695	£47,333
QuiremSpheres	0.467	£36,692
SIR-Spheres	0.467	£36,692
Sorafenib	0.497	£33,838
Lenvatinib	0.527	£54,062
Regorafenib	0.492	£34,993

Table 23: Results ranked by incremental cost model outputs

Intervention	Δ Costs	Δ QALYs	ICER
Sorafenib	£0	0.000	Referent
Regorafenib	£1,155	-0.005	Dominated
SIR-Spheres	£2,854	-0.029	Dominated
QuiremSpheres	£2,854	-0.029	Dominated
TheraSphere	£13,495	0.198	£68,224

Lenvatinib	£20,224	0.030	Dominated

Use of the AG HRs

Table 24: Raw model outputs (unranked)

Intervention	QALYs (Disc)	Costs (Disc)
TheraSphere	0.695	£50,376
QuiremSpheres	0.408	£35,873
SIR-Spheres	0.408	£35,873
Sorafenib	0.450	£35,842
Lenvatinib	0.466	£56,254
Regorafenib	0.695	£50,376

Table 25: Results ranked by incremental cost model outputs

Intervention	Δ Costs	Δ QALYs	ICER
Sorafenib	£0	0.000	Referent
SIR-Spheres	£31	-0.041	Dominated
QuiremSpheres	£31	-0.041	Dominated
TheraSphere	£14,534	0.245	£59,320.81
Lenvatinib	£20,412	0.016	Dominated

Update of the age-adjusted utilities

Table 26: Raw model outputs (unranked)

Intervention	QALYs (Disc)	Costs (Disc)
TheraSphere	0.993	£50,376
QuiremSpheres	0.682	£37,516
SIR-Spheres	0.682	£37,516
Sorafenib	0.722	£37,152
Lenvatinib	0.752	£60,496
Regorafenib	0.717	£34,993

Table 27: Results ranked by incremental cost model outputs

Intervention	Δ Costs	Δ QALYs	ICER
Regorafenib	£0	0.000	Referent
Sorafenib	£2,159	0.005	Ext dominated
SIR-Spheres	£2,523	-0.036	Dominated
QuiremSpheres	£2,523	-0.036	Dominated
TheraSphere	£15,383	0.276	£55,726
Lenvatinib	£25,502	0.035	Dominated

Regorafenib removed as a comparator

Table 28: Raw model outputs (unranked)

Intervention	QALYs (Disc)	Costs (Disc)
TheraSphere	0.993	£50,376
QuiremSpheres	0.682	£37,516
SIR-Spheres	0.682	£37,516
Sorafenib	0.722	£37,152
Lenvatinib	0.752	£60,496
Regorafenib	0.717	£34,993

Table 29: Results ranked by incremental cost model outputs

Intervention	Δ Costs	Δ QALYs	ICER
Sorafenib	£0	0.000	Referent
SIR-Spheres	£364	-0.029	Dominated
QuiremSpheres	£364	-0.029	Dominated
TheraSphere	£13,224	0.198	£66,854
Lenvatinib	£23,343	0.030	Dominated
Regorafenib	£3,939,703	-0.005	Dominated

Subsequent systemic therapy costs

Scenario 1a

Table 30: Raw model outputs (unranked)

Intervention	QALYs (Disc)	Costs (Disc)
TheraSphere	0.695	£37,946
QuiremSpheres	0.467	£41,928
SIR-Spheres	0.467	£41,928
Sorafenib	0.497	£44,279
Lenvatinib	0.527	£60,496
Regorafenib	0.492	£34,993

Table 31: Results ranked by incremental cost model outputs

Intervention	Δ Costs	Δ QALYs	ICER
Regorafenib	£0	0.000	Referent
TheraSphere	£2,952	0.203	£14,569
SIR-Spheres	£6,935	-0.025	Dominated
QuiremSpheres	£6,935	-0.025	Ext dominated
Sorafenib	£9,286	0.005	-£32,019

Lenvatinib	£25,502	0.035	£544,889

Scenario 2

Table 32: Raw model outputs (unranked)

Intervention	QALYs (Disc)	Costs (Disc)
TheraSphere	0.695	£44,588
QuiremSpheres	0.467	£35,949
SIR-Spheres	0.467	£35,949
Sorafenib	0.497	£44,279
Lenvatinib	0.527	£60,496
Regorafenib	0.492	£34,993

Table 33: Results ranked by incremental cost model outputs

Intervention	Δ Costs	Δ QALYs	ICER
Regorafenib	£0	0.000	Referent
SIR-Spheres	£956	-0.025	Dominated
QuiremSpheres	£956	-0.025	Dominated
Sorafenib	£9,286	0.005	Ext dominated
TheraSphere	£9,595	0.203	£47,348
Lenvatinib	£25,502	0.035	Dominated

Scenario 3

Table 34: Raw model outputs (unranked)

Intervention	QALYs (Disc)	Costs (Disc)
TheraSphere	0.695	£48,232
QuiremSpheres	0.467	£44,712
SIR-Spheres	0.467	£44,712
Sorafenib	0.497	£44,279
Lenvatinib	0.527	£60,496
Regorafenib	0.492	£34,993

Table 35: Results ranked by incremental cost model outputs

Intervention	Δ Costs	Δ QALYs	ICER
Regorafenib	£0	0.000	Referent
Sorafenib	£9,286	0.005	Ext dominated
SIR-Spheres	£9,719	-0.025	Dominated
QuiremSpheres	£9,719	-0.025	Dominated
TheraSphere	£13,239	0.203	£65,333.66

Aggregated results

Table 36: Raw model outputs (unranked) – with scenario 1a

Intervention	QALYs (Disc)	Costs (Disc)
TheraSphere	0.993	£45,911
QuiremSpheres	0.594	£39,781
SIR-Spheres	0.594	£39,781
Sorafenib	0.652	£35,477
Lenvatinib	0.664	£50,260

Table 37: Results ranked by incremental cost model outputs – with scenario 1a

Intervention	Δ Costs	Δ QALYs	ICER
Sorafenib	£0	0.000	Referent
SIR-Spheres	£4,303	-0.058	Dominated
QuiremSpheres	£4,303	-0.058	Dominated
TheraSphere	£10,434	0.341	£30,590.50
Lenvatinib	£14,782	0.011	Dominated

Table 38: Raw model outputs (unranked) – with scenario 3

Intervention	QALYs (Disc)	Costs (Disc)
TheraSphere	0.993	£37,550
QuiremSpheres	0.594	£37,518
SIR-Spheres	0.594	£37,518
Sorafenib	0.652	£35,477
Lenvatinib	0.664	£50,260

Table 39: Results ranked by incremental cost model outputs – with scenario 3

Intervention	Δ Costs	Δ QALYs	ICER
Sorafenib	£0	0.000	Referent
SIR-Spheres	£2,040	-0.058	Dominated
QuiremSpheres	£2,040	-0.058	Dominated
TheraSphere	£2,073	0.341	£6,077
Lenvatinib	£14,782	0.011	Dominated

NICE Multiple Technology Appraisal ID1276

Selective internal radiation therapies for treating hepatocellular carcinoma

SIRTEX Medical

Response to the Assessment Group Report

SIR-Spheres Y-90 resin microspheres

15th October 2019

This document contains AIC and CIC information.

Abbreviations

Acronym	Definition
AE	Adverse event
AFP	Alpha-fetoprotein
AIC	Akaike information criteria
ALBI	Albumin-bilirubin grade
BCLC	Barcelona clinic liver cancer staging
BD	Twice daily
BIC	Bayesian information criteria
BSA	Body surface area
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CIRT	CIRSE Registry for SIR-Spheres Therapy
CMA	Cost-minimisation analysis
coeff	Coefficient
CR	Complete response
CS	Company submission
CT	Computed tomography
cTACE	Conventional transarterial chemoembolisation
DEBDOX	Drug eluting beads of doxorubicin
DEB-TACE	Drug-eluting bead- transarterial chemoembolisation
(DEB-)TACE	Transarterial chemoembolisation using either conventional administration or drug eluting beads
DIC	Deviance information criteria
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EASL	European Association for the Study of the Liver
ECOG	Eastern Cooperative Oncology Group
EHD	Extrahepatic disease
EHS	Extrahepatic spread
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
exp	Exponential
FACT-G	Functional Assessment of Cancer Therapy - General
gen	Generalised
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
INB	Incremental net benefit
INR	International normalised ratio
IPTW	Inverse probability of treatment weighting
IQR	Interquartile range
ISPOR-SMDM	International Society for Pharmacoeconomics and Outcomes Research- Society for Medical Decision Making
ITT	Intention-to-treat
KM	Kaplan-Meier
KOL	Key opinion leader
LCI	Lower confidence interval
LYG	Life-years gained

LTX	Liver transplant
MAIC	Matched adjusted indirect comparison
MCMC	Markov chain Monte Carlo
MIRD	Medical Internal Radiation Dose
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic resonance imaging
MVI	Macroscopic vascular invasion
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NLHCC	Hepatocellular carcinoma with normal liver
NMA	Network meta-analysis
NR	Not reported
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PP	Per-protocol
PR	Partial response
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PVA	Polyvinyl alcohol
PVI	Portal vein involvement
PVT	Portal vein thrombosis
PVTT	Portal vein tumour thrombosis
QALY	Quality-adjusted life-year
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	Radiofrequency ablation
SAE	Serious adverse events
SD	Stable disease OR standard deviation
SE	Standard error
SIR-Spheres	SIR-Spheres® Y-90 resin microspheres
SIRT	Selective internal radiation therapy
SLR	Systematic literature review
SPECT/ CT	Single-photon emission computed tomography
TA	Technology appraisal
TACE	Transarterial chemoembolisation
TAE	Transarterial embolisation
TARE	Transarterial radioembolisation
^{99m}Tc-MAA	Technetium-99m macroaggregated albumin
TEAE	Treatment-emergent adverse events, treatment-related adverse events
TNM	Tumour node metastasis
TTD	Time to treatment discontinuation
TTO	Time trade-off
TTP	Time to progression
TTUP	Time to untreatable progression
TTV	Total tumour volume
UCI	Upper confidence interval
vs	Versus

1 Introduction

Thank you for the opportunity to comment on the assessment report of selective internal radiation therapies for treating hepatocellular carcinoma (HCC). Please find below a summary of the key points that Sirtex Medical would like the Committee and the Assessment Group (AG) to consider:

- Selective internal radiation therapy (SIRT) is an addition to existing alternatives for the treatment of unresectable HCC in the UK, for which therapeutic options remain limited. SIRT will not replace NICE-recommended systemic therapies for the majority of patients who are ineligible for conventional transarterial therapies (CTT-ineligible). SIR-Spheres would only be used in a clinically relevant subgroup of patients.
- The subgroup of patients who would receive SIRT in routine clinical practice in the UK and who are most likely to benefit from SIRT using SIR-Spheres was defined in accordance with UK clinical experts, with significant experience with SIRT and/or the management of HCC.
- This subgroup comprises patients with a smaller tumour burden (defined as a tumour volume ≤25% of the total liver volume) and a well-preserved liver function (defined as an Albumin-Bilirubin [ALBI] grade 1). This subgroup is defined based on clinical parameters which are routinely collected in the UK for the management of patients with HCC and based on thresholds which are clinically validated to stratify patients for locoregional therapy or already used by NHS England to determine eligibility for SIRT in another indication.
- This subgroup is relevant to SIR-Spheres, because SIRT is a locoregional therapy with a radiobiological mechanism of action, that differs completely from systemic therapy. Therefore, individual tumour morphology and other relevant baseline clinical parameters may act as treatment effect modifiers, in the comparison of SIRT vs systemic therapy.
- Further due to its different mechanism of action, SIRT can result in the downstaging of initially unresectable HCC for patients to receive subsequent therapies with curative intent (including liver transplantation, liver resection and percutaneous tumour ablation), whereas this is very rarely observed for patients treated with sorafenib or lenvatinib. Downstaging to treatments with curative intent is consistently observed for patients with unresectable HCC receiving SIR-Spheres across the available evidence base, and more frequently observed in the subgroup of patients with a tumour burden ≤25% and an ALBI grade 1.
- The main comparator for SIRT is sorafenib, because lenvatinib would only be used in a small fraction of patients considered for SIRT in the UK. If lenvatinib is included in the economic model, treatments should be compared in the comparable populations reported in the trials.
- Equal efficacy and safety should not be assumed between the different devices used for SIRT. SIR-Spheres are the only device supported by evidence from Phase III randomised trials.
- The administration of SIR-Spheres does not require an additional imaging procedure compared with TheraSphere or QuiremSpheres. However, SIR-Spheres are the only device with which single-session treatment of patients with bi-lobar HCC can be performed in a selective manner, with multiple infusions of a single source dose of SIR-Spheres. This results in a lower number of treatments received by patients and lower costs compared with other SIRT devices.
- SIR-Spheres are a cost-saving alternative to sorafenib in the base case model and result in (quality-adjusted) life-year gains, especially in the relevant subgroup of patients.
- In conclusion, SIR-Spheres would be an option for well-selected patients with unresectable HCC who are CTT-ineligible, depending on tumour morphology and patient preference. SIR-Spheres can reduce treatment costs and increase the proportion of patients with initially unresectable HCC receiving downstaging to therapies with curative intent.

2 Major issues

2.1 *Use of lenvatinib as a comparator*

- **Sorafenib is more commonly used than lenvatinib, and lenvatinib is unlikely to be considered a clinically relevant alternative to SIRT. Therefore, it is important to conduct an incremental analysis excluding lenvatinib as a comparator to inform decision-making for patients who would not receive lenvatinib.**
- **When SIRT is compared to lenvatinib, the populations need to be adjusted for the main differences in the trials' inclusion criteria**

Lenvatinib was recommended by NICE in December 2018 (1). However as second line regorafenib is recommended by NICE only after sorafenib (NICE in December 2018), and not after lenvatinib (2). This limits the use of lenvatinib, leading to the majority of patients receiving sorafenib. As the Assessment Group (AG) notes on page 187 "The AG was advised that current NICE recommendations mean that lenvatinib is rarely used in practice, as this would preclude second-line use of regorafenib"(3).

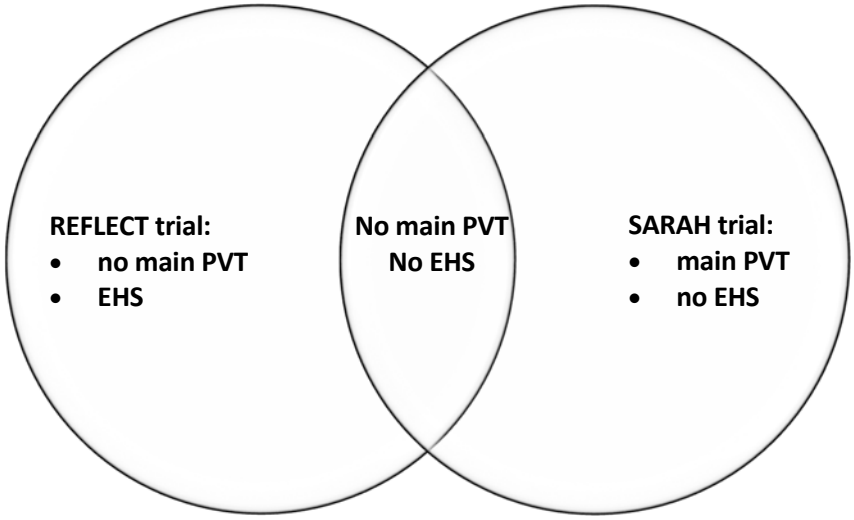
Clinical expert opinion elicited by Sirtex indicated that lenvatinib is rarely used in practice and that the absence of NICE-recommended second-line treatment options following progression on lenvatinib is one of the key factors explaining this. In addition, clinical experts have indicated that among patients considered for systemic therapy and because of the increased tumour response observed with lenvatinib compared with sorafenib, lenvatinib would typically be used in patients with larger intrahepatic tumours and therefore a larger tumour burden. As a result, lenvatinib is unlikely to be a clinically relevant alternative to SIRT in patients with HCC, especially in the subgroup of patients with a tumour burden ≤25% and an ALBI grade 1, who are most likely to benefit from SIRT and to receive this therapy in UK clinical practice.

Lenvatinib should therefore not be a comparator to SIR-Spheres in a fully incremental analysis which treats options as mutually exclusive. We suggest that the base case incremental analysis should be presented without lenvatinib, retaining sorafenib.

If any comparison with lenvatinib is conducted, it is important to account for differences in inclusion and exclusion criteria of the REFLECT and SARAH trials:

- REFLECT excluded patients with main portal vein thrombosis (main PVT) and included patients with extrahepatic spread (EHS);
- SARAH included patients with main PVT but excluded patients with EHS.

Figure 1. Inclusion of patients with MPV/EHS in the REFLECT and SARAH trials



The comparable population for the SARAH and REFLECT trials are therefore patients with neither main PVT nor EHS. The REFLECT trial reported subgroup results for patients with no main PVT and/or EHS. When this subgroup is compared to the same subgroup from SARAH, the indirect comparison shows very similar efficacy for SIR-Spheres compared to lenvatinib vs. sorafenib (Table 1). Inclusion of the below hazard ratios (HRs) in the model leads to the cost-effectiveness results presented in Table 2.

When using the appropriate comparison with similar populations, lenvatinib is dominated, and sorafenib is either dominated with the model structure including downstaging or not cost-effective when downstaging is excluded (Table 2).

Table 1. Results from the indirect comparison of the REFLECT and SARAH trials' comparable subgroups: Overall survival (OS) hazard ratios (HRs)

	No main PVT/no EHS OS, mean (95% CrI)	
	Fixed Effects	**Random Effects**
Sorafenib (reference)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
SIR-Spheres	1.05 (0.75, 1.46)	1.05 (0.43, 2.53)
Lenvatinib	1.05 (0.79, 1.39)	1.05 (0.44, 2.51)
DIC	-2	-2

DIC: deviance information criteria; OS: Overall survival; MPV: invasion of the main portal vein; EHS: Extrahepatic spread; CrI: Credible Interval
Included as Table 10, page 50 in the company submission

Table 2. Cost-effectiveness results for fully incremental analyses including lenvatinib using comparable populations

Intervention	**Costs**	**QALYs**	**NMB (threshold of £20,000/QALY)**	**ICER (fully incremental)**
ITT population excluding EHS/main PVT – No downstaging				
Lenvatinib	£36,032	0.909	-17,862	Dominated
SIR-Spheres	£23,357	0.927	-£4,827	-
Sorafenib	£27,917	0.964	-£8,632	£120,774
ITT population excluding EHS/main PVT – With downstaging				
Lenvatinib	£36,328	0.931	-£17,713	Dominated
Sorafenib	£28,266	0.986	-£8.548	Dominated
SIR-Spheres	£23,451	1.039	-£2,673	-

main PVT: main portal vein thrombosis; EHS: Extrahepatic spread; QALYs: quality-adjusted life-years; NMB: net monetary benefit; ICER: incremental cost-effectiveness ratio; ITT: intention-to-treat

2.2 *Subgroup of low tumour burden and good liver function*

- **Patients with low tumour burden (≤25%) and good liver function (ALBI score 1) are a clinically plausible and appropriate target population for SIR-Spheres in the CTT- ineligible population based on the available evidence and the opinion of clinicians with extensive experience with SIRT.**

As a locoregional treatment with a radiobiological mechanism of action, SIRT is most likely to benefit patients with suitable tumour morphology, whose tumours can effectively be targeted for irradiation, and with adequate liver functional reserve, who can therefore tolerate some degree of radiation exposure to the non-tumoural liver. Clinical decision-making for the treatment of HCC in the UK is generally based on a combination of factors including tumour burden and liver function. UK clinicians with extensive experience of SIRT (see Table 13, in Appendix) have recommended patients with a low tumour burden (tumour replacement of ≤25% of the total liver volume) and a well-preserved liver function (ALBI grade 1) as the most appropriate candidates for SIRT in the UK.

Tumour burden is defined in terms of volume, diameter and/or number of tumours to quantify the spread of disease within the liver. The measure of tumour burden as a fraction of liver volume is expected to capture the qualitative variability of tumour morphology, which drives the ability to deliver a tumouricidal radiation dose. The threshold of a tumour burden ≤25% of the total liver volume is already used in the UK for SIRT as a patient selection criterion according to the NHS England commissioning policy for SIRT in patients with colorectal liver metastases (4); this is also the case in other countries such as France(5). The threshold of a tumour burden ≤25% also was a predefined subgroup in the SARAH trial (6) .

Liver function is defined based on a number of blood tests, of which serum albumin and bilirubin are the most important. Liver function has historically been classified in UK clinical practice using the Child-Pugh classification, which includes albumin and bilirubin as factors, however due to limitations of this classification especially in capturing the hepatic functional reserve (8,9), the albumin-bilirubin (ALBI) grade has more recently been introduced (10). The ALBI grade was further validated as an instrument to stratify patients in prognostic subgroups, for treatment allocation to locoregional therapy within the Child-Pugh A class (10–15), including SIRT (16,17), with the potential to outperform the Child-Pugh classification as a predictor for OS following SIRT (17). Serum albumin and bilirubin are routinely collected and used in both clinical decision-making and in clinical trials for SIRT. The ALBI grade is currently used in the UK to predict outcomes of transarterial chemo-embolisation, however its use is not widespread for systemic therapies as it was not required, sorafenib and lenvatinib being recommended for patients within the broader Child-Pugh A class. The ALBI grade ((log10 bilirubin × 0.66) + (albumin × − 0.085)) can be easily estimated using freely available web-based calculators[1]; Sirtex is further committed to develop a smartphone app for this purpose.

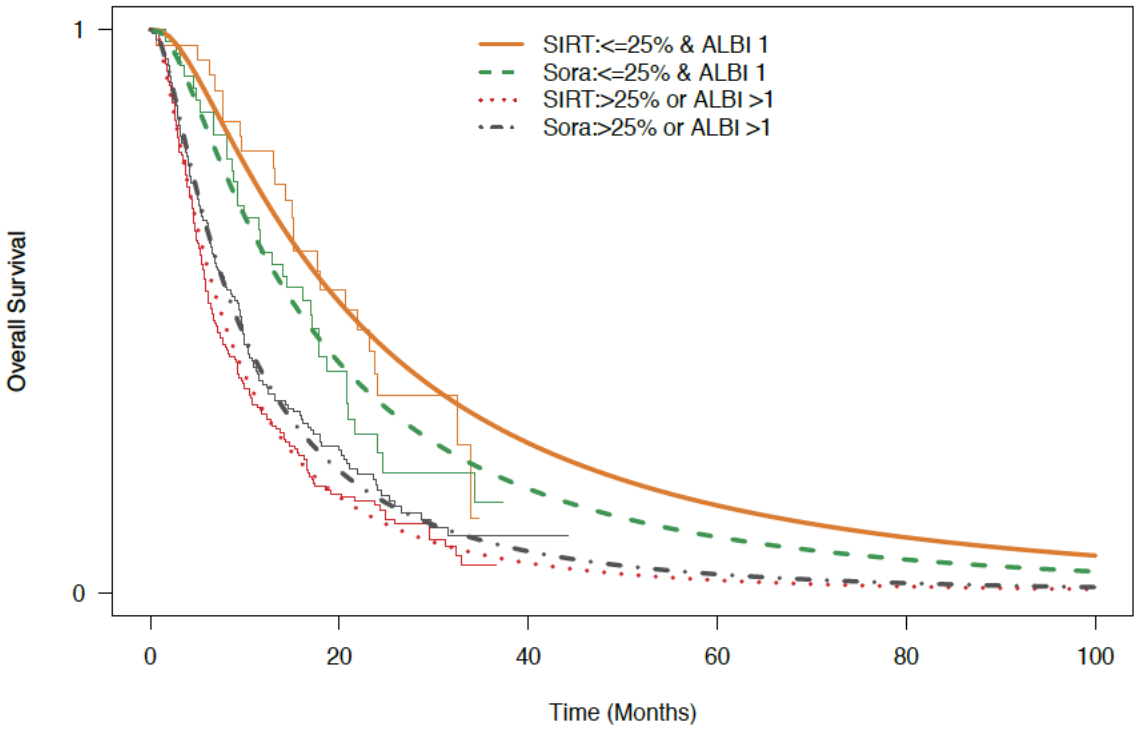
[1] Free web-based calculators include:

- https://www.mdcalc.com/albi-albumin-bilirubin-grade-hepatocellular-carcinoma-hcc
- http://web.stanford.edu/~akoong/nomogram.html (with a focus around SBRT)
- https://www.uptodate.com/contents/table-of-contents/calculators (subscription required)

While the combination of low tumour burden and good liver function is not a predefined subgroup in the SARAH trial, they have been shown to be both highly prognostic and an important treatment effect modifier both separately and together (Table 3 and Figure 2, page 8) (18,19).

Their relevance as patient selection criteria for SIRT is supported by clinicians with substantial experience with SIRT and HCC (see Table 13, in Appendix). Analyses of survival outcomes for patients in this subgroup recently led to an abstract presentation at the European Society for Medical Oncology (ESMO) 2019 congress (20) and are currently being submitted for publication.

Figure 2. Overall survival for patients with and without good liver function (ALBI 1) and low tumour burden (≤25%)



<=25%: Tumour burden less or equal to 25% of liver volume; ALBI: Albumin-Bilirubin Grade; SIRT: selective internal radiation therapy; Sora: sorafenib

Table 3. Overall survival for patients with and without good liver function (ALBI 1) and low tumour burden (≤25%)

Subgroup	SIRT		Sorafenib		Interaction Effect (Hazard Ratio)			
	Mean OS	N	Mean OS	N	P-Value	HR	95% CI	
Remaining Patients	12.74	200	14.95	174	-	1	1	1
Good Liver Function & Low Tumour Burden	34.3	37	26.22	48	0.086	0.61	0.34	1.08

2.3 *Downstaging to treatments with curative intent*

- **Downstaging and subsequent treatments with curative intent should be included in the base case because there is evidence from randomised trials and non-randomised studies that treatment with SIRT is associated with increased use of treatments with curative intent.**
- **This is an important part of the patients' pathway with SIRT in the CTT-ineligible population**

Downstaging with systemic treatments

Systemic treatments rarely lead to the downstaging of patients with advanced HCC to receive subsequent treatments with curative intent (liver transplant, liver resection or percutaneous tumour ablation) as mentioned by the AG ("with very few if any of these patients receiving curative therapies" (assessment report page 136)). This is also seen in the sorafenib arm of the SARAH trial (6), where in the ITT population only 1.4% of patents received treatments with curative intent after sorafenib (Table 4). In UK clinical practice, clinicians confirmed this would be extremely rare (0.1% of patients after sorafenib) (21). This is consistent with the AG remark that "none of the previous TAs which assessed systemic cancer treatments for advanced HCC modelled the possibility of curative therapies" (assessment report page 136).

Downstaging with SIRT

SIRT is a locoregional treatment, with a radiobiological mechanism of action that is completely different to systemic therapy. Compared with sorafenib, SIRT resulted in improved tumour response in the SARAH and SIRveNIB trials. Depending on the selected subgroup, probabilities of [redacted] to 29% were reported for patients with initially unresectable HCC to receive potentially curative treatments after SIRT, including a 13.5% downstaging rate in the subgroup of patients with a tumour burden ≤25% and ALBI grade 1 in the SARAH trial (Table 4). UK clinicians with experience using SIRT further reported that in current practice 5.6% of patients with initially unresectable HCC who are ineligible for CTT receive treatments with curative intent after SIRT (Table 4).

While there is uncertainty around the precise proportion of patients downstaged to treatments with curative intent, there is well-established and diverse evidence to support that SIR-Spheres does lead to downstaging in clinical practice.

Table 4. Proportion of patients receiving subsequent treatments with curative intent after SIR-Spheres

Source	After SIR-Spheres	After sorafenib
SARAH trial: patients with tumour burden ≤25% and ALBI grade 1	13.5%	2.1%
SARAH trial: ITT population	5.1%	1.4%
SARAH trial: PP population	6.9%	1.5%
CIRT Registry (22)	[redacted]	-
Physician survey (See Appendix O of Sirtex company submission (18))	5.6%	0.1%
Regnault 2019 (23)	24%	-
Inarrairaegui et al. 2012 (24)	29%	-

Included as Table 12 in the Sirtex company submission on page 53

As treatments with curative intent have major implications for life expectancy, quality of life of patients and costs, their exclusion from the cost-effectiveness modelling may underestimate the benefit of SIRT compared to systemic treatments.

The survival benefit of treatments with curative intent was not fully captured in the SARAH trial outcomes, as all but one patient in each arm remained alive at the end of the trial following treatment with curative intent – for these patients censoring was informative. Therefore, explicit modelling of the OS consequences of treatments with curative intent more accurately captures outcomes for these patients.

2.4 *Costs of SIRT administration procedures*

- **No additional imaging costs should be considered for the administration of SIR-Spheres compared to TheraSphere.**

The Assessment Report notes (page 186) that: "*The Sirtex company submission stated that SIR-Spheres administration procedures use intermittent contrast medium injection to assess the distribution of the microspheres under x-ray over the course of approximately one hour. The AG therefore included an additional cost of £209 for the SIR-Spheres administration procedure (RD32Z – Contrast Fluoroscopy Procedures with duration of more than 40 minutes) for a total of £2,999*."

This cost assumption is incorrect. No additional imaging is required for the administration of SIR-Spheres compared to TheraSphere: both types of yttrium-90 microspheres are administered during a hepatic angiography with contrast material injection under two-dimensional X-ray (fluoroscopy) and/or C-arm computed tomography (CT) guidance, with the use of three-dimensional cone-beam CT being an emergent imaging approach for SIRT in the UK, as is also the case for TACE. The administration costs for SIR-Spheres and TheraSphere is therefore equal.

Furthermore, the costs of contrast fluoroscopy or other imaging techniques are included in the HRG tariff applicable to both TACE and SIRT (YR57Z 'Percutaneous, Chemoembolisation, or Radioembolisation, of Lesion of Liver) and TACE is also performed using contrast fluoroscopy. The addition of a fluoroscopy cost therefore results in double counting.

2.5 *Differences between SIRT devices and relative clinical effectiveness*

- **Evidence from the Phase III randomised trials of SIR-Spheres should not be applied to other SIRT devices.**
- **There is no relevant clinical evidence comparing TheraSphere or QuiremSpheres with any of the comparators for CTT-ineligible patients.**

Despite SIR-Spheres and TheraSphere carrying the same radioactive isotope yttrium-90, there are differences between the products in both dosage and administration methods which are likely to result in differences in both the clinical efficacy and toxicity profiles (cf. Sirtex company submission (CS), section 2.2, pages 23-25 (18)). There is no evidence of equivalence between products (25,26). Higher

amounts of injected radioactivity (25) and of tumour-absorbed dose (26,27) are recommended for the administration of TheraSphere compared to SIR-Spheres due to the differences in the microspheres. This suggests alternative toxicity profiles, as higher injected radioactivity and radiation dose to the non-tumoural liver parenchyma are associated with increased risks of liver complications (27,28). This may also influence efficacy. Equal efficacy and safety can therefore not be assumed between these devices or with QuiremSpheres.

We encourage the Committee to acknowledge that the available data on TheraSphere and QuiremSpheres do not provide relevant evidence on the relative effectiveness and safety of these devices compared to any other comparator in the appraisal.

As there is no evidence on equal efficacy and safety of QuiremSpheres, TheraSphere and SIR-Spheres, the inclusion of TheraSphere or QuiremSpheres in the economic model for the CTT-ineligible population using the assumption of equal efficacy/safety, even as a sensitivity analysis, is therefore misleading.

In a scenario analysis including TheraSphere (assessment report (3) pages 93-94, 99-106, 198-200), an additional comparison was made primarily based on the Biederman *et al.* study (29) which was a single-centre, retrospective study comparing SIR-Spheres and TheraSphere. This study was described by the AG as being at "high risk of bias" because it included "patients with different prognostic characteristics at baseline in the two different treatment groups" and because "it was unclear whether outcome assessors were blinded in any of the studies." (3) Additional limitations include the unbalanced, low sample size of the study (n=21 patients treated with SIR-Spheres, n=69 with TheraSphere) and its design as a non-consecutive retrospective review. Patient selection criteria were not documented by the authors, despite the study considering a limited sample (90 patients included out of 709 treated from January 2005 to September 2014) and covering a long enrolment period over which changes in clinical practice are likely.

We further refute that studies selected by the AG should be "included as a sensitivity analysis as they are the only studies with direct evidence between TheraSphere and SIR-Spheres" (assessment report page 83): this is because Biederman *et al.* study is at major risk of overestimating the relative effectiveness of TheraSphere versus other comparators in the network meta-analysis, which can invalidate the results of this analysis as a whole. The inclusion of this study can further lead to misrepresentation of the effectiveness of TheraSphere, especially considering that the HR for overall survival between SIR-Spheres and TheraSphere reported in the Biederman et al. study can be considered a statistical outlier compared to the other studies identified by the AG. Although this study is limited to a sensitivity analysis in the AG report, we argue that this presentation is very misleading as it does confer some form of credibility to the HR estimates for TheraSphere versus other comparators in the network meta-analysis, whereas other connections in the network of studies are based on large, Phase III randomised trials considered at low risk of bias.

As a result, we recommend that the Committee dismiss evidence from the Biederman *et al.* study from sensitivity analyses conducted for this appraisal and to consider that the evidence on the relative clinical effectiveness and safety of TheraSphere is not established in this population.

2.6 *Evolution from the SARAH trial protocol to current clinical practice*

- **Clinical practice of SIRT using SIR-Spheres has evolved from treatment approaches mandated by the SARAH trial protocol to more selective and less costly approaches especially for patients with bi-lobar HCC.**

Patients with bi-lobar HCC have tumour nodules in both lobes of the liver: for these patients, SIRT must be administered to tumours in both lobes (i.e. in the whole liver) to obtain disease control. This can be performed using one of three different treatment approaches:

- **Sequential treatment:** one SIRT infusion to each of the two lobes in two separate hospital admissions. This approach was mandated by the SARAH trial protocol, which also stipulated that infusions be performed at the lobar level: this is performed by positioning the tip of the microcatheter used to infuse SIRT microspheres in the right of left hepatic artery, directing the microspheres towards tumours in the entire right or left liver lobe.
- **Whole-liver treatment:** a single SIRT infusion to both lobes of the liver simultaneously at one hospital admission. This is performed by positioning the tip of the microcatheter more proximally, in the proper hepatic artery, and allowing blood flow to preferentially direct SIRT towards tumour nodules in both lobes of the liver. This approach is used to treat patients with diffuse disease throughout the liver and without underlying cirrhosis, limiting it to well-selected patients with HCC.
- **Single-session treatment with a split administration:** multiple (typically 2 to 4) SIRT infusions for a single patient and during a single session and a single hospital admission. This is performed by positioning the tip of the microcatheter more distally in different arterial feeders of tumour nodules. This procedure can only be performed with SIR-Spheres: while a single V-vial of SIR-Spheres is prepared from the source vial provided by Sirtex in the case of a single injection, this particular procedure is performed by splitting the total amount of radioactivity to deliver in multiple V-vials of the product. This procedure can be applied to treat a few (typically ≤5) nodules spread in both lobes of the liver, or to treat different parts of a larger nodule with multiple arterial afferences. This procedure allows a minimisation of the number of treatment sessions and device units used per patient, while adopting selective treatment approaches, thereby minimising the radiation exposure to the non-tumoural liver.

The Committee should be aware that the clinical practice for treatment with SIR-Spheres has evolved since the SARAH trial protocol development (ethics committee approval received in June 2011). This protocol mandated sequential treatments for all patients. While clinical advisors to the AG contended that "*in UK practice it is likely that sequential treatment would be used as per the SARAH trial*" (assessment report page 138) and, consequently, that "*patients would not receive whole liver treatment in one session"* (assessment report page 51), real-world observational studies of SIR-Spheres demonstrate that routine clinical practice differs from the SARAH trial protocol in that sequential treatment is only used for a small minority of patients with bi-lobar HCC.

This is first observed in the ENRY register, which enrolled 325 consecutive patients with a confirmed diagnosis of unresectable HCC in 8 European centres: authors report that "the majority of whole-liver treatments were performed in a single session (141/147 [95.9%]) through one or more injections".

This is further supported by an interim analysis of the CIRT register, which enrolled [redacted] patients treated in 6 European countries (Belgium, France, Germany, Italy, Spain and Switzerland) and excluding Turkey, for which data were not provided to Sirtex. All patients had a confirmed diagnosis of HCC. These patients received a total [redacted] treatments, with a mean [redacted] treatments per patient. Of these, [redacted] patients [redacted] had single-lobe HCC (Table 5) and [redacted] patients [redacted] had had bi-lobar HCC (Table 6). Patients overall received between [redacted] SIR-Spheres treatments, with the distribution of number of treatments per patient being reported and compared with ENRY data in Table 5, for patients with single-lobe HCC, and in Table 6, for patients with bi-lobar HCC. In the CIRT registry, [redacted] of patients with single-lobe HCC and [redacted] of patients with bi-lobar respectively received a single administration of SIR-Spheres.

Pooling results from both observational studies of SIR-Spheres results in a mean 1.12 administrations of SIR-Spheres per patient; this figure is observed both for patients with single-lobe HCC (Table 5) and those with bi-lobar HCC (Table 6), providing unambiguous confirmation that bi-lobar disease is not associated with an increased number of treatments with SIR-Spheres.

Although neither the CIRT nor ENRY registers included patients treated with SIR-Spheres in the UK, as SIRT has not been routinely available in the NHS for patients with HCC, these European real-world studies therefore indicate that sequential treatment is very unlikely to be adopted for SIR-Spheres in routine clinical practice in the UK.

Table 5. CIRT and ENRY data for patients with single-lobe HCC

Number of patients with:	**CIRT Europe register**						**ENRY register**	**Pooled analysis**	
	BE	**FR**	**DE**	**IT**	**ES**	**SW**			
1 treatment	[redacted]						148	[redacted]	88.7%
2 treatments	[redacted]						5	[redacted]	10.8%
3 treatments	[redacted]						0	[redacted]	0.3%
4 treatments	[redacted]						0	[redacted]	0.3%
TOTAL	[redacted]						**153**	[redacted]	**100%**
Treatments per patient	[redacted]						**1.03**	**1.12**	

BE: Belgium; FR: France; DE: Germany; IT: Italy; ES: Spain; SW: Switzerland

Table 6. CIRT and ENRY data for patients with bi-lobar HCC

Number of patients with:	**CIRT Europe register**						**ENRY register**	**Pooled analysis**	
	BE	**FR**	**DE**	**IT**	**ES**	**SW**			
1 treatment	[redacted]						155	[redacted]	89.5%
2 treatments	[redacted]						14	[redacted]	9.2%
3 treatments	[redacted]						3	[redacted]	1.3%
4 treatments	[redacted]						0	[redacted]	0.0%
TOTAL	[redacted]						**172**	[redacted]	**100%**
Treatments per patient	[redacted]						**1.12**	**1.12**	

BE: Belgium; FR: France; DE: Germany; IT: Italy; ES: Spain; SW: Switzerland

2.7 *Summary table of key issues and proposed changes*

Table 7. Comparators

Place in the Assessment Report	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Section 5.3: Page 95 Section 8.4.1: Pages 191-193	In section 8.4.1 of the assessment report, lenvatinib is included in the fully incremental analyses. However, sorafenib is more commonly used than lenvatinib, therefore it is important to conduct an incremental analysis excluding lenvatinib as a comparator to inform decision-making for patients who would not receive lenvatinib. In additional, when SIRT is compared to lenvatinib, the populations need to be adjusted for the main differences in the trials' inclusion criteria, which include both extrahepatic spread (EHS) and main portal vein thrombosis (main PVT). On page 95, the AG states, that: "*The REFLECT trial, which compares lenvatinib and sorafenib included patients with extra-hepatic spread (61% in the lenvatinib arm and 62% in the sorafenib arm). All the other trials excluded patients with extra-hepatic spread, therefore the subgroup of patients without extra-hepatic spread or portal vein invasion was used for the REFLECT trial, a more appropriate subgroup was not reported.*" See section 2.1 of this document for detailed explanation.	Sirtex proposes AG revises the statement on page 95 with the following: "The REFLECT trial, which compares lenvatinib and sorafenib included patients with extra-hepatic spread (61% in the lenvatinib arm and 62% in the sorafenib arm). All the other trials excluded patients with extra-hepatic spread, therefore the subgroup of patients without extra-hepatic spread or portal vein invasion was used for the REFLECT trial, as a more appropriate subgroup was not reported. **Similarly, the SARAH trial included patients with main portal vein invasion, while these patients were excluded from the REFLECT trial. Therefore, the subgroup of patients without extra-hepatic spread or main portal vein invasion was selected from the SARAH trial**." Consequently, Sirtex proposes the NMA results are updated accordingly on page 95-99. Sirtex proposes the AG to exclude lenvatinib from the base-case analyses in addition to both the deletion of lenvatinib from Table 33 and Figure 19 on page 193 and the surrounding interpretation. Sirtex proposes that the comparisons with lenvatinib are included in the scenario analyses from page 194. However, the populations in the scenario analyses need to	This has a major effect on the results. Using an appropriate comparison with similar populations, SIR-Spheres is the most cost-effective option and lenvatinib is dominated.

		be adjusted for the main differences in the trial populations inclusion criteria (i.e. excluding patients with main PVT and/or EHS).	
Section 8.4.1: Pages 191-193	In section 8.4.1, TheraSphere and QuiremSpheres are included in the fully incremental analyses assuming equal efficacy and safety with SIR-Spheres. However, evidence from the Phase III randomised trials of SIR-Spheres should not be applied to other SIRT devices. There is no relevant clinical evidence comparing TheraSphere or QuiremSpheres with any of the comparators for the population of CTT-ineligible patients.	Sirtex proposes TheraSphere and QuiremSpheres are excluded from the base-case analyses, and therefore are deleted from Table 33 and Figure 19 on page 193, and that the surrounding interpretation is also removed.	When TheraSphere, QuiremSpheres, and lenvatinib are excluded from the base case, SIR-Spheres is the most cost-effective option.

Table 8. Subgroup of patient with low tumour burden (≤25%) and good liver function (ALBI grade 1)

Place in the Assessment Report	**Description of problem**	**Description of proposed amendment**	**Result of amended model or expected impact on the result (if applicable)**
Section 4.2.2.2, page 52 Section 6.3.2.3, page 135	The AG states on page 135: "*this definition did not represent a widely accepted clinically distinct subgroup of patients*". The AG also notes on page 52: "*This is not a clinically recognised subgroup*" However, patients with low tumour burden (≤25%) and good liver function (ALBI score 1) are a clinically plausible and appropriate target population for SIR-Spheres in the CTT-ineligible population based on the available evidence and the opinion of clinicians with extensive experience with SIRT. Please see section 2.2 of this document.	Sirtex proposes the amendment of these statements to clarify that the components of the subgroup - both the low tumour burden (≤25%) and the good liver function (ALBI score 1) separately are clinically recognised subgroups, however the combination is not relevant to systemic treatments. It is relevant specifically to SIRT. Additionally, Sirtex proposes that the subgroup is presented in the base case in Table 33 and Figure 19 on page 193, and is included in the current base case with the ITT population in Table 35 on page 195.	The use of the recommended subgroup has a significant effect on the cost-effectiveness results. Using the Low tumour burden/ALBI grade 1 subgroup (Table 35 of the AG Report) increased the QALY for SIR-Spheres from 0.764 to 1.153 and the costs from £30,107 to £34,267.

Table 9. Downstaging

Place in the Assessment Report	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Section 6.3.2.3, page 136	Page 136 of the assessment report states: "*The AG was advised that downstaging of patients with advanced HCC to transplant and other curative options is rare in UK clinical practice, with very few if any of these patients receiving curative therapies.*" This is however only true in the context of systemic therapies, as discussed in section 2.3 of this document, and does not preclude the use of curative treatments for a new treatment option, such as SIRT. The AG also states (page 136): "*Similarly, none of the previous TAs which assessed systemic cancer treatments for advanced HCC modelled the possibility of curative therapies. The AG is therefore concerned that the very sizable benefits resulting from curative therapy would not be realised in practice, and that the rarity of downstaging means any resulting incremental benefits are subject to very considerable uncertainty.*" As stated previously, the lack of modelling curative treatment with systemic therapies is due to the systemic therapies not allowing downstaging to potentially curative treatments. However, this does not preclude the inclusion of potentially curative treatment in the cost-effectiveness model for treatments that do result in downstaging such as SIRT. The AG did not include downstaging in the base-case cost-effectiveness analyses based on historic data	Sirtex proposes the statement is changed to: "The AG was advised that downstaging of patients with advanced HCC to transplant and other curative options is rare in **current** UK clinical practice **with systemic treatment**, with very few if any of these patients receiving curative therapies." Sirtex proposes the exclusion of the second statement on the over-estimation of benefits resulting from curative therapy because of the evidence laid out in Section 2.3 of this document. Sirtex also proposes including downstaging in the base-case analyses based on the evidence presented instead of the scenario analyses, i.e. the inclusion in Table 33 and Figure 19 on page 193 and the inclusion of the current base case without downstaging in Table 38 on page 202.	This has a major effect on the results, as downsizing to potentially curative treatments has important implications on both health benefits and costs. Excluding downstaging, excludes an important benefit of SIRT to the patients, that can be quantified and included in the cost-effectiveness model. Using the current AG results the inclusion of downstaging, even in the ITT population, increased the QALY for SIR-Spheres from 0.764 to 0.842 and reduced the costs from £30,107 to £29,208. While these changes seem small, in the context of the small differences between the different treatment options, they are influential.

	with systemic treatments. However, there is sufficient evidence in the literature and from clinicians, that with SIRT (as opposed to systemic therapies) do result in downstaging to potentially curative treatment option. Please see more details in section 2.3 of this document.		
Section 6.3.2.3, page 136	On page 136 the AG states: "*It is also notable that the SIRveNIB trial, which recruited a similar population, makes no mention of any patients going on to receive curative therapy.*" However, as the AG report stated (pages 48-49), SIRveNIB was conducted in Asia where prognosis and treatment pattern are different to that of patients in Europe, therefore it is not relevant for the UK population. This is also consistent with other technology appraisals for interventions in HCC(1,30).	Sirtex proposes the deletion of this statement.	This has a major effect on the results, as downstaging to potentially curative treatments has important implications on both health benefits and costs. Excluding downstaging, excludes an important benefit of SIRT to the patients, that can be quantified and included in the cost-effectiveness model. As stated above, using the current AG results the inclusion of downstaging, even in the ITT population, increased the QALY for SIR-Spheres from 0.764 to 0.842 and reduced the costs from £30,107 to £29,208. While these changes seem small, in the context of the small differences between the different treatment option, they are influential.
Section 4.2.2.2, page 50	On page 50, the AG presents the "*Rate of liver transplantation or resection*" As mentioned in the Background section of assessment report (pages 29-30), treatments with curative intent "include radiofrequency ablation (which uses the heat generated by alternating current to destroy solid tumour tissue), resection (where the tumour-containing portions of the liver are removed),	Sirtex proposes the rates from the SARAH trial and in Table 4 are revised to report according to treatment option. Sirtex therefore proposes the title and subsequent text are changed to: "Rate of transplantation ~~**or,**~~ **liver** resection **or percutaneous tumour ablation**"	This has a major effect on the results, as downstaging to potentially curative treatments has important implications on both health benefits and costs. Excluding downstaging, excludes an important benefit of SIRT to the patients, that can be quantified and included in the cost-effectiveness model.

	and liver transplantation", therefore a title excluding ablations is incorrect. Additionally, combining rates observed in SARAH and SIRveNIB is inappropriate, because treatment patterns in Asia are different, and not applicable to the UK population, as acknowledged in the assessment report (pages 48-49). Combining rates observed for sorafenib and SIRT is also misleading, because both treatments differ in their mechanism of action and because this would result in different rates of downstaging, as claimed in Section 2.3 of the present document.	A ~~very~~ small proportion of patients in **the SIRT** ~~**both**~~ treatment arm~~s~~ of the SARAH ~~**and SIRveNIB**~~ trial~~s~~ went on to have subsequent liver transplantation**, liver resection or percutaneous tumour ablation with SIRT (5.1%) vs. 1.4% with sorafenib ~~(<1%), liver surgery (0.6-1.3%) or tumour ablation (0.5-2.5%)~~**. **Additional evidence shows, depending on the selected subgroup, probabilities of 3.5% to 29% for patients to receive potentially curative treatments after SIRT, including a 13.5% downstaging rate in the subgroup of patients with a tumour burden ≤25% and ALBI grade 1 in the SARAH trial.**"	Using the current AG results the inclusion of downstaging, even in the ITT population, increased the QALY for SIR-Spheres from 0.764 to 0.842 and reduced the costs from £30,107 to £29,208. While these changes seem small, in the context of the small differences between the different treatment option, they are influential.

Table 10. Cost and number of SIR-Spheres administration procedures

Place in the Assessment Report	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Section 8.2.3.1: Page 186	The duration of "approximately one hour" mentioned in the Sirtex company submission (section 2.1, page 21, paragraph "Treatment administration") refers to the full duration of the SIRT administration procedure, including the preparation of the patient in the interventional room, the hepatic angiography, the infusion of the microspheres and the discharge of the patient from the interventional room, rather than the infusion of the microspheres alone. Durations of the treatment procedures are not expected to materially differ between SIR-Spheres and TheraSphere. The additional cost of £209 for the SIR-Spheres administration (based on the tariff RD32Z – Contract Fluoroscopy procedures with duration of more than 40 minutes) is not relevant. These costs are	Sirtex proposes the additional administration cost of £209 which has been applied for SIR-Spheres is removed from the economic model. Sirtex proposes therefore that the corresponding statement is deleted: "~~The Sirtex company submission stated that SIR-Spheres administration procedures use intermittent contrast medium injection to assess the distribution of the microspheres under x-ray over the course of approximately one hour. The AG therefore included an additional cost of £209 for the SIR-Spheres administration procedure (RD32Z –~~	Treatment costs with SIR-Spheres would be reduced by £209 per treatment procedure.

	already included in the HRG tariff applicable to SIRT YR57Z 'Percutaneous, Chemoembolisation, or Radioembolisation, of Lesion of Liver.	~~Contrast Fluoroscopy Procedures with duration of more than 40 minutes) for a total of £2,999."~~	
Section 4.2.2.2: Page 51 Section 6.3.2.3: Page 138	The Assessment Report notes that: *"No patient had a whole liver treatment approach in one session* [in the SARAH trial]. *Clinical advisors confirmed that this is reflective of their experience, where patients would not receive whole liver treatment in one session, in order to reduce the risk of radioembolisation induced liver disease (REILD)"* However, neither the AG nor Sirtex provided evidence of an increased toxicity of SIRT for patients with bi-lobar disease receiving simultaneous treatment. While whole-liver treatment could theoretically result in increased toxicity due to a higher exposure of the non-tumour liver, the evolution in clinical practice highlighted in Section 2.6 above would on the contrary result in more selective treatment approaches being utilised even for patients with bi-lobar HCC. These selective treatment approaches would reduce the radiation exposure of non-tumour liver parenchyma and therefore could reduce in decreased toxicity. No REILD or radiation hepatitis adverse events were observed in the ENRY register, and 2/130 (1.5%) patients treated with SIRT had radiation hepatitis in the SIRveNIB trial, in which more than 95% of patients received a single administration of SIR-Spheres. There are differences in the treatment of single lobe versus bi-lobar HCC between SIR-Spheres and TheraSphere: for TheraSphere as many vials as injections are required. Therefore, two vials are required for bi-lobar treatments, which are administered in a sequential manner. Conversely, due to differences in administration, bi-lobar treatments with SIR-Spheres only require a single vial, and therefore can be administered in the same treatment session. It is likely that these differences would	Sirtex proposes that the number of administrations of SIR-Spheres elicited from UK clinical experts is used as the base case of the model, and that sensitivity analyses is included for SIR-Spheres including alternative values ranging from 1.02 to 1.20 treatments per patients, as detailed in Section 7.2.4.1.1 of the Sirtex CS. These sensitivity analyses should be conducted only for SIR-Spheres as single-session treatment with split administration can only be performed using SIR-Spheres. Sirtex recommends that the report is updated to suggest that the toxicity observed in the SARAH and SIRveNIB trials and the ENRY register would not be significantly different from that observed in real-life clinical practice. Sirtex proposes the corresponding statements in sections 4.2.2.2 and 6.3.2.3 are removed or amended. Sirtex proposes that the committee includes sensitivity analyses with alternative numbers of procedures based on the number of treatments observed for TheraSphere in the available single-arm evidence for this product.	Treatment costs with SIR-Spheres would be reduced in sensitivity analyses.

	result in a higher mean number of treatments per patient for TheraSphere. Large-scale observational data from a retrospective analysis of 1,000 patients with HCC receiving TheraSphere in a single leading US centre have reported a mean 1.577 treatments per patient (range: 1 to 8); in this series, 36.1% of patients presented with bi-lobar HCC. While the above data does not report on routine clinical practice in the UK, as SIRT has not been routinely available in the NHS for the treatment of HCC, the difference in number of treatments received with either device is supported by the only UK-specific evidence found by Sirtex in this context. This evidence was from a recent audit of patients receiving SIRT at a specialist centre in England, which found that patients received a mean of [redacted] treatments with SIR-Spheres vs. [redacted] treatments with TheraSphere(31).		
Section 4.2.2.2: Page 51	Evidence from the ENRY register was dismissed on the grounds that the "*register is likely to include a majority of patients with colorectal cancer liver metastases, who do not have underlying cirrhosis, whereas in HCC patients the cirrhotic liver is likely to be more susceptible to REILD*". However, the ENRY register only included patients with HCC, 78.5% of whom had underlying cirrhosis. The ENRY register therefore provides confirmation that patients with bi-lobar HCC receive a single-session administration of SIR-Spheres in routine clinical practice, outside of the SARAH trial.	Sirtex recommends that the AG considers evidence from the ENRY register especially in terms of number of treatment procedures with SIR-Spheres, and to delete the following statement: ~~"This variance is likely to be due to the clinical indication for SIRT; the ENRY register is likely to include a majority of patients with colorectal cancer liver metastases, who do not have underlying cirrhosis, whereas in HCC patients the cirrhotic liver is likely to be more susceptible to REILD."~~	Clarification point without direct impact on the model.

3 Additional issues

Table 11. Extrapolation of survival data

<table>
<tr><th>Place in the Assessment Report</th><th>Description of problem</th><th>Description of proposed amendment</th><th>Result of amended model or expected impact on the result (if applicable)</th></tr>
<tr>
<td>Section 6.3.2.3, page 137

Section 8.2.1, page 176</td>
<td>On page 137, the AG claims the Sirtex model double counted survival for those downstaged:

“In the economic model, the outcomes for these patients are modelling independently, and therefore using the uncensored data means that the OS benefits experienced by these patients are double counted. The impact of this double counting is significant, and leads to a substantial overestimation of survival gain.”

Similarly, on page 138:

“The AG is also concerned that the modelled data were not censored for downstaging events and therefore double counts patients who were downstaged to receive curative treatment. As with OS, this results in PFS gains being overestimated, though to a lesser degree than OS.”

This is incorrect. The methodology used is reported on page 53 of the Sirtex CS: the survival benefit of treatments with curative intent is not captured in the SARAH trial outcomes, as only 1 patient in each arm died after treatments with curative intent. The remaining patients were alive and censored at the end of the follow-up period.

The Sirtex CS explains, that the scenario including downstaging excluded those patients from the survival analyses who had</td>
<td>Sirtex proposes to delete all mention of double counting on pages:

• 137
• 138
• 176
• 214

In the AG model, the following survival parameters should be used:

Survival parameters for independently fitted curves in the ITT population estimated from the SARAH trial:

<table>
<tr><th>Model</th><th>Coeff. name</th><th>Coeff. SIRT</th><th>Coeff. sorafenib</th></tr>
<tr><td>Exponential</td><td>rate</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Weibull</td><td>shape</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Weibull</td><td>scale</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>log normal</td><td>Mean log</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>log normal</td><td>Sd log</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>log Logistic</td><td>shape</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>log Logistic</td><td>scale</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Gamma</td><td>shape</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Gamma</td><td>rate</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Gen Gamma</td><td>mu</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Gen Gamma</td><td>sigma</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Gen Gamma</td><td>Q</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Gompertz</td><td>shape</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td>Gompertz</td><td>rate</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td>
<td>Due to the confidential nature of the survival parameters, it is not possible to ascertain if the AG model used the parameters in Appendix 2. If these parameters were used, the model and the results are not impacted.</td>
</tr>
</table>

<table>
<tr><th>Place in the Assessment Report</th><th>Description of problem</th><th>Description of proposed amendment</th><th>Result of amended model or expected impact on the result (if applicable)</th></tr>
<tr><td></td><td>received potentially curative treatments, thus avoiding any double counting.

The AG proposes censoring these patients on page 176:

“To avoid the double counting of patients who are downstaged to receive curative therapies, the data included from SARAH, for both SIR-Spheres and sorafenib are censored for downstaging.”

This is also incorrect, these patients do not need to be censored, as they have been excluded from the analyses.</td><td>Survival parameters for independently fitted curves in the low tumour burden (≤25%) and good liver function (ALBI grade 1) population estimated from the SARAH trial:

<table><tr><th>Model</th><th>Coeff. name</th><th>Coeff. SIRT</th><th>Coeff. sorafenib</th></tr><tr><td>Exponential</td><td>rate</td><td></td><td></td></tr><tr><td>Weibull</td><td>shape</td><td></td><td></td></tr><tr><td>Weibull</td><td>scale</td><td></td><td></td></tr><tr><td>log normal</td><td>Mean log</td><td></td><td></td></tr><tr><td>log normal</td><td>Sd log</td><td></td><td></td></tr><tr><td>log Logistic</td><td>shape</td><td></td><td></td></tr><tr><td>log Logistic</td><td>scale</td><td></td><td></td></tr><tr><td>Gamma</td><td>shape</td><td></td><td></td></tr><tr><td>Gamma</td><td>rate</td><td></td><td></td></tr><tr><td>Gen Gamma</td><td>mu</td><td></td><td></td></tr><tr><td>Gen Gamma</td><td>sigma</td><td></td><td></td></tr><tr><td>Gen Gamma</td><td>Q</td><td></td><td></td></tr><tr><td>Gompertz</td><td>shape</td><td></td><td></td></tr><tr><td>Gompertz</td><td>rate</td><td></td><td></td></tr></table>
coeff.: coefficient</td><td></td></tr>
<tr><td>The AG model

Section 8.2.1, page 176</td><td>It is not clear, how in the AG model the survival curve parameters were estimated.

This requires clarification. The Sirtex CS and subsequent clarification submitted all survival parameters and also the underlying summary data.

It is not clear in the AG model if any differentiation is included for the OS curves for the two model structures:

• for patients not receiving curative treatments and
• the total patient population including those receiving treatments with curative intent.</td><td>Sirtex proposes further clarification is added on how the survival parameters were calculated. This includes information on whether new curves were fitted, or if the submitted parameters were included in the model, and additional information on how patients were censored for downstaging.</td><td>This is a clarification request and as such does not result in changes in the model results.</td></tr>
</table>

Place in the Assessment Report	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
	The Sirtex CS includes two model structures in the cost-effectiveness model: • Traditional partitioned survival analyses, where the survival curves were fitted onto the patient level data of the SARAH trial for both PFS and OS without any modifications. This assumes, that any effect of downstaging is included in the survival curves, which we know not to be the case. • Model structure that includes separately patients receiving potentially curative treatment. For this structure, in the OS curves from the SARAH trial, all patients receiving potentially curative treatments have been excluded. The survival of these patients was taken from external source. So, the survival of the whole population should be estimated from adding the survival of patients not receiving curative treatments (from SARAH trial) and of those receiving curative treatment (from literature)		
Section 6.3.2.3, page 137	Page 137 of the AG report states that "*based on a log-normal extrapolation (used in the Sirtex base-case) and using the uncensored data, estimated OS gain on SIR-Spheres is 8.27 months. Using the log-normal function on the same data censored for downstaging results in a much-reduced predicted OS gain of 1.55 months*." The survival curves mentioned here are from different populations and therefore are not comparable. The comparable populations would be the following:	Sirtex proposes the following amendments: "based on a log-normal extrapolation (used in the Sirtex base-case) and using the uncensored data, estimated OS **~~gain~~** on SIR-Spheres is 8.27 months. Using the log-normal function **~~on the same data~~** **where patients downstaged were modelled through external data and the patients not downstaged were modelled using data from the SARAH trial for those not downstaged** **~~censored~~** **~~for downstaging~~** results in **~~a much reduced~~** predicted OS **~~gain~~** of **10.8** **~~1.55~~** months. **Additionally, using the**	This will not have implications on the results.

Place in the Assessment Report	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
	The OS from the structure that does not model separately patients with potentially curative treatment can be compared from the other model structure to the sum of the survival from patients receiving curative treatments AND the survival of those receiving curative treatments.	**lognormal function on the data that excludes patients who underwent therapies with curative intent results, as expected when excluding patients who do well on treatment, in a much-reduced predicted OS gain of 1.55 months**."	
Section 6.3.2.3, page 136	Page 136 of the AG assessment report discusses the preferred use of the Weibull curve instead of the lognormal curve, among others, because the tail fits Weibull better and fits with KOL opinion. However, tail has very limited data, and the opinion of 5 KOLs experienced with SIRT supported this extrapolation. Additionally, in the latest sorafenib NICE TA, lognormal distribution was found to fit the OS curves the best in advanced HCC for both sorafenib and best supportive care.	Sirtex proposes the use of lognormal distributions in the base case analyses presented in in Table 33 and Figure 19 on page 193, and the inclusion of the current base case with Weibull distribution in Table 38 on page 203 in scenario analyses.	This has only minor effect on the results. Using the current AG results the use of lognormal distribution, even in the ITT population, increased the QALY for SIR-Spheres from 0.764 to 0.795 and the costs from £30,107 to £ £30,426.
Section 6.3.2.3, page 139	The AG report states that: "*Assuming that patients who fail work-up receive sorafenib outcomes is therefore likely to overestimate the PFS and OS for those allocated to receive SIR-Spheres*" The Sirtex CS overestimates, not the survival, but the cost of patients on the SIRT arm. OS and PFS used are from the SARAH trial, that includes the efficacy of those who received sorafenib and those who did not. It is not possible to overestimate PFS/OS this way. We have, however, been conservative by overestimating the costs of patients dropping off by assuming the cost of sorafenib for all patients, but not the efficacy.	Sirtex proposes this statement is deleted.	This does not influence the results.

Table 12. Time on treatment

Place in the Assessment Report	Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
Section 6.3.2.3, page 139	The AG report states that "The approach taken to define ToT was inconsistent, as median values were used for sorafenib and lenvatinib, while a mean value was used for regorafenib" This is however incorrect. As reported on page 58 of the SIRTEX CS the median value was not used for sorafenib and lenvatinib but the patient level data for sorafenib and HR for lenvatinib as per the submission and Appendix F.	Sirtex proposes to delete this statement.	This does not influence the results.
Section 8.2.3.1, page 186 AG model	ToT by AG: "*was calculated by applying an exponential function to the median ToT reported in the SARAH trial (exponential mean 122.95 days)*" When fitting ToT curves to the patient level data, the exponential distribution has the worse fit after Weibull. Using the patient level data submitted, even an exponential distribution results in higher ToT (139.15 days), but the mean ToT for sorafenib using the distribution with the best fit (lognormal distribution) is 146.41 days. The AG model therefore underestimates the cost of sorafenib.	Sirtex recommends a revision of ToT for sorafenib in the model by using the parameters estimated based on the patient level data using the best fitting, lognormal distribution: **ITT** [redacted] [redacted] **Low tumour burden / good liver function** [redacted] [redacted]	These changes will increase the cost of sorafenib, and improve the cost-effectiveness of SIR-Spheres. The mean duration of sorafenib will increase by 23.46 days with a cost of £2,429.

4 References

1. NICE. Lenvatinib for untreated advanced hepatocellular carcinoma [Internet]. National Institute for Health and Care Excellence; [cited 2019 Oct 14]. Report No.: TA551. Available from: https://www.nice.org.uk/guidance/TA551

2. NICE. Regorafenib for previously treated advanced hepatocellular carcinoma [Internet]. National Institute for Health and Care Excellence; [cited 2019 Oct 14]. Report No.: TA555. Available from: https://www.nice.org.uk/guidance/TA555

3. Walton M, Wade R, Claxton L, Sharif-Hurst S, Harden M, Patel J, et al. Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276] Assessment Report. Centre for Reviews and Dissemination and Centre for Health Economics - York; 2019 Sep. Report No.: ID1276.

4. NHS England Specialised Services Clinical Reference Group for Radiotherapy. Clinical Commissioning Policy: Selective internal radiation therapy (SIRT) for chemotherapy refractory / intolerant metastatic colorectal cancer (adults). NHS England; 2018 Dec. Report No.: 170102P.

5. Commission Nationale d'Evaluation des Dispositifs Médicaux et des Technologies de Santé. SIR-SPHERES, Microsphères d'Yttrium-90. HAS; 2015 Mar. Report No.: CEPP-4825.

6. Vilgrain V, Abdel-Rehim M, Sibert A, Ronot M, Lebtahi R, Castéra L, et al. Radioembolisation with yttrium–90 microspheres versus sorafenib for treatment of advanced hepatocellular carcinoma (SARAH): study protocol for a randomised controlled trial. Trials [Internet]. 2014 Dec 3 [cited 2019 Jul 5];15. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4265525/

8. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182–236.

9. Villanueva A. Hepatocellular Carcinoma. N Engl J Med. 2019 Apr 11;380(15):1450–62.

10. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol Off J Am Soc Clin Oncol. 2015 Feb 20;33(6):550–8.

11. Hiraoka A, Kumada T, Michitaka K, Toyoda H, Tada T, Ueki H, et al. Usefulness of albumin-bilirubin grade for evaluation of prognosis of 2584 Japanese patients with hepatocellular carcinoma. J Gastroenterol Hepatol. 2016 May;31(5):1031–6.

12. Pinato DJ, Sharma R, Allara E, Yen C, Arizumi T, Kubota K, et al. The ALBI grade provides objective hepatic reserve estimation across each BCLC stage of hepatocellular carcinoma. J Hepatol. 2017;66(2):338–46.

13. Waked I, Berhane S, Toyoda H, Chan SL, Stern N, Palmer D, et al. Transarterial chemo-embolisation of hepatocellular carcinoma: impact of liver function and vascular invasion. Br J Cancer. 2017 Feb 14;116(4):448–54.

14. Hickey R, Mouli S, Kulik L, Desai K, Thornburg B, Ganger D, et al. Independent Analysis of Albumin-Bilirubin Grade in a 765-Patient Cohort Treated with Transarterial Locoregional Therapy for Hepatocellular Carcinoma. J Vasc Interv Radiol JVIR. 2016 Jun;27(6):795–802.

15. Han G, Berhane S, Toyoda H, Bettinger D, Elshaarawy O, Chan A, et al. Prediction of Survival Among Patients Receiving Transarterial Chemoembolization: A Response-Based Approach. Publ Rev. 2019;

16. Ali R, Yang Y, Antkowiak M, Gabr A, Mora R, Abouchaleh N, et al. Prognosticating Survival in Hepatocellular Carcinoma with Elevated Baseline Alpha-fetoprotein Treated with Radioembolization Using a Novel Laboratory Scoring System: Initial Development and Validation. Cardiovasc Intervent Radiol. 2019 May;42(5):700–11.

17. Antkowiak M, Gabr A, Das A, Ali R, Kulik L, Ganger D, et al. Prognostic Role of Albumin, Bilirubin, and ALBI Scores: Analysis of 1000 Patients with Hepatocellular Carcinoma Undergoing Radioembolization. Cancers. 2019 Jun 24;11(6).

18. Sirtex Medical. NICE Multiple Technology Appraisal ID1276 Selective internal radiation therapies for treating hepatocellular carcinoma: SIR-Spheres Y-90 resin microspheres. 2019 May.

19. Chow PKH, Gandhi M, Tan S-B, Khin MW, Khasbazar A, Ong J, et al. SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma. J Clin Oncol. 2018 Jul;36(19):1913–21.

20. Palmer DH, Hawkins NS, Vilgrain V, Pereira H, Chatellier G, Ross PJ. [734P] Selection of patients with hepatocellular carcinoma for selective internal radiation therapy based on tumour burden and liver function: A post-hoc analysis of the SARAH trial. Ann Oncol [Internet]. 2019 Oct 1 [cited 2019 Oct 14];30(Supplement_5). Available from: https://academic.oup.com/annonc/article/30/Supplement_5/mdz247.061/5576648

21. Visible Analytics. Clinician questionnaire: Resource use in the treatment of hepatocellular carcinoma patients. 2019.

22. CIRSE Registry for SIR-Spheres Therapy. CIRSE Registry for SIR-Spheres Therapy (CIRT): preliminary data on patients with HCC. 2019.

23. Regnault H, Perrin C, Amaddeo G, Chalaye J, Tacher V, Luciani A, et al. P07-06 yttrium -90 trans arterial radioembolisation (tare) is an effective treatment for the downstaging of patients with hepatocellular carcinoma: a monocentric experience in a tertiary center. In Lisbon, Portugal: EASL; 2019.

24. Iñarrairaegui M, Pardo F, Bilbao JI, Rotellar F, Benito A, D'Avola D, et al. Response to radioembolization with yttrium-90 resin microspheres may allow surgical treatment with curative intent and prolonged survival in previously unresectable hepatocellular carcinoma. Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol. 2012 Jul;38(7):594–601.

25. Kennedy A, Nag S, Salem R, Murthy R, McEwan AJ, Nutting C, et al. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. Int J Radiat Oncol Biol Phys. 2007 May 1;68(1):13–23.

26. Pasciak AS, Bourgeois AC, Bradley YC. A Microdosimetric Analysis of Absorbed Dose to Tumor as a Function of Number of Microspheres per Unit Volume in 90Y Radioembolization. J Nucl Med Off Publ Soc Nucl Med. 2016;57(7):1020–6.

27. Walrand S, Hesse M, Jamar F, Lhommel R. A hepatic dose-toxicity model opening the way toward individualized radioembolization planning. J Nucl Med Off Publ Soc Nucl Med. 2014 Aug;55(8):1317–22.

28. Sangro B, Martínez-Urbistondo D, Bester L, Bilbao JI, Coldwell DM, Flamen P, et al. Prevention and treatment of complications of selective internal radiation therapy: Expert guidance and systematic review. Hepatol Baltim Md. 2017;66(3):969–82.

29. Biederman DM, Titano JJ, Tabori NE, Pierobon ES, Alshebeeb K, Schwartz M, et al. Outcomes of Radioembolization in the Treatment of Hepatocellular Carcinoma with Portal Vein Invasion: Resin versus Glass Microspheres. J Vasc Interv Radiol. 2016 Jun;27(6):812-821.e2.

30. NICE. Sorafenib for treating advanced hepatocellular carcinoma [Internet]. National Institute for Health and Care Excellence; 2017 Sep [cited 2019 Oct 15]. Report No.: TA474. Available from: https://www.nice.org.uk/guidance/ta474

31. Christie NHS Foundation Trust. Data on File. 2019.

32. Wasan HS, Gibbs P, Sharma NK, Taieb J, Heinemann V, Ricke J, et al. First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. Lancet Oncol. 2017;18(9):1159–71.

33. NHS England. Commissioning through Evaluation Registry [Internet]. [cited 2019 Oct 15]. Available from: https://www.england.nhs.uk/commissioning/spec-services/npc-crg/comm-eval/

5 Appendix

Table 13. Experience of interviewed clinicians

Expert and interview type	Specialty	No. of unresectable HCC patient treated with SIRT / year	No. of unresectable HCC patient treated who are eligible for SIRT	Total new HCC patients / year	Relevant experience
KOL1: resource use interview	Medical oncology	N/A	N/A	180	Experience with SIRT in trials (FOXFIRE trial (32)) and clinical practice. Lead UK investigator for systemic therapy trials in HCC, author of HCC UK audit for sorafenib.
KOL2: resource use interview	Medical oncology	2-4	N/A	400	Experience with SIRT in trials (FOXFIRE trial (32), Commissioning through Evaluation registry (33)) and clinical practice. Lead UK investigator for systemic therapy trials in HCC, author of HCC UK audit for sorafenib.
KOL3: resource use interview	Hepatology	6	N/A	150-200	Experience with SIRT in trials (FOXFIRE trial (32)) and clinical practice.
KOL4: resource use interview	Nurse	Up to 15	N/A	250-300	Experience with SIRT in trials (FOXFIRE trial (32), Commissioning through Evaluation registry (33)) and clinical practice.
KOL5: resource use interview	Nurse	64	N/A	585	Experience with SIRT in trials (FOXFIRE trial (32), Commissioning through Evaluation registry (33)) and clinical practice.
KOL6: short survey	Radiology	<5	30	N/A	Experience with SIRT in trials (FOXFIRE trial (32)) and clinical practice. Last author for three publications on yttrium-90 SIRT.
KOL7: short survey	Radiology	5	20	N/A	Experience with SIRT in trials (FOXFIRE trial (32), Commissioning through Evaluation registry (33)) and clinical practice, author for one publication on yttrium-90 SIRT.
KOL8: short survey	Radiology	5	10	N/A	Experience with SIRT in trials (FOXFIRE trial (32)) and clinical practice.
KOL9: short survey	Radiology	4	20	N/A	Experience with SIRT in trials (FOXFIRE trial (32), Commissioning through Evaluation registry (33)) and clinical practice.
KOL10: short survey	Radiology	0	12	N/A	Experience with SIRT in trials (FOXFIRE trial (32) – largest enrolment site globally and Commissioning through Evaluation registry (33)) and clinical practice (not currently treating patients with HCC using SIRT due to lack of funding for the technology in this indication)
KOL11: resource use interview	Nurse	20 (Total SIRT patients)	N/A	N/A	Experience with SIRT in trials (FOXFIRE trial (32), Commissioning through Evaluation registry (33)) and clinical practice.

KOLx: clinical expert number; N/A: data not available

Selective Internal Radiation Therapies (SIRT) for treating unresectable hepatocellular carcinoma [ID1276]

Response to the Assessment Report

TERUMO EUROPE (distributor)/QUIREM MEDICAL (manufacturer)

15 October 2019

We are grateful for the opportunity to comment on this document

Section/Theme	Comment	Change proposed
General	We congratulate the Centre for Reviews and Dissemination and Centre for Health Economics in York for their thorough and clear report. Terumo/Quirem Medical is however disappointed by the conclusion of the Evaluation report. We believe that SIRT has a place in the treatment pathway in HCC. We are concerned that dosimetry is not discussed in the report, despite the evidence available showing the correlation between the dose absorbed by the tumour and treatment outcomes. We highlight below the importance of pre-treatment dosimetry for predicting clinical outcomes (for example in the post-hoc analysis of the SARAH RCT[1]) and in the recent DOSISPHERE RCT[2] We are disappointed that the York assessment group overlooked the current usage of SIRT in HCC in the NHS. It is already a treatment option available in the UK, but not consistently across the country. We believe the NICE Guidance would allow for a more consistent access to this therapy rather than the postcode lottery currently taking place.	
DOSIMETRY is critical	Summary The Assessment report and the evidence considered by the Committee should take into account dosimetry in the SIRT evaluation, and in particular tumour-absorbed dose. **Dosimetry, the measurement and calculation of ionizing radiation dose to tissue, can be considered an indicator of treatment success**. Indeed, it has been shown that there is a strong correlation between dose to the tumour and response[3]. This is further underlined by a recent post-hoc	**We would suggest that the Assessment Group considers the post-hoc analysis from SARAH for the subgroup receiving**

[1] Poster 736P at ESMO 2019 by Hawkins et al. - Overall survival of patients with hepatocellular carcinoma receiving sorafenib versus selective internal radiation therapy with predicted dosimetry in the SARAH trial (ID 5562)

[2] Presentation at CIRSE 2019 by Garin et al. – MAA based personalised dosimetry with TheraSphere for HCC: interim analysis of the phase II DOSISPHERE study

[3] Cremonesi M *et al.* Front Oncol., (2014). https://doi.org/10.3389/fonc.2014.00210

	analysis of the SARAH study which was presented at ESMO 2019 showing that overall survival was considerably longer in patients with a predicted tumour-absorbed dose >=100Gy than those with a predicted tumour-absorbed dose <100Gy. Conclusions drawn from the SARAH and SIRveNIB studies should therefore be considered in the light of methodological choices made in an era when the importance of dosimetry was not yet understood. Since then, many steps have been taken which may not invalidate these studies but indicate that they should be interpreted with nuance. Dosimetry and personalised treatment are undeniable factors in SIRT success. **We would suggest that the Assessment Group considers the post-hoc analysis from SARAH for the subgroup receiving >=100Gy presented at ESMO in their model and addresses the importance of predicted tumour-absorbed dose in their conclusions.** Rationale When reading the York assessment group evaluation report, we noted the absence of a discussion on dosimetry. Dosimetry is the measurement and calculation of ionizing radiation dose to tissue. Within the community it is now considered to be a key indicator of treatment success[4]. Over the last decade, the field of SIRT has taken a strong interest in developing a better understanding of the strong relation between (tumour) dose and outcome, also known as dose-effect relationships. It has been shown that there is a strong correlation between dose to the tumour and response, using any of the three products under evaluation and in several indications[4]. For example, in the case of SIRT with holmium microspheres, Bastiaannet et al.[5] established that there is a significant effect of absorbed dose on lesion response in liver metastases. Based on recently published studies, it is widely recognised that a better understanding of the SIRT procedure and the use of dosimetry will positively impact treatment outcome[6].	>=100Gy presented at ESMO in their model and addresses the importance of predicted tumour-absorbed dose in their conclusions.

[4] Cremonesi M *et al.* Front Oncol., (2014). https://doi.org/10.3389/fonc.2014.00210
[5] Bastiaannet R et al. J Nucl Med., (2019). https://doi.org/10.2967/jnumed.119.232751
[6] Bastiaannet R *et al.* EJNMMI Phys., (2018). https://doi.org/10.1186/s40658-018-0221-z.

	There is ample evidence to suggest that patients receiving sufficient dose to the tumour have better outcomes than patients that have been underdosed[7]. This has been prospectively validated in the recent DOSISPHERE trial[8] in HCC, a multicentre randomised study demonstrating the impact of 99mTc-MAA based dosimetry on tumour response with yttrium-90 glass microspheres in HCC. Patients were randomised between the personalised dosimetry arm (PDA) and standard dosimetry arm (SDA). Response rates were 79% vs. 43% respectively. On a tumour level, they showed that tumours that received a dose ≥ 205 Gy, 76.6% responded, whereas for tumours that received less than 205 Gy, only 22.2% responded. These outcomes clearly indicate the need to personalise treatment, aiming to reach sufficient target dose for each individual. Secondly, these results highlight the need to grade studies, based on how they take dosimetry and personalised treatment into consideration. Relevance for the SIRT Appraisal These aspects are of intrinsic importance for the NICE Appraisal as the SARAH trial is the basis of the conclusions of the Assessment report for the patients not eligible for CTT. The 2 randomised phase III trials, evaluated in the report, have indeed been criticised for their lack of endpoints regarding tumour-absorbed dose and liver absorbed dose from the moment they were published[9]. The methods used in these studies for calculating the activity needed to treat a patient, are now known not to allow for a personalised treatment, resulting in insufficient tumour dose[10]. The occurrence of underdosing in a subcohort of the SARAH study and the subsequent effects on tumour control and outcomes were demonstrated by Allimant et al.[11]	

[7] Garin E *et al.* J Nucl Med., (2012). https://doi.org/10.2967/jnumed.111.094235
[8] Presentation at CIRSE 2019 by Garin et al. – MAA based personalised dosimetry with TheraSphere for HCC: interim analysis of the phase II DOSISPHERE study
[9] Sposito C *et al.* HepatoBiliary Surg Nutr., (2018). https://doi.org/10.21037/hbsn.2018.10.06 and Garin E *et al.* Lancet Oncol., (2018). https://doi.org/10.1016/S1470-2045(18)30024-X
[10] Kafrouni M *et al.* J Nucl Med., (2018). https://doi.org/10.2967/jnumed.117.202937
[11] Allimant C *et al.* J Vasc Interv Radiol., (2018). https://doi.org/10.1016/j.jvir.2018.07.006

	A recent abstract presented at the ESMO Congress[12] (September 2019), is instrumental in highlighting the importance of predicted tumour dose on outcomes. The aim of the post-hoc analysis of survival from the SARAH trial is to assess the impact of predicted dosimetry on OS following SIRT and to compare outcomes of SIRT using Yttrium-90 resin microspheres versus sorafenib in specific patient subgroups. A subgroup analysis was performed for patients with a predicted tumour-absorbed dose >=100Gy. Patients in the SIRT arm receiving a tumour absorbed dose of >=100Gy had statistically significant prolonged survival and improved tumour response compared to patients receiving sorafenib (OS 23.0 months vs 18.2 months, and PFS 10.05 months vs. 6.91 months). The authors indicate that, crucially for the purposes of patient selection, the predicted tumour-absorbed dose is estimated prior to the administration of SIRT using 99mTc-MAA SPECT/CT imaging. This sub-analysis was presented during ESMO 2019 alongside the results from the subgroup presented by SIRTEX in their submission (low liver burden/ALBI Grade 1).[13] The conclusions of the SARAH and SIRveNIB studies should therefore be considered in the light of this new evidence. This nuance should be made when interpreting the outcomes obtained using dated methodology. The QuiremSpheres® submission to NICE already discussed the importance of patient selection for an optimal treatment outcome. It was highlighted that QuiremScout® – the first SIRT workup product that utilises the same particle (poly-L-lactic acid microspheres loaded with holmium-166) as the therapeutic microspheres – has been shown to be a safe and more effective option than 99mTc-MAA for predicting intrahepatic distribution (and therefore to predict tumour-absorbed dose) Since the submission in May, Smits et al[14] have shown that 166Ho-scout has shown to have a superior predictive value for intrahepatic distribution (and therefore for actual	

[12] Poster 736P at ESMO 2019 by Hawkins et al. - Overall survival of patients with hepatocellular carcinoma receiving sorafenib versus selective internal radiation therapy with predicted dosimetry in the SARAH trial (ID 5562)

[13] Poster 734P at ESMO 2019 - Selection of patients with hepatocellular carcinoma for selective internal radiation therapy based on tumour burden and liver function: A post-hoc analysis of the SARAH trial (ID 4338)

[14] Smits MLJ *et al.* Eur J Nucl Med Mol Imaging., (2019). https://doi.org/10.1007/s00259-019-04460-y

	therapeutic dose) in comparison to 99mTc-MAA prior treatment with 166Ho-radioembolization. **We would suggest that the Assessment Group considers the post-hoc analysis from SARAH for the subgroup receiving >=100Gy presented at ESMO in their model and addresses the importance of predicted tumour-absorbed dose in their conclusions.**	
Summary of SARAH and SIRTEX cost-effectiveness results Subgroup : low tumour burden (<=25%) and preserved liver function (ALBI 1)	We wanted to provide the Assessment group with some relevant publications highlighting that parameters of low tumour burden (<25%) and the ALBI score to measure liver function are relevant parameters to look at SIRT effectiveness. Although we agree that they have not been looked at as a composite parameter. Low tumour burden The ESMO HCC guidelines indicate that: "*Absolute contraindications for transarterial therapies are decompensated cirrhosis,* ***extensive tumor burden****, reduced portal vein flow, renal failure or any technical contraindication*" In the publication of Sangro et al[15] a better OS is obtained for 1-5 nodules vs >5 nodules. (see graph and table below). This is another indication that the tumour burden has an impact on procedural effectiveness.	

[15] Sangro B, et al. Survival After Yttrium-90 Resin Microsphere Radioembolization of Hepatocellular Carcinoma Across Barcelona Clinic Liver Cancer Stages: A European Evaluation. HEPATOLOGY, Vol. 54, No. 3, 2011

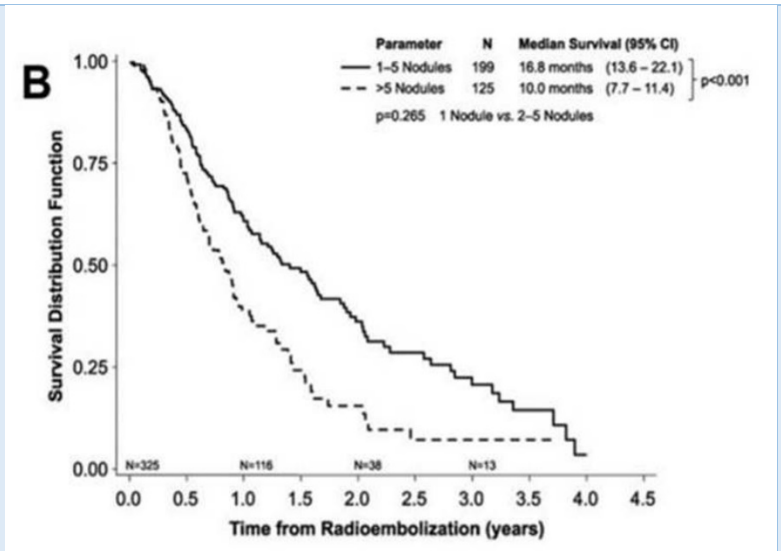


Table 5. Multivariate Analysis of Significant Single-Vector Prognostic Indicators

Variable	HR (95% CI)	P
All patients		
No. of nodules >5	1.76 (1.32-2.35)	<0.001
ECOG performance status	1.39 (1.14-1.70)	0.001
Extrahepatic disease	1.91 (1.17-3.13)	0.010
INR >1.2	1.47 (1.04-2.09)	0.028
BCLC stage A		
INR >1.2	5.26 (1.72-16.09)	0.004
BCLC stage B		
AFP >400 ng/mL	2.98 (1.62-5.48)	<0.001
Total bilirubin >1.5 mg/dL	2.91 (1.20-7.06)	0.019
BCLC stage C		
No. of nodules >5	1.59 (1.10-2.29)	0.014
INR >1.2	1.52 (1.05-2.21)	0.028

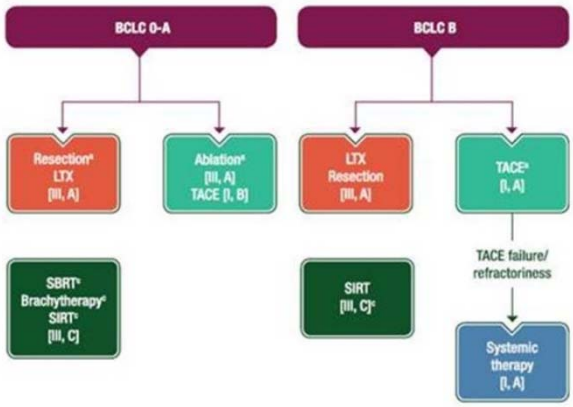
Abbreviation: AFP, alpha-fetoprotein.
Model selection was made according to the best subsets approach using input variables that are statistically significant in the univariate Cox proportional hazards model ($P < 0.05$). Data contributing to the multivariate model: n = 319/325 (98.2%).

ALBI grading

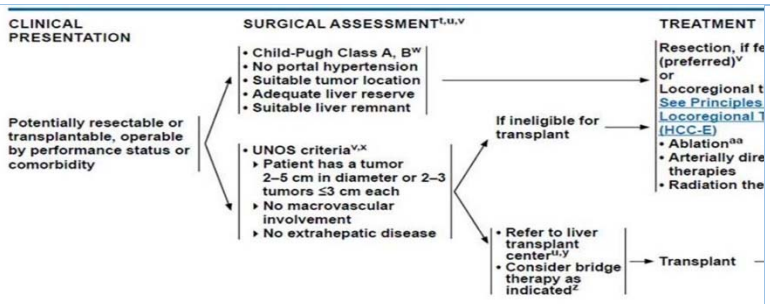
Although this score is mentioned in guidelines, its role in clinical decision making or stratification in is not consistently used.

However, a paper by Antkowiak et al[16] recently compared the relevance of the ALBI score vs Child–Pugh (CP) in 1000 HCC patients treated with yttrium-90.
It reports that median OS for ALBI 1, 2, and 3 grades was 46.7, 19.1, and 8.8 months, respectively and median OS for CP A, B, and C was 21.7, 11.3, and 6.0 months, respectively.
The authors conclude that ***ALBI outperforms CP in survival prognosis in Y90 treated patients***.

[16] Antkowiak M, et al., Cancers (2019). doi:10.3390/cancers11060879

Population 1 « Patients eligible for transplant » The 2 RCTs available (PREMIERE & Kulik et al) are not relevant to the UK clinical practice : transplant waiting times are short (on average 50 days) and SIRT is rarely the (bridging) option of choice	<u>SIRT is a well-established « bridging » option</u> Both European and US guidelines include SIRT as part of the options available for bridge to transplant. In <u>*ESMO HCC guidelines*</u>, SIRT is listed as an option for bridge to transplant, and appears in the treatment flowchart (See below) possible, SIRT may be considered. Additionally, SIRT may be considered instead of TACE for the treatment of small tumours in patients waiting for liver transplantation, in an attempt to avoid drop-out from the list due to tumour progression [106].  In <u>*EASL guidelines*</u>, the use of SIRT as bridge to transplant, is mentioned (although not reflected in the treatment flowchart) **Other indications** Few studies have evaluated SIRT as a bridge to liver transpl In a small series, patients treated with SIRT showed be tumour control and a higher proportion received liver tr plantation than those with TACE, leading to speculation SIRT could reduce drop-out from transplant waiting list SIRT has also been tested in patients with borderline resect HCC. Besides its effect on tumour control, SIRT might prepar select patients for surgery as it induces substantial hypertro in the liver lobe contralateral to the target.[561] Both guidelines refer to the Salem study[17] that compares the efficacy of Y90 vs TACE in HCC liver transplant candidates. SIRT also appears as an option for liver transplant in the <u>*US guidelines*</u>	

[17] Salem R, et al. Gastroenterology (2016). doi: 10.1053/j.gastro.2016.08.029

		
Continued access to SIRT treatment in the NHS	The Evaluation report concludes that there is not enough robust and relevant evidence to create a NMA in « early » and « intermediate » patient groups. The evidence provided by manufacturers is criticised and mostly overlooked. It gives the unfortunate impression that SIRT will not be considered in these populations. However, SIRT is already being offered as a treatment option in some hospitals in England. Data gathered from Hospital Episode Statistics for the period July 2018-June 2019 shows that primary HCC is the primary diagnosis of about a third of patients treated with SIRT. However, anecdotal evidence suggests that access is not consistent across the country. The NICE recommendations would provide very clear guidance and a consensus which would be welcome and allow a more consistent access to this therapy rather than the postcode lottery currently taking place. A network of 10 hospitals specialised in providing SIRT is already in place across the country following the Commissioning through evaluation process. A clear recommendation similar to the commissioning policy available for mCRC would be beneficial.	The current SIRT practice in the NHS should be taken into account
Equivalence of efficacy between the 3 SIRT technologies (Evaluation report base-case	The Assessment Group's base-case analysis assumes equivalence between SIRT technologies due to a lack of randomised evidence on the relative effectiveness of each SIRT. This is in line with the analysis submitted AiC by Terumo Europe as an addendum. Although it is a very small pilot study with several methodological limitations, clinical outcomes appear to be similar between treatment groups. The Terumo/Quirem Medical submission highlighted that, on the basis of an identical therapeutic mode of action based on emission of beta radiation, holmium-166 microspheres (QuiremSpheres®) is regarded as a technical	No change required. Consider the procedure irrespectively of the technology used (as per

presented p.23, p.176 ; addendum presented by Terumo Europe page 60)	variant of yttrium-90 resin (SIR-Spheres®) and glass (TheraSphere®) microspheres within the framework of selective internal radiation therapy (SIRT). It is important to note that this rationale has been confirmed by the Interventional Procedure team at NICE that considers the SIRT procedure irrespectively of the product used (SIR-Spheres®, TheraSphere® and QuiremSpheres®). It is therefore reassuring that the Technology Appraisal process follows the same direction.	the NICE Interventional Procedure Committee)
8.5 page 207-208 *In all scenarios, QuiremSpheres was not cost-effective compared with other SIRTs due to higher work-up costs*	The Terumo Europe/Quirem Medical submission is built on list prices rather than NHS acquisition costs. Indeed, as holmium-166 work-up product (QuiremScout®) and microspheres (QuiremSpheres®) are not fully commercial in the UK, the commercial price (acquisition costs) are not fully defined yet. It is important to note that the competitive environment for medical technologies (and therefore their price) is very different to pharmaceuticals. There are already two SIRT technologies being used in the NHS, and three in many other European healthcare systems. The commercial price will be subject to these competitive market forces. We are modifying our PAS with the Patient Access Scheme Liaison Unit so it can be more reflective of a price at full commercial availability. Moreover, the Assessment report considers QuiremScout® work-up costs solely with SIRT using QuiremSpheres®, thereby considerably increasing the costs of holmium SIRT. However, it is important to note that it is not compulsory to use QuiremScout® as a work-up prior to SIRT using QuiremSpheres® The traditional work-up surrogate (99mTc-MAA) can be used prior to SIRT using QuiremSpheres®. Conversely, QuiremScout® can be used as a work-up prior to SIRT using resin yttrium-90 (SIR-Spheres®) or glass yttrium-90 (TheraSphere®) microspheres. **The model should consider a scenario in which all 3 SIRT technologies have the same work-up costs.**	Please adapt the cost of QuiremSpheres® in the evaluation following updated Patient Access Scheme Please create a scenario in which work-up acquisition costs are the same for all 3 SIRT technologies
4.2.2.5 p.58-59 Description and critique	We value the opinion and critique of the York assessment group. However, we do not understand this comment « *patients in the TheraSphere group had poorer prognosis at baseline compared with the other two treatment groups* ». Could you please expand on this point as the authors do not concur?	We would be grateful for an answer as the authors do not

of the Terumo addendum		understand this comment

Overall survival of patients with hepatocellular carcinoma receiving sorafenib versus selective internal radiation therapy with predicted dosimetry in the SARAH trial

Hawkins N[1], Ross P[2,3], Palmer D[4], Chatellier G[5,6], Pereira H[5,6], Vilgrain V[7]

[1] Institute of Health & Wellbeing, University of Glasgow, Glasgow, UK [2] Medical Oncology, Guy's and St. Thomas' NHS Foundation Trust, London, UK [3] Medical Oncology, King's College Hospital, London, UK [4] Molecular and Cancer Medicine, University of Liverpool, Liverpool, UK
[5] Hôpital européen Georges-Pompidou (AP-HP), Unité d'épidémiologie et de Recherche Clinique, Paris, France [6] INSERM, Centre d'Investigation Clinique 1418, module Épidémiologie Clinique, Paris, France [7] Radiology, Hôpital Beaujon (AP-HP), Clichy, France

Introduction

Background

Hepatocellular carcinoma (HCC) is a complex disease with a heterogenous patient population presenting at different disease stages, with different degrees of tumour burden, various morphologies, and liver function impairment as common comorbidity.

Two randomised controlled trials (RCTs) in Europe (SARAH)[1] and Asia Pacific (SIRveNIB) compared selective internal radiation therapy (SIRT) using ^{90}Y resin microspheres with sorafenib 400mg *bid*, the standard of care systemic therapy for patients not eligible for transarterial chemoembolisation (TACE). The trials did not show a statistically significant benefit of SIRT over sorafenib in terms of overall survival (OS), but did show improved tumour response rates, a lower frequency of treatment-related adverse events, and lower rates of progression in the liver as first site in the SIRT arm.

Correlations between the predicted dose of radiation to the tumour and outcomes of SIRT in HCC have been observed, including in provisional data from SARAH showing that patients in the SIRT arm receiving a tumour-absorbed dose ≥100 Gy had prolonged survival and improved tumour response.[2]

Crucially for the purposes of patient selection, the predicted tumour-absorbed dose is estimated prior to the administration of SIRT using ^{99m}technetium macroaggregated albumin (^{99m}Tc-MAA) SPECT/CT imaging.

Objective

The aim of this *post hoc* analysis of survival data from the SARAH trial was to assess the impact of predicted dosimetry on OS following SIRT and to compare outcomes of SIRT using ^{90}Y resin microspheres versus sorafenib in specific patient subgroups.

Methods

Trial

Main inclusion criteria for SARAH were a diagnosis of HCC, either advanced HCC (Barcelona Clinic Liver Cancer [BCLC] stage C), intermediate HCC (BCLC stage B) having failed up to two rounds of TACE, or a recurring HCC lesion not eligible for resection, transplantation or ablation.[1]

Eligible patients were randomly assigned (1:1) to receive either SIRT using ^{90}Y resin microspheres or sorafenib 400mg *bid*. Patients assigned to SIRT underwent a work-up consisting of angiography of the hepatic artery, protective coiling of extrahepatic branches and ^{99m}Tc-MAA SPECT/CT scintigraphy. Prescribed activity was calculated according to the modified body surface area (BSA) model. Patients underwent SIRT during a subsequent hospital admission.[1]

Dosimetry was calculated retrospectively, using imaging collected in the work-up phase prior to the SIRT treatment. ^{99m}Tc-MAA-SPECT/CT imaging was analysed using dosimetry software to delineate volumes of interest and estimate absorbed dose in the volumes of interest with a voxel-based estimation method.

Statistical analysis

Analyses were performed in patients from the intent-to-treat (ITT) population for whom dosimetric data were available. The primary endpoint was OS, defined as time from randomisation to death from any cause or date of last follow-up in patients still alive.

A subgroup analysis was performed for patients with a predicted tumour-absorbed dose ≥100 Gy, selected based on a previously-established association with greatest effectiveness with SIRT using ^{90}Y resin microspheres in HCC. Propensity score matching (PSM) was conducted to correct for loss of randomisation in the comparison.

Table 1: Comparison of baseline characteristics

Characteristic		Total in SIRT arm, n (%) N=237	Proportion in SIRT arm with predicted dose ≥100 Gy, % N=64	Total in sorafenib arm, n (%) N=216
Child-Pugh grade	A	196 (83%)	86%	187 (85%)
	B	38 (16%)	14%	34 (15%)
Tumour involvement	Bi-lobar	50 (21%)	20%	35 (16%)
	Unilobar	187 (79%)	80%	187 (84%)
Portal vein thrombosis	Present	143 (60%)	48%	118 (53%)
	Absent	94 (40%)	52%	104 (47%)
Number of tumour nodules	<4	225 (95%)	94%	211 (95%)
	≥4	12 (5%)	6%	11 (5%)
Previous TACE	No	119 (50%)	34%	114 (51%)
	Yes	118 (50%)	66%	108 (49%)
Tumour burden	<25%	157 (66%)	84%	146 (66%)
	≥25%	80 (34%)	16%	76 (34%)
ALBI grade	1	52 (22%)	21%	70 (32%)
	2 or 3	174 (73%)	79%	148 (68%)
BCLC stage	A	9 (4%)	5%	12 (5%)
	B	66 (28%)	39%	61 (27%)
	C	162 (68%)	56%	149 (67%)

ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolisation.

PSM was based on inverse propensity score weights to account for potential sample selection bias into the ≥100 Gy SIRT group. The matching considered pre-specified variables for subgroup analysis in the SARAH trial and those identified as prognostic by Sangro *et al.*[3] Variables used for the matching were: complete portal vein occlusion of the main vein; Child-Pugh A vs. B; bilobar vs. unilobar disease; alcohol-induced aetiology; hepatitis B and/or C virus infection; cirrhosis; portal branch occlusion; tumour number (<4 nodules vs. ≥4 nodules); prior TACE; and tumour burden (≤25% vs. >25%). ALBI grade was also included as a recently-developed measure of liver function.[4] Sorafenib patients were re-weighted to match the SIRT ≥100 Gy group.

Results

Between December 2011 and March 2015, 467 patients were recruited to the SARAH trial; 237 patients were randomly assigned to SIRT, but 53 (22%) of these did not receive SIRT, leaving 184 patients receiving SIRT, of whom dosimetry data were available for 127 patients.

Figure 1: Balance between ≥100 Gy and sorafenib groups after propensity score matching based on inverse propensity score weights

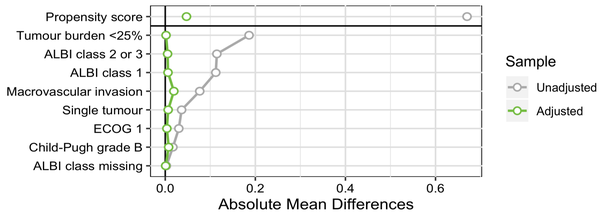
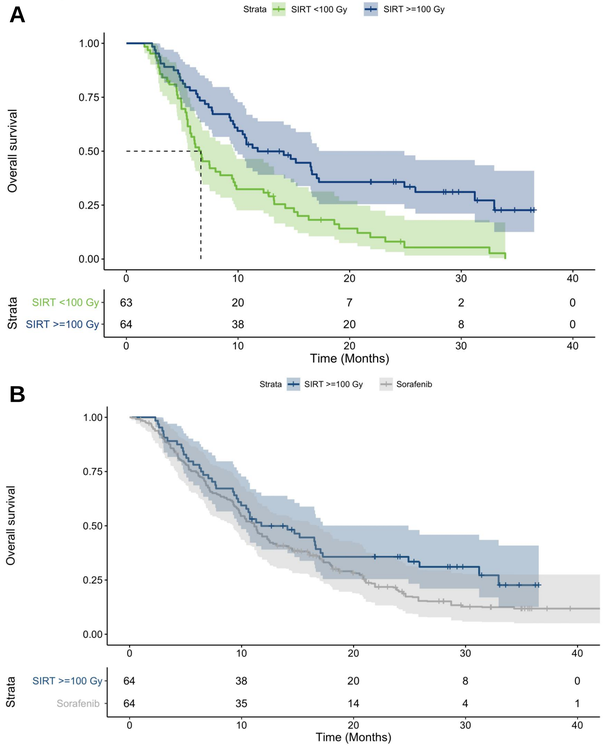


Figure 2: Kaplan-Meier curves of A) overall survival with SIRT ≥100 Gy and SIRT <100 Gy and B) matched comparison of overall survival between SIRT ≥100 Gy and sorafenib

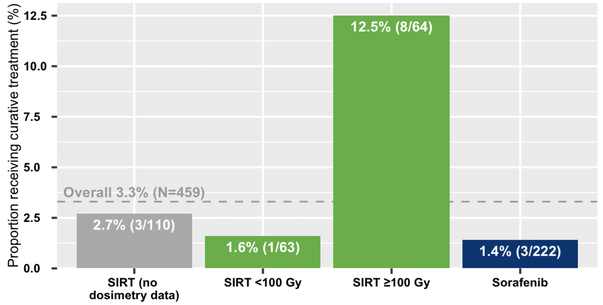


For the dosimetry subgroups, key baseline variables were similar between the patients receiving SIRT ≥100 Gy and the sorafenib population (Table 1). PSM by inverse propensity score weighting was successful in further reducing the absolute mean differences between the matched cohorts (Figure 1).

OS was considerably longer in patients with a predicted tumour-absorbed dose ≥100 Gy than those with a predicted dose <100 Gy (Figure 2A). Furthermore, patients who received SIRT with a predicted dose ≥100 Gy had a statistically significant increase in OS compared to patients who received sorafenib (Figure 2B); mean OS in the matched SIRT ≥100 Gy group was 23.0 months versus 18.2 months in the corresponding sorafenib group.

Mean progression-free survival was also higher in the SIRT ≥100 Gy group at 10.05 months versus 6.91 months with sorafenib.

Figure 3: Proportion of patients receiving treatment with curative intent



A regression analysis indicated that low tumour burden (≤25%) is associated with a significant increase in mean predicted dose of 77 Gy (mean predicted dose: 93 Gy and 170 Gy in the high and low tumour burden groups, respectively, p = 0.015).

A small number of patients (n=15) in SARAH received curative treatments (surgical resection, liver transplantation, tumour ablation) after the study-allocated treatments. Of these, three had received sorafenib, one had received a predicted SIRT dose of <100 Gy, and eight had received a predicted SIRT dose of ≥100 Gy (p<0.001) (Figure 3).

Discussion and conclusions

A predicted dosimetry ≥100 Gy was associated with prolonged OS following SIRT with ^{90}Y resin microspheres compared with sorafenib.

The present analysis also demonstrates that patients receiving SIRT with a tumour-absorbed dose ≥100 Gy are significantly more likely to undergo subsequent curative treatment than those receiving sorafenib.

In conclusion, this analysis of the SARAH data suggests that predicted dosimetry may be relevant for patient selection for SIRT versus sorafenib in patients with HCC who are not eligible for TACE.

Conflicts of interest

DP reports fees/honoraria/travel support from Bayer, Eisai, BMS, MSD, and AstraZeneca. **PR** reports honoraria from Amgen, Servier, Shire, Sirtex, BMS, Pierre Fabre, and Roche; participation in advisory board meetings for Shire, Celgene, BMS, Pierre Fabre; receipt of travel support from Amgen, BMS, Bayer, and Servier; his institution has received research funding from Sanofi. **NH** is a partner for Visible Analytics, which conducted the statistical analyses and received consultancy, research grant and expenses from Sirtex. **VV** reports research grants and personal fees from Sirtex during the conduct of the SARAH study, and subsequent participation in an advisory board meeting for Sirtex. **GC** and **HP** declare no competing interests. Editorial assistance was provided by Covalence Research Ltd, London, UK.

References

1. Vilgrain V *et al.*; SARAH Trial Group. Efficacy and safety of selective internal radiotherapy with yttrium 90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. Lancet Oncol. 2017;18(12):1624–1636.
2. Hermann A-L *et al.* Role of 99mTc-Macroaggregated Albumin SPECT/CT based dosimetry in predicting survival and tumour response of patients with locally advanced and inoperable hepatocellular carcinoma (HCC) treated by selective intra-arterial radiation therapy (SIRT) with yttrium-90 resin microspheres, a cohort from SARAH study. J Hepatol. 2018;68((Suppl)):S13.
3. Sangro B *et al.* Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. Hepatology. 2011 Sep 2;54(3):868–78.
4. Johnson PJ, *et al.* Assessment of Liver Function in Patients With Hepatocellular Carcinoma: A New Evidence-Based Approach—The ALBI Grade. J Clin Oncol. 2015;33(6):550-8.

Further information is available on request.

Funding for this analysis was provided by Sirtex. SIR-Spheres® is a registered trademark of Sirtex SIR-Spheres Pty Ltd.

Assessment report for consultation to C&Cs: Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276]

The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments.

Page 23 – " the proportion of patients who completed the questionnaires was low" – the questionnaire return rates should be stated in order to justify this statement.

Page 25 – it is not helpful that the two submissions have compared SIRT to different standard treatments (Sirtex to DEB-TACE and TheraSphere to regorafenib) – perhaps that should have been specified in the scope that was offered to the companies by NICE?

It is not clear why Therasphere is cost-saving (presumably due to a hypothetical 50% discount) relative to SIR-Spheres. Notably, the price for NHS hospitals is currently equivalent for the 2 products, so the terms of this hypothetical discount are not clear.

Recently, the cost for SIR-Spheres has halved in clinical practice in certain hospitals in the UK and Europe since we have been able to deliver a single dose of SIR-Spheres to two patients on the same day. This is using a selective approach, where individual arteries are feeding multiple tumours or different parts of a large single tumour. As far as we are aware, this approach is not possible with TheraSphere.

Page 26 – the report states that Therasphere was cost effective compared to sorafenib at a TWP threshold of £30,000. However, the comparators were allowed to be considered with "confidential PAS discounts" – was the same playing field offered to the SIRT manufacturers for PAS by NICE?

Page 27 – the report seems to jump within sections between sorafenib and lenvatinib with no clear justification for using one or other as comparator. In particular, greater consistency and justification is required for the comparison to lenvatinib (rather than sorafenib) on page 27. Currently, lenvatinib is only used in approximately 5% of patients with HCC who are not eligible for TACE. Despite its non-inferiority compared with sorafenib, this current practice results from the lack of evidence-based second-line options after lenvatinib and the generalised experience of sorafenib available among UK clinicians.

Rest of document (no page references):

It is correct that ALBI score is not routinely used in clinical practice for HCC – Child Pugh is the principal scoring system for clinical practice. ALBI 1 is mainly Child Pugh score 5.

The evidence that ALBI 1 (which is mainly Child Pugh 5) and low tumour volume benefit from SIRT has been presented in abstract form at a scientific meeting (ESMO 2019) by Professor Dan Palmer of the University of Liverpool and Dr Paul Ross of Kings College London. It reports positive findings for patients receiving SIRT vs sorafenib in the subgroup of patients with an ALBI grade 1 and a tumour burden ≤25%. This abstract has not yet been published as a full paper, but I understand from the scientific investigators that it is likely to be published within the next 6 months.

The only published Phase III randomised trials of SIRT for HCC have used SIR-Spheres. The effectiveness and safety observed in the SARAH and SIRveNIB trials cannot be generalised to TheraSphere or QuiremSpheres.

Downsizing patients to hepatic resection or transplantation or ablation is potentially curative and therefore the best chance for long-term survival in this patient group. The authors should not dismiss the importance of hepatic resection (the reason stated is that “resection” is not “transplantation” as stated in the BTG case). Both types of surgery are important clinical outcomes for patients with this disease, with important health economic implications. There is also evidence from the SARAH trial that 5% of patients treated with SIR-Spheres, although initially unresectable, had sufficient tumour response to be downstaged to potentially curative treatments (these include liver transplantation, hepatectomy and percutaneous tumour ablation). There is preliminary evidence that improved patient selection can result in even higher rates of downstaging following SIRT (see Palmer D et al. ESMO 2019 poster). The message is that, for some patients with HCC, downstaging following SIRT can dramatically alter the progression of the disease, as opposed to the palliative intent of systemic therapies such as sorafenib and regorafenib.

Selective Internal Radiation Therapy for treating HCC

Feedback on Assessment Report from Teik Choon See

- Overall a very detailed assessment with comprehensive evidence review and robust methodologies given the complexity of the subject and limitation of level 1 evidence.
- No head to head study for direct comparison of costs.
- Inference from cost effectiveness comparison with lenvatinib may not be relevant in the UK given that it is not the commonest systemic therapy used.
- Is the difference in cost between Theraspheres and Sirspheres related to single versus two treatment sessions for bilobar disease? In practice doses for sirspheres can be divided to > 1 targeted delivery, during the same session.
- There is a standard HRG, irrespective of the products.
- Difficult to infer the available evidence given that a number of the completed trials (e.g. SARAH) were set up many years ago.
- SIRveNIB and SARAH trials included different patient group which may not be comparable with UK patients.
- Level 1 evidence on down staging will not be available due to current clinical practice and medical ethics.
- Evidence on SIRT for tumour burden ≤25% rumor burden or ALBI grade of 1 deserved further exploration.
- Late Intermediate stage patients?

Assessment report for consultation to C&Cs: Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276]

Kelvin Marshall – Patient Representative for the above appraisal.

I have no submission regarding the appraisal documentation, but I would ask that any patient information material/leaflets relating to the following be made available for the meeting, and if possible, copies/attachments emailed to me in advance.

- Lenvatinib
- Sorafenib
- TheraSphere
- SirSpheres
- Quiremspheres

Thank you

Kelvin Marshall

Liver4Life Helpline Manager

Assessment Group's Response to consultation comments

Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma

26th October 2019

1 Plausibility of equal efficacy of SIRTs

AG response: The comparative effectiveness of alternative SIRT technologies (SIR-Spheres, TheraSphere and QuiremSpheres) in all HCC populations is largely unknown. The technologies are similar in that all aim to achieve targeted destruction of the tumour by internal deliver of a radioactive isotope. As such it is not unreasonable to *a priori* consider that the effectiveness of individual SIRTs would be similar. However, there are differences in the technologies that may impact on effectiveness, including important differences in terms of the size of micro beads and the radioactive isotope used, see Table 2 of the AG report for comparison of the SIRTs.

The empirical evidence on the comparative effectiveness of the different SIRTs is weak. There is currently is no comparative evidence regarding the relative effectiveness of QuiremSpheres and only 5 retrospective non-randomised studies comparing SIR-Spheres with TheraSpheres. Two of these studies Bhangoo, 2015[17] and Biederman, 2015[20] did not report survival outcomes. In D'Abadie, 2018[21] the population recruited was unclear and appeared to be a mix of patients eligible and ineligible for TACE. The results appear to suggest similar survival outcomes for the two different SIRTs, though no formal analysis is implemented.

Van Der Gucht, 2017[18]	42 (subgroup of 77 patients)	SIR-Spheres	TheraSphere	Retrospective comparative	Subgroup of advanced stage HCC patients.
Biederman, 2016[19]	90	SIR-Spheres	TheraSphere	Retrospective comparative	Patients with unresectable HCC and main or lobar PVT.
D'Abadie, 2018[21]	45	SIR-Spheres	TheraSphere	Retrospective comparative	Population unclear. Appears to include both patients eligible and ineligible for TACE.
Bhangoo, 2015[17]	17	TheraSphere	SIR-Spheres	Retrospective comparative	Mixed population of patients with unresectable HCC, who had either failed or were not amenable to other locoregional therapies. No relevant outcomes reported.
Biederman, 2015[20]	97	SIR-Spheres	TheraSphere	Retrospective comparative	Adults with unresectable HCC with PVT. No relevant outcomes reported.

The Van Der Gucht, 2017[18] and Biederman, 2016[19] syudies, both suggest that TheraSpheres is superior to SIR-Spheres, though only the latter comparison reports a statistically significant difference. In the quality assessment carried out as part of the systematic review, both studies were rated at high risk of bias, with concerns raised regarding differences in base-line characteristics and lack of blinded outcome assessment, see Table 1.

Table 1 Risk of bias assessment results for retrospective comparative studies

Trial	Biederman 2015 (abstract only)	Biederman 2016	Van Der Gucht 2017	Bhangoo 2015	d'Abadie 2018
Inclusion criteria clearly defined	No	Yes	Yes	Yes	No
Representative sample from relevant population	Unclear	Yes	Yes	Yes	Unclear
Groups similar at baseline	Unclear	No (see table below)	No ("Patients with small-tumor volumes were preferentially addressed to 90Y glass microspheres")	Unclear	No
Clearly described and consistently delivered intervention	No	Yes	Yes	Yes	No
Clearly described and consistently delivered comparator	No	Yes	Yes	Yes	No
Outcome assessors blinded	Unclear	Unclear	Unclear	Unclear	Unclear
Missing outcome data balanced across groups	Unclear	Unclear	Yes	Unclear	Unclear
Free from suggestion of selective reporting	Unclear	Unclear	Yes	Yes	Yes
Overall judgement of risk of bias	High	High	High	Unclear	High

A comparison of base-line characteristics in Biederman, 2016[19] (Table 2) does not show any consistent differences in base-line characteristics that would favour one group over the other. The AG is, however, is concerned that the results of Biederman, 2016[19] lack face validity. The reported HR from Biederman, 2016[19] was 0.39 (CI 0.23 to 0.67) with patients receiving TheraSpheres reported to have substantially longer median survival (9.5 vs 3.7 months). This is sizable survival advantage given the inherent similarities in the treatments. Further the AG notes that the reported median OS for SIR-Spheres of 3.7 months is much shorter than the median OS reported in SARAH and SIRveNIB, 8.0 and 8.8 months respectively.

A similar comparison of base-line characteristics in Van Der Gucht, 2017[18] suggests that TheraSpheres patients may have better prognosis than the SIR-Spheres patients as they appear to have smaller tumours on average, were less heavily pre-treated and were less likely to have bilobar disease. The results of Van Der Gucht, 2017[18] show a more modest benefit in favour of TheraSphere HR 0.77,

(CI 0.27 to 2.18). It is important to note the results of NMA used in the model were primarily driven by the Biederman, 2016[19] study as this is a larger study and therefore carried more weight in the meta-analysis. The plausibility of the Biederman, 2016[19] results are therefore of primary concern when considering the relevant scenario analysis in the economic model.

Table 2 Summary of Baseline characteristics

	Biederman 2016 Baseline Patient Characteristics		**Van Der Gucht, 2017 Baseline Patient Characteristics***	
	SIR-Spheres (n=21)	**TheraSphere (n=69)**	**SIR-Spheres (n=41)**	**TheraSphere (n=36)**
Age	60.0 ± 11.5	65.6 ± 11.3	68 (58–72)	71 (62–75)
Male	20 (95.2%)	54 (78.3%)	37 (90.2)	6 (83.3)
Ethnicity caucasian	15 (71.4%)	31 (44.9%)	NR	NR
Prior therapy naive	14 (66.7%)	35 (50.7%)	11 (26.8)	16 (44.4)
Prior therapy TACE	5 (23.8%)	29 (42%)	13 (31.7)	6 (16.7)
Sorafenib before	6 (28.6%)	31 (44.9%)	0.0 (0.0)	0.0 (0.0)
Tumour size <5 cm ≥5 cm	NR	NR	 14 (34.1) 27 (65.9)	 17 (47.2) 19 (52.8)
Tumour distribution Solitary Multifocal	 14 (66.7) 7 (33.3)	 42 (60.9) 27 (39.1)	 21 (51.2) 20 (28.8)	 15 (41.7) 21 (58.3)
ECOG PS 1 ECOG PS 2	12 (57.1%) 1 (4.8%)	31 (44.9%) 10 (14.5%)	NR	NR
Cirrhosis present	15 (71.4%)	58 (84.1%)	36 (87.8)	30 (83.3)

*Reported characteristics are for the whole population not just advanced patients

2 Overall survival (OS) extrapolation

AG response: The AG approach to extrapolating OS sought to account for the desire incorporate lenvatinib as a comparator in the economic analysis. As discussed in the AG report the generalised gamma model had the best fit along with the log-normal and log-logistic curves which had similar statistical fit. The generalised gamma, log-normal, and log-logistic models are, however, all accelerated failure time models and as such, a hazard ratio cannot be applied to them. This prevents them from being used if we wish to include lenvatinib as a comparator. The AG therefore took the pragmatic step to select this best fitting curve from amongst those that a HR could be applied i.e. a Weibull curve. The AG considered this reasonable given the available data and the small variation in predicted incremental survival across all six functions; but acknowledge this as a limitation of the presented base-case analysis. To reassure the committee we therefore also presented scenario analysis in which the generalised gamma, log-normal and log-logistic functions are used to model OS. In these scenarios, equivalence is assumed between sorafenib and lenvatinib.

The AG also notes that other methods of modelling time to even data were proposed as a potentially solution to this issue including spline and piecewise modelling. The AG considered these as options and agrees that these could be used to model OS and would allow a HR to be applied to the extrapolated curves. These approaches, however, have limitations particularly in the context of the present appraisal. Specifically, these methods fit to part of the observed data, and as such the extrapolated portion of these models would be driven by the tail of the observed data. The tails of the observed data, however, show a degree of divergence between SIR-Sphere and SIRT, extrapolation using a spline or piecewise model may therefore result in a divergence in predicted survival during the extrapolated period. This is not present using either the Weibull or generalised gamma function to model OS.

3 Dosimetry in the AG's analysis

AG response: A subgroup analysis based on predicted dosimetry in the SARAH trial was presented in Section 7.1.7 of the original Sirtex submission, and a similar analysis as described in the Terumo consultation response was presented in late September at the ESMO Congress 2019. While there initially appeared to be a significant difference in OS between SIR-Spheres patients with a predicted dose of ≥100 Gy and the ITT sorafenib population [redacted] following adjustment for differences in baseline characteristics, this difference was no longer significant [redacted]

Further investigation by Sirtex identified a strong correlation between tumour burden and predicted dose. Regression analysis indicated that a tumour burden of ≥25 was associated with a reduction of [redacted] in the mean predicted dose, with patients with a low tumour burden (<25%) having a mean predicted dose of [redacted] The implication of this finding is that the predicted dosimetry in the SARAH trial appeared to identify healthier patients, it is therefore unsurprising that these patients had a longer OS than the ITT sorafenib population, and that this benefit was lost in a matched comparison.

The AG concluded that given the strong correlation between patients having a predicted dose of ≥100 and a tumour burden of <25%, the company's subgroup analysis focusing on patients with a tumour burden <25% and an ALBI grade of 1 was preferable to one based on predicted dosimetry, and appeared to comprise a roughly equivalent group of patients. The use of this subgroup had a number of important benefits: a) it permitted direct comparison with sorafenib patients (who understandably had no predicted dosimetry data); b) tumour burden/ALBI score data was available for the whole SIR-Spheres population (compared to 65.7% with recorded predicted dosimetry data); c) patients would be prospectively definable in current clinical practice, thus would not require an unnecessary work-up procedure. The company also stated that it was unclear whether 99mTc-MAA based dosimetry was part of the way SIRT was currently used on the NHS.

The concept of predicted dosimetry was not further examined in the AG Report partly because the interim analysis of the Phase II DOSISPHERE study discussed by Terumo in their consultation response was only presented at CIRSE following the submission of the AG report, and thus was not considered. The AG note that the cut-offs used in this analysis (≥205 Gy) were substantially higher than those used in the *post hoc* analysis of the SARAH trial. Given the correlation between tumour burden and predicted dosimetry, it is unclear whether this analysis truly reflects the dose the tumour will receive, or instead separates out the healthiest patients in terms of baseline tumour burden.

The AG again reiterate that neither subgroup analysis found a statistically significant difference in OS between SIR-Spheres and sorafenib, as the trial was not appropriately powered for these *post hoc* analyses.

4 Treatment of curative intent

AG response: The results of the SARAH Trial in Table 4 of Sirtex's response show that in the low tumour burden and ALBI 1 subgroup that a greater proportion of SIRT patients went on to receive curative therapy than those that received sorafenib. This reported difference is, however, based on a post-hoc analysis of the SARAH trial, which breaks the randomisation of the trial. As such there is a risk of confounding and that these results are spurious. The AG notes there is significant imbalance in the size of the two groups within this subgroup suggesting the potential for selection bias and as can be in seen Table 1, that a number of base-line characteristics appear imbalanced. Importantly the proportion of patients with a single tumour nodule is higher in the SIRT arm, as well as greater proportion of patients having BCLC B disease. Both characteristics are likely linked to the probability of receiving curative treatment.

Table 3 Baseline characteristics: low tumour burden and ALBI 1 subgroup

Baseline characteristics	Sorafenib (n=48)	SIRT (n=37)
Age, years		
≥65	48%	43%
<65	52%	57%
ECOG performance status		
0	79%	62%
1	21%	38%
2	0%	0%
BCLC stage		
A	6%	3%
B	35%	43%
C	58%	54%
Number of tumour nodules (multifocal vs. single nodule)		
Multiple	67%	57%
Single	33%	43%
Number of tumour nodules		
<4	92%	92%
≥4	8%	8%
Macroscopic vascular invasion		
No	48%	46%
Yes	52%	54%
Child-Pugh grade		
A	98%	95%
B	2%	5%

Even if we take the results of the SARAH trial at face value, the AG is concerned about the generalisability of downstaging to UK practice. The AG was advised that downstaging of patients with advanced HCC to transplant and other curative options is rare in UK clinical practice, with very few if any of these patients receiving curative therapies. It is also notable that the SIRveNIB trial, which recruited a similar population, makes no mention of any patients going on to receive curative therapy. The AG also notes that the recent TA for sorafenib and lenvatinib (TA474 and TA551) did not model downstaging. Given these uncertainties the AG therefore considered that it was inappropriate to include these benefits in the base-case. To explore the possibility of benefits associated with downstaging scenario analysis was presented for both full advance population and the low tumour burden/ALBI 1 subgroup.

5 Equal administration costs of SIRT

AG response: The addition of a contrast fluoroscopy procedure into the administration costs for SIR-Spheres in the AG model was done to reflect the difference between the descriptions of the administration procedure defined in the respective submissions from Sirtex and BTG. The BTG submission for TheraSphere states on page 15: *"Administration of TheraSphere® is carried out on an outpatient basis, is quick and easy* ***and requires no contrast.****"* This is supported by the package insert for TheraSphere, which makes no mention of fluoroscopy, CT-guidance, or the use of a contrast medium injection in its detailed description of the administration procedure.

In their consultation response, Sirtex goes on to state that the HRG tariff YR57Z 'Percutaneous, Chemoembolisation, or Radioembolisation, of Lesion of Liver' already accounts for the cost of contrast fluoroscopy, thus the additional cost included by the AG for SIR-Spheres results in double counting. If the AG's assessment is correct, £209 should have instead been deducted from the administration cost for TheraSphere. However, as there is no net effect upon relative costs of SIR-Spheres and TheraSphere, no new analysis has been undertaken.

6 Treatment of bilobar disease

AG response: The AG acknowledges that the evidence provided in the Sirtex consultation response supports the companies assertion that patients with bilobar disease will have both lobes treated simultaneously. However, clinical experts consulted by the AG were of the view that simultaneous treatment of both lobes would not be undertaken in the UK due to the risks of radiation induced liver disease. Further, the AG emphasises that observed data from SARAH are based on separate treatment of each lobe and therefore the estimated survival gains are based on patients receiving sequential treatment.

7 Adjusting for portal vein involvement

AG response: The SARAH and SIRveNIB trials both exclude patients with extra-hepatic spread. The REFLECT trial[23], which compares lenvatinib and sorafenib, however, included a proportion of patients with extra-hepatic spread (61% in the lenvatinib arm and 62% in the sorafenib arm). To ensure that the population hazard ratio drawn from REFLECT reflected the modelled population, the NMA drew data from the reported subgroup of patients without extra-hepatic spread or portal vein invasion. Sirtex are therefore correct in their assertion that this population does not fully reflect the population in the SARAH and SIRveNIB trials which included patients with portal vein invasion. This inconsistency, will however, only impact on model results to the extent that the relative effectiveness of lenvatinib and sorafenib differ across the population of patients with and without portal vein invasion. The AG consider this to be relative small risk given that only a minority of patients enrolled had portal vein involvement and the relative stability of reported HR across a range of subgroups presented in REFLECT trial publication. The adjusted analysis suggested by SIRTEX excluding PVI patients are effectively presented in Scenario 3 where the no MVI subgroup is modelled. As can be seen this scenario lenvatinib and sorafenib both still dominate the SIRTs.

8 Appropriateness of lenvatinib as a comparator

AG response: The AG's interpretation of the NICE Scope decision problem to be addressed in this appraisal is that we were assess the effectiveness and cost-effectiveness of SIRT therapies relative to

currently available NHS treatments. In the context of advanced HCC this therefore includes both lenvatinib and sorafenib, as eligible to receive both therapies. Reflecting this the AG included lenvatinib as a relevant comparator. The AG further notes, that while lenvatinib is used in only a minority of patients, it is used in practice and therefore a comparison solely against sorafenib will misrepresent the additional incremental costs and QALYs generated resulting from implementing SIRTs in the NHS. For completeness, Table 4 and Table 5 present scenario analyses in which lenvatinib is excluded as a comparator.

Table 4 Results of AG base-case and scenarios 1-4 *SW quadrant ICERs not presented

Intervention	Total			Incremental (vs baseline)						ICER (fully incremental)	ICER (vs sorafenib)
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER	NMB (30k)	NMB (20k)		
AG Deterministic base-case											
TheraSphere	£29,888	1.110	0.764								-
SIR Spheres	£30,107	1.110	0.764	£218	0.000	0.000	More costly	-£218	-£218	Ext. dom.	-
Sorafenib	£32,082	1.243	0.841	£2,194	0.133	0.076	£28,728	£97	-£667	£28,728	-
QuiremSpheres	£36,503	1.110	0.764	£6,614	0.000	0.000	More costly	-£6,614	-£6,614	Ext. dom.	-
AG Probabilistic base-case											
TheraSphere	£30,017	1.111	0.765								-
SIR Spheres	£30,230	1.111	0.765	£213	0.000	0.000	Dominated	-£217	-£216	Dominated	-
Sorafenib	£32,495	1.244	0.841	£2,478	0.133	0.077	£32,302	-£177	-£944	£32,302	-
QuiremSpheres	£36,618	1.111	0.765	£6,600	0.000	0.000	Dominated	-£6,604	-£6,603	Dominated	-
Deterministic Scenario 1: Efficacy data from SARAH only											
TheraSphere	£29,395	0.976	0.671								-
SIR Spheres	£29,614	0.976	0.671	£218	0.000	0.000	More costly	-£218	-£218	Ext. dom.	-
Sorafenib	£31,951	1.209	0.817	£2,556	0.233	0.147	£17,424	£1,845	£378	£17,424	-
QuiremSpheres	£36,010	0.976	0.671	£6,614	0.000	0.000	More costly	-£6,614	-£6,614	Ext. dom.	Dominated
Deterministic Scenario 2: Low tumour burden/ALBI grade 1 subgroup											
Sorafenib	£33,388	1.420	1.037								
TheraSphere	£34,021	1.542	1.153	£633	0.122	0.116	£5,466	£2,841	£1,683	£5,466	£5,466
SIR Spheres	£34,267	1.542	1.153	£879	0.122	0.116	£7,594	£2,594	£1,436	Ext. dom.	£7,594
QuiremSpheres	£40,931	1.542	1.153	£7,544	0.122	0.116	£65,152	-£4,070	-£5,228	Ext. dom.	£65,152
Deterministic Scenario 3: No macroscopic vascular invasion (SARAH)											

TheraSphere	£29,949	1.078	0.740								£15,923
SIR Spheres	£30,167	1.078	0.740	£218	0.000	0.000	More costly	-£218	-£218	Ext. dom.	£14,535
Sorafenib	£32,452	1.326	0.897	£2,503	0.248	0.157	£15,923	£2,213	£641	£15,923	-
QuiremSpheres	£36,563	1.078	0.740	£6,614	0.000	0.000	More costly	-£6,614	-£6,614	Dominated	Dominated
Deterministic Scenario 4: TheraSphere HR from Biederman and Van Der Gucht NMA Scenario											
SIR Spheres	£30,107	1.110	0.764								£25,870
Sorafenib	£32,082	1.243	0.841	£1,976	0.133	0.076	£25,870	£315	-£448	Ext. dom.	-
TheraSphere	£33,373	1.883	1.297	£3,267	0.773	0.533	£6,130	£12,722	£7,392	£6,130	£2,828
QuiremSpheres	£36,503	1.110	0.764	£6,396	0.000	0.000	More costly	-£6,396	-£6,396	Dominated	Dominated
Deterministic Scenario 10: Low tumour burden/ALBI 1 subgroup including possibility of downstaging											
TheraSphere	£31,255	1.752	1.316								Dominant
SIR Spheres	£31,501	1.752	1.316	£246	0.000	0.000	More costly	-£246	-£246	Ext. dom.	Dominant
Sorafenib	£33,007	1.457	1.066	£1,752	-0.295	-0.250	Dominated	-£9,240	-£6,744	Dominated	-
QuiremSpheres	£38,166	1.752	1.316	£6,911	0.000	0.000	More costly	-£6,911	-£6,911	Ext. dom.	£20,669

Table 5 Results of AG base-case excluding lenvatinib, gen. gamma on OS.

Intervention	Total			Incremental (vs baseline)						ICER (fully incremental)	ICER (vs sorafenib)
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER	NMB (30k)	NMB (20k)		
AG Deterministic base-case (Gen. gamma OS)											
TheraSphere	£30,992	1.277	0.875								
SIR Spheres	£31,211	1.277	0.875	£218	0.000	0.000	More costly	-£218	-£218	Ext. dom.	-
Sorafenib	£32,854	1.357	0.916	£1,862	0.080	0.040	£46,103	-£650	-£1,054	£46,103	-
QuiremSpheres	£37,607	1.277	0.875	£6,614	0.000	0.000	More costly	-£6,614	-£6,614	Ext. dom.	Dominated

Addendum (1) to Assessment Group's Response to consultation comments

Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma

Table 1 Results of AG base-case and scenarios 1-4 with equal SIRT work-up costs, no PAS discounts

Intervention	Total			Incremental (vs baseline)						ICER (fully incremental)	ICER (vs sorafenib)
	Costs	LYs	QALYs	Costs	LYs	QALYs	ICER	NMB (30k)	NMB (20k)		
AG Deterministic base-case											
TheraSphere	£29,888	1.110	0.764								-
Lenvatinib	£30,005	1.183	0.805	£117	0.073	0.040	£2,911	£1,090	£688	£2,911	-
SIR Spheres	£30,107	1.110	0.764	£218	0.000	0.000	More costly	-£218	-£218	Extendedly dominated	-
QuiremSpheres	£31,868	1.110	0.764	£1,980	0.000	0.000	More costly	-£1,980	-£1,980	Extendedly dominated	-
Sorafenib	£32,082	1.243	0.841	£2,194	0.133	0.076	£28,728	£97	-£667	£57,488	-
Deterministic Scenario 1: Efficacy data from SARAH only											
TheraSphere	£29,395	0.976	0.671								-
SIR Spheres	£29,614	0.976	0.671	£218	0.000	0.000	More costly	-£218	-£218	Extendedly dominated	-
Lenvatinib	£29,893	1.150	0.782	£498	0.174	0.111	£4,475	£2,840	£1,727	£4,475	-
QuiremSpheres	£31,375	0.976	0.671	£1,980	0.000	0.000	More costly	-£1,980	-£1,980	Extendedly dominated	-
Sorafenib	£31,951	1.209	0.817	£2,556	0.233	0.147	£17,424	£1,845	£378	£58,080	-
Deterministic Scenario 2: Low tumour burden/ALBI grade 1 subgroup											
Lenvatinib	£31,388	1.366	1.000								-
Sorafenib	£33,388	1.420	1.037	£2,000	0.054	0.038	£53,320	-£875	-£1,250	Extendedly dominated	-
TheraSphere	£34,021	1.542	1.153	£2,633	0.176	0.153	£17,175	£1,966	£433	£17,175	£5,466
SIR Spheres	£34,267	1.542	1.153	£2,879	0.176	0.153	£18,783	£1,720	£187	Dominated	£7,594
QuiremSpheres	£36,256	1.542	1.153	£4,868	0.176	0.153	£31,759	-£270	-£1,803	Dominated	£24,774
Deterministic Scenario 3: No macroscopic vascular invasion (SARAH)											
TheraSphere	£29,949	1.078	0.740								-

SIR Spheres	£30,167	1.078	0.740	£218	0.000	0.000	More costly	-£218	-£218	Extendedly dominated	-
Lenvatinib	£30,399	1.272	0.865	£451	0.194	0.125	£3,594	£3,310	£2,056	£3,594	-
QuiremSpheres	£31,929	1.078	0.740	£1,980	0.000	0.000	More costly	-£1,980	-£1,980	Extendedly dominated	-
Sorafenib	£32,452	1.326	0.897	£2,503	0.248	0.157	£15,923	£2,213	£641	£64,437	-
Deterministic Scenario 4: TheraSphere HR from Biederman and Van Der Gucht NMA Scenario											
Lenvatinib	£30,005	1.183	0.805								-
SIR Spheres	£30,107	1.110	0.764	£101	-0.073	-0.040	Dominated	-£1,308	-£906	Dominated	-
QuiremSpheres	£31,868	1.110	0.764	£1,863	-0.073	-0.040	Dominated	-£3,070	-£2,668	Dominated	-
Sorafenib	£32,082	1.243	0.841	£2,077	0.060	0.036	£57,488	-£993	-£1,354	Extendedly dominated	-
TheraSphere	£33,373	1.883	1.297	£3,368	0.700	0.493	£6,835	£11,413	£6,486	£6,835	£2,828
Deterministic Scenario 10: Low tumour burden/ALBI 1 subgroup including 13.5% downstaging											
Lenvatinib	£31,072	1.404	1.029								-
TheraSphere	£31,467	1.736	1.303	£395	0.332	0.274	£1,440	£7,826	£5,086	£1,440	-
SIR Spheres	£31,713	1.736	1.303	£641	0.332	0.274	£2,339	£7,579	£4,839	Extendedly dominated	-
Sorafenib	£33,007	1.457	1.066	£1,935	0.053	0.037	£52,685	-£833	-£1,200	Extendedly dominated	-
QuiremSpheres	£33,702	1.736	1.303	£2,630	0.332	0.274	£9,599	£5,590	£2,850	Dominated	£2,931

Network 2: Adults with unresectable HCC who are eligible for conventional transarterial therapies

The second model is for patients with unresectable HCC who are eligible for conventional transarterial therapies (CTT). Patients in this population tend to have intermediate stage HCC (BCLC B), however patients with advanced stage HCC (BCLC C) can also be eligible if they do not have portal vein thrombosis (PVT)/portal vein involvement (PVI) or extra-hepatic spread. Studies in which the majority of patients had intermediate stage HCC (BCLC B) and ≤ 30% of patients had advanced disease (BCLC C) were included. If studies reported results split by disease stage, they were included. A small proportion of patients in this population may also be eligible for downstaging to transplant. However, there was very little evidence to inform this. Furthermore, clinicians advised that the role of downstaging HCC for liver transplantation is currently under evaluation in the UK and SIRT is not specifically required for downstaging as this can be achieved using existing therapies, most commonly TACE.

After screening the 39 studies described in the previous section, 7 studies were identified as relevant for the population of patients who are eligible for CTT: 6 RCTs and 1 retrospective comparative study. The reasons for inclusion and exclusion are listed in Table 8 of the AG report. The main reason for exclusion was the population being substantially mixed in terms of stage of HCC disease or patients having advanced stage disease, which made them ineligible for CTT. SIR-TACE, which is an RCT comparing SIR-Spheres and TACE, included a mixed population of patients with early, intermediate or advanced stage HCC. The trial was funded by Sirtex Medical; therefore, data split by disease stage was requested. However, Sirtex Medical were unable to provide the data as they did not have access to it, and it could not be included in the NMA.

The studies included in Network 2 were an RCT directly comparing SIR-Spheres to DEB-TACE (Pitton *et al*.), 5 RCTs comparing different CTT therapies and one retrospective comparative study comparing SIR-Spheres and TheraSphere (Van Der Gucht *et al*.), which had a high risk of bias, as reported in Table 13.8 of the AG report appendices. The two treatment groups in Van Der Gucht et al. were not similar at baseline as patients with small tumour volumes were preferentially treated with TheraSphere. It was also unclear whether outcome assessors were blinded. There were no studies comparing TheraSphere and CTT.

The RCT that compared SIR-Spheres and DEB-TACE (Pitton *et al)*. is a pilot study that included only 24 patients and was the only direct evidence between SIR-Spheres and CTT. There were some concerns regarding bias as there was no information about allocation concealment. Treatment groups appeared reasonably similar at baseline, although more patients in the SIRT group had received prior local ablation (4 versus 1) and more patients in the DEB-TACE group had received prior resection (5 versus 3). The full risk of bias assessment for Pitton et al. is reported in Table 13.5 of the AG report appendices

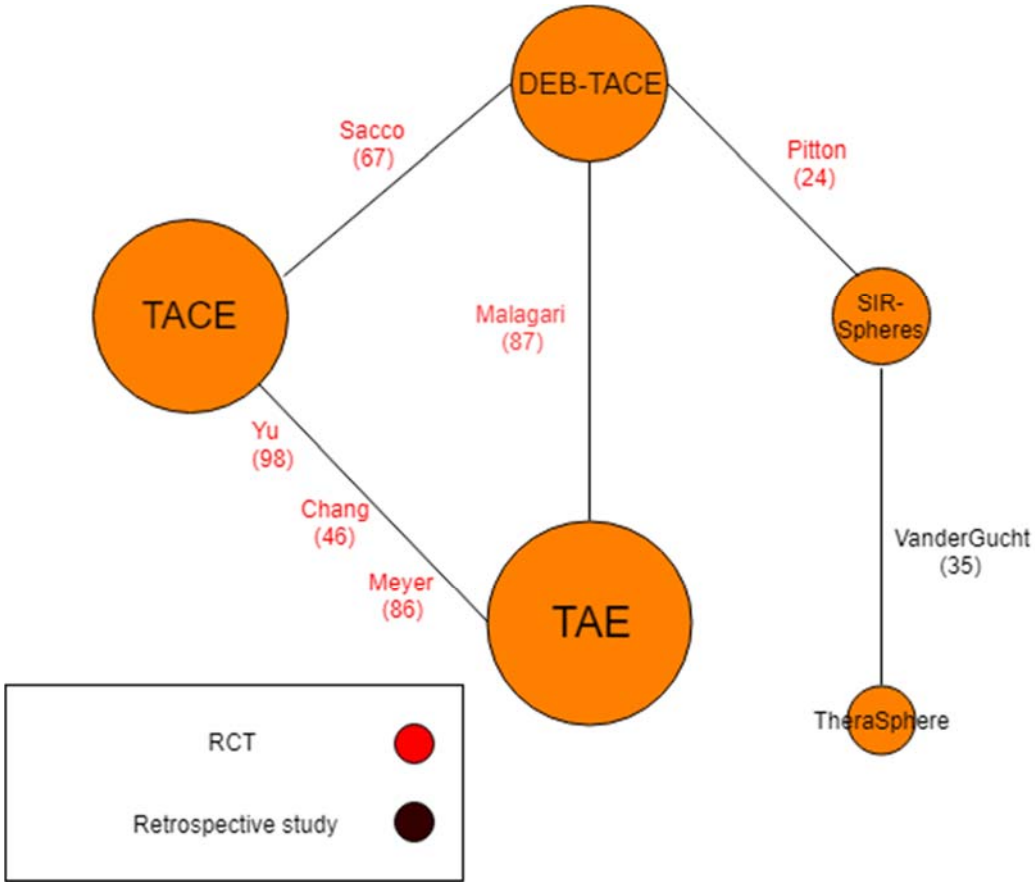
The five RCTs comparing different CTTs, which were deemed relevant for this population, were included to inform the network. The risk of bias assessment for all five trials is reported in Table 13.9 of the AG report appendices. There were 3 RCTs comparing TACE and transarterial embolization (TAE): Yu *et al*., Chang *et al*. and Meyer *et al*. The risk of bias assessment reported some concerns regarding bias in the randomisation process for all three trials. There was no information on the allocation sequence being randomised or concealed and there was no information on blinding of participants or outcome assessors in the Chang et al. trial. There did not seem to be allocation concealment in the Yu et al. trial and there was no information on allocation concealment or blinding of participants or outcome assessors in the Meyer et al. trial.

There was one RCT comparing DEB-TACE and TAE: Malagari *et al*. The risk of bias assessment reported some concerns with this study as there was no information on allocation concealment or blinding of participants or outcome assessors.

The remaining RCT compared DEB-TACE and TACE: Sacco *et al*. This trial had a high overall risk of bias, due to an open randomisation process and no information on allocation concealment. Full results of the risk of bias judgements are presented in Appendix 13.9 and the study details and results are presented in Appendix 13.10 of the AG report.

The network diagram representing the model is shown in Figure 1.

Figure 1: Network 2: Patients eligible for conventional transarterial therapies



The AG have run this network as requested by NICE. However, implementing an NMA in this population produces very uncertain results as it relies on a single small trial by Pitton *et al*. to connect SIR-Spheres to the other interventions in the network. Furthermore, it does not provide reliable evidence on TheraSphere comparisons with CTT as there is only one small, retrospective, low-quality study connecting TheraSphere in the network (Van Der Gucht et al.). Therefore, the AG consider the results of this network unsuitable for decision making.

In response to BTG's comments regarding combining randomised and non-randomised evidence in an NMA, the AG have looked at the articles provided[1-3]. The techniques reported have not been used by the AG because, as stated by the articles, the methods for incorporating non-randomised

evidence in an NMA of RCTs should be employed after researchers have performed a formal assessment of the risk of bias and the applicability of the identified studies.

'Before performing a joint analysis of randomized and non-randomized evidence, researchers need to ensure the compatibility of the different pieces of evidence, for each treatment comparison. If studies are deemed incompatible a priori (i.e. before comparing effect estimates across study designs), their inclusion in the NMA should not be considered.'

The AG excluded several non-randomised studies because the population was not appropriate or because the studies were deemed to have a high risk of bias. The exclusion of each non-randomised comparative study was sufficiently justified in the AG report. The decision to focus on comparative evidence was made due to the sheer volume of evidence and the lower quality of non-comparative studies. A total of 1085 records appeared to meet the study selection criteria based on title and abstract screening. In view of the high number of potentially eligible records, the evidence was scoped before deciding which studies to order for full paper screening. There were a large number of comparative studies (177), therefore these were prioritised over non-comparative studies. However, six large non-comparative studies that included over 500 patients were included for full paper screening and 11 non-comparative studies of QuiremSphere. As described on page 55 of the AG report, only one non-comparative study of QuiremSphere was eligible after full paper screening.

Results of Network 2: Adults with unresectable HCC who are eligible for conventional transarterial therapies

There were five studies included in both the OS and PFS NMA's. Malagari et al. was included in the network diagram above however, could not be analysed because it did not report the appropriate outcomes. Chang et al. was only included in the OS NMA as it did not report PFS. Yu et al. was only included in the PFS NMA as it did not report a Kaplan Meier curve or hazard ratio for OS.

A Bayesian evidence synthesis approach was employed. The Schoenfeld residuals were visually inspected and statistically tested for each survival curve. Although, the Kaplan-Meier curves for each study cross over, which suggests that there are some concerns about the proportional hazards assumption, there is no clear statistical evidence that the assumption is violated for all the included studies. The viability of the network depends on the proportional hazards assumption. Therefore, hazard ratios were synthesised across studies. Only one out of the five studies (Meyer et al.) reported hazard ratios. Therefore, Kaplan Meier plots were digitised and IPD was reconstructed using methods reported by Guyot et al.[5] Three studies did not report the number of patients at risk. The method is less reliable when not all the data is available, therefore it is important to note that the results of this NMA may not be accurate.

The choice of prior distributions for the between-study variance was explored. A half-normal (0, 0.19^2) prior was chosen as there was no evidence to update the uniform (0, 3) prior from the posterior. According to the deviance information criterion (DIC) and total residual deviance statistics, the random effects model did not provide an improvement in fit and the DIC was comparable to the fixed effects model for both overall survival (OS) and progression free survival (PFS) outcomes. For OS, the DIC is marginally higher; 10.85 for the random effects model, compared to 8.82 for the fixed effects model (lower DIC values are preferred, with differences of 2-5 considered important).[4] Additionally, the high level of uncertainty around the random effects credible interval indicates that there is little information to inform the random effect parameter. Therefore, the fixed effects model was chosen, as it is the simpler model, for both OS and PFS outcomes.

The results of both the fixed effect and the random effects analysis for OS are shown in Table 1. There were no meaningful differences in overall survival between any of the five treatments and all treatments appear to have a similar effect. TheraSphere shows a marginal improvement in OS when compared to SIR-Spheres (HR: 0.96, 95% C.I: 0.34-2.18) and DEB-TACE and TAE show improvements in OS when compared to TACE (HR: 0.88, 95% C.I: 0.29-2.09 and HR: 0.98, 95% C.I: 0.61-1.57, respectively). However, all estimates have very wide credible intervals which include no effect and are therefore uncertain. Table 2 shows the treatment effect estimates for each comparison.

Table 3 presents the cumulative ranking for each treatment, with rank 1 being the best and rank 5 being the worst. TheraSphere was ranked as the most efficacious treatment, but with a low probability of being the best of 0.39. TACE had the lowest probability of being the best of 0.05 and SIR-Spheres was ranked as third best, with a probability of 0.13. However, the confidence intervals for the mean rank of each treatment were 1 to 5. This indicates that the results are extremely uncertain and unreliable.

Table 1 OS results for the NMA of patients eligible for CTT

Intervention	**Comparator**	**Hazard ratio (95% CrI) - fixed effects**	**Hazard ratio (95% CrI) – random effects**
SIR-Spheres	TACE	1.06 (0.21-3.31)	1.08 (0.18-3.55)
SIR-Spheres	TAE	0.83 (0.19-3.64)	0.84 (0.17-4.00)
SIR-Spheres	DEB-TACE	1.20 (0.39-2.82)	1.22 (0.37-3.01)
TheraSphere	TACE	1.02 (0.13-3.77)	1.06 (0.11-4.14)
TheraSphere	TAE	0.71 (0.12-4.09)	0.72 (0.11-4.54)
TheraSphere	DEBTACE	0.90 (0.23-3.53)	0.91 (0.21-3.81)
DEBTACE	TACE	0.88 (0.29-2.09)	0.89 (0.27-2.19)
TAE	TACE	0.98 (0.61-1.57)	0.98 (0.57-1.68)
TheraSphere	SIR-Spheres	0.96 (0.34-2.18)	0.98 (0.32-2.36)
SD		-	0.14 (0.005-0.408)
DIC		8.82	10.85
pD		4	4.2

CrI: credible interval, SD: standard deviation, DIC: deviance information criterion, pD: number of parameters

Table 2 OS hazard ratio estimates for each treatment comparison for the NMA of patients eligible for CTT

	COMPARATOR				
TREATMENT	**TACE**	-	-	-	-
	1.06 (0.21-3.31)	**SIR-Spheres**	-	-	-
	1.02 (0.13-3.77)	0.96 (0.34-2.18)	**TheraSphere**	-	-
	0.88 (0.29-2.09)	0.95 (0.35-2.56)	1.41 (0.28-4.34)	**DEBTACE**	-
	0.98 (0.61-1.57)	1.60 (0.27-5.25)	2.08 (0.24-8.01)	1.48 (0.42-3.77)	**TAE**

Table 3 Mean rank and probability of being the best treatment

Treatment	Mean rank (95% CI)	Probability of being the best treatment
TheraSphere	2.6 (1-5)	0.39
DEB-TACE	2.7 (1-5)	0.21
SIR-Spheres	3.0 (1-5)	0.13
TAE	2.9 (1-5)	0.22
TACE	3.7 (1-5)	0.05

The results of both the fixed effect and the random effects analysis for PFS are shown in Table 4. There were no meaningful differences in progression free survival between any of the five treatments and all treatments appear to have a similar effect. TheraSphere shows a marginal improvement when compared to SIR-Spheres (HR: 0.95, 95% CI: 0.36-2.05) and DEB-TACE and TAE show slight improvements in OS when compared to TACE (HR: 0.86, 95% CI: 0.26-2.15 and HR: 0.87, 95% CI: 0.61-1.20, respectively). However, like the OS results, all estimates have wide credible intervals, which include no effect and are therefore very uncertain. Table 5 shows the treatment effect estimates for PFS for each comparison.

Table 4 PFS results for the NMA of patients eligible for CTT

Intervention	Comparator	Hazard ratio (95% CrI) - fixed effects	Hazard ratio (95% CrI) – random effects
SIR-Spheres	TACE	1.20 (0.22-3.82)	1.26 (0.20-4.32)
SIR-Spheres	TAE	1.42 (0.25-4.67)	1.49 (0.22-5.29)
SIR-Spheres	DEB-TACE	1.39 (0.47-3.23)	1.43 (0.44-3.50)
TheraSphere	TACE	1.14 (0.15-4.20)	1.22 (0.13-4.79)
TheraSphere	TAE	0.93 (0.17-5.08)	0.93 (0.14-5.82)
TheraSphere	DEBTACE	1.32 (0.29-3.90)	1.39 (0.26-4.36)
DEBTACE	TACE	0.86 (0.26-2.15)	0.88 (0.24-2.32)
TAE	TACE	0.87 (0.61-1.20)	0.89 (0.56-1.35)
TheraSphere	SIR-Spheres	0.95 (0.36-2.05)	0.97 (0.34-2.21)
SD		-	0.16 (0.008-0.426)
DIC		9.56	10.67
pD		4	4.2

Table 5 PFS hazard ratio effect estimates for each treatment comparison for the NMA of patients eligible for CTT

	COMPARATOR				
TREATMENT	**TACE**	-	-	-	-
	1.20 (0.22-3.84)	**SIR-Spheres**	-	-	-
	1.14 (0.15-4.20)	0.95 (0.36-2.05)	**TheraSphere**	-	-
	0.86 (0.26-2.15)	0.92 (0.31-2.12)	0.94 (0.26-3.44)	**DEBTACE**	-
	0.87 (0.61-1.20)	0.93 (0.21-4.05)	1.58 (0.20-5.97)	1.35 (0.38-3.50)	**TAE**

References

1. Cochrane Training. Combining randomised and non-randomised evidence in network meta-analysis (NMA): Cochrane Training; 2016 [cited 2019. Available from: https://training.cochrane.org/resource/combining-randomised-and-non-randomised-evidence-network-meta-analysis-nma.

2. Efthimiou O, Mavridis D, Debray TP, Samara M, Belger M, Siontis GC, et al. Combining randomized and non-randomized evidence in network meta-analysis. Statistics in medicine. 2017;36(8):1210-26.

3. Mueller M, D'Addario M, Egger M, Cevallos M, Dekkers O, Mugglin C, et al. Methods to systematically review and meta-analyse observational studies: a systematic scoping review of recommendations. BMC Medical Research Methodology. 2018;18(1):44

4. 83. Dias S, Welton NJ, Sutton AJ, Ades AE. *NICE DSU Technical Support Document 2: A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials*. Sheffield: Decision Support Unit, ScHARR, University of Sheffield; 2014.

5. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012; 12:9.

BTG

Selective internal radiation therapies for treating hepatocellular carcinoma ID1276

Company Evidence Submission for TheraSphere®

Contents

Figures and tables in this document

Abbreviations

(G) Bq	(Giga) Becquerel
95% CI	95% confidence interval
AASLD	American Association for the Study of Liver Diseases
AFP	Alpha-fetoprotein
ALARA	As Low as Reasonably Achievable
Alb	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APAC	Asia and the Pacific
APASL	Asian Pacific Association for the Study of the Liver
AST	Aspartate aminotransferase
BCLC	Barcelona Clinic Liver Cancer
Bili	Bilirubin
Bq	Becquerel
BSC	Best supportive care
BTG	British Technology Group
CC	Cholangiocarcinoma
CI	Confidence interval
CLCC	Comprehensive Liver Cancer Clinic
CLIP	Cancer of the Liver Italian Program
CR	Complete response
CT	Computed tomography
cTACE	Conventional transarterial chemoembolisation
CTP	Child-Turcotte-Pugh
CUPI	Chines University Prognostic Index
DC	Disease control rate
DCR	Disease Control Rate
DEB	Drug-Eluting Beads
DEB-DOX	Drug-eluting beads loaded with doxorubicin
DEB-TACE	Drug-eluting beads plus transarterial chemoembolization
DNA	Desoxy-Ribonucleic Acid
EASL	European Association for the Study of the Liver
eCC	Extrahepatic cholangiocarcinoma
ECOG	Eastern Cooperative Oncology Group
EHD	Extrahepatic disease
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	EuroQol Five Dimensions
ESDO	European Society of Digestive Oncology
ESMO	European Society for Medical Oncology
EU	European Union
FACT	Functional Assessment of Cancer Therapy
FDA	(US) Food and Drug Administration
FHSI	FACT Hepatobiliary Symptom Indexes
FLR	Future liver remnant
Gd-EOB-DTPA	Gadolinium-Ethoxybenzyl-Diethylenetriamine Pentaacetic Acid
GVD	Global value dossier
Gy	Unit of Gray
HAIC	Hepatic arterial infusion chemotherapy
HBV	Hepatitis B Virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C Virus
HDE	Humanitarian device exemption
HR	Hazard ratio
HRQoL	Health-related quality of life
HUD	Humanitarian use device
iCC	Intrahepatic cholangiocarcinoma
JIS	Japan Integrated Staging

JSH	Japan Society of Hepatology
KLCSG	Korean Liver Cancer Study Group
LAASL	Latin American Association for the Study of the Liver
LATAM	Latin American countries
M	Months
mBreast	Metastatic breast cancer
mCRC	Metastatic colorectal cancer
mNET	Metastatic neuroendocrine tumour
mRECIST	Modified Response Evaluation Criteria in Solid Tumours
MRI	Magnetic resonance imaging
NCC	National Cancer Centre, Korea
NCCN	National Comprehensive Cancer Network
NCCS	National Cancer Centre Singapore
NET	Neuroendrocrine tumour
NICE	National Institute for Health and Care Excellence
NS	Non-significant
OLT	Orthotopic liver transplant
OR	Odd Ratio
OR	Overall response
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PR	Partial tumour response
PS	Performance status
PVT	Portal vein thrombosis
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RFS	Recurrence-free survival
RMB	Chinese Yuan
RR	Relative risk
SD	Standard deviation
SD	Stable disease
SEER	Surveillance, Epidemiology, and End Results
SF-36	Short-Form 36
SIRT	Selective internal radiation therapy
SLR	Systematic literature review
SR	Systematic review
TACE	Transarterial chemoembolisation
TAE	Transarterial embolisation
TARE	Transarterial radioembolisation
TACE	Transarterial chemoembolisation
TNM	Tumour node metastasis
TRAE	Transplant related adverse events
TS	TheraSphere®
TTP	Time-to-progression
TTST	Time to secondary therapy
UK	United Kingdom
UNOS	United Network for Organ Sharing
WGO	World Gastroenterology Organisation
WHO	World Health Organization
^{90}Y	Yttrium-90

Section 1: Executive Summary

1.1 THE TECHNOLOGY

TheraSphere® is a selective internal radiation therapy (SIRT) used in the treatment of hepatocellular carcinoma (HCC).

TheraSphere® is licenced for the treatment of hepatic neoplasms including operable and inoperable HCC. It may be used as palliative treatment or with curative intent, the latter involving the use of TheraSphere® to remove the tumour, downstage disease to enable patients to undergo curative treatments or as locoregional tumour control in patients on the transplant list.

TheraSphere® consists of insoluble glass microspheres with radioactive yttrium-90 (^{90}Y) as an integral constituent of the glass. It is delivered to the tumour site via transfemoral catheterisation of the hepatic artery and provides localised, targeted high dose radiation to destroy the tumour. TheraSphere® has a high specific activity per microsphere, which allows local delivery of a standardised therapeutic radiation dose with a low volume of microspheres. The low volume of microspheres avoids reflux to other areas, avoids embolic events, maintains blood and oxygen flow and allows the use of subsequent arterial therapies. The minimal embolic effect and avoidance of reflux also makes TheraSphere® a treatment option in patients with portal vessel thrombosis (PVT).

TheraSphere® is available in a wide range of doses, giving clinicians the flexibility to adjust dose according to patients' needs. Treatment can be administered to the whole liver or localised to specific areas, as required. Clinician/technician exposure to radiation is minimised since there is no need for dose preparation, it is provided with shielding materials and is administered within 5 minutes.

Other SIRT products include SIR-Spheres® and QuiremSpheres®. Unlike, other SIRT products, no physical manipulation of the microspheres is needed, and a smaller number of microspheres is required to deliver high-dose effective therapy.

Over 55,000 patients have been treated with TheraSphere® world-wide since launch in 2000.

1.2 HEALTH CONDITION AND POSITION OF THE TECHNOLOGY IN THE TREATMENT PATHWAY

Although liver cancer is not a particularly common cancer, it is a common cause of cancer death and accounts for 3% of cancer deaths (8th most common cause of cancer death, 5,200, per year in the UK). Patients often receive their diagnosis at a late stage of the disease, with correspondingly poor prognosis.

HCC is often described using the Barcelona Clinic Liver Cancer (BCLC) staging system, where stage 0/A corresponds to early disease and stage D to end-stage terminal disease.

The heterogeneous nature of HCC and associated underlying co-morbidities make evaluation and treatment extremely complex, and treatment should be individualised to each patient to ensure optimal outcomes. Several treatment options exist and can be broadly divided into curative treatment for early stage disease, or palliative treatment for later stage disease. Curative treatments included in the existing NICE pathway for liver cancer, include liver transplantation, surgical liver resection and local destructive methods such as radiofrequency ablation or microwave ablation. Palliative treatments included in the pathway are interventional procedures such as SIRT, transarterial embolisation (TAE), transarterial chemoembolisation (TACE), either as conventional TACE (cTACE) or as drug eluting bead TACE (DEB-TACE), and systemic chemotherapy, such as sorafenib. The level of evidence for most therapeutic options in HCC is limited, with few randomised controlled trials.

TheraSphere® can be used as an alternative to palliative systemic chemotherapy in patients with advanced disease (BCLC C) or as an alternative to liver-directed interventional procedures e.g. chemoembolisation, in patients with intermediate disease (BCLC B). It can also be used in earlier stage disease (BCLC A, selected B patients) as:

- a potentially curative treatment in patients with small tumours not suitable for other curative treatments (radiation segmentectomy)
- a treatment to downstage disease in order that patients can undergo resection
- locoregional tumour control in patients on the transplant list
- as radiation lobectomy, which is a lobar treatment for patients who have insufficient remaining normal tissue to undergo other curative treatments. Following treatment with TheraSphere® in the diseased lobe, the un-diseased lobe increases in size, improving overall liver function and permitting the diseased lobe to be resected

1.3 CLINICAL EFFECTIVENESS

In terms of clinical outcomes [1], comparative evidence indicates better or equivalent outcomes for TheraSphere® in most studies. This pattern of benefit is seen in both later stage and earlier stage disease.

The comparative evidence available for TheraSphere® vs SIRSpheres® includes three studies and one network meta-analysis [NMA]. There are 13 studies vs TACE and one NMA vs sorafenib. Much of the comparative evidence is in later stage disease. In patients with PVT, overall outcomes are poorer than for patients without PVT or than the overall HCC population, however TheraSphere® has better or equivalent outcomes to the comparators in this challenging patient group, when used in later stage disease.

Two comparative studies evaluated health related quality of life (QoL) after treatment with TheraSphere® vs. TACE or systemic chemotherapy (cisplatin) in later stage HCC patients. QoL was not adversely affected after treatment with TheraSphere®. Some QoL subscales were significantly improved with TheraSphere® when compared with TACE including social

[1] overall survival (OS); progression (defined previously as progression free survival (PFS)); time to progression (TTP); time to subsequent treatment (TTST) or relapse free survival (RFS); overall response (OR).

and functional well-being. The study comparing TheraSphere® vs. TACE also used a QoL scale which specifically assessed QoL parameters most relevant to patients undergoing embolisation (pain, impact of treatment side effects, ability to work, diarrhoea and good appetite) and found that QoL improved with TheraSphere® and worsened with TACE.

There is no comparative evidence against QuiremSpheres® or bland TAE in any stage of disease.

Non-comparative evidence supports the value of TheraSphere® when used as palliative treatment in later stage disease. Non-comparative evidence in early stage disease also demonstrates benefit in radiation segmentectomy, downstaging, locoregional control and radiation lobectomy:

- Median OS for TheraSphere® was found to be comparable to that seen with curative therapies (up to 7 years). when used as radiation segmentectomy in patients with early stage, non-resectable, single small HCC tumours.
- When used for downstaging or locoregional control in patients on the transplant list, median OS for TheraSphere® was 2 to 4 years
- In studies where TheraSphere® was specifically used for downstaging to curative intent, downstaging was achieved in 33% to 66% of patients.
- Studies using TheraSphere® treatment for bridging resulted in a high success rate, ranging from 90% to 100%.
- In studies where TheraSphere® was used as radiation lobectomy, survival was over 2 years (mean OS 31 months, median OS 37 months and not reached in three studies).

1.4 ADVERSE EVENTS

Overall, the clinical safety data generated from the literature, clinical studies and post-marketing surveillance data, confirms an acceptable and reproducible safety profile for TheraSphere® when it is used according to the manufacturer's instructions. There are no unanswered questions regarding safety and no new risks have been identified. Given the depth of existing safety information, TheraSphere® can be considered to have an acceptable safety profile.

In the clinical papers reviewed in this submission, the most frequent adverse events were flu-like symptoms such as fatigue, abdominal pain and nausea. Biochemical toxicities were generally low (<10% frequency). The most frequently observed severe adverse event (grade III-IV) was increased bilirubin. These results are consistent with the list of adverse events (for all types of patients) included in the investigator's brochure which incorporates post-marketing surveillance information.

There is a lack of head-to-head evidence comparing TheraSphere® vs. SIR-Spheres® or sorafenib. Broad explorative comparisons of TheraSphere® vs. SIR-Spheres® show that some adverse events are more commonly reported with TheraSphere® and others are more commonly reported with SIR-Spheres®.

There is evidence from one RCT that more patients treated with cTACE experienced grade I-II diarrhoea and hypoalbuminemia compared with TheraSphere®. Data from non-randomised comparative studies generally show higher percentages of patients with abdominal pain, nausea/vomiting, diarrhoea, increased AST/ALT, increased bilirubin and hypoalbuminemia with TACE compared with TheraSphere®. Rates of post-embolisation syndrome were significantly lower with TheraSphere® than with TACE. This is a key benefit with TheraSphere® since post-embolisation syndrome after TACE has been shown to be associated with a worse survival and a two-fold increased risk of death, even after adjusting for important confounders.

1.5 COST-EFFECTIVENESS

The TAE eligible population[2] (i.e. patients with BCLC A and selected BCLC B stage disease) and the TAE-ineligible[2] population (i.e. patients with selected BCLC B and BCLC C stage disease) were modelled separately. Structural design followed the NICE reference case, with an NHS direct health cost perspective being adopted. A 20-year time horizon was used, reflecting the maximum likely life expectancy in this population. Cycle length was 4 weeks. Standard discounting of 3.5% pa was applied to both costs and utilities.

Treatment with TheraSphere® was modelled versus the comparators defined in the NICE final scope for both populations. Despite the use of a different nucleotide and an overall absence of clinical data relating to patients with QuiremSpheres®, for modelling purposes the assumption was made that it was equivalent to other SIRTs.

In the TAE-eligible population, TheraSphere® produces a quality adjusted life year (QALY) gain equivalent to other SIRT treatment and superior to cTACE, DEB-TACE and bland embolisation. In this patient group, the costs associated with SIRT treatments are similar. Despite an absence of specific evidence for SIR-Spheres® or QuiremSpheres® a conservative assumption of therapeutic equivalence to TheraSphere® was made. Thus, in this population, all SIRTs share an incremental cost-effectiveness ratio (ICER) of approximately £24,600/QALY when the price of treatment is £8,000. All other treatments are dominated.

In the TAE-ineligible population, TheraSphere® was found to be the most costly treatment option as well as the most beneficial in terms of QALYs gained. The ICER for TheraSphere® is approximately £64,700/QALY, with all other treatments dominated or extended dominated. A merged estimated ICER of £52,894/QALY was calculated, based on the expected distribution of TAE-eligible and ineligible patients in the UK population.

1.6 SUMMARY AND CONCLUSIONS

There is comparative evidence for TheraSphere® vs. SIR-Sphere® in later stage disease, but no evidence vs. QuiremSpheres® at any stage of disease. TheraSphere® and SIR-

[2] As defined in the NICE Final Scope [See Appendix F]. NB The NICE scope also defines TAE as a comparator, therefore, we refer to the comparator as bland embolisation and define the TAE-ineligible/eligible populations as those ineligible/eligible for TACE or bland embolisation.

Spheres® are broadly comparable, with some studies showing a survival advantage with TheraSphere®. In a NMA comparing TheraSphere® and SIR-Spheres®, TheraSphere® was non-inferior to SIR-Spheres® with [redacted]year survival of [redacted] vs. [redacted]. Patients with PVT have improved outcomes with TheraSphere® vs. SIR-Spheres®, which may result from the higher activity in the smaller TheraSphere® microspheres. TheraSphere® is an effective alternative treatment to SIR-Spheres®, particularly in patients with PVT.

In earlier and later stage disease, TheraSphere® is an effective alternative treatment to TACE, particularly in patients with PVT for whom TACE is unsuitable, patients unable to tolerate TACE, those who have failed previous TACE or whose vasculature has changed as a result of prior treatments and are now unsuitable for TACE.

In later stage disease, TheraSphere® is an effective alternative treatment to sorafenib. TheraSphere® has the added benefits of no dose-limiting systemic side effects, no lifetime twice daily dosing and no treatment resistance.

In early stage disease treatment for HCC can be potentially curative. TheraSphere® can be used as a potentially curative treatment in patients with small tumours not suitable for other curative treatments (radiation segmentectomy), as a lobar treatment for patients who have insufficient remaining normal tissue to undergo other curative treatments (radiation lobectomy), to downstage disease in order that patients can undergo resection or ablation or as locoregional tumour control in patients on the transplant list.

Overall, the data demonstrates that TheraSphere® is effective and safe in the treatment of early and later stage HCC. The high variability in results is likely due to of a number of confounding factors, such as differing patient populations, study methods, differences in dosing, or even the refinement of administration techniques over time. Nevertheless, there is clear evidence to suggest that TheraSphere® can be used to make curative options available for patients who may not otherwise have that option. It also has similar or better outcomes to other recommended therapies, such as TACE.

We acknowledge that the data are limited as most of the studies are retrospective or prospective cohort studies, and these studies were collectively considered to present low quality evidence. Despite these limitations, the extensive body of studies and consistent results supporting the use of TheraSphere® in the palliative and curative intent settings, provides evidence that TheraSphere® can be used as an alternative to well accepted therapies included in staging algorithms.

TheraSphere® is likely to be a cost-effective treatment at the listed price of £8,000 for patients who may be downstaged to curative treatments. TheraSphere® may also be a cost-effective treatment for later stage, unresectable HCC in certain scenarios, if considered to meet NICE end of life criteria or if adjustments are made for the cost of sorafenib in pre-progressed patients. When the two sub populations are considered collectively (i.e. TAE-eligible and TAE-ineligible), TheraSphere® has a merged ICER of approximately £52,900/QALY.

Section 2: The Technology

TheraSphere® is a selective internal radiation therapy (SIRT) used in the treatment of hepatocellular carcinoma (HCC).

TheraSphere® consists of insoluble glass microspheres with radioactive yttrium-90 (^{90}Y) as an integral constituent of the glass.

TheraSphere® is delivered to the tumour site via transfemoral catheterisation of the hepatic artery and provides localised targeted high dose radiation to destroy the tumour.

TheraSphere® has a high specific activity per microsphere, which allows local delivery of a standardised therapeutic radiation dose with a low volume of microspheres. The low volume of microspheres avoids reflux to other areas, avoids embolic events, maintains blood and oxygen flow and allows the use of subsequent arterial therapies.

TheraSphere® is available in a wide range of doses, which gives clinicians the flexibility to adjust the dose according to patient needs. Treatment can be administered to the whole liver or localised to specific areas, as required.

Clinician/technician exposure to radiation is minimised with TheraSphere® since there is no need for dose preparation, it is provided with shielding materials and is administered within 5 minutes.

Over 55,000 patients have been treated with TheraSphere® world-wide since launch in 2000.

TheraSphere® is licenced for the treatment of hepatic neoplasms. It may be used with curative intent in HCC (to remove the tumour or downstage disease in order that patients can undergo curative treatment or as used as locoregional tumour control in patients on the transplant list) or as a palliative treatment in HCC depending on the individual patient and their disease stage.

TheraSphere® has the advantage over other SIRT products in that no physical manipulation of the microspheres is needed and a smaller number of microspheres are required to deliver high-dose effective therapy. This minimises any embolic effects and reflux of spheres into non target areas, as observed with other devices and makes TheraSphere® a valuable treatment option in patients with portal vessel thrombosis (PVT).

2.1 DESCRIPTION OF THE TECHNOLOGY

TheraSphere® is one of the three SIRTs for the treatment of HCC which NICE has selected for appraisal in a Multiple Technology Appraisal (MTA). Other available forms of SIRT are SIR-Spheres® which are ^{90}Y resin microspheres and QuiremSpheres® which are polyester microspheres containing a different radioactive isotope: holmium-166 (^{166}Ho).

This document outlines the clinical and health economic evidence for TheraSphere®.

TheraSphere® is considered as a therapeutic brachytherapy device, and consists of insoluble glass microspheres in which radioactive yttrium-90 (^{90}Y) is an integral constituent of the glass.

TheraSphere® microspheres are delivered to the HCC tumour vasculature via transfemoral catheterisation of the hepatic artery. The liver is supplied by two sources of blood: the hepatic artery and the portal vein. Tumour tissue is mainly supplied (80%-100%) by blood from the hepatic artery [1], whereas normal liver tissue receives the majority (75%) of blood flow from the portal vein [2]. Delivering the microspheres via the hepatic artery means that the radiation dose is delivered preferentially to the tumour, minimising the risk of radiation damage to healthy surrounding tissues.

Arterial blood flow together with flushing fluid (usually saline) delivers the microspheres into the tumour. The microspheres are then trapped in the vasculature of the tumour and emit a therapeutic radiation dose which ultimately necrotizes the tumour while minimising damage to the normal surrounding tissue. This technique allows TheraSphere® to deliver a targeted radiation dose as close as possible to the tumour (Pellerin *et al.* 2013) [3].

Table 2-1: Description of the Technology

Brand name	TheraSphere®
UK approved name	TheraSphere®
Therapeutic device	TheraSphere® is a radiotherapy device delivering internal locoregional cytotoxic doses of radiation (radioactive ^{90}Y).
Indication	For the treatment of hepatic neoplasms
Use in practice	TheraSphere® can be used to treat operable and inoperable HCC. It may be used with curative intent (to remove the tumour or downstage disease in order that patients can undergo curative treatment or as used as locoregional tumour control in patients on the transplant list) or as a palliative treatment depending on the individual patient and their disease stage.
Mechanism of action	This device delivers locoregional beta radiation via insoluble glass microspheres where ^{90}Y is an integral constituent of the glass matrix. The microspheres are delivered to the liver tumour through a catheter placed into the hepatic artery that supplies blood to the tumour. The microspheres, unable to pass through the vasculature of the liver due to arteriolar capillary blockade, are trapped in the tumour and exert a local radiotherapeutic effect (Oken *et al.* 1982) [4].

^{90}Y included in each TheraSphere® is a pure beta emitter which decays to stable zirconium-90 with a physical half-life of 64.1 hours. After 10 half-lives, radiation drops to below detectable levels and only 6% of the dose will be active after 11 days.

TheraSphere® microspheres have a mean diameter range of 20–30 micrometres and a specific activity of 2,500 Bq per microsphere. One GBq (27 mCi) of ^{90}Y per kilogram of tissue gives a radiation dose of 13 Gy (1.297 rad) per day, thus the radiation dose delivered by ^{90}Y over complete radioactive decay for 1 GBq (27 mCi) per kilogram of tissue is 50 Gy (5,000) of

radiation. The average energy of the beta emissions from ^{90}Y is 0.9367 MeV with a short tissue penetration (mean 2.5 mm and a maximum of 11 mm) (Package insert) [5].

Such a high specific activity per microsphere allows local delivery of a standardised therapeutic radiation dose with a low volume of microspheres. This has several important advantages (Harrison *et al.* 2004, Fournier *et al.* 2010) ([6], [7]).

- Avoids reflux of microspheres back into the artery. It is important to avoid reflux, since deposition of the microspheres in other areas may cause complications, for example, if spheres reflux and then move down the gastric duodenal artery they can potentially cause a gastroduodenal ulcer.
- Avoids tumour hypoxia. It has been demonstrated that tumour hypoxia or lack of oxygen decreases the impact of radiation, the low volume of microspheres means that blood flow and oxygen continue to be delivered to the tumour area maximising the impact of radiation.
- Avoids embolism (slowing or blockage of blood flow) and maintains vessel patency, allowing subsequent arterial therapies to be used [3, 8].

The recommended dose to the liver tissue is 80-150 Gy (Package insert) [5]. The amount of radioactivity needed to deliver the desired dose (in Gy) to the liver is calculated from liver volume converted to liver mass. The appropriate time of ordering and then injection of the TheraSphere microspheres is calculated by determining the amount of physical decay of the ^{90}Y. Doses are scheduled to arrive the day before treatment and the dose vial remains sterile for 12 days [9].

TheraSphere® is available in dose sizes ranging from 3 GBq to 20 GBq (at 0.5 GBq intervals), each supplied in 0.6 mL of sterile, pyrogen-free water contained in a 1.0 mL vial secured within a clear acrylic vial shield. The wide range of available doses gives clinicians the flexibility to adjust the dose according to their patients' needs.

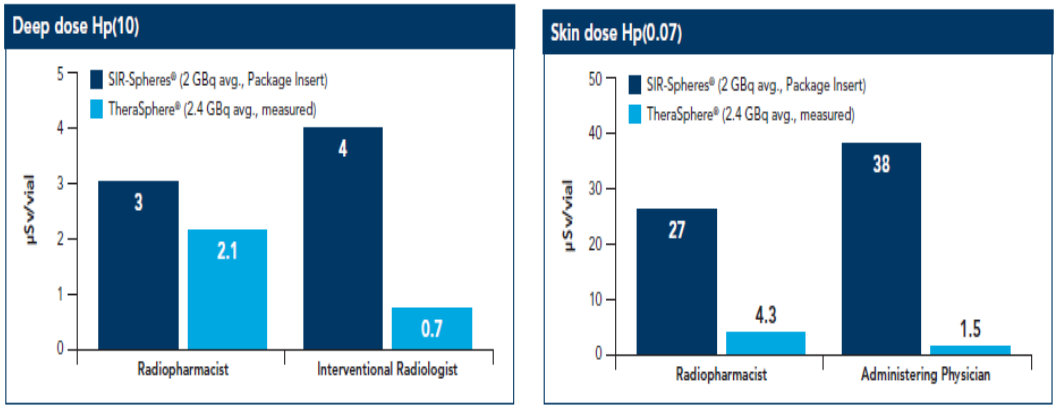
TheraSphere® can be administered to target the whole liver, an individual lobe or select smaller Couinaud segment(s) with the goal of maximising tumour exposure to beta radiation while minimising surrounding healthy tissue exposure. Each patient receives an individualised treatment dosing plan, where the dose required is determined via pre-treatment planning.

Administration of TheraSphere® is carried out on an outpatient basis, is quick and easy and requires no contrast. TheraSphere® is supplied with one single use Administration Set, gamma radiation or ethylene oxide and one re-usable Administration Accessory Kit. TheraSphere® has an infusion time of less than 5 minutes and patients are usually discharged within 6 hours of treatment completion.

The simplified administration process for TheraSphere®, reduces exposure to the radiation emitted by the device (Acuff *et al.* 2016) [10]. Exposure time is further reduced by a common shipping and administration vial which contains pre-specified doses, removing the need for dose preparation and/or manipulation steps (BTG 2015) [11]. The TheraSphere® packaging contains shielding materials, which compared to other ^{90}Y manufacturer's packaging, reduces

β-particle emissions. Combined with a rapid infusion process (without the need for in procedure angiographic monitoring), TheraSphere® significantly reduces radiation exposure compared to other products (BTG 2016) [12]. These precautions adhere to As Low As Reasonably Achievable (ALARA) requirements for radiation exposure, and result in a ten-times lower finger radiation exposure in hospital personnel compared to other microspheres such as SIR-Spheres® (Laffont *et al.* 2016) [13]. Additionally, radiopharmacists and interventional radiologists administering TheraSphere®, are exposed to lower levels of average chest dose compared to other products such as SIR-Spheres® (Laffont *et al.* 2016; Garin *et al.* 2003) [13, 14] (see Figure 2-1)).

Figure 2-1: Average chest dose received by hospital personnel during ^{90}Y microsphere therapy (Laffont *et al.* 2016) [13]



2.2 LICENCED INDICATION

The current licenced indication is for the treatment of hepatic neoplasms.

TheraSphere® can be used to treat operable and inoperable HCC. It may be used with curative intent (to remove the tumour or downstage disease in order that patients can undergo curative treatment or as used as locoregional tumour control in patients on the transplant list) or as a palliative treatment depending on the individual patient and their disease stage. TheraSphere® may be a treatment option for patients with PVT, which is an adverse prognostic factor in patients with HCC. [9]

A medical device CE mark was obtained for TheraSphere® in September 2014 for operable and inoperable hepatic neoplasms. The CE mark covers the ^{90}Y glass microspheres, administration set and administration accessory kit.

TheraSphere® was initially approved in the USA in 1999. It is indicated for HCC as a Humanitarian Use Device (HUD) available to patients through the Humanitarian Device Exemption (HDE). Outside of the UK, TheraSphere® is approved worldwide to treat HCC and other hepatic neoplasias.

Over 55,000 patients have been treated with TheraSphere® world-wide since launch in 2000.

2.3 THERASPHERE® AND OTHER SELECTIVE INTERNAL RADIATION DEVICES

Other SIRT devices are available and include SIR-Spheres® and QuiremSpheres®. TheraSphere® differs from other devices as shown in Table 2-2 below.

Table 2-2: Comparison of technologies

	TheraSphere®[5]	**SIR-Spheres®[15]**	**QuiremSpheres®[16]**
Matrix	Glass	Resin	Polyester
Diameter (μm)	20-30	20-60	15-60
Density (g/cm^3)	3.2	1.6	1.4
Number of spheres per administration	4 million	33 million	33 million
Isotope	^{90}Y	^{90}Y	^{166}Ho
Half life	64 hours	64 hours	26.8 hours
Dose of radiation per microsphere (Bq)	2500	50	240-375
Indication	Treatment of hepatic neoplasia	Treatment of patients with advanced non-operable liver cancer	Treatment of unresectable liver tumours
Device status	CE marked class III active medical device	CE marked class III active medical device	CE marked class III active medical device
Physical manipulation needed prior to use	No	Yes	Yes
Available in different doses	Yes Six standard dose sizes and custom doses also available in 0.5 GBq increments between 3 and 20 GBq	No	No
Assessed by NICE in Medtech innovation briefing	Yes (2016, MIB 62)	Yes (2016, MIB 63)	No

Key differences are that TheraSphere® is available for order in different doses, there is no need for physical manipulation of the microspheres before administration and TheraSphere® has a smaller microsphere size and higher dose of radiation per microsphere (2500 Bq vs. 50 Bq vs. 240-375 Bq) than other SIRTs.

TheraSphere® has a smaller microspheres with a higher levels of radiation per single microsphere compared to other SIRTS. Therefore, fewer TheraSphere® microspheres are required to attain an effective radiation dose. This is clinically important since it minimises the embolic effect (blockage of the vessels) and risk of microsphere reflux into non-target areas. These characteristics allow TheraSphere® to be used in patients with compromised portal venous flow or PVT.

Section 3: Health Condition and Position of the Technology in the Treatment Pathway

Although liver cancer is not a particularly common cancer, it is a relatively common cause of cancer death, accounting for 3% of cancer deaths (eighth most common cause of cancer death, 5,200 per year in the UK). Patients often receive their diagnosis at a late stage of the disease, with correspondingly poor prognosis.

The heterogeneous nature of HCC and associated underlying co-morbidities make the evaluation and treatment of HCC extremely complex.

Treatment for HCC should be individualised to each patient to ensure optimal outcomes.
There are a number of treatment options for HCC (surgery, interventional procedures, systemic chemotherapy) and careful selection of the appropriate treatment option and the expert application of these treatments is essential. The level of evidence for most therapeutic options is limited with few randomised controlled trials.

Treatment for HCC is broadly divided into curative treatment for earlier stage disease (surgical liver resection, liver transplantation and local destructive methods such as radiofrequency ablation or microwave ablation) and palliative treatment (interventional procedures such as SIRT, TAE, TACE/DEB-TACE and chemotherapy such as sorafenib).

In earlier stage disease (BCLC A and selected B patients), TheraSphere® can be used a potentially curative treatment in patients with small tumours not suitable for other curative treatments, used as lobar treatment for patients who have insufficient remaining normal tissue to undergo other curative treatments, used to downstage disease in order that patients can undergo resection or ablation or used as locoregional tumour control treatment in patients on the transplant list.

In later stage disease, TheraSphere® can be used as an alternative to other liver-directed interventional procedures such as chemoembolisation in patients with intermediate disease (selected BCLC B) or as an alternative to palliative systemic chemotherapy in patients with advanced disease (BCLC C).

3.1 HEALTH CONDITION

In the UK, liver cancer is the 15th most common cancer in men and 20th most common in women, with 3,700 and 2,100 cases each year (2015 data) [17]. However, it is the eighth most common cause of cancer death, resulting in around 5,200 deaths each year.

The incidence of liver cancer has increased by 151% since the early 1990s, due to changes in lifestyle. It is thought that around 50% [17] of liver cancers are due to lifestyle factors such as smoking, obesity and alcohol intake.

Liver cancer is often diagnosed at a late stage of disease and UK data shows that around 40% of people with liver cancer are diagnosed as an emergency [17]. Prognosis is poor for patients diagnosed with advanced disease, with median survival of <1 year (Nordenstedt *et al.* 2010, El-Serag *et al.* 2007) [18, 19]).

HCC is the most common primary liver cancer, accounting for 80% to 90% of liver cancers. In 2016, 4,925 people (3,235 men and 1,690 women) were diagnosed with HCC in England [20].

The development of HCC is a complex process involving sustained inflammation resulting from chronic liver disease which may lead to HCC include hepatitis (B or C), chronic alcohol use, NAFLD (non-alcoholic fatty liver disease), NASH (non-alcoholic steatohepatitis). In HCC, inflammation leads to fibrosis (scarring), cell necrosis (death) and eventually cirrhosis [21]. Cirrhosis is present in approximately 80% of patients with HCC and once cirrhosis is established, HCC is almost inevitable. HCC carries a poor prognosis for many patients given that diagnosis occurs at an advanced disease stage when median survival time is less than one year (Nordenstedt *et al.* 2010, El-Serag *et al.* 2007) [18, 19]. Left untreated, HCC is uniformly fatal, with an incidence to death ratio close to 1.0 (El-Serag *et al.* 2007) [19]. The mean age at diagnosis is approximately 65 years of age, however, the incidence rate has risen over the past decades and the number of new cases in patients 45-60 years of age has also risen (El-Serag *et al.* 2007) [19]. In 2016, 4,925 people (3,235 men and 1,690 women) were diagnosed with HCC in England [20].

HCC is a is a heterogeneous cancer; it may present as solitary or multinodular tumours with varying degrees of tumour burden, unilobar or bilobar involvement, invasion into the liver vascular system, PVT, extrahepatic disease spread and metabolic liver dysfunction. Given that HCC is primarily a disease of older people, it is often accompanied by co-morbidities as well as the underlying liver disease. These factors make the treatment of HCC uniquely challenging amongst cancers. These variables introduce an additional level of complexity in evaluating HCC disease and choosing optimal therapy for a patient (Villaneuva *et al.* 2008) [22]. Given the presence of both progressive cirrhosis and liver cancer in most HCC patients, optimal treatment should be directed at both preserving liver function and halting cancer progression. Patients must be monitored continually, and treatment choices re-evaluated as the dynamics of both diseases change over time.

3.2 POSITION OF THE TECHNOLOGY IN THE TREATMENT PATHWAY

3.2.1 Current Management and Guidelines

The aim of treatment in HCC is to increase survival while maintaining quality of life. Treatment for HCC should be individualised to each patient to ensure optimal outcomes. Careful selection of candidates for each treatment option and the expert application of these treatments is essential. Given the complexity of the disease and the large number of potentially useful treatments, patients diagnosed with HCC should be referred to multidisciplinary teams for their management.

Treatment for HCC is dependent on stage of disease, liver function, the distribution and volume of tumours within the liver, portal vein involvement and extra-hepatic metastases. Several staging systems are used including the Barcelona Clinic Liver Cancer (BCLC) system, which incorporates the Child–Pugh assessment of liver impairment, tumour characteristics and performance status (Eastern Cooperative Oncology Group [ECOG] score).

In patients with early stage disease (BCLC stage 0 or A), treatment can be curative. The European Society for Medical Oncology (ESMO) guidelines [23] updated and published in 2018 recommend surgical liver resection, liver transplantation and local destructive methods (radiofrequency ablation or microwave ablation) for early stage disease. In the UK, 70% of people with early disease undergo surgical liver resection compared with only 8% of those with late stage disease [17]. However, given that most patients are diagnosed with later stage disease, only around 30% to 40% are eligible for curative treatment (Llovet *et al.* 2003) [24].

The predominant arterial vascularisation of HCC has led to the development of interventional procedures which utilise the hepatic artery to deliver a blockage/chemotherapy/radiotherapy to the tumour. These procedures include:

- Transarterial embolisation (TAE) which physically blocks the blood supply to the tumour.
- Transarterial chemoembolisation using lipiodol (TACE) which blocks the blood supply to the tumour and may also include chemotherapy.
- Transarterial chemoembolisation using drug-eluting beads with doxorubicin or cisplatin (DEB-TACE) which blocks the blood supply and delivers chemotherapy to the tumour.
- SIRT which delivers radiation to the tumour.

The ESMO guidelines suggest that these interventional procedures may be used in a number of ways [23]:

- To provide complete tumour destruction in well-selected candidates.
- As a treatment for downstaging unresectable disease to potentially curative therapy, such as liver resection or transplantation or as a bridge to transplantation.
- As a palliative treatment to extend life and control disease and symptoms.

For unresectable early stage disease (BCLC stage 0 or A) or intermediate/advanced disease (BCLC stage B or C), potential treatment options include TAE, TACE, DEB-TACE and SIRT and/or systemic chemotherapy (sorafenib, levatinib or regorafenib) [23]. For some patients, however, systemic therapy may not be suitable due to severe systemic side effects and the need for twice daily dosing with inherent compliance risks. Furthermore, sorafenib has only a modest survival benefit of 2.8 months when compared with best supportive care (BSC) (Llovet *et al.* 2008) [25].

For patients with BCLC stage D disease, treatment is best supportive care (BSC).

Table 3-1: BCLC staging and treatment options (ESMO guidelines, 2018) [23]

BCLC stage	Definition	Standard of care	Alternative treatment
0-A	Single tumour any size or up to 3 nodules ≤3 cm Preserved liver function ECOG PS 0	Resection Transplantation Thermal ablation TACE	SIRT Radiotherapy High dose brachytherapy
B	Multinodular Preserved liver function ECOG PS 0	TACE	SIRT Transplantation Resection Systemic treatment
C	Portal invasion Extrahepatic spread Preserved liver function ECOG PS 1-2	Sofefenib (first-line) Lenvatinib (first-line) Regorafenib (second-line)	SIRT Nivolumab (second-line) Pembrolizumab (second-line)
D	End-stage liver function ECOG PS 3-4	Best supportive care	

Guidance from NICE broadly reflects the ESMO guidelines [23], with resection, transplant or ablation recommended for early resectable disease and interventional procedures and/or systemic chemotherapy for later stage disease (BCLC stage B or C) or unresectable early stage disease. Sorafenib is recommended by NICE for the treatment of advanced disease in people with Child-Pugh grade A liver impairment [26]. Lenvatinib is recommended as an option for untreated advanced, unresectable HCC for people with Child-Pugh grade A liver impairment and ECOG performance status of 0 or 1 [27]. Regorafenib is recommended as an option for advanced unresectable hepatocellular carcinoma as a second-line treatment (post-sorafenib) in people with Child-Pugh grade A liver impairment and an ECOG performance status of 0 or 1 [28].

3.2.2 Places in the Treatment Pathway for TheraSphere®

Figure 3-1 illustrates the potential places in the treatment pathway for TheraSphere®.

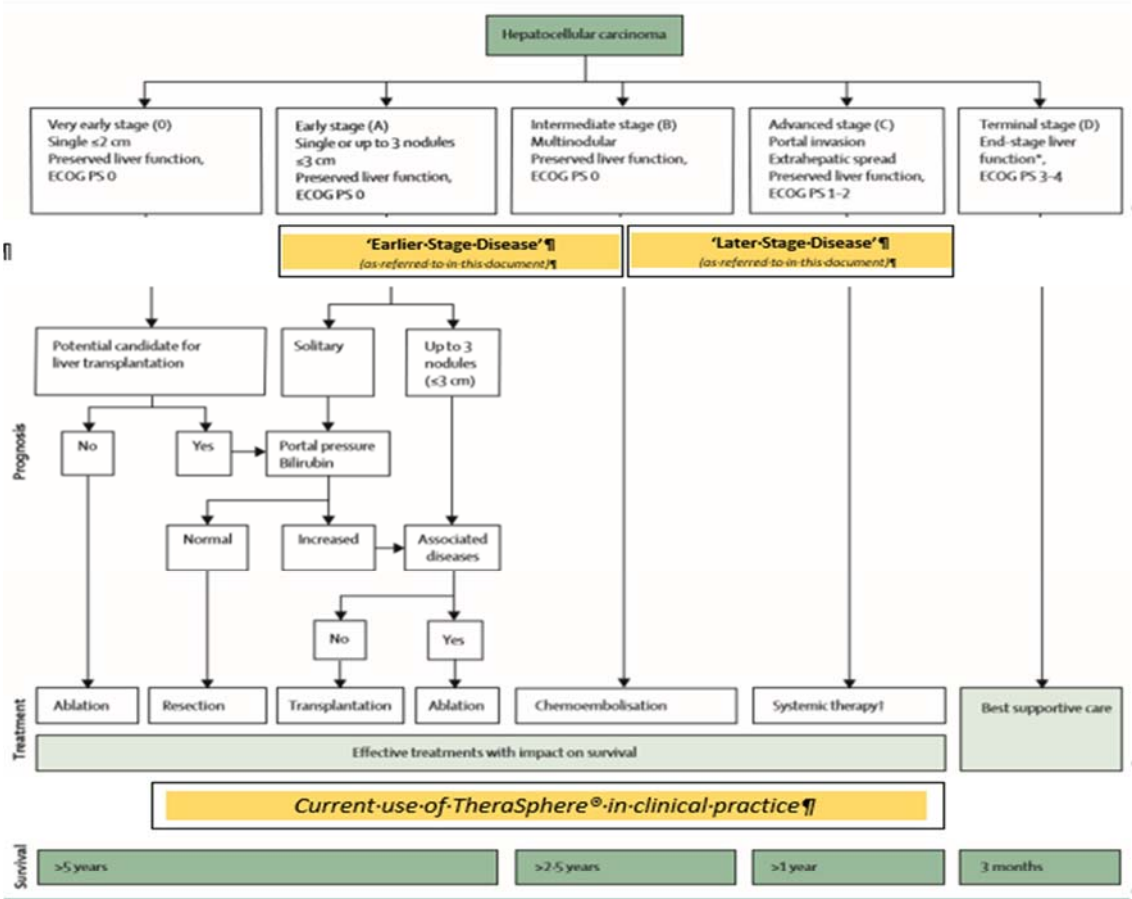
For the purposes of this document, we refer to “earlier stage disease” as patients with BCLC A[3], and selected patients with intermediate BCLC B disease (early/intermediate stage) in whom TheraSphere® is used with curative intent.

“Later stage disease” refers to patients with BCLC B or BCLC C disease (intermediate/advanced stage) who might benefit from TheraSphere® as a palliative treatment to control disease and symptoms.

[3] Patients with earlier stage disease may also include BCLC 0 patients but are not typically treated with TheraSphere®.

It is important to remember that these delineations are arbitrary, since the clinician may initiate treatment according to the categories above, with no certainty as to how the patient will actually respond.

Figure 3-1: Modified BCLC staging classification including proposed TheraSphere® treatment population (Forner *et al.* 2018)[21]



The BCLC system establishes a prognosis in accordance with the five stages that are linked to first-line treatment recommendation. The expected outcome is expressed as median survival of each tumour stage according to the available scientific evidence. Note that liver function should be evaluated beyond the conventional Child-Pugh classification or the Model of End-stage Liver Disease (MELD) score. None of them serves to properly gauge the liver function status, and this evaluation should take into account biochemistry parameters as well as the compensated or decompensated status of the patient. Preserved liver function includes a group of patients with different degrees of liver function reserve that has to be carefully evaluated. For most treatment options, compensated liver disease (Child-Pugh stage A without ascites) is required to obtain optimal outcomes. The sole option that could be applied irrespective of liver function is liver transplantation. ECOG PS=Eastern Cooperative Oncology Group Performance Status. *Patients with end-stage cirrhosis due to heavily impaired liver function (Child-Pugh stage C or earlier stages with predictors of poor prognosis or high a MELD score) should be considered for liver transplantation. In these patients, hepatocellular carcinoma might become a contraindication if it exceeds enlistment criteria. †Currently, sorafenib followed by regorafenib has been shown to be effective. Lenvatinib has been shown to be non-inferior to sorafenib, but no second-line option after lenvatinib has been explored.

3.2.3 Treatment of Later Stage HCC with TheraSphere®

For patients with later stage disease, TheraSphere® can be:

- Used in patients for whom chemoembolisation is not optimal therapy e.g. in patients with PVT whose underlying disease precludes TACE use.
- Used in patients who cannot tolerate chemoembolisation.
- Used in patients who have failed previous chemoembolisation therapy.
- Used in patients whose vasculature has changed due to prior treatments such that a chemoembolic agent such as TACE are no longer appropriate.

Patients with advanced HCC (BCLC C) are usually considered for palliative systemic chemotherapy (Forner *et al.* 2018) [21].

In this patient population, TheraSphere® can be:

- Used in patients who are unable to take or tolerate systemic chemotherapy.

3.2.4 Treatment of Earlier Stage HCC with TheraSphere®

For earlier stage disease, TheraSphere® can be used with curative intent. It can be:

- Used as a potentially curative treatment for patients with small HCC tumours (≤5 cm) which are not amenable to ablation or are otherwise unresectable due to location and/or proximity to critical structures. In such cases TheraSphere® is administered super-selectively using radiation segmentectomy to apply high dose radiation to ≤2 liver segments.
- Used for lobar treatment in patients who cannot undergo resection due insufficient remaining normal tissue (radiation lobectomy). These treated patients experience hypertrophy of the contralateral untreated lobe such that resection of the diseased lobe becomes an option. This response occurs while the tumours in the diseased lobe are being irradiated and atrophy. Other agents used to effect hypertrophy (e.g. portal vein embolisation) do so without treating the diseased lobe, whereas radiation lobectomy with TheraSphere® does both.
- Used to downstage disease to make patients eligible for potentially curative treatment (resection or ablation). For example, patients outside the Milan transplant criteria who experience a tumour burden reduction or 'downstaging' (e.g. a decrease from United Network for Organ Sharing (UNOS) stage T3 to T2), thus becoming candidates for potentially curative treatment.
- Used as locoregional tumour control treatment in patients on the transplant list currently recommended by NHS Blood and Transplant) [29].

Downstaging of HCC in order for patients to become eligible for transplant is not currently permitted in the UK, however TheraSphere® should be included as an option in the proposed service development for this population.

Section 4: Clinical Effectiveness

Comparative evidence for TheraSphere® in terms of clinical outcomes, including overall survival (OS), progression (defined variously as PFS, time to progression [TTP], time to subsequent treatment [TTST] or relapse free survival [RFS]) and overall response, indicate that TheraSphere® has either better or comparable outcomes to comparators (SIR-Spheres®, TACE, DEB-TACE and sorafenib) in most studies. This pattern of benefit is seen in both earlier and later stage disease.

Comparative evidence is available for TheraSphere® vs. SIR-Spheres® (three studies and one network meta-analysis [NMA]), TACE (13 studies including three with DEB-TACE and two which also included DEB-TACE) and sorafenib (one NMA). There is no comparative evidence against QuiremSpheres® or bland TAE. The majority of the comparative evidence is in later stage disease.

Overall, outcomes for patients with PVT are poorer than for patients without PVT or for the overall HCC population, however, TheraSphere® has either better or comparable outcomes to the comparators in this challenging patient group when used in later stage disease.

Non-comparative evidence provides supportive evidence of the value of TheraSphere® in later stage disease when used as a palliative treatment and in early stage disease (including radiation segmentectomy, radiation lobectomy, downstaging disease and use as locoregional tumour control in patients on the transplant list).

Two comparative studies evaluated health-related QoL after treatment with TheraSphere® in later stage HCC patients. Some QoL subscales were significantly improved with TheraSphere® when compared with TACE or with systemic chemotherapy, including functional well-being. QoL was not adversely affected after treatment with TheraSphere®

4.1 IDENTIFICATION AND SELECTION OF RELEVANT STUDIES

Two systematic literature reviews (SLRs) have been undertaken by BTG to evaluate the clinical effectiveness, safety and QoL of TheraSphere® [30] [31]. These SLRs have different inclusion criteria in terms of population characteristics than defined in the final NICE scope; one SLR had a broader focus and the other had a narrower focus. However, taken together, along with regular publication notifications received by BTG, they provide a comprehensive list of studies from which to screen for eligibility against the inclusion/exclusion criteria for this submission. Details of the search strategies presented in these SLRs are reported in Appendix A.

The inclusion criteria for this submission, following the final NICE scope, were as follows (Table 4-1):

Table 4-1: Inclusion/exclusion criteria

PICOS	Inclusion criteria	Exclusion criteria
Population(s)	• Group A: Patients with early and intermediate stage HCC, with the subgroup: o Patients receiving downstaging or bridging therapy prior to surgical intervention (resection, transplant) This group also included patients undergoing radiation lobectomy or radiation segmentectomy • Group B: Patients with intermediate and advanced stage HCC, with the subgroup: o Patients with PVT	• Studies conducted in Asian populations. It is well documented that in Asian countries, HBV is an important etiological factor for HCC. This differs from the USA in which HCV prevalence is greater than HBV as a contributory factor (Cheng *et al.* 2009; Llovet *et al.* 1999) [32, 33] to HCC development. In addition, in Asia TACE is used more aggressively and frequently to treat HCC compared to in Western practice • Mixed disease populations in which HCC outcomes are not reported separately were excluded
Intervention(s)	• TheraSphere®	• Studies which evaluated TheraSphere® and other SIRT devices were excluded unless data was available for TheraSphere® separately • Publications only reporting TheraSphere® use in combination with another therapy
Comparator(s)	• For patient group A: o SIR-Spheres® or QuiremSpheres®; o Bland TAE or cTACE or DEB-TACE • For patient group B: o SIR-Spheres® or QuiremSpheres®; o Sorafenib; lenvatinib, or regorafenib • Non-comparative studies were also included	
Outcome(s)	• OS • PFS • TTP (where applicable) • Response Rates • Rates of liver transplant or surgical resection (for patient group A) • Adverse effects of treatment • HRQoL	
Study design(s)	• Randomised controlled trials (RCTs), non-randomised control studies, case-control studies, and cohort studies (prospective and retrospective) • Data from network meta-analyses (where available) were included only if no head-to-head studies were available	• Publications in which patient efficacy and/or safety outcomes using TheraSphere® were not reported or were only descriptive only in nature • Case studies and case series were excluded • Abstracts, letters to editors or editorials were also excluded.
Limits	• Studies published after 2004 only were included as prior to this time, patient selection and administration techniques for TheraSphere® were still evolving. This cut-off date is consistent with other systematic reviews[4]	

Key: (c)TACE – (conventional) transarterial chemoembolisation; DEB-TACE – drug-eluting beads plus transarterial chemoembolisation; HCC – hepatocellular carcinoma; HBV – hepatitis B virus; HCV – hepatitis C virus; OS – overall survival; PFS – progression free survival; PVT – portal vein thrombosis; HRQoL – health related quality of life; RCT – randomised controlled trial; SIR(T) – selective internal radiation (therapy); TAE – transarterial embolisation; TTP – time to progression

[4] In one of SLRs, the cut off point for the search (January 2004) was chosen after consultation with clinical experts, with the rationale being that since earlier studies employing radioembolisation were likely based on sub-optimal clinical techniques that do not represent current clinical practice for HCC treatment (Precision Xtract. A network meta-analysis to compare the efficacy and safety of TheraSphere® and sorafenib for the treatment of unresectable hepatocellular carcinoma. 2018).

Data extraction was undertaken by one reviewer and checked by a second reviewer, with any disagreements resolved by discussion. For any randomised controlled trials, the Cochrane Collaboration's Risk of Bias tool was applied [34]. Given the number of comparative retrospective/prospective cohort studies that are included in this submission, and time restrictions, a comprehensive quality assessment of these types of studies (i.e. using the ROBINS-I tool) was not be completed.

However, for the purposes of this submission, the GRADE system[5] was used to assess the quality of evidence for each outcome (Schunemann *et al.* 2008) [35], starting with a low initial quality level for all observational studies (as per GRADE methodology).

4.2 LIST OF RELEVANT STUDIES

Overall, 43 studies met the inclusion criteria for this clinical effectiveness section. In addition, data from one NMA [30] and one systematic review [31] have been considered in this submission as they aimed to provide comparative data of TheraSphere® vs. other treatments. A list of these 43 individual studies is presented in Appendix B. A list of studies that were also screened, but did not meet the inclusion criteria is presented in Appendix C. In addition, ongoing relevant studies are presented in Appendix D.

Some research groups reported multiple publications using the same or overlapping patient groups. These papers were collated and cross-checked, and where significant overlap and identical endpoints were reported, only the most relevant (or recent) papers were included in this submission. As such, it may appear that many relevant papers will have been missed, but this is not the case.

In the following sections, summaries of the results are reported by outcome, with full data tables contained in Appendix E. Within each outcome, the results are presented separately (where possible[6]) by patients with later stage disease (BCLC C and select BCLC B) and earlier stage disease (BCLC A and select BCLC B) and then further divided into comparative and non-comparative studies.

When a subgroup analyses on PVT patients was presented, this data is reported in a 'PVT subgroup analyses' section. When a study specifically aimed to compare outcomes in patients with PVT compared with patients with no PVT, these publications were grouped and described separately from studies which only reported subgroup data.

Several papers reviewed within this document reported transplant and resection outcomes incidentally rather than as a primary or secondary endpoint. These data have been reported in a separate table from those studies that specifically examined TheraSphere® as a downstaging or bridge to transplant treatment.

[5] Using the four standard GRADE levels of quality (high, moderate, low and very low) we assigned evidence from RCTs an initial quality rating of high and evidence from non-RCTs an initial rating of low. We upgraded (for observational studies only) or downgraded these levels based on our judgments regarding risk of bias, precision, consistency, directness and publication bias.
[6] In many HCC studies, patients with all BCLC stages are included, without separate analysis by stage.

Details of study and patient characteristics for the studies described in the sections below are presented in Appendix E.

4.3 SUMMARY OF CLINCIAL EFFECTIVENESS RESULTS

The three tables (Table 4-2 to Table 4-4) below summarise the evidence for OS, progression (defined variously as PFS, TTP, TTST or RFS) and overall response. They indicate that TheraSphere® has better outcomes than the comparator or is comparable to the comparator in the majority of studies and in later and earlier stage disease. The majority of the evidence is in later stage disease (BCLC B and C).

Comparative evidence is available for TheraSphere® vs. SIR-Spheres® (three studies and one NMA), TACE (13 studies including three with DEB-TACE and two which also included DEB-TACE) and sorafenib (one NMA). There is no comparative evidence against QuiremSpheres® or bland TAE.

Where available, we have also listed outcomes for patients with PVT (either subgroup analyses or trials limited to patients with PVT). Overall, outcomes for this patient group are poorer than for patients without PVT or for the overall HCC population, however, TheraSphere® has better outcomes than the comparator or is comparable to the comparator in this challenging patient group.

Non-comparative evidence provides supportive evidence of the value of TheraSphere® in later stage disease when used as a palliative treatment and in early stage disease (including radiation segmentectomy, radiation lobectomy, downstaging disease and use as locoregional tumour control in patients on the transplant list).
Two comparative studies evaluated health related quality of life (QoL) after treatment with TheraSphere® vs. TACE or systemic chemotherapy (cisplatin) in later stage HCC patients. QoL was not adversely affected after treatment with TheraSphere®. Some QoL subscales were significantly improved with TheraSphere® when compared with TACE including social and functional well-being. The study vs. TACE used a QoL scale which specifically looked at the QoL parameters most relevant to patients undergoing embolisation (pain, impact of treatment side effects, ability to work, diarrhoea and good appetite) and found that QoL improved with TheraSphere® and worsened with TACE.

Full details of the clinical evidence for these outcomes is presented from section 4.4 onwards.

Table 4-2: Summary of Overall Survival data for TheraSphere®

Comparator	Number of studies	Results	OS	Population
Comparative studies				
QuiremSpheres®	0			
Bland TAE	0			
SIR-Spheres®	2	Comparable	Median: 11.7 M vs 9.9 M 2 year OS: 14% vs. 11%	Later stage disease
SIR-Spheres®	1 (NMA)	Comparable (non-inferior)	Approximately [redacted] survival at [redacted] years Approximately [redacted] survival at [redacted] years	Later stage disease Non-Asian
SIR-Spheres®	1	TheraSphere® better	Median: 9.5 M vs 3.7 M	Later stage disease with PVT
TACE	4	Comparable	Median: 18.6 M vs 17.7 M Median: 16.4 M vs 18 M Median: 27.6 M vs 27.4 M Median: Not reached vs 87.2 M	Earlier stage disease
TACE	2	TheraSphere® better	Median: 11.5 M vs 8.5 M Median: 35.7 M vs 18.7 M	Later stage disease
TACE (two studies also included DEB-DOX)	4	Comparable	Median: 15 M vs 14.4 M Median: 39.9 M vs 34.7 M No significant difference (median OS not given) Median: 20.5 M vs 17.4 M	Later stage disease
TACE (DEB-DOX)	1	Competitor better	Median: 4 M versus 13 M	Later stage disease
TACE (DEB-DOX)	2	Comparable	Median: 3 M vs 6 M Median: 5 M vs 7 M	Later stage disease with PVT
Sorafenib	1 (NMA)	Comparable (non-inferior)	Approximately [redacted] survival at [redacted] years Approximately [redacted] survival at [redacted] years	Later stage disease Non-Asian
Non-comparative studies				
TheraSphere®	9		Median: 12.3 M to 22.1 M	Mixed stage unresectable disease (most patients with later stage disease)
TheraSphere®	6		Median: 3.2 M to 17.5 M	Subgroup analyses of PVT patients in mixed stage unresectable disease (most patients with later stage disease)

TheraSphere®	4		Median: 3.9 M to not reached	Later stage disease with PVT
TheraSphere®	4		Median: 26.4 M (2.2 years) to 80.4 M (6.7 years)	Earlier stage disease Radiation segmentectomy
TheraSphere®	6		Median: 25.4 M (2.1 years) to 46 M (3.8 years)	Earlier stage disease Downstaging disease and/or bridging to transplant
TheraSphere®	3		Mean: 31 M Median: 36.6 M to not reached	Earlier stage disease Radiation lobectomy

NMA: Network meta-analysis

Table 4-3: Summary of Progression data for TheraSphere®

Comparator	Number of studies	Results	PFS or TTP or TTST or RFS	Population
Comparative studies				
QuiremSpheres®	0			
Bland TAE	0			
SIR-Spheres®	2	Comparable	Median PFS: 5.9 M vs 2.8 M 2 year PFS: 6% versus 0%	Later stage disease
SIR-Spheres®	1	Comparable/TheraSphere® better	Median PFS: 8.8 M vs 2.8 M (lobar PVT) p=0.77 Median PFS: 5.4 M vs 2.0 M (main PVT) p=0.02	Later stage disease with PVT
TACE	4	TheraSphere® better	Median TTST: 23.3 M vs 8.2 M Median TTP: 13.3 M vs 6.8 M Median TTP: Not reached vs 6.8 M Median RFS: 79 M vs 76.8 M	Earlier stage disease
TACE (study in DEB-DOX)	1	Competitor better	Median PFS: 5 M vs 15 M	Later stage disease
TACE	3	TheraSphere® better	Median TTP: 33.3 M vs 12.8 M Median PFS: 18.8 M vs 9 M Median TTP: 13.3 M vs 8.4 M	Later stage disease
Sorafenib	0			
Non-comparative studies				
TheraSphere®	6		Median TTP: 6 M to 11.3 M Median PFS: 5.9 M	Mixed stage unresectable disease (most patients with later stage disease)
TheraSphere®	3		Median: 1.4 M to 8 M	Subgroup analyses of PVT patients in mixed stage unresectable disease (most patients with later stage disease)
TheraSphere®	2		Median: 9 M to 11 M	Later stage disease with PVT
TheraSphere®	3		Median TTP: 25.2 M (2.1 years) to 32.4 M (2.7 years)	Earlier stage disease Radiation segmentectomy
TheraSphere®	6		Median time to recurrence: 10.1 M to 36.8 M % of patients experiencing recurrence post-transplant: 0% to 23%	Earlier stage disease Downstaging disease and/or bridging to transplant
TheraSphere®	3		Median TTP: 11 M to 34.3 M	Earlier stage disease Radiation lobectomy

Table 4-4: Summary of Response data for TheraSphere®

Comparator	Number of studies	Results	Response	Population
Comparative studies				
QuiremSpheres®	0			
Bland TAE	0			
SIR-Spheres®	1	Comparable	Overall response: 40% vs 13%	Later stage disease
TACE	2	TheraSphere® better	Overall response: 92.1% vs 52.6% Overall response: 75% vs 50%	Earlier stage disease
TACE	1	Comparable	Overall response: 52% vs 63%	Earlier stage disease
TACE	1	Comparable	Overall response: 33% vs 28%	
TACE (DEB-DOX)	1	Comparable	Overall response: 41% vs 34%	Later (or predominantly later) stage disease
TACE (two studies also included DEB-DOX)	5	TheraSphere® better	Overall response: 46% vs 60% Overall response: 61% vs 13% Overall response: 51% vs 51% Overall response: 95% vs 84% Overall response: 49% vs 36%	Later (or predominantly later) stage disease
Sorafenib	0			
Non-comparative studies				
TheraSphere®	8		Overall response (EASL): 40% to 76% Overall response (WHO): 21% to 42% Overall response (RECIST/mRECIST): 48% to 66%	Later (or predominantly later) stage disease
TheraSphere®	1		Overall response (WHO): 37%	Subgroup analyses of PVT patients in later (or predominantly later) stage disease
TheraSphere®	2		Overall response (EASL): 70% to 83%	Studies in PVT patients with later (or predominantly later) stage disease
TheraSphere®	4		Overall response (EASL): 67% to 83% Overall response (WHO): 46% to 71%	Earlier stage disease Radiation segmentectomy
TheraSphere®	2		Overall response (EASL): 87% Overall response (WHO): 76% Overall response (RECIST): 45%	Earlier stage disease Downstaging disease and/or bridging to transplant
TheraSphere®	3		Overall response (EASL): 94% to 95% Overall response (WHO): 65%	Earlier stage disease Radiation lobectomy

4.4 OVERALL SURVIVAL

Comparative Studies

Two retrospective comparative cohort studies comparing TheraSphere® and SIR-Spheres® revealed comparable median OS in patients with predominantly later stage unresectable disease. A third cohort study in difficult to treat later stage patients with PVT reported significantly longer median OS in TheraSphere® treated patients vs. SIR-Spheres® regardless of PVT severity. In an NMA comparing TheraSphere® and SIR-Spheres® in later stage disease, TheraSphere® was non-inferior to SIR-Spheres®.

Results from one RCT and three cohort studies reported comparable OS in patients with earlier stage disease with TheraSphere® and TACE. In seven cohort studies of patients with predominantly later stage disease, results were broadly comparable or showed benefit with TheraSphere® (two studies OS showed benefit with TheraSphere®, four studies comparable OS and one study OS benefit with TACE). Of two studies reporting subgroup analyses of PVT patients, both reported comparable OS with TheraSphere® and TACE.

In a network analysis comparing TheraSphere® and sorafenib in later stage disease, TheraSphere® was non-inferior to sorafenib with respect to OS.

Non-comparative Studies

The evidence suggests that TheraSphere® is an effective locoregional therapy for palliative care in both later stage and earlier stage disease. Across nine cohort studies in patients with later stage disease, median OS ranged from 12.3 to 22.1 months. In patients with PVT, median OS was shorter (3.2 to 14.3 months), with main PVT having shorter OS than other PVT locations. Across four cohort studies in patients with earlier stage disease, median OS ranged from 2.2 to 6.7 years.

Median OS in early stage unresectable disease patients using TheraSphere® was up to 7 years, which is comparable to that seen with curative therapies. Median OS was 2-4 years in patients who received TheraSphere® for downstaging or locoregional control whilst on the transplant list. Similarly, patients who received a radiation lobectomy with TheraSphere® had a mean OS of 31 months in one cohort study and a median OS of 36.6 months in another cohort study. In a third cohort study, median OS had not yet been reached.

The variability in OS across these studies may be confounded by differences in patient populations, reporting styles (e.g. by BCLC type or PVT status), censoring, dosing or differences in administration techniques over time. In addition, OS may be confounded in HCC patients by underlying progressing cirrhosis, concurrent treatment, previous and post-treatment. All of which emphasise the importance of individualised treatment selection.

Extending OS is the objective of any cancer therapy, with the best therapy offering the best chance of extending OS while balancing side effects and QoL. As such, these results should be considered in light of the safety profile and QoL data as reported in 4.7 below and Section 5.

4.4.1 Comparative Studies Reporting on Overall Survival

No studies were found that compared TheraSphere® with QuiremSpheres® or bland TAE.

4.4.1.1 TheraSphere® vs. SIR-Spheres® in Later Stage Disease

Three retrospective comparative cohort studies compared TheraSphere® vs. SIR-Spheres® in patients with predominantly later stage unresectable HCC (BCLC B or C), median OS in patients treated with TheraSphere® ranged from 7 to 9.5 months, and from 3.7 to 7.8 months with SIR-Spheres®. Two of the studies showed comparable OS with the two SIRTs and one study in patients with PVT reported a significant benefit with TheraSphere® (all BCLC C patients). The OS benefit with TheraSphere® vs. SIR-Spheres® in patients with PVT is confirmed by data from a sub-analysis.

Three retrospective comparative cohort studies compared TheraSphere® vs. SIR-Spheres® with respect to OS in patients with predominantly later stage unresectable HCC (BCLC B or C) (Biederman *et al.* 2016; Bhangoo *et al.* 2015, Van de Gucht *et al.* 2017) [36-38].

Two studies did not demonstrate a difference in median OS (Bhangoo *et al.* 2015; Van de Gucht *et al.* 2017) [37, 38], despite differing sized patient populations and percentage of patients with PVT (see Table E14 in Appendix E), In contrast, Biederman *et al.* 2016 [36] treated patients who all had PVT and reported a significantly longer median OS in patients who received TheraSphere® compared with SIR-Spheres® (hazard ratio (HR) of 0.39 (95% CI 0.23 to 0.67, p<0.001) (see Table 4-5).

The overall GRADE quality assessment for this group of studies, and for this outcome is: low quality[7].

Data is also available from a NMA and network analysis of seven studies which excluded studies in Asian populations [30]. This compared TheraSphere® with SIR-Spheres®, sorafenib and no treatment (see 4.4.1.3). TheraSphere® was non inferior to SIR-Spheres® and sorafenib (see Figure 4-1).

4.4.1.1.1 Subgroup analysis in PVT patients

Subgroup analysis demonstrated longer OS with TheraSphere® compared with SIR-Spheres® in patients with lobar PVT (HR of 2.1 [95% CI 1.1 to 4.3], p=0.027) and in patients with main PVT (HR of 2.7 [95% CI 1.1 to 6.4], p=0.024) (Biederman *et al.* 2016) [36].

[7] Using GRADE criteria, all observational studies start with a low initial quality of evidence. The evidence for this outcome was not further downgraded or upgraded. We note that in Biederman *et al.* (2016) the baseline characteristics were similar between treatment groups and both univariate and multivariate analyses were conducted, so this study was considered to be well-conducted for this type of design.

Table 4-5: Comparative studies of TheraSphere® vs. SIR-Spheres® in Later Stage Disease: Overall Survival

Study	Study country	Study design	Treatment	Sample size (n) analysed	Definition	Statistical analysis	Results
Bhangoo MS *et al.* J Gastrointest Oncol 2015, 6: 469-478 [37]	USA	Retrospective comparative cohort	TheraSphere®	15 amongst TheraSphere® and Sir-Spheres®	Time between date of first treatment and date of death	K	Median Survival since ^{90}Y: 8.4 M (range 1.3 to 21.1) Median Survival since diagnosis: 11.7 (range 3.4-43.2)
			SIR-Spheres®				Median Survival since ^{90}Y: 7.8 M (range: 2.3 to 12.5) Median Survival since diagnosis: 9.9 (range 3.8-19.4)
Van der Gucht A *et al.* J Nucl Med 2017, 58: 1334-1340 [38]	Switzerland	Retrospective comparative cohort	TheraSphere®	36	Time from date of the ^{90}Y TARE until death or tumour progression	K, LR	OS: 7 M (95% CI 1.6-12.4) OS at 6 M: 57% OS at 1y: 29% OS at 2y: 14%
			SIR-Spheres®	41			OS: 7.7 M (95% CI 7.2-8.2) P=0.77 OS at 6 M: 63% OS at 1y: 22% OS at 2y: 11%
Biederman DM *et al.* J Vasc Interv Radio 2016, 27: 812-821 [36]	USA	Retrospective comparative cohort	TheraSphere® (mean 2.63 Gbq)	69	From time of first ^{90}Y therapy for HCC with PVT censored for curative therapy or transplant	K, LR, Cox proportional hazards	Median: 9.5 M (95% CI 7.6-15.0) HR 0.39; 95% CI 0.23-0.67; p<0.001 Multivariate analysis: HR 0.19; 95% CI 0.10-0.37; p<0.0001 *Subgroup analysis*: Lobar PVT: 11.4 M (8.8-15.7) HR 2.1 (95%CI, 1.1-4.3) P=0.027 Main PVT: 8.6 M (4.2-15.) HR 2.7 (95%CI, 1.1-6.4) P=0.024
			SIR-Spheres® (mean 1.07 Gbq) *in both treatment groups, some patients also received sorafenib	21			Median: 3.7 M (95% CI 2.3-6.0) *Subgroup analysis*: Lobar PVT: 3.5 M (2.1-6.6) Main PVT: 3.7 M (2.7-6.0)

Key – Gbq – giga Becquerel; HCC – hepatocellular carcinoma; HR – hazard ratio; K – Kaplan-Meier estimates for univariate survival curves; LR – log-rank test for differences in median and 95% confidence interval (CI); M – months; n – number; OS – overall survival; PVT – portal vein thrombosis; SIR – selective internal radiation; TARE - transarterial radioembolisation

4.4.1.2 TheraSphere® vs. TACE in Earlier and Later Stage Disease

OS was comparable in four studies of patients with earlier stage disease, suggesting equivalence between TheraSphere® and TACE for this group of patients. For those with later stage disease, two comparative cohort studies reported significantly longer median OS with TheraSphere® compared with TACE, four cohort studies did not demonstrate a difference and one showed OS benefit with TACE. Of two studies reporting subgroup analyses of PVT patients, both reported comparable OS with TheraSphere® and TACE.

TACE (either conventional TACE (cTACE) or drug-eluting beads TACE [DEB-TACE]) is the standard of care for intermediate stage (BCLC B) patients according to ESMO guidelines [23]. Given that TACE is not appropriate for all patients, a number of studies have been conducted comparing TACE with TheraSphere® to determine whether TheraSphere® could be an alternative therapy to TACE. As previously described, we have included BCLC B patients in both earlier and in later stage treatment discussions and several publications below have done the same. In order to better group the studies by patient population, we have discussed earlier stage and later stage disease studies separately.

Eleven studies comparing TheraSphere® vs. TACE reported on OS, including one RCT (Salem *et al.* 2016) [39] and ten comparative cohort studies (Akinwande *et al.* 2016; Biederman *et al.* 2018; Carr *et al.* 2010; El Fouly *et al.* 2015; Gabr *et al.* 2017; Lewandowski *et al.* 2009; Moreno-Luna *et al.* 2013, Padia *et al.* 2015, Padia *et al.* 2017, Salem *et al.* 2011)[8, 40-48]. Of these studies, three included earlier stage HCC patients as follows: BCLC A and BCLC B (Salem *et al.* 2016) [39], BCLC B patients (El Fouly *et al.* 2015) [43] and "early stage" HCC patients (but no BCLC status provided) (Biederman *et al.* 2018) [41]. One study (Gabr *et al.* 2017) [44] reported OS (largely BCLC A and B with a low number from other stages) in patients who had received prior TheraSphere® or TACE as a bridging or downstaging therapy prior to transplant. The remaining studies were predominantly in patients with later stage disease or included patients more evenly distributed across all disease stage.

Of the four studies in patients with earlier (or predominantly earlier) stage disease, the RCT (Salem *et al.* 2016) [39] reported a median survival time (censored to liver transplantation) of 18.6 months for TheraSphere® and 17.7 months for cTACE (p=0.99) which was lower than expected due for both groups in part due to the number of patients with advanced underlying cirrhosis included in the study. In a group of BCLC B patients only, El Fouly *et al.* 2015 [43] reported that median OS was 16.4 months (95% CI: 7.9, 25.3) with TheraSphere® and 18 months (95% CI: 12.1, 25.5) with cTACE, but there was no statistically significant difference. Similarly, (Biederman *et al.* 2018) [41] did not demonstrate a difference in OS between the HCC groups after propensity score matching; OS was 27.6 months with TheraSphere® and 27.4 months with TACE (p=0.71). In a very different type of study, the median OS in transplanted patients with prior TACE was 87.2 months but was not reached for the TheraSphere® arm (57% alive at 100 months, p=0.42) demonstrating no difference between the two prior treatments on OS (Gabr *et al.* 2017) [44].

Of the remaining seven studies in predominantly later stage disease patients, two studies demonstrated benefit with TheraSphere®: Carr *et al.* (2010) [42], and Lewandowski *et al.* (2009) [45].

In Carr *et al.* (2010) [42], OS was significantly longer with TheraSphere® (11.5 months versus 8.5 months, p<0.05), however the authors noted that patients in the ^{90}Y group had milder disease. In Lewandowski *et al.* (2009) [45] OS was significantly longer with TheraSphere® compared with TACE (censored 35.7 vs. 18.7 months; p = 0.18; uncensored 41.6 vs. 19.2 months, p = 0.008).

Four studies demonstrated no significant difference in OS and one demonstrated a lower OS with TheraSphere®. In Akinwande *et al.* (2016) [40], median OS was significantly lower for patients treated with TheraSphere® than for patients treated with drug-eluting beads loaded with doxorubicin (DEB-DOX) (4 months vs. 13 months, p=0.008 in propensity matched populations).

The RCT was considered to have an unclear risk of bias[8], and the GRADE quality assessment for this overall group of studies is: low quality[9]

4.4.1.2.1 Subgroup analysis in PVT patients

In both Akinwande *et al.* (2016) [40] and Carr *et al.* (2010) [42], no significant difference in OS was demonstrated between treatment groups in patients with PVT (see Table 4-6).

[8] This study was considered to have an unclear risk of bias because details regarding the method of randomisation and allocation concealment were not reported (although baseline characteristics were balanced). Blinding was not possible and the outcome variable (OS) was objective. It is unclear if there was selective outcome reporting. Outcome data were available for all patients. We note, however, that this study was stopped early.

[9] Using GRADE criteria, all observational studies start with a low initial quality of evidence. The evidence for this outcome was not further downgraded or upgraded.

Table 4-6: Comparative Studies of TheraSphere® vs. TACE in Earlier and Later Stage Disease: Overall Survival

Study	Study country	Study design	Treatment	Sample size (n) analysed	Definition	Statistical analysis	Results
Studies of patients with earlier stage disease							
Biederman DM *et al.* J Vasc Interv Radiol 2018, 29: 30-37 [41]	USA	Retrospective comparative cohort	TheraSphere®	55 before, 38 after PSM	From date of initial therapy censored for curative therapy	K +LR Comparison between groups used LR before PSM and stratified LR after PSM.	Before PSM: Median: 37.6 M (95% CI 32.0-43.2) vs TACE: HR: 0.79 (95% CI 0.51-1.22) p=0.29
							After PSM: Median: 27.6 M (95% CI 25.0-30.4) vs TACE: HR: 1.33 (95% CI 0.30-5.98) p=0.71
			TACE	57 before, 38 after PSM			Before PSM: Median: 39.9 M (95% CI 33.6-46.3) HR: 1.00
							After PSM: Median: 27.4 M (95% CI 23.4-31.4) HR: 1.00
El Fouly A *et al.* Liver Int 2015, 35: 627-635 [43]	Germany and Egypt	Prospective, non RCT	TheraSphere®	44	NR	Survival probabilities displayed by K calculated by LR	Overall median survival rate: 16.4 M (95% CI 7.9-25.3) 1 year survival rate: 59% 2 year survival rate: 40% 3 year survival rate: 31%
			cTACE	42			Overall median survival rate: 18 M (95% CI 12.1-25.5) 1 year survival rate: 64% 2 year survival rate: 36% 3 year survival rate: 11%
Salem R *et al.* Gastroenterology 2016, 151: 1155-1163 [39]	USA	RCT	TheraSphere® 120Gy	24	From day of randomisation	K using ITT population HR and 095% CI by proportional hazard regression.	Censored to liver transplant: Median 18.6 M (95% CI 7.4-32.5) P=0.99
			cTACE Drug NR	21			Median 17.7 M (95% CI 8.3-not calculable)
Gabr A *et al.* Eur J Radiol 2017, 93: 100-106 [44]	USA	Retrospective comparative cohort	TheraSphere® followed by transplant	93	From first liver-directed therapy	K, LR	Median OS from first liver-directed therapy: ^{90}Y: not reached but 57% alive at 100 M TACE: 87.2 M p=0.42 5y OS probability:

Study	Study country	Study design	Treatment	Sample size (n) analysed	Definition	Statistical analysis	Results
							^{90}Y: 67% (95% CI 52-82%) TACE: 68% (95% CI 57-81%) Post-transplant OS: ^{90}Y: 57% alive at 100 months p=0.5654 TACE: 84.2 M No significant difference in OS between TheraSphere® or TACE given pre transplant
			cTACE followed by transplant	79			
Studies of patients with later (or predominantly later) stage disease							
Akinwande O *et al.* Anticancer Res 2016, 36: 239-246 [40]	USA	Retrospective comparative cohort	TheraSphere®	Pooled: 67	Time between the treatment start date and death from any cause	K, LR	Pooled: median survival: DEBDOX: 15 M vs ^{90}Y: 6 M (log rank, p<0.0001)
				Pooled 291			
			DEBDOX	Matched 48			Matched**:** median survival**:** DEBDOX; 13 M ^{90}Y: 4 M (LR, p=0.0077) PVT subgroup showed trend toward longer OS for DEBDOX (6 M) vs ^{90}Y (3 M) p=0.13 NSS
				Matched 48			
Carr BL *et al.* Cancer 2010, 116: 1305-1314 [42]	USA	Prospective Cohort	TheraSphere®	691	Time between date of 1st treatment and death date	K+ LR, Cox	Median survival= 11.5 M (95% CI 8-16) vs TACE+ p<0.0146; modestly sustained difference over 50 M Absence of PVT: TS: 16 M (95% CI 12-20 M); TACE: 12 M (95% CI, 10-14 M): p<0.05 Presence of PVT: TS: 5 M (95% CI 4-9 M); TACE: 7 M (95% CI 5-9 M): NSS
		Observational Retrospective Cohort	cTACE	99			Median survival= 8.5M

Study	Study country	Study design	Treatment	Sample size (n) analysed	Definition	Statistical analysis	Results
		Observational Cohort	No treatment	NR			Median survival= 2M
Lewandowski RJ *et al.* Am J Transplant 2009, 9: 1920-1928 [45]	USA	Prospective, non-random cohort comparison	TheraSphere®	43	From date of 1st cTACE or ^{90}Y	K, LR	**Median follow up:** 34.1 M (15.7-39.8) p=0.008 **Median OS:** censored: 35.7 M (95% CI 17.3-41.6) p=0.18 uncensored: 41.6 M (95% CI 29.6-) p=0.008 **EFS:** 17.7 M (95% CI 10.8-33.3) p=0.0017 **1 year RFS rate:** 89%
			cTACE	43			**Median follow up:** 51.9 M (95% CI 32.2-65.2) **Median OS :** censored: 18.7 M (95% CI 13-23.6) uncensored: 19.2 M (95% CI 14.7-26.5) **EFS:** 7.1 M (95% CI 6-10.6) **1 year RFS rate:** 73%
Moreno-Luna LE *et al.* Cardiovasc Intervent Radiol 2013, 36: 714-723 [46]	USA	Retrospective comparative cohort	TheraSphere®	61	From initial treatment until last follow up or death	K + LR. Cox	Median OS=15 M P=0.47 2y survival= 30% 3y survival=21% 5y survival= 9%-
			cTACE	55			Median OS=14.4 M 2y survival= 24% 3y survival=16% 5y survival= 5%
Padia SA *et al.* J Vasc Interv Radiol 2017, 28:777-785 [48]	USA	Retrospective comparative cohort	TheraSphere® Median radiation activity=1.59GBq (IQR, 1.11-2.18 GBq)	101	From day of treatment	K Groups were weighted using IPTW for PS	Median OS: 1,198 d When censored for transplant chemo had higher mortality rate HR=2.26; p=0.015, but the effect decreased when IPTW adjusted: HR=1.83; P=0.064. Excluding PVT patients: HR=1.41; P=0.33
			TACE: DEB DOX or cTACE: 50 mg doxorubicin	77	From day of treatment	K Groups were weighted using IPTW form PS	Median OS: 1,043 d
Padia SA *et al.* Cardiovasc Intervent Radiol 2015, 38: 913-921 [47]	USA	Retrospective comparative cohort	TheraSphere®: intended dose 120Gy	4	From 1st treatment	C, cumulative incidence curves	Patients with transjugular intrahepatic portosystemic shunts (TIPS): NSS difference

Study	Study country	Study design	Treatment	Sample size (n) analysed	Definition	Statistical analysis	Results
			TACE: 50 mg doxorubicin in LC beads OR cTACE	9			in survival between any of the treatment groups (p>0.82). When censored for transplant: Supportive care vs ^{90}Y: HR=5.9 (95% CI 0.7-49), p=0.045 Supportive care vs TACE: HR=5.0 (95% CI 0.9-27), p=0.035) NSS difference between treatment groups (p>0.33)
			Supportive Care	19			
Salem R *et al.* Gastroenterol 2011, 140: 497-507 [8]	USA	Prospective comparative cohort	TheraSphere®	123	From date of first therapy; data censored to curative therapy	K, CCox , p value corrected for multiple comparisons	Overall Survival: 20.5 M (95% CI 15.7-29.1) p=0.232
			cTACE 30 mg mitomycin, 30 mg hemoembol, 100 mg cisplatin	122			Overall Survival: 17.4 M (95% CI13.9-18.7)

Key: BCLC – Barcelona Clinic Liver Cancer; Ccox - Cox proportional regression model for Hazard ratios; C – Chi square test; CI – confidence interval; CP – Child-Pugh score; ITACE – (conventional) transarterial 40hemoembolization; d – days; DEBDOX – drug-eluting beads loaded with doxorubicin; EFS – event free survival; GBq – gigabecquerel; Gy – Gray (units); HCC – Hepatocellular carcinoma; HR – hazard ratio; IPTW – inverse probability of treatment weights; IQR – inter-quartile range; ITT – intent to treat; ; K – Kaplan-Meier for univariate survival curves; LR – log-rank test; M – months; mg – milligram; n – number; NSS – no statistical significance; OS – overall survival; PS – propensity score model; PSM – propensity score matching; PVT – portal vein thrombosis; RCT – randomised controlled trial; RFS – relapse free survival; y – years

4.4.1.3 TheraSphere® vs. Sorafenib in Later Stage Disease

A network meta-analysis (NMA), intended to demonstrate non-inferiority, showed TheraSphere® was a non-inferior treatment to sorafenib with respect to OS using non-Asian population studies and the best fit statistical model. Approximate survival at [redacted] years was [redacted] with TheraSphere® and [redacted] with sorafenib.

No direct head-to-head studies have been conducted comparing TheraSphere® with sorafenib. Comparisons between these treatments have been considered in a NMA and network analysis of [redacted] studies which excluded studies in Asian populations [30]. Based on results from the best fit model (proportional hazards fixed effects model), the comparison between TheraSphere® and sorafenib was [redacted] (HR: [redacted] 95% CrI: [redacted]), [redacted] follow up period. This result suggests that TheraSphere® is an alternative option to sorafenib. A random-effects model showed similar results, with a HR of [redacted] (95% CrI: [redacted]). Meta-regression analyses adjusting for BCLC class, Child-Pugh, macrovascular invasion, EHD, and PVT did not substantially change the estimates of the relative treatment effect.

Estimated survival curves from these models are presented in Figure 4-1 (fixed-effects) and Figure 4-2 (random-effects). These plots show similar estimated survival, with TheraSphere® showing approximately [redacted] survival at [redacted] years post-treatment vs. approximately [redacted] with sorafenib. This estimate holds with both fixed and random-effects models, although the width of the credible intervals differed.

Figure 4-1: Estimated survival of TheraSphere® and other interventions from 2nd order fractional polynomial (p_1=0, p_2=-1) network meta-analysis with fixed-effects and proportional hazards for the primary network of studies

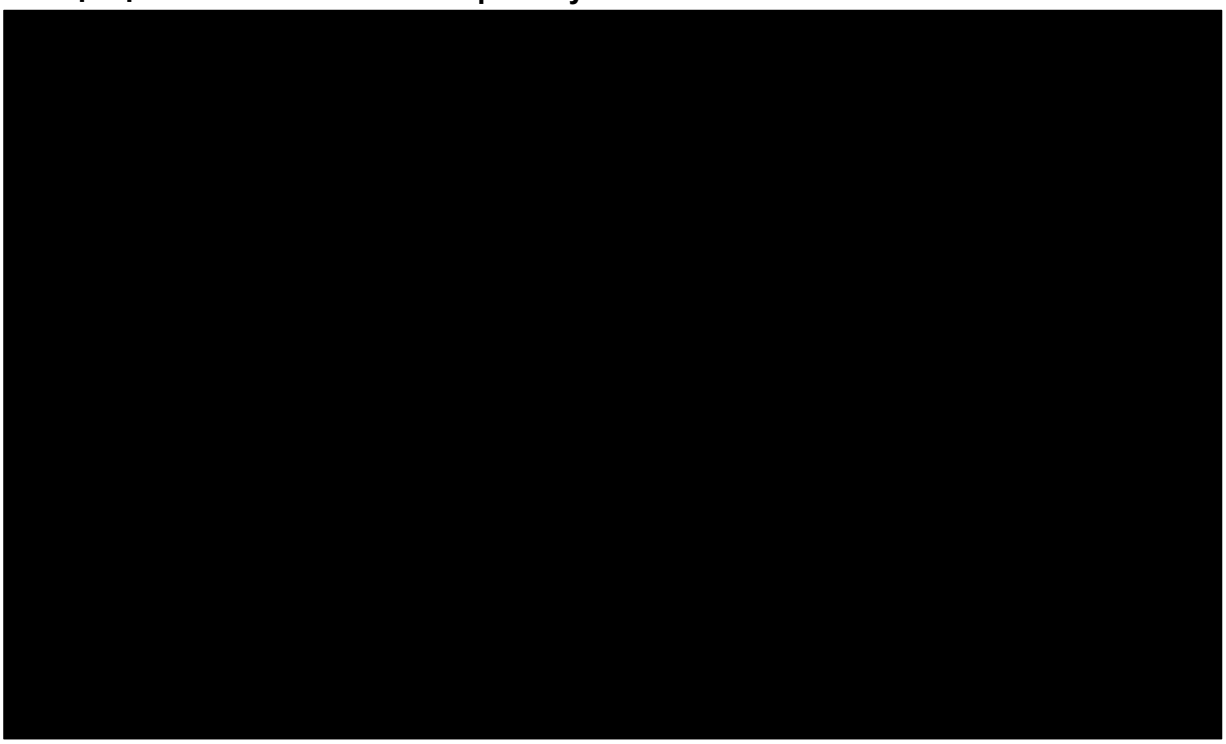


Figure 4-2: Estimated survival of TheraSphere® and other interventions from 2nd order fractional polynomial (p_1=0, p_2=-1) network meta-analysis with random-effects and proportional hazards for the primary network of studies

4.4.2 Non-Comparative Studies Reporting on Overall Survival

4.4.2.1 TheraSphere® Treatment in Later Stage Disease

The evidence suggests that TheraSphere® is an effective locoregional therapy for palliative care in later stage disease. Across nine cohort studies, median OS ranged from 12.3 to 22.1 months. In patients with PVT, median OS was shorter (from 3.2 to 14.3 months) – with main PVT having poorer outcomes compared with other PVT locations.

The variability in OS across these studies may reflect differing patient populations, different reporting styles of the study authors (e.g. by BCLC type or PVT status), differences in censoring, and differences in administration techniques over time – which continued to be refined over the 10 year period when these studies were published.

Nine non-comparative cohort studies assessed OS in patients with mixed stage unresectable HCC (although most patients had later stage disease) who were treated with TheraSphere® (Ali *et al.* 2017; Biederman *et al.* 2015; Hilgard *et al.* 2010; Garin *et al.* 2017; Lambert *et al.* 2011; Mazzaferro *et al.* 2013; Salem *et al.* 2010; Woodall *et al.* 2009) [41, 49-56] Although Woodall *et al.* (2009) [56] compared supportive care with TheraSphere®, we have only focused on the TheraSphere® results in this section. Across all of these studies, median OS ranged from 12.3 to 22.1 months (Table 4-7). Some of the variability across these studies may be due in part to patient characteristics, which are discussed below.

The Salem *et al.* (2010) [55], Mazzaferro *et al.* (2013) [54] and Woodall *et al.* (2009) [56] publications set the stage for reporting on TheraSphere® use in unresectable HCC. The earliest of these studies demonstrated a median OS of 13.9 months in non-PVT patients (Woodall *et al.* 2009) [56]. Salem *et al.* (2010) [55] further reported an OS of 17.2 months in BCLC B patients and 7.3 months in BCLC C patents. Mazzaferro *et al.* (2013) [54] treated later stage patients who were initially considered for downstaging or transplant but were considered ineligible due to tumour extension – and reported a median OS of 15 months post-TheraSphere®.

In addition to these studies, Biederman *et al.* (2015) [50] reported and OS of 19.3 months in hepatitis B patients[10] and mostly BCLC C with some BCLC B patients. A later study by Biederman *et al.* (2018) [57] reported on patients with marginal functional hepatic reserve treated with TheraSphere® (mostly BCLC C) and found the OS was 21.9 months.

In European patients, Hilgard *et al.* (2010) [51] found the OS in patients with later stage disease (mostly BCLC C or BCLC B TACE-ineligible patients) and with cirrhosis to be 16.4 months. Lambert *et al.* (2011) [53] reported a slighter lower OS of 12.3 months in a much smaller study, but at the time of their analysis 55% of patients had died. The author suggested that the degree of censoring for transplant might account for OS differences between this study and that of Salem *et al.* 2010 [55] in the BCLC B group.

Ali *et al.* (2017) [49] assessed TheraSphere® administered to patients with unresectable recurrent HCC post-resection, and reported an OS of 22.1 months.

Garin *et al.* (2017) [52] reported on outcomes (in 43 haemoembolisation–ineligible patients) as a function of dosimetry-determined tumour dosing and reported that OS was 18.7 months in the overall patient group.

The overall GRADE quality assessment for this group of studies, and for this outcome is: low quality.[11]

4.4.2.1.1 Subgroup Analysis in PVT Patients

Six studies also reported OS data in patients with PVT albeit in small patient numbers in two studies. Overall survival was reported as 3.2 months (n=15) (Woodall *et al.* 2009) [56], 4.6 months (n=8) (Ali *et al.* 2017) [49], 12 months (n=31) (Garin *et al.* 2017) [52] and 13 months (n=35) (Mazzaferro *et al.* 2013) [54]. Salem *et al.* (2010) [55] stratified PVT patients based on BCLC status, CP status and presence /absence of extrahepatic disease. The majority of PVT patients had no extrahepatic disease of which BCLC C with CP A liver status patients had an OS of 10.4 months, and in BCLC C with CP B status patients OS was 5.6 months. Seven studies reported inferior survival in PVT patients compared with

[10] Most HCC patients with a viral aetiology in the Western world have hepatitis C.
[11] Using GRADE criteria, all observational studies start with a low initial quality of evidence. The evidence for this outcome was not further downgraded or upgraded.

no PVT (Ali *et al.* 2017; Biederman *et al.* 2015; 2018; Garin *et al.* 2017; Mazzaferro *et al.* 2013; Salem *et al.* 2010; Woodall *et al.* 2009) [49, 50, 52, 54-57].

4.4.2.1.2 Studies in PVT Patients

In addition to the above studies, four cohort studies reported OS in patients with PVT (Abouchaleh *et al.* 2018: Kokabi *et al.* 2015; Kulik *et al.* 2008 and Pracht *et al.* 2013) [58-61] In these studies, OS differed depending on disease stage and type (Kokabi studied infiltrative HCC) as well as the type of PVT. For example, patients with main PVT had shorter OS than segmental PVT. This was also noted in the Salem *et al.* (2010) [55] paper. Amongst these groups, and across studies, OS ranged from 4.6 months to 14.3 months (see Table 4-8).

Table 4-7: Non-Comparative Studies of TheraSphere® in Later Stage Disease: Overall Survival

Study	Study country	Study design	Treatment	Sample size (n) analysed	Definition	Statistical analysis	Results
Ali R *et al.* Eur J Nucl Med Mol Imaging 2017, 44: 2195-2202 [49]	USA	Observational Retrospective Cohort	TheraSphere®	41	From day of ^{90}Y treatment	K censored to subsequent liver transplantation	Median survival from ^{90}Y: 22.1M (95% CI 10.3-31.3) With PVT: 4.6 M (95% CI 3.0-6.2) No PVT: 30.4 M (17.2-43.6)
Biederman DM *et al.* J Vasc Interv Radiol 2015, 26: 1630-1638 [50]	USA	Observational Retrospective Cohort	TheraSphere®	38	From time of first radioembolisation censored for curative therapy	K	Median OS: 19.3M (95% CI 11.2-22.7) Inferior survival seen in PVT patients (p=0.2)
Biederman DM *et al.* Clin Imaging 2018, 47:34-40 [57]	USA	Observational Retrospective Cohort	TheraSphere®	36	From time of first ^{90}Y therapy	K, LR, univariate analysis for PVT subgroups	Mean OS: 21.9 (95%CI 14.8-29.0) Absence of PVT improved survival: p=0.005 HR: 0.14 (95% CI 0.04-0.56)
Hilgard P *et al.* Hepatology 2010, 52: 1741-1749 [51]	Germany	Observational Retrospective Cohort	TheraSphere®	108	From day of first ^{90}Y treatment	K	Median OS: 16.4 (95% CI 12.1-∞) Survival probability at 6 M: 75% (95% CI 66%-85%) Survival probability at 1y: 59% (95% CI 47%-75%)
Garin E *et al.* Liver Int. 2017, 37: 101-110 [52]	France	Consecutive Prospective Cohort	TheraSphere®	85	From time between treatment and last follow or death	K	Median OS: 18.7M (95% CI 12-25) Non-PVT: 24.0M (95% CI: 14-29) PVT: 12.0 (95%CI: 8-20.2) p=0.0391 Mortality rate: 0% at 1 M and 5.8% at 3 M PVT patients:

Study	Study country	Study design	Treatment	Sample size (n) analysed	Definition	Statistical analysis	Results
							25 patients were good candidates (and had an OS of 17.5 M (95%CI 11-26.6) 6 were poor candidates (e,g, TD<205GY, 2 with poor PVT targeting with dose administration) and OS was only 3.6 M (95% CI 2-8) I comparison HR of 12.85 (95%CI 3.68-44.77)
Lambert B *et al.* Eur J Nucl Mol Imaging 2011, 38: 2117-2124 [53]	Belgium	Observational Retrospective Cohort	TheraSphere®	29	NR Censored at maximum follow up	K	At a median follow up of 17.0 M (95% CI 4.7-29.2): Overall median survival: 12.3 M (95% CI 9.4-15.2)
Mazzaferro V *et al.* Hepatology2013, 57: 1826-1837 [54]	Italy	Prospective single arm	TheraSphere®	52	From 1st radio-embolization to death from any cause	K, C	Median OS: 15 M (95%CI, 12-18) PVT Absent: BCLC B: 18 M (95%CI 12-38) PVT Present: BCLC C: 13 M (95% CI 9-17)
Salem R *et al.* Gastroenterology 2010, 138: 52-64 [55]	USA	Observational Prospective Cohort	TheraSphere®	NR (245 for entire study)	From date of 1st ^{90}Y treatment	K, LR	**Without EHD** Classified by BCLC BCLC B overall: 17.3 M (95% CI 13.5-29.6) BCLC C overall: 7.3 M (95% CI 6.5-10.1) BCLC C, CP A with PVT:10.4 M (95% CI 7.2-6.6) BCLC C, CP A No PVT: 47.4 (95% CI n.c.)

Study	Study country	Study design	Treatment	Sample size (n) analysed	Definition	Statistical analysis	Results
							BCLC C, CP B with PVT: 5.6 M (95% CI 4.5-6.7) BCLC C, CP B No PVT: 11.8 (95% CI nc.-34) **Classified by CP** Overall CP A: 17.2 (95% CI 14.0-24) Overall CP B: 7.7 (95% CI 6.5-11.2) **Classified by PVT type** CP A branch: 16.6 (95% CI 8.8-24) CP A main: 7.7 (95% CI 3.3-13.2) CP B branch: 6.5 (95% CI 5-8.5) CP B main: 4.5 (95% CI 2.9-6.6) **With EHD** BCLC C overall: 5.4 (95% CI 2.7-7.5) BCLC C, CP A with PVT: 6.3 M (95% CI n.c.-12.9) BCLC C, CP A No PVT: 9.5 M (95% CI 8.4-13) BCLC C, CP B with PVT: 2.7 M (95% CI 2.4-3.6) BCLC C, CP B No PVT: 6.4 (95% CI 2.1-14.1) BCLC C, CP A 8.7 (95% CI 6.3-11.3) BCLC C, CP B 6.4 (95% CI 2.1-14.1)

Study	Study country	Study design	Treatment	Sample size (n) analysed	Definition	Statistical analysis	Results
Woodall CE *et al.* J Am Coll Surg 2009, 308: 375-382 [56]	USA	Prospective single arm	TheraSphere®	NR	NR	K, LR	Treated without PVT: median OS: 13.9 M Treated with PVT: median OS: 3.2 M Supportive care: median OS: 5.2 M p=0.01 for without PVT vs with PVT or supportive care)
			Supportive care				

Key: BCLC – Barcelona Clinic Liver Cancer; c – Chi-square test; EHD – extrahepatic disease; HR – hazard ratio; K – Kaplan-Meier estimates for univariate survival curves; LR – log-rank test for differences in median and 95% confidence interval (CI); Gy – gray (unit); M – months; n – number; NR – not reported; OS – overall survival; PVT – portal vein thrombosis; RFS – recurrence-free survival; SS – statistically significant; y – years

Table 4-8: Non-Comparative Studies of TheraSphere® in PVT patients: Overall Survival

Study	Study country	Study design	Treatment	Sample Size (n) Analysed	Definition	Statistical Analysis	Results
Abouchaleh J *et al.* Nucl Med 2018, 59: 1042-1048 [58]	USA	Retrospective Cohort	TheraSphere® 80-150 Gy	CP A: 74 CP B7: 51 CP ≥B8: 60	NR	K, univariate analysis using K+ LR	CP A:13.3 M (95% CI 8.7-15.7) Segmental PVT: 14.3 M (95% CI 12.0-17.8), lobar: 14.2 M (95% CI 7.3-19.5) main: 7.7 M (95% CI 4.6-13.8) CP B7: 6.9 M (95% CI 5.3-10.1) Segmental PVT: 6.5 M (95% CI 3.4-38), lobar: 6.9 M (95% CI 4.6-13.3) main: 7.7 M (95% CI 4.8-11.1) CP ≥B8: 3.9 M (95% CI 2.9-5.0) Segmental PVT: 8.4 M (95% CI 1.2-75.2) lobar: 4.4 M (95% CI 2.5-9.7) main: 3.4 M (95% CI 2.5-4.6) Univariate analyses showed segmental or branch PVT patients had better survival than main portal vein PVT (p=0.008)

Study	Study country	Study design	Treatment	Sample Size (n) Analysed	Definition	Statistical Analysis	Results
Kokabi M *et al.* Cancer 2015, 12: 2164-2174 [59]	USA	Prospective single arm	TheraSphere®	30	From time of 1st ^{90}Y therapy	K	Median OS: 13M (95% CI, 4.4-22) Main vs branch PVT: 1.696 M (95% CI 0.55-5.25) Occlusive vs non occlusive: 1.23 M (95% CI 0.39-3.82)
Kulik L *et al.* Hepatology 2008, 47: 71-81 [60]	USA	Prospective cohort	TheraSphere®	Total: 82 No PVT:71 Branch:25 Main: 12	From 1st day of treatment	K, LR	Median OS No PVT: 467d (95% CI 322-629) Branch: 304d (95% CI 217-481) Main: 133.5d (95% CI 88-225) No PVT vs PVT: 0.0052
Pracht M *et al.* Int J Hepatol 2013, doi: 10.1155/2013/827649 [61]	France	Retrospective Cohort	TheraSphere®	18	From date of first treatment until the date of death from any cause or of last follow up	K, LR	Not reached (95% CI 9.0-∞) Overall survival at 6 M: 88.5 M± 95% CI 14.7 Overall survival at 1y: 70.3 M± 95% CI 21.1

Key: d – days; Gy – gray (unit); K – Kaplan-Meier estimates for univariate survival curves; LR – log-rank test for differences in median and 95% confidence interval (CI); M – months; OS – overall survival; PVT – portal vein thrombosis

4.4.2.2 TheraSphere® Treatment in Earlier Stage Disease: Radiation Segmentectomy

The evidence suggests that TheraSphere® is an effective locoregional therapy in earlier stage unresectable HCC. Across four cohort studies, median OS ranged from 2.2 to 6.7 years in earlier stage disease patients treated with TheraSphere®, which is comparable to that seen with other curative treatments. Differences in patient groups and dosing may account for the wide range in OS in these studies.

Four non-comparative cohort studies assessed OS in patients with earlier stage HCC (predominantly BCLC A or B) treated with TheraSphere® (Lewandowski *et al.* 2018; Riaz *et al.* 2018; Salem *et al.* 2010; Vouche *et al.* 2014).[55, 62-64]. Across these studies, median OS ranged from 2.2 to 6.7 years.

One study (Riaz *et al.* 2018) [63] selected patients with CP ≤B7 and solitary tumour HCC (any size tumour) and reported on survival times of responders (patients with a complete response (CR) or partial tumour response (PR)) compared with non-responders (patients with stable disease (SD) or progressive disease (PD)) post-TheraSphere® using Landmark statistical analyses. Responders survived statistically significantly longer than non-responders when estimated at 3 M, 6 M and 12 M post-treatment with the longest survival times being c. 4.5 years (using EASL[12]) (Table 4-9). These data suggest that treatment to response should be the goal, which may prolong OS in earlier stage disease.

Lewandowski *et al.* (2018) [62] treated early stage HCC patients with preserved liver function (CP A5 and A6) and solitary tumours ≤5 cm, with radiation segmentectomy giving doses of >190Gy. Median OS was 6.7 years, which compares favourably with outcomes reported in other curative therapies (resection, ablation or transplantation). Thus, the authors suggested that radiation segmentectomy could be considered curative in this population.

Salem *et al.* (2010) [55] assessed all BCLC staged patients, of which 48 BCLC A patients had a median OS of 26.9 months.

Vouche *et al.* (2014) [64] examined the effects of TheraSphere® given via radiation segmentectomy in patients with solitary HCC lesions (median 3 cm) and CP A, B or C, not amenable to resection or ablation (e.g. close proximity to critical structures). Median OS in these patients was 53.4 months (4.5 years). Of the 33 (32%) patients who went on to receive a transplant, median OS was 56.5 months (4.7 years).

The overall GRADE quality assessment for this group of studies, and for this outcome is: low quality[13]

[12] Median survival differed depending on the criteria used (i.e. WHO, RECIST 1.1, EASL).
[13] Using GRADE criteria, all observational studies start with a low initial quality of evidence. The evidence for this outcome was not further downgraded or upgraded.

Table 4-9: Non-Comparative Studies of TheraSphere® in Earlier Stage Disease: Overall Survival

<table>
<tr><th>Study</th><th>Study Country</th><th>Study design</th><th>Treatment</th><th>Sample Size (n) Analysed</th><th>Definition</th><th>Statistical Analysis</th><th>Results (n,%)</th></tr>
<tr><td>Lewandowski RJ et al. Radiology 2018, 287: 1050-1058 [62]</td><td>USA</td><td>Observational Retrospective Cohort</td><td>TheraSphere®</td><td>70</td><td>From the first treatment with ^{90}Y until day of last follow up or death</td><td>K, LR</td><td>Median overall survival was 6.7 years (95% CI 3.1- 6.7)
1y, 3y and 5y survival probability:98%, 66%, and 57% respectively</td></tr>
<tr><td>Riaz A et al. Heptatology 2018, 67: 873-883 [63]</td><td>USA</td><td>Observational Retrospective Cohort</td><td>TheraSphere®</td><td>3M: 134
6M: 116
12M: 81</td><td>Landmark analysis: OS is estimated from set time points onwards (3, 6, 12M post therapy)</td><td>K, LR, C used to compare rates of death</td><td>Landmark Analysis: Median Survival (M)
<table><tr><th></th><th colspan="2">3M</th><th colspan="2">6M</th><th colspan="2">12M</th></tr><tr><th></th><th>R</th><th>NR</th><th>R</th><th>NR</th><th>R</th><th>NR</th></tr><tr><td rowspan="2">WHO</td><td>34.3</td><td>27.3</td><td>61.5</td><td>23.6</td><td>56.7</td><td>31.8</td></tr><tr><td colspan="2">P=0.51</td><td colspan="2">P=0.027</td><td colspan="2">P=0.0066</td></tr><tr><td rowspan="2">RECIST 1.1</td><td>51.6</td><td>46.0</td><td>56.1</td><td>36.3</td><td>52.3</td><td>35.2</td></tr><tr><td colspan="2">P=0.32</td><td colspan="2">P=0.021</td><td colspan="2">P=0.049</td></tr><tr><td rowspan="2">EASL</td><td>44.3</td><td>22.1</td><td>33.5</td><td>13.9</td><td>53.5</td><td>18.2</td></tr><tr><td colspan="2">P=0.002</td><td colspan="2">P<0.001</td><td colspan="2">P<0.001</td></tr><tr><td colspan="7">R – Responder(CR, PR) NR=non responder (SD, PD)</td></tr></table></td></tr>
<tr><td>Salem R et al. Gastroenterology 2010, 138: 52-64 [55]</td><td>USA</td><td>Observational Prospective Cohort</td><td>TheraSphere®</td><td>NR (245 for entire study)</td><td>From date of first ^{90}Y treatment</td><td>K, LR</td><td>Median OS (BCLC A): 26.9 M (17-30.2)
CP-A 17.2
CP- B 7.7
CP-B with PVT – 5.6</td></tr>
<tr><td>Vouche M et al. Hepatology 2014, 60: 192-201 [64]</td><td>USA</td><td>NR</td><td>TheraSphere®</td><td>102</td><td>NR</td><td>K with LR then C with censoring for transplant</td><td>Median overall survival: 53.4 M with median F/up of 27.1M
When censored for transplant: survival was 34.5 M</td></tr>
</table>

Key: BCLC – Barcelona Clinic Liver Cancer; C – Chi-square test; EASL – European Association for the Study of the Liver; K – Kaplan-Meier estimates for univariate survival curves; LR – log-rank test for differences in median and 95% confidence interval (CI); M – months; n – number; NR – not reported; OS – overall survival; RECIST – Response Evaluation Criteria in Solid Tumours; WHO – World Health Organization; y – years

4.4.2.3 TheraSphere® Treatment in Earlier Stage Disease: Downstaging to Curative Treatment or Bridge to Transplant

In earlier stage disease, TheraSphere® can be used to downstage disease such that curative treatments may become an option. Additionally, TheraSphere® can be used as locoregional control to maintain a patients' status on the transplant list. TheraSphere® used for downstaging to curative treatment or bridge to transplant resulted in a median OS ranging from 25.4 months to 46 months across studies. Longer OS values were reported in some of the cohort studies, but it is unclear if these were calculated pre- or post-transplantation.

Six non-comparative cohort studies reported on OS or survival rates in patients treated with TheraSphere® for downstaging or bridging to transplant intent (Abdelfattah *et al.* 2015; Ibrahim *et al.* 2012; Kulik *et al.* 2006; Kulik *et al.* 2014; Radunz *et al.* 2017; Tohme *et al.* 2013) [65] [66-70] Where reported, these studies included patients in all BCLC stages, with higher proportions of patients with BCLC A or B stage HCC, but the studies and/or patients were heterogeneous: For example, Ibrahim *et al.* (2012) [66], assessed downstaging in patients with caudate lobe HCC – a rarer location for HCC and difficult to resect making transplantation the only viable curative option; Kulik *et al.* (2014) [68] examined whether TheraSphere® alone or with sorafenib was the more effective bridging therapy[14]; Radunz *et al.* (2017) [69] examined tumour recurrence and survival post liver transplant, and evaluated the potential relationship of recurrence with pathological tumour response attained with TheraSphere® treatment (see Table 4-10).

Reporting on OS in this group of studies was also variable. In one study, the authors only reported that all patients were alive at follow-up (Abdelfattah *et al.* 2015) [65]. In other studies, survival was found to be relatively high, but it was not always clear whether or not the data were censored for transplantation. Tohme *et al.* (2013) [70] reported that survival at 1, 3 and 5 years was 95%, 84% and 79% respectively, with an overall median OS of 75.1 months (OS not defined). Kulik *et al.* (2014) [68] reported a similarly high survival rate of 70% at year 3 (from date of randomisation). In Kulik *et al.* (2006) [67] OS for all the patients at 1, 2 and 3-years was 84%, 54% and 27%, respectively, with a median survival not reached at 800 days (OS not defined). Ibrahim *et al.* (2012) [66] reported that OS was 27.8 months (uncensored – from time of first treatment) and 25.4 months (censored to transplantation). In Radunz *et al.* (2017) [69], median OS (from the day of liver transplantation) was 46 months.

The overall GRADE quality assessment for this group of studies, and for this outcome is: low quality.[15]

[14] Although Kulik *et al.* (2014) also included a TheraSphere® plus sorafenib treatment arm, we have only extracted data from the TheraSphere® arm (as per our inclusion criteria) and thus treated this study as a non-comparative study.
[15] Using GRADE criteria, all observational studies start with a low initial quality of evidence. The evidence for this outcome was not further downgraded or upgraded.

Table 4-10: Non-Comparative Studies of TheraSphere® used for Downstaging or Bridge to Transplant: Overall Survival

Study	Study country	Study design	Treatment	Sample size (n) analysed	Definition	Statistical analysis	Results
Abdelfattah MR *et al.* Transplant Proc 2015, 47: 408-411 [65]	Saudi Arabia	Observational Retrospective Cohort	TheraSphere®	Group A[16]: 3 Group B[17]: 6	NR	NR	All 9 patients were alive and recurrence free with follow up assessments occurring 13.6 – 70.1 M after OLT
Ibrahim, SM, *et al.* Cardiovasc Intervent Radiol. 2012, 35:1094-1101. [66]	USA	Observational Retrospective Cohort	TheraSphere®	8 5 outside Milan criteria (≥T3)	From time of first treatment, uncensored and censored to transplantation	K	OS (uncensored): 27.8 M (95% CI 6.2- not reached) OS for OLT (censored): 25.4 M (95% CI 6.3-30.4)
Kulik L, *et al.* J Hepatol 2014, 61: 309-317 [68]	USA	Unblinded prospective randomized pilot study	TheraSphere® (vs sorafenib + TheraSphere® – data not shown)	10 All on transplant list; all within Milan criteria	From date of randomization on a MITT	Descriptive, Mann Whitney and F to compare groups	Survival rate at 3y: 70% (p = 0.57)
Kulik, LM *et al.* J Surg Oncol. 2006, 94 :572-86. [67]	USA	Observational Retrospective Cohort	TheraSphere®	35 All T3 requiring downstaging	NR	Descriptive	Alive at publication time: 24 (69%) including all 8 transplanted and 1 resected patient. OS: 84%, 54%, and 27% at 1, 2, and 3 years respectively Median OS not reach at 800 days
Radunz S *et al.* Ann Transplant 2017, 22: 215-221 [69]	Germany	Observational Retrospective Cohort	TheraSphere®	40 All underwent transplant post TheraSphere®	From the day of liver transplantation. Patents who died within 30d post-transplant were excluded	K, LR	Median OS: 46 M Survival was SS longer in recurrence-free patients compared to those with recurrence (p=0.0193)
Tohme S,*et al.* J Vasc Interv Radiol 2013, 24: 1632-1639 [70]	USA	Observational Retrospective Cohort	TheraSphere®	20 All on transplant list; 6 of which require downstaging	NR	K, LR	Median OS: 75.1 M (IQR 36.9–106.0 M) 1-,3- and 5-year survival rates: 95%, 84%, and 79% respectively

Key: d- days; IQR – interquartile range; K – Kaplan-Meier estimates for univariate survival curves; LR – log-rank test for differences in median and 95% confidence interval (CI); F – Fischer's exact test; M – months; MITT – modified intention to treat; n – number; NR – not reported; OLT – orthotopic liver transplant; OS – overall survival; RFS – recurrence-free survival; SS – statistically significant; y – years

[16] TheraSphere indicated for downstaging
[17] TheraSphere indicated for bridging

4.4.2.4 TheraSphere® Treatment in Earlier Stage Disease: Radiation Lobectomy

Patients who had received a radiation lobectomy with TheraSphere® had a mean OS of 31 months in one cohort study and a median OS of 36.6 months in another cohort study. In a third cohort study, median OS had not yet been reached.

As described above, radiation lobectomy is a procedure whereby the diseased lobe is irradiated with TheraSphere® resulting in treatment of HCC lesions with hypertrophy in the contralateral untreated lobe. Radiation lobectomy may allow resection of the diseased liver lobe as the increase in volume of the untreated liver is sufficient to sustain (at least) the minimum liver function required to survive, post-resection. Other agents used to effect hypertrophy (e.g. portal vein embolisation) do so without treating the diseased lobe, whereas radiation lobectomy with TheraSphere® does both.

Three retrospective cohort studies reported on OS or survival rates in patients who were treated with lobar TheraSphere® and manifested a hypertrophy in the untreated lobe (see Table 4-11). Gabr *et al.* (2018) [71] reported on outcomes post-radiation lobectomy and subsequent resection, whereas the other two studies focused on characteristics of the atrophy-hypertrophy phenomena which is radiation lobectomy.

Median survival was reported as 36.6 months in one study (Gaba *et al.* 2009) [72] and mean survival was reported as 31 months in another study (Goebel *et al.* 2017) [73]. In Gabr *et al.* (2018) [71], the survival rate (from date of resection) at year 1-2 year was 96% and 86% by year 3 (median OS not reached).

The overall GRADE quality assessment for this group of studies, and for this outcome is: low quality.[18]

[18] Using GRADE criteria, all observational studies start with a low initial quality of evidence. The evidence for this outcome was not further downgraded or upgraded.

Table 4-11: TheraSphere® used in Radiation Lobectomy: Overall Survival

Study	Study country	Study design	Treatment	Sample size (n) analysed	Definition	Statistical analysis	Results
Gaba *et al.* Ann Surg Oncol 2009, 16: 1587-1596 [72]	USA	Observational Retrospective Cohort	TheraSphere®	17	From date of first ^{90}Y until death or date of most recent clinical follow up censored to transplant or resection	K	Median survival: 36.6 M (95%CI 21.7-∞) 1 y survival: 100%, 2y: 76%, 5y: 46% 13/17 patients alive at time of publication
Goebel *et al.* PloS One 2017, 12(7): e0181488 [73]	Germany	Observational Retrospective Cohort	TheraSphere®	75	NR	K	Mean OS: 31±3.4 M
Gabr A *et al.* J Vasc Interv Radiol 2018 29: 1502-1510 [71]	USA	Observational Retrospective Cohort	TheraSphere®	31	RFS from the date of resection to death or last follow-up	K, LR	Survival rates: 1y and 2y: 96% (95% CI 81–99) 3y: 86% (95% CI 52– 99). Median was not reached Median recurrence-free survival: 34.2M (95% CI 18.7-34.2)

Key: CI – confidence interval; K – Kaplan-Meier for univariate survival curves; HCC – hepatocellular carcinoma; M – months; n – number; NR – not reported; OS – overall survival; y – years

4.5 PROGRESSION (OR TIME TO SECONDARY THERAPY)

Comparative Studies
Two retrospective comparative cohort studies that compared the effect of TheraSphere® vs. SIR-Spheres® on TTP or PFS in patients with predominantly later stage HCC (BCLC B or C) demonstrated no significant difference between treatments. In a subgroup analysis with main PVT, TTP was significantly longer in patients treated with TheraSphere® compared with SIR-Spheres®.

Eight studies presented data on progression, with evidence largely showing significantly longer TTP in both earlier and later stage HCC patients treated with TheraSphere® compared with TACE.

Non-comparative Studies
Median TTP ranged from 6 to 11.3 months across studies in patients with later stage disease who were treated with TheraSphere®. In patients with earlier stage disease, median TTP ranged from 2.1 to 2.7 years across three cohort studies.

TheraSphere® used for downstaging or bridge to transplant resulted in a median time to recurrence after resection or transplant of 10.1 months to 36.8 months across the studies. The percentages of patients experiencing a recurrence after transplant ranged from 0% to 23%.

Recurrence rates in patients who received a radiation lobectomy with TheraSphere® ranged from 20% to 51% across three cohort studies.

4.5.1 Comparative Studies Reporting on Progression

No studies were found that compared TheraSphere® with QuiremSpheres® or bland TAE.

4.5.1.1 TheraSphere® vs. SIR-Spheres® in Later Stage Disease

Two retrospective comparative cohort studies that compared the effect of TheraSphere® vs. SIR-Spheres® on TTP or PFS in patients with predominantly later stage HCC (BCLC B or C) had comparable results. In a subgroup analysis of patients with main PVT, TTP was significantly longer in patients treated with TheraSphere® compared with SIR-Spheres®.

Two retrospective comparative cohort studies compared the effect of TheraSphere® vs. SIR-Spheres® on TTP or PFS in patients with predominantly later stage HCC (BCLC B or C) (Biederman *et al.* 2016; Van Der Gucht *et al.* 2017) [36, 38]. Neither study demonstrated a significant difference for these outcomes (see Table 4-12).

The overall GRADE quality assessment for this group of studies, and for this outcome is: low quality[19]

4.5.1.1.1 Subgroup Analysis in PVT Patients

Subgroup analysis demonstrated longer TTP with TheraSphere® compared with SIR-Spheres® in patients with main PVT (HR not reported, p=0.02) but the difference for lobar PVT was not reported to be statistically significant (Biederman *et al.* 2016) [36].

[19] Using GRADE criteria, all observational studies start with a low initial quality of evidence. The evidence for this outcome was not further downgraded or upgraded. We note that in Biederman *et al.* (2016), the baseline characteristics were similar between treatment groups and both univariate and multivariate analyses were conducted, so this study was considered to be well-conducted for this type of design.

Table 4-12: Comparative studies of TheraSphere® vs. SIR-Spheres®: Time to Progression or Progression Free Survival

Study	Study country	Study design	Treatment	Sample size (n) analysed	Definition	Statistical Analysis	Results
Biederman DM *et al.* J Vasc Interv Radio 2016, 27: 812-821 [36]	USA	Retrospective comparative cohort	TheraSphere® (mean 2.63 Gbq)	57	Time from initial treatment to disease progression censored for curative therapy and loss of imaging follow up	K, LR Proportional hazards model applied for competing risk of death	Median 5.9 M (95% CI 4.2-9.1) HR 1.31 (95% CI 0.62-2.75) p=0.48 Lobar PVT (n=39): 8.8 M (95% CI 4.2-11.7) p=0.77 Main PVT (n=18): 5.4 M (95% CI 3.6-8.5) p=0.02
			SIR-Sphere® (mean 1.07 Gbq) *in both treatment groups, some patients also received sorafenib	15			Median 2.8 M (95% CI 1.9-4.3) Lobar PVT (n=8): 2.8 M (95% CI 2.8-14.4) Main PVT (n=18): 2.0 M (95% CI 1.4-4.3)
Van der Gucht A *et al.* J Nucl Med 2017, 58: 1334-1340 [38]	USA	Retrospective comparative cohort	TheraSphere®	36	PFS defined as time from date of the ^{90}Y TARE until first occurrence of disease progression determined by biological and contrast-enhanced MRI	K, LR	PFS: 5 M (95% CI 0.9-9.2) PFS at 6 M: 47% PFS at 1y: 18% PFS at 2y: 6%
			SIR-Spheres®	41			PFS: 6.1 M (95% CI 4.7-7.4) p=0.53 PFS at 6 M: 52% PFS at 1y: 7% PFS at 2y: 0%

Key: Gbq – gigabecquerel; HR – hazard ratio; K – Kaplan-Meier estimates for univariate survival curves; LR – log-rank test for differences in median and 95% confidence interval (CI); M – months; MRI – magnetic resonance imaging; PFS – progression-free survival; PVT – portal vein thrombosis; TARE – transarterial radioembolisation

4.5.1.2 TheraSphere® vs. TACE in Earlier and Later Stage Disease

Eight studies presented data on progression, with evidence largely showing significantly improved outcomes in patients treated with TheraSphere® compared with TACE. One RCT (with an unclear risk of bias) demonstrated that time to progression (TTP) was significantly longer in earlier disease stage patients treated with TheraSphere® compared with patients treated with cTACE. Longer TTP with TheraSphere® was also observed in two other comparative cohort studies in patients with earlier stage disease, and also in two studies that included patients with all BCLC states.

Two comparative cohort studies also found that progression free survival (PFS) was significantly longer with TheraSphere® compared with TACE in later stage HCC patients. One study reported that recurrence-free survival was similar between TheraSphere® and TACE when data were collected post-transplant.

Eight studies that compared TheraSphere® with TACE reported TTP, PFS or time to secondary therapy (TTST) (Akinwande *et al.* 2016; Biederman *et al.* 2018; El Fouly *et al.* 2015; Gabr *et al.* 2017; Lewandowski *et al.* 2009; Padia *et al.* 2017; Salem *et al.* 2011; Salem *et al.* 2016) [8, 39-41, 43-45, 48] (see Table 4-13). Of these, one RCT (Salem *et al.* 2016) [39], and two comparative cohort studies provided comparative data on TheraSphere® vs. TACE in BCLC A or BCLC B (Salem *et al.* 2016) [39], BCLC B patients (El Fouly *et al.* 2015) [43] or 'early-stage' HCC patients (Biederman *et al.* 2018) [41]. In addition, Gabr *et al.* (2017) [44] reported on recurrence-free survival (RFS) in patients who had received TheraSphere® or TACE, followed by transplant. This study was largely in BCLC A and B patients, but also included C and D patients. The remaining studies were predominantly in patients with later stage disease or included patients in all disease stages.

4.5.1.2.1 TTP (or TTST)

In the studies of patients with earlier stage disease, the RCT showed that TheraSphere® was associated with a significantly longer TTP than cTACE (>26 months vs. 6.8 months (p=0.0012) (Salem *et al.* 2016) [39]. In the study by El Fouly *et al.* (2015) [43], median TTP was longer with TheraSphere® than cTACE (13.1 vs 6.8 months, respectively), but a significant difference was not demonstrated. Biederman *et al.* (2018) [41], reported that patients were more likely to need secondary treatment (TTST) if treated with TACE compared with those treated with TheraSphere® (HR 1.39; 95% CI 1.08-1.79; p=0.001) and reported a significantly longer TTST with TheraSphere® compared to TACE before propensity score matching (HR 0.71, 95% CI 0.55-0.92; p=0.009) or after (HR: 0.21, 95% CI 0.08-0.55; p=0.001).

Two further comparative prospective studies reported on TTP in patients with all BCLC states (Lewandowski *et al.* 2009; Salem *et al.* 2011) [8, 45]. Median time to overall progression was 33.3 months with TheraSphere® and 12.8 months with TACE (p=0.005) in Lewandowski *et al.* (2009) [45]. In Salem *et al.* (2011) [8], TheraSphere® also demonstrated a longer median TTP than cTACE (13.3 vs 8.4 months), p=0.005. The authors suggested

that the longer tumour control could potentially lower dropout rate from the transplant waitlist and provide higher rates of successful bridging to transplant.

4.5.1.2.2 RFS and PFS

Gabr *et al.* (2017) [44] reported on recurrence free survival (RFS) in post-transplant patients. This study was largely in BCLC A and B patients, but also included C and D patients. Median RFS was similar in patients treated with TheraSphere® (followed by transplant) and those treated with cTACE (followed by transplant) (79 vs. 77 months).

The remaining two studies reported on PFS in patients with intermediate or late stage HCC (Akinwande *et al.* 2016; Padia *et al.* 2017) [40, 48]. In Akinwande *et al.* (2016) [40], PFS was significantly longer in patients who were treated with TheraSphere® compared to those who were treated with DEBDOX group (15 months vs. 6 months, $p<0.0001$). Padia *et al.* (2017) [48] also reported a significant benefit of TheraSphere® compared with TACE (median PFS 564 days vs. 271 days, $p<0.001$).

The RCT was considered to have an unclear risk of bias[20], and the GRADE quality assessment for this overall group of studies is: low quality.[21]

[20] This study was considered to have an unclear risk of bias because details regarding the method of randomisation and allocation concealment were not reported (although baseline characteristics were balanced). Blinding was not possible and the outcome variable (OS) was objective. It is unclear if there was selective outcome reporting. Outcome data were available for all patients. We note, however, that this study was stopped early.

[21] Using GRADE criteria, all observational studies start with a low initial quality of evidence. The evidence for this outcome was not further downgraded or upgraded.

Table 4-13: Comparative studies of TheraSphere® vs TACE: Time to Progression or Progression Free Survival or Time to Second Therapy

Study	Study country	Study design	Treatment	Sample size (n) analysed	Definition	Statistical analysis	Results
Studies of patients with earlier Stage Disease							
Biederman DM *et al.* J Vasc Interv Radiol 2018, 29: 30-37 [41]	USA	Observational Retrospective Cohort	TheraSphere®	55 before, 38 after PSM	TTST included all forms of treatment e.g. locoregional, surgical, systemic. Censored at date of transplant where initial therapy resulted in CR and radiologic progression before transplant	K+LR Comparison between groups used LR before PSM and stratified LR after PSM.	**Before PSM TTST:** Median: 700d (95% CI 308-812) vs TACE: HR: 0.71 (95% CI 0.55-0.92) p=0.009 **After PSM TTST:** Median: 812d (95% CI 363-812) vs TACE: HR: 0.21 (95% CI 0.08-0.55) p=0.001
			TACE	55 before, 38 after PSM			**Before PSM TTST:** Median: 246d (95% CI 135-350) HR: 1.00 **After PSM TTST**: Median: 161d (95% CI 76-350) HR: 1.00 TTST outcomes showed patients are more likely to need secondary treatment if treated with TACE vs TheraSphere® (HR 1.39; 95% CI 1.08-1.79; P=.001)
El Fouly A *et al.* Liver Int 2015, 35: 627-635 [43]	Europe and others	Prospective, non RCT	TheraSphere®	44	TTP (definition not reported)	K=LR	13.3 M (95% CI 3.4-23.1) 1y progression rate: 42% 2y progression rate: 73%
			cTACE	42			6.8 M (95% CI 3.9-8.8) 1y progression rate: 66% 2y progression rate: 88%
Salem R *et al.* Gastro-enterology 2016, 151: 1155-1163 [39]	USA	Prospective 1:1 randomized study Study terminated early	TheraSphere®	24	TTP: from day or randomization using ITT population; applying WHO and EASL criteria	K + LR HR and 95% CI by proportional hazard regression. Inverse probability of censoring weighting	13/15 (87%) of patients listed on transplant were successfully bridged and received a transplant Median TTP not reached: > 26 M (95% CI 14.5-not calculable) P=0.0012 (HR: 0.122 , 95%CI 0.027-0.557, p=0.007 With competing risk analysis or IPCW the difference remained significant

			cTACE	21		(IPCW). Gray's test for cumulative incidence of progression with transplant /death as competing risks. Proschan and Jitlal methods for early terminated studies, applied.	7/10 (70%) of patients listed on transplant were successfully bridged and received a transplant Median time to PR/CR: 1.7M (95% CI 1.6-3.4) Median TTP: 6.8M
Gabr A *et al.* Eur J Radiol 2017, 93: 100-106 [44]	USA	Observational Retrospective Cohort	TheraSphere® followed by transplant	93	RFS from first liver directed therapy	K	Median RFS: 79.0 M (p=0.71) 5-year RFS probability 59% (95% CI 43-74%)
			cTACE followed by transplant	79			Median RFS: 76.8 M 5-year RFS probability 66% (95% CI 54-78%)
Studies of patients with later (or predominantly later) stage disease							
Akinwande O *et al.* Anticancer Res 2016, 36: 239-246 [40]	USA	Observational Retrospective Cohort	TheraSphere®	Pooled 67	^{90}Y 48	PFS: Time between start of treatment and image-based disease progression or death	K, LR	Pooled PFS: DEBDOX: 15 M, ^{90}Y: 5 M (p<0.0001)
			DEB-DOX	Pooled 291	^{90}Y 48			Matched PFS: DEBDOX: 6 M, ^{90}Y:5 M (p=0.42) but PFS in ^{90}Y was due to some deaths vs disease progression
Lewandowski RJ *et al.* Am J Transplant 2009, 9: 1920-1928 [45]	USA	Prospective, non-random cohort comparison	TheraSphere®	43		From first treatment to response to progression assessed by WHO/EASL/UNOS or UNOS/new lesion	K, LR	**TACE (n=35)** / **^{90}Y (n=43)** / **p-Value** **WHO 1y progression rate (%)**: 25 / 11 / 0.008 **EASL 1y progression rate (%)**: 40 / 8 / 0.01 **UNOS 1y progression rate (%)**: 28 / 19 / 0.098

							UNOS/new lesion 1y progression rate	36	22	0.096
							Overall progression 1y (%)	32	15	0.005
							1-year progression rate for ^{90}Y: 15% Median time to overall progression: 33.3 M (95% CI,17.8–33.8), p=0.005 vs TACE			
			TACE	43			1-year progression rate: 32% Median time to overall progression: 12.8 M (95% CI, 7.9–19.6)			
Padia SA *et al.* J Vasc Interv Radiol 2017, 28:777-785 [48]	USA	Observational Retrospective Cohort	TheraSphere®	131 Tumour progression 101 PFS	PFS: local or distant tumour progression or death	K+LR	Index tumour progression at 1y: 7.7%; 2y: 15% Median PFS: 564 d Chemo has worse PFS with or without IPTW adjustment HR=3.2 (95% CI 2.0-5.2) p<0.001; with or without censoring for transplant. Chemo had higher rate of index tumour progression with or without IPTW HR=8.2 (95% CI, 4.0-17.1) p<0.001 when censored for OLT and death or as competing risks: PS adjusted HR=7.1 (95% CI, 3.4-15.1) p<0.001			
			TACE	103 Tumour progression 77 PFS			Index tumour progression at 1y: 30%; 2y: 42% Median PFS: 271 d			
Salem R *et al.* Gastroenterol 2011, 140: 497-507 [8]	USA	Observational Prospective Cohort	TheraSphere®	123	Time to response TTP: From date of first therapy; data censored to curative therapy (WHO criteria)	Adjusted p for multiple comparisons	Overall TTP: 13.3 (95% CI 9.3-25) p=0.046			
			cTACE	122			Overall TTP: 8.4 (95% CI 7.3-10.6)			

Key: BCLC - Barcelona Clinic Liver Cancer; CI – confidence interval; CP – Child-Pugh score; CR – complete response; (c)TACE - conventional) transarterial chemoembolisation; d – days; DEB-DOX - drug-eluting beads loaded with doxorubicin; EASL – European Association for the Study of the Liver; EHD – Extrahepatic disease; HR – hazard ratio; IPCS – inverse probability of censoring; IPTW - inverse probability of treatment; ITT – intent to treat; K – Kaplan-Meier for univariate survival curves; LR – Log-Rank test; M – months; OLT - orthotopic liver transplantation PFS – progression free survival; PSM - propensity score matching; RCT – randomised controlled trial; RFS – recurrence-free survival; TTP – time to progression; TTST - time to secondary therapy; WHO – World Health Organization; y - years

4.5.2 Non-Comparative Studies Reporting on Progression

4.5.2.1 TheraSphere® Treatment in Later Stage disease

Median TTP ranged from 6 to 11.3 months across studies in patients with later stage disease who were treated with TheraSphere®. One study reported a median PFS of 5.9 months. In patients with PVT, median PFS ranged from 7 to 11 months.

Six non-comparative cohort studies assessed TTP or PFS in patients with mixed stage disease (but mostly later stage unresectable HCC) after treatment with TheraSphere® (Ali *et al.* 2017; Biederman *et al.* 2015; Biederman *et al.* 2018; Hilgard *et al.* 2010; Mazzaferro *et al.* 2013; Salem *et al.* 2010) [49-51, 54, 55, 57]. Where reported, median TTP ranged from 6 to 11.3 months. One study reported on median PFS, which was 5.9 months (Biederman *et al.* 2018) [57]. Salem *et al.* (2010) [55] reported progression for patients with and without extrahepatic disease, and by BCLC stage. Not surprisingly, progression was longer in patients without extrahepatic disease (EHD) and with earlier stage disease (see Table 4-14).

The overall GRADE quality assessment for this group of studies, and for this outcome is: low quality[22].

4.5.2.1.1 Subgroup Analysis in PVT Patients

Three of these studies also reported progression data in patients with PVT. PFS in this group of patients was reported as 7 months (Mazzaferro *et al.* 2013) [54] and 8 months (Hilgard *et al.* 2010) [51]. Salem *et al.* (2010) [55] reported that progression was longer in PVT patients without EHD.

4.5.2.1.2 Studies in PVT Patients

In addition to these studies, two cohort studies reported PFS in patients with PVT (Kokabi *et al.* 2015; Pracht *et al.* 2013) [59. 61]. Across these two studies, median PFS was 9 months and 11 months (see

Table **4-15**).

[22] Using GRADE criteria, all observational studies start with a low initial quality of evidence. The evidence for this outcome was not further downgraded or upgraded.

Table 4-14: Non-Comparative Studies of TheraSphere® in Later Stage Disease: Progression

Study	Study country	Study design	Treatment	Sample size (n) analysed	Definition	Statistical analysis	Results
Ali R *et al.* Eur J Nucl Med Mol Imaging 2017, 44: 2195-2202 [49]	USA	Observational Retrospective Cohort	TheraSphere®	41	Progression defined by WHO and EASL	K censored to day of last imaging	Median TTP: 11.3 M (95%CI 6.5-15.5)
Biederman, DM *et al.* J Vasc Interv Radiol 2015, 26: 1630-1638 [50]	USA	Observational Retrospective Cohort	TheraSphere®	38	Time from initial treatment to disease progression censored for curative therapy and death	K	Mean TTP: 8.6 M (95% CI 5.3-11.9) Median TTP: 5.6 M (95% CI 4.4-7.9)
Biederman, DM *et al.* Clin Imaging 2018, 47:34-40 [57]	USA	Observational Retrospective Cohort	TheraSphere®	36	PFS was censored for curative therapy and loss to follow up imaging	K, LR	Median PFS: 5.9 M (95%CI 4.4-7.7)
Hilgard P *et al.* Hepatology 2010, 52: 1741-1749 [51]	Germany	Observational Retrospective Cohort	TheraSphere®	76	TTP: from 1st ^{90}Y treatment to time of first detection of progression	K	Median TTP: 10.0 M (95% CI 6.1-16.4) Median TTP with PVT: 8.0 M (95% CI 5.9-∞) Without PVT: 11.8 M (95% CI 6.1-17.2)
Mazzaferro V *et al.* Hepatology2013, 57: 1826-1837 [54]	Italy	Prospective single arm	TheraSphere®	52	From 1st radio-embolization to first progression at any site	K, C	Mean TTP: 11 M (6-11) Tumour progression rate at 2y= 62% Mean TTP with PVT: 7 M; no PVT: 13 M NSS
Salem R *et al.* Gastroenterology 2010, 138: 52-64 [55]	USA	Observational Prospective Cohort	TheraSphere®	197	From date of 1st ^{90}Y, progression as defined by WHO, EASL and UNOS stage	K, LR	**Without EHD** BCLC B: 13.1 M (95% CI 4.4-18.1) BCLC C: 6.0 M (95% CI 4.6-8.8) BCLC C, CP A with PVT: 5.6 M (95% CI 2.3-7.6) BCLC C, CP B with PVT: 5.9 M (95% CI 4.2-7.9) **With EHD** BCLC C: 3.1 M (95% CI 1.2-5.1) BCLC C and CP A with PVT: 3.7 M (95% CI 1.1-5.2)

Study	Study country	Study design	Treatment	Sample size (n) analysed	Definition	Statistical analysis	Results
							BCLC C and CP B with PVT: 1.4 M (95% CI 1.1-6.3)

Key: BCLC – Barcelona Clinic Liver Cancer; C – Chi-square test; EASL – European Association for the Study of the Liver; EHD – extrahepatic disease; K – Kaplan-Meier for univariate survival curves; LR – log-rank test for differences in median and 95% confidence interval (CI); M – months; n – number; NR – not reported; NSS – no statistical significance; PFS – progression-free survival; PVT – portal vein thrombosis; TTP – time to progression; UNOS – United Network for Organ Sharing; WHO – World Health Organization

Table 4-15: Non-Comparative Studies of TheraSphere® in PVT Patients: Progression

Study	Study country	Study design	Treatment	Sample size (n) analysed	Definition	Statistical analysis	Results
Kokabi M *et al.* Cancer 2015, 12: 2164-2174 [59]	USA	Prospective single arm	TheraSphere®	NR	From first ^{90}Y therapy to 1st imaging follow up	K	Median: 9 M (95% CI 6.2-13.1) Main vs branch PVT:1.68 M (95% CI 0.55-5.17) Occlusive vs non occlusive: 1.19 M (95% CI 0.39-3.66)
Pracht M *et al.* Int J Hepatol 2013, doi: 10.1155/2013/827649 [61]	France	Retrospective Cohort	TheraSphere®	NR	PFS: date of first treatment until date of progression to treated liver	K	Median PFS: 11.0 M (95% CI 8.0-16.5)

Key: CI – confidence interval; K – Kaplan-Meier for univariate survival curves; M – months; n – number; NR – not reported; PFS – progression-free survival; PVT – portal vein thrombosis

4.5.2.2 TheraSphere® Treatment in Earlier Stage Disease: Radiation Segmentectomy

Across three non-comparative cohort studies, median TTP ranged from 2.1 to 2.7 years in earlier staged disease patients treated with TheraSphere®.

Three non-comparative cohort studies reported on progression in patients with earlier stage HCC (BCLC A or B) treated with TheraSphere® (Lewandowski *et al.* 2018; Salem *et al.* 2010; Vouche *et al.* 2014) [55, 62, 64]. Across these studies, median time to progression ranged from 2.1 to 2.7 years.

The overall GRADE quality assessment for this group of studies, and for this outcome is: low quality[23].

[23] Using GRADE criteria, all observational studies start with a low initial quality of evidence. The evidence for this outcome was not further downgraded or upgraded

Table 4-16: Non-Comparative Studies of TheraSphere® in Earlier Stage Disease: Progression

Study	Study country	Study design	Treatment	Sample size (n) analysed	Definition	Statistical Analysis	Results
Lewandowski RJ *et al.* Radiology 2018, 287: 1050-1058 [62]	USA	Observational Retrospective Cohort	TheraSphere®	70	Progression as defined by WHO or EASL criteria, development of PVT, new lesions	K	Median TTP: 2.4y (95% CI: 2.1, 5.7) For target liver tumour, median time to progression was not reached regardless of tumour size. The 5 and 7-year progression-free probability both at 72%
Salem R *et al.* Gastroenterology 2010, 138: 52-64 [55]	USA	Observational Prospective Cohort	TheraSphere®	48	From date of first ^{90}Y, progression as defined by WHO, EASL and UNOS stage	K, LR	BCLC A: 25.1 M (95% CI 8-27)
Vouche M *et al.* Hepatology 2014, 60: 192-201 [64]	USA	NR	TheraSphere®	102	TTP and Time to local recurrence from first ^{90}Y date.	Descriptive statistics	Rate of disease progression: 27/102 (26%) Median time to disease progression: 33.1 M (IQR 10-35) based on mostly appearance of new intrahepatic lesions (16/27, 59%). Median time to local progression: 17.1 M(IQR 4.4-27.8) Time to local recurrence (after a mRECIST CR)= 10.5 M (IQR 1.9-15.9)

Key: BCLC – Barcelona Clinic Liver Cancer; EASL – European Association for the Study of the Liver; IQR – interquartile range; K - Kaplan-Meier for univariate survival curves; LR – log-rank test for differences in median and 95% confidence interval (CI); M – months; mRECIST – modified RECIST; n – number; NR-not recorded in publication; PVT – portal vein thrombosis; TTP – time to progression; UNOS – United Network for Organ Sharing; WHO – World Health Organization; y - years

4.5.2.3 TheraSphere® Treatment in Earlier Stage Disease: Downstaging to Curative Treatment or Bridge to Transplant

TheraSphere® used for downstaging or bridge to transplant resulted in a median time to recurrence after resection or transplant ranging from 10.1 months to 36.8 months across the studies. The percentages of patients experiencing a recurrence after transplant ranged from 0% to 23%.

Six non-comparative cohort studies reported on progression in patients treated with TheraSphere® for downstaging or bridging to transplant (Abdelfattah *et al.* 2015; Ibrahim *et al.* 2012; Kulik *et al.* 2006; Kulik *et al.* 2014; Radunz *et al.* 2017; Tohme *et al.* 2013) [65-70] (see Table 4-17). Where reported, these studies included patients in all BCLC stages, with higher proportions of patients with BCLC A or B state HCC.

In this group of studies, median time to recurrence after resection or transplant was variously reported to be 10.1 months (Ibrahim *et al.* 2012) [66], 13 months (Radunz *et al.* 2017) [69], or 36.8 months (Tohme *et al.* 2013) [70].

Kulik *et al.* (2014) [68] reported that at the last follow-up there were no recurrences in patients who received TheraSphere® (and incidentally, no recurrence in patients who received TheraSphere® plus sorafenib). In an earlier study by Kulik *et al.* (2006) [67] the rate of progression was reported as 4/35 (11.4%). The percentage of patients experiencing a recurrence after transplant was 9/40 (23%) in Radunz *et al.* (2017) [69] and 4/20 (20%) in Tohme *et al.* (2013) [70].

In one study, 1/9 (11%) patients evaluated experienced a recurrence after TheraSphere®, but *before* liver transplantation (Abdelfattah *et al.* 2015) [65].

The overall GRADE quality assessment for this group of studies, and for this outcome is: low quality.[24]

[24] Using GRADE criteria, all observational studies start with a low initial quality of evidence. The evidence for this outcome was not further downgraded or upgraded.

Table 4-17: Non-Comparative Studies of TheraSphere® used for Downstaging or Bridge to Transplant: Progression

Study	Study country	Study design	Treatment	Sample size (n) analysed	Definition	Statistical Analysis	Results
Abdelfattah MR *et al.*Transplant Proc 2015, 47: 408-411 [65]	Saudi Arabia	Observational Retrospective Cohort	TheraSphere®	Group A[25]: 3 Group B[26]: 6	NR	Descriptive	1 patient had recurrence 1y after ^{90}Y but before OLT; no recurrence in transplanted patients
Kulik L, *et al.* J Hepatol 2014, 61: 309-317 [68]	USA	Unblinded prospective randomised pilot study	TheraSphere®	10 All on transplant list; all within Milan criteria	NR	Descriptive	At the time of last follow-up there were no recurrences
Kulik, LM *et al.* J Surg Oncol. 2006, 94: 572-86. [67]	USA	Observational Retrospective Cohort	TheraSphere®	35 All T3 requiring downstaging	NR	Descriptive per patients living or no OLT/resection	PFS at end of follow up: 4 patients (11.4%)
Ibrahim, SM, *et al.* Cardiovasc Intervent Radiol. 2012, 35:1094-1101. [66]	USA	Observational Retrospective Cohort	TheraSphere®	8 5 outise Milan criteria (≥ T3)	PFS: From time of first treatment uncensored and censored to transplantation	K	Median PFS (uncensored): 10.1 M (95% CI 2.0-not attained) Median PFS for OLT (censored): 10.1 M (95% CI 5.4- not attained)
Radunz S *et al.* Ann Transplant 2017, 22: 215-221 [69]	Germany	Observational Retrospective Cohort	TheraSphere®	40 All underwent transplant post TheraSphere®	NR	Descriptive	9 (23%) had recurrence post-transplant. Median time to recurrence: 13 M (range 4–56 M). Trend towards lower risk of tumour recurrence for patients with complete pathologic necrosis
Tohme S *et al.* J Vasc Interv Radiol 2013, 24: 1632-1639 [70]	USA	Observational Retrospective Cohort	TheraSphere®	20 All on transplant list; 6 of which require downstaging	NR	Descriptive	Median time to recurrence: 36.8 M (IQR, 9.4–62.1) in 4 patients. Patients with no recurrence showed more complete pathologic necrosis (31% in no recurrence vs 0% in recurrence)

Key: K - Kaplan-Meier for univariate survival curves; LR – log-rank test for differences in median and 95% confidence interval (CI); M – months; n – number; NR – not reported; OLT – orthotopic liver transplant; PFS – progression-free survival; RFS – recurrence-free survival; y - years

[25] TheraSphere indicated for downstaging
[26] TheraSphere indicated for bridging

4.5.2.4 TheraSphere® Treatment in Earlier Stage Disease: Radiation Lobectomy

Recurrence rates in patients who received a radiation lobectomy with TheraSphere® ranged to 20% to 51% across three cohort studies.

Three retrospective cohort studies reported on progression in mostly earlier stage disease patients who received a radiation lobectomy with TheraSphere® (Palard *et al.* 2018; Vouche *et al.* 2013; Gabr *et al.* 2018) [71, 74, 75] (see Table 4-18). Palard *et al.* (2018) [74] reported a recurrence of 29% in the treated liver and 51% in the non-treated liver, with a mean TTP of 11 months, and Vouche *et al.* (2013) [75] reported a recurrence rate of 20% in the left untreated lobe. Gabr *et al.* 2018 [71] reported a median time to recurrence after resection or transplant of 34.3 months, with fewer progressions in patients who were responders (CR or PR) to treatment. Recurrence occurred more often in patients who did not demonstrate >50% pathological necrosis.

The overall GRADE quality assessment for this group of studies, and for this outcome is: low quality.[27].

[27] Using GRADE criteria, all observational studies start with a low initial quality of evidence. The evidence for this outcome was not further downgraded or upgraded.

Table 4-18: Non-Comparative Studies of TheraSphere® used in Radiation Lobectomy: Time to Progression or Progression Free Survival

Study	Study country	Study design	Treatment	Sample size (n) analysed	Definition	Statistical analysis	Results
Gabr A *et al.* J Vasc Interv Radiol 2018 29: 1502-1510 [71]	USA	Observational Retrospective Cohort	TheraSphere®	31	RFS from the date of resection to death or last follow-up	K, LR	9 (29%) developed recurrence Median time to recurrence: 34.3 M (95% CI 18.8– 34.3) Of the 18 responders (CR+PR), 2 (11%) had recurrence whereas of the 13 non-responders, 7 (54%) had recurrences 6/7 (86%) with <50% pathologic necrosis develop recurrence whereas only 3 (24%) of the 24 patients with 50%-99% necrosis developed recurrence (p=0.004):
Palard *et al.* Eur J Nucl Med Mol Imaging 2018, 45: 392-401 [74]	France	Observational Retrospective Cohort	TheraSphere®	73	NR	K; descriptive	TTP at 3 M and 6 M At time of analysis: 79.4% of patients had recurrence with a mean TTP: 11.0 M (CI 95%: 8.5–14.0 M). Recurrence in non-treated liver: 50.7% Recurrence in treated liver: 28.8
Vouche *et al.* J Hepatol 2013, 59: 1029-1036 [75]	USA	Observational Retrospective Cohort	TheraSphere®	67 at baseline	NR	Descriptive at time ranges after TARE (1, 1.5-3, 3-6, 6-9, >9 M	Total recurrences: 13/67 (19.5%) in the untreated left lobe after 224d (23-539 f/up) No difference in frequency of the untreated left lobe progression between patients with PVT (7/37 (19%) or without PVT (6/30, 20%), p=1.0 At ~1 M: 4/65 (6); at ~3 M: 2/29(7%); at 3-6 M 3/33(9%); at 6-9 M: 5/23(21.7%); at >9 M: 6/18 (33.3%)

Key: d – days; f/up – follow up; HCC – hepatocellular carcinoma; K - Kaplan-Meier for univariate survival curves; LR – log-rank test for differences in median and 95% confidence interval (CI); M – months; n – number; NR – not reported; PVT – portal vein thrombosis; TARE – transarterial radioembolisation; TTP – time to progression

4.6 RESPONSE

Comparative Studies
Results from one retrospective comparative cohort study demonstrated that overall response was 40% with TheraSphere® and 13% with SIR-Spheres® in patients with later stage HCC, but this difference was not found to be statistically significant.

Overall response rates in HCC patients receiving TheraSphere® was comparable or significantly better than TACE. This was true for studies of patients with earlier stage (BCLC A and select BCLC Bs) (one RCT and two cohort studies) and with later (BCLC C and select BCLC Bs) stage disease (seven cohort studies).

Non-comparative Studies
In patients with later stage disease, overall response according to EASL criteria ranged from 40% to 76%, from 21% to 42% using WHO criteria, and from 48% to 66% using RECIST/mRECIST criteria. Rates of overall response in two cohort studies of PVT patients ranged from 70% to 83% using EASL criteria.

In patients with earlier stage disease, overall response according to EASL criteria ranged from 67% to 83% (at the last follow-up) and from 46% to 71% (at the last follow-up) using WHO criteria. These results with TheraSphere® are consistent with treatments considered to be curative (resection, ablation or transplantation).

In one study using TheraSphere® for downstaging to curative treatment, overall response was 87% according to EASL criteria and 76% using WHO criteria. In another study using TheraSphere® for downstaging in some patients and also bridging to transplant in other patients, overall response according mRECIST/WHO criteria was 45%.

When TheraSphere® was specifically used for downstaging to curative intent, downstaging was achieved in 33% to 66% of the patients across three cohort studies. Using TheraSphere® treatment for bridging resulted in a high success rate, ranging from 90% to 100% across three cohort studies.

Overall response in patients who received a radiation lobectomy with TheraSphere® was very high, ranging from 94 to 95% with EASL criteria, and 65% with WHO criteria.

4.6.1 Comparative Studies Reporting on Response

No studies were found that compared TheraSphere® with QuiremSpheres® or bland TAE.

4.6.1.1 TheraSphere® vs. SIR-Spheres® in Later Stage Disease

One retrospective comparative cohort study compared the impact of TheraSphere® vs. SIR-Spheres® on tumour response in patients with later stage HCC. Although overall response was 40% with TheraSphere® and 13% with SIR-Spheres®, this difference was not reported to be statistically significant.

One retrospective comparative cohort study compared TheraSphere® vs. SIR-Spheres® on tumour response in patients with later stage HCC (Biederman *et al.* 2016)[28], [36] but no difference significant difference in overall response (OR) was demonstrated (see Table 4-19). GRADE: low quality[29]

4.6.1.1.1 Subgroup Analysis in PVT Patients

Subgroup analysis in PVT patients was not conducted in Biederman *et al.* (2016) [36] for this outcome.

[28]Another study evaluated tumour response in patients who received TheraSphere and SIR-Spheres, but they did not report results by treatment type (Bhangoo *et al.* 2015).

[29] Using GRADE criteria, all observational studies start with a low initial quality of evidence. We note, however, that baseline characteristics were similar between treatment groups and both univariate and multivariate analyses were conducted, so this study was considered to be well-conducted for this type of design.

Table 4-19: Comparative studies of TheraSphere® vs. SIR-Spheres® in Later Stage Disease: Tumour Response

Study	Study country	Study design	Treatment	Sample size (n) analysed	Definition	Statistical Analysis	Follow-up assessment	Results n (%)
Biederman DM *et al.* J Vasc Interv Radio 2016, 27: 812-821 [36]	USA	Retrospective comparative cohort	TheraSphere® (mean 2.63 Gbq)	57	mRECIST	C	NR (the authors only stated that patients were followed at regular 4 to 6 weeks intervals)	CR= 5 (8.8) PR = 18 (31.6) SD = 8 (14) PD = 26 (45.6) OR = 23 (40.4) DC = 23 (40.4)
			SIR-Spheres® (mean 1.07 Gbq) *in both treatment groups, some patients also received sorafenib	15				CR=0 (0) P=0.12 PR= 2 (13.3) SD=4 (26.7) PD= 9 (60) OR=2 (13.3) P=0.07 DC=6 (37.5) P=0.39 P values were not reported for all response outcomes

Key: C – Chi-square test; CR – complete response; DC – disease control (CR+PR+SD); Gbq – Gigabecquerel; mRECIST – modified RECIST; n – number; NR – not reported; OR – objective response (CR+PR); PD – progressive disease; PR – partial response; SD – stable disease

4.6.1.2 TheraSphere® vs. TACE in Earlier and Later Stage Disease

Overall response rates in HCC patients receiving TheraSphere® was comparable or significantly better than TACE. This was true for studies of patients with earlier stage (BCLC A and select BCLC Bs) (one RCT and two cohort studies) and studies of patients with later (BCLC C and select BCLC Bs) stage disease (seven cohort studies).

Ten studies comparing TheraSphere® vs. TACE or cTACE reported on tumour response, including one RCT (Salem *et al.* 2016) [39] and nine comparative cohort studies (Akinwande *et al.* 2016; Biederman *et al.* 2018; Carr *et al.* 2010; El Fouly *et al.* 2015; Lewandowski *et al.* 2009; Moreno-Luna *et al.* 2013; Padia *et al.* 2015; Padia *et al.* 2017; Salem *et al.* 2011) [8, 40-43, 45-48] (see Table 4-20). Of these studies, three were in patients with earlier stage disease: BCLC A or BCLC B (Salem *et al.* 2016) [39], BCLC B patients (El Fouly *et al.* 2015) [43] or 'early-stage' HCC patients as described by Biederman *et al.* 2018 [41]. The remaining studies were predominantly in patients with later stage disease or included patients in all disease stages.

Biederman *et al.* (2018) [41] assessed response to treatment of the first targeted lesion and the overall response of all lesions before and after propensity score matching using mRECIST. In the unmatched groups, a greater percentage of patients had a significantly greater overall response with TheraSphere® compared with TACE (81.8% vs. 49.1%; odds ratio 2.12 (95% CI 1.40-3.32)). After adjustment for the propensity score, the significance levels were retained: 92.1% (TheraSphere®) compared with 52.6% (TACE) (odds ratio: 18.0 (95% CI 2.41-135) p=0.005).

El Fouly *et al.* (2015)[43], also using mRECIST, found a higher overall response rate in the TheraSphere® group compared with cTACE. Significance was reached in the DC group (p=0.04) comprising CR+PR+SD.

The RCT by Salem *et al.* (2016) [39] compared response rates using both WHO and EASL. Response rates were similar between the two groups using both types of assessments, however baseline lesion size was generally small in both groups. Followed over time, TheraSphere® showed better local tumour control than cTACE. In fact, 13/24 (54%) patients treated with TheraSphere® went on to transplantation compared to 7/21 (33%) in the TACE group.

Similar to Biederman *et al.* (2018) [41], Akinwande *et al.* (2016) [40] also compared response rate to TheraSphere® treatment with TACE in an unmatched pooled population as well as matched cohorts. In the pooled population, overall response was not significantly different between the groups, however the disease control rate (DCR) was significantly greater in the DEBDOX group (p=0.0041). These results held true for the matched populations. It is worth noting that there was a significantly higher proportion of patients with PVT in the TheraSphere® group (p=0.0001) compared to the DEBDOX group. Portal vein thrombosis has been shown to be a negative prognostic factor for treatment response and survival post treatment [76, 77].

In Carr *et al.* (2010) [42] overall tumour response rates did not demonstrate a significant difference between TheraSphere® and cTACE (89% vs. 76%, respectively).

Lewandowski *et al.* (2009) [45] compared TheraSphere® with TACE as a potential downstaging agent and found that response rates were similar between groups, but the time to achieve a partial response was significantly shorter with TheraSphere®. Notably, significantly more patients were downstaged from UNOS stage T3 to T2 (transplant eligible) with TheraSphere® (58%) compared to TACE (31%) (p=0.023) indicating a superior ability to downstage with radiation.

Morena-Luna *et al.* (2013) [46] compared TheraSphere® with cTACE in a mixed population of BCLC A–C patients without PVT. No significant differences in the percentage of patients with CR, DC or overall response were observed between treatment groups.

Padia *et al.* (2017) [48] evaluated response in patients treated segmentally with either TheraSphere® or TACE or cTACE in a propensity score matched study. Results showed that when adjusted for the propensity score, the difference in complete response rate for the index tumour (23%, 95% CI 9.8%-36%, p=0.001) and overall tumour response (29%, 95% CI, 15%-43%, p<0.001) was significantly higher with TheraSphere® compared to TACE.

In a smaller study by Padia *et al.* (2015) [47] outcomes from HCC patients with transjugular intrahepatic portosystemic shunts, and who were treated with either TACE or TheraSphere® or ablation or supportive care only, showed no significant difference in tumour response between TACE and TheraSphere® cohorts when measured using WHO and EASL criteria.

As with the Lewandowski *et al.* (2009) [45] study, Salem *et al.* (2011) [8] found that although there were no significant differences in overall tumour response between TheraSphere® and cTACE, the median time to response was significantly shorter with TheraSphere® as measured either by WHO or EASL. We also note that in a subgroup analysis in Salem *et al.* (2011) [8], a higher proportion of patients (who received treatment for bridge to transplant intent) were transplanted after TheraSphere® compared with cTACE (13/15 (87%) vs. 7/10 (70%), respectively).

The RCT was considered to have an unclear risk of bias[30], and the GRADE quality assessment for this overall group of studies is: low quality.[31]

[30] This study was considered to have an unclear risk of bias because details regarding the method of randomisation and allocation concealment were not reported (although baseline characteristics were balanced). Blinding was not possible and the outcome variable (OS) was objective. It is unclear if there was selective outcome reporting. Outcome data were available for all patients. We note, however, that this study was stopped early.

[31] Using GRADE criteria, all observational studies start with a low initial quality of evidence. The evidence for this outcome was not further downgraded or upgraded.

Table 4-20: Comparative studies of TheraSphere® vs. TACE in Earlier and Later Stage Disease: Tumour Response

Study	Study Country	Study design	Treatment	Sample Size (n) analysed	Definition	Statistical Analysis	Results n (%)	
Studies of patients with earlier stage disease								
Biederman DM *et al.* J Vasc Interv Radiol 2018, 29: 30-37 [41]	USA	Observational Retrospective Cohort	TheraSphere®	55 before, 38 after PSM	mRECIST (best response within 90d)	Logistic regression before PSM and conditional logistic regression after PSM. Conditional LR was used for matching pairs K+LR	**Before PSM** Target lesion response: CR 48/55 (87.3%) Odds ratio:)2.48 (95% CI 1.5-3.99) p<0.001 Overall response: CR 45/55 (81.8%) Odds ratio: 2.12 (95% CI 1.40-3.32) p<0.001	**After PSM** Target lesion response: CR 36/38 (94.7%) Odds ratio: 19.0 (95% CI 1.90-142) p=0.004 Overall response: CR: 35/38 (92.1%) Odds ratio: 18.0 95% CI 2.41-135) p=0.005
			TACE	57 before, 38 after PSM			**Before PSM** Target lesion response: CR: 30/57 (52.6%) Odds ratio: (95%CI)=1.00 Overall response: CR 28/57 (49.1) Odds ratio: (95%CI)=1.00	**After PSM** Target lesion response: CR: 18/38 (47.4%) Odds ratio: (95%CI)=1.00 Overall response: CR 18/38 (52.6%) Odds ratio: (95%CI)=1.00
El Fouly A *et al.* Liver Int 2015, 35: 627-635 [43]	Germany and Egypt	Prospective, non RCT	TheraSphere®	44	mRECIST	NR	CR= 3 (7) PR= 30 (68) SD= 8 (18) PD= 3 (7) DR=41 (75) p=0.04 vs TACE	
			cTACE	42			CR= 2 (5) PD= 12 (29) PR= 19 (45) DR= 30 (50) SD= 9 (21)	
Salem *et al.* R.Gastro-enterology 2016, 151: 1155-1163 [39]	USA	Prospective randomised study	TheraSphere®	23	WHO and EASL	LR	**Primary index lesion:** Response using WHO: 12/23 (52%) P=0.542 Median time to PR: 7.6M; (95%CI, 4.5-11.3), P=0.85, log-rank Response using EASL: 20/23 (87%) P=0.443 Median time to PR/CR: 1.7M (95% CI 1.6-3.4)	

<table>
<tr><th>Study</th><th>Study Country</th><th>Study design</th><th>Treatment</th><th>Sample Size (n) analysed</th><th>Definition</th><th>Statistical Analysis</th><th>Results n (%)</th></tr>
<tr><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td><td></td><td></td><td rowspan="2"></td><td rowspan="2"></td><td>13/15 (87%) on the transplant waitlist were successfully bridged and received a transplanted</td></tr>
<tr><td>cTACE</td><td>19</td><td>Response using WHO: 12/19 (63%)
Median time to PR: 7.3M; 95% CI, 3.9-12.6

Response using EASL: 14/19 (74%)
Median time to PR/CR: 1.4M (95% CI 1.3-4.9)
P=0.62 log-rank

7/10 (70%) on the transplant waitlist were successfully bridged and received a transplanted</td></tr>
<tr><td colspan="8">Studies of patients with later (or predominantly later) stage disease</td></tr>
<tr><td>Akinwande O et al. Anticancer Res 2016, 36: 239-246 [40]</td><td>USA</td><td>Observational Retrospective Cohort</td><td>See results</td><td>See results</td><td>EASL or mRECIST</td><td></td><td>Pooled OR: DEBDOX: 41% ^{90}Y: 34% NSS
DCR: DEBDOX vs ^{90}Y: p=0.0041 for DEBDOX
Pooled Cohort
<table>
<tr><th></th><th>DEBDOX (n=263)</th><th>^{90}Y (n=61)</th></tr>
<tr><td>CR</td><td>19(7)</td><td>5(8)</td></tr>
<tr><td>PR</td><td>89(34)</td><td>16(26)</td></tr>
<tr><td>SD</td><td>98(37)</td><td>11(18)</td></tr>
<tr><td>PD</td><td>28(11)</td><td>1(2)</td></tr>
</table>
Post study ^{90}Y patients: 1% liver resection
Post study DEBDOX patients: 9 proceeded to RFA, 4 transplanted.</td></tr>
</table>

<table>
<tr><th>Study</th><th>Study Country</th><th>Study design</th><th>Treatment</th><th>Sample Size (n) analysed</th><th>Definition</th><th>Statistical Analysis</th><th>Results
n (%)</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>Matched Data OR: DEBDOX: 47% vs ^{90}Y 35% NSS
Matched DCR: DEBDOX 72% vs ^{90}Y 48% p=0.02
<table><tr><th></th><th>DEBDOX (n=47)</th><th>^{90}Y (n=46)</th></tr><tr><td>CR</td><td>6(13)</td><td>5(11)</td></tr><tr><td>PR</td><td>16(34)</td><td>11(24)</td></tr><tr><td>SD</td><td>12(26)</td><td>6(13)</td></tr><tr><td>PD</td><td>7(15)</td><td>1(2)</td></tr></table>Post study ^{90}Y patients: 1 (2%) received liver resection
Post study DEBDOX patients: 3 (6%) proceeded to RFA</td></tr>
<tr><td rowspan="3">Carr BL et al. Cancer 2010, 116: 1305-1314 [42]</td><td rowspan="3">USA</td><td>Observational Prospective Cohort</td><td>TheraSphere®</td><td>99</td><td>WHO criteria at 6M post treatment</td><td rowspan="3">NR</td><td>CR=3 (3) SD=35 (35)
PR= 38 (38) PD= 23 (23)
Overall tumour control rate (CR=PR+SD)= 76%</td></tr>
<tr><td>Observational Retrospective Cohort</td><td>cTACE</td><td>691</td><td>WHO criteria after 3 chemo cycles</td><td>CR=37(5) SD= 199 (29)
PR= 380 (55) PD=75 (11)
Overall tumour control rate (CR=PR+SD)= 89%</td></tr>
<tr><td>Observational Cohort</td><td>No treatment</td><td>142</td><td>NR</td><td>NR</td></tr>
<tr><td rowspan="3">Lewandowski RJ et al. Am J Transplant 2009, 9: 1920-1928 [45]</td><td rowspan="3">USA</td><td rowspan="3">Prospective, non-random cohort comparison</td><td>TheraSphere®</td><td>43</td><td rowspan="3">Downstaging to RFA defined as a decreased in the maximum tumour dimension to ≤3cm</td><td rowspan="3">Descriptive</td><td><table><tr><th></th><th>WHO</th><th>EASL</th></tr><tr><td>CR</td><td>0 (0)</td><td>20 (47)</td></tr><tr><td>PR</td><td>26 (61)</td><td>17 (39)</td></tr><tr><td>SD</td><td>16 (37)</td><td>6 (14)</td></tr><tr><td>PD</td><td>1 (2)</td><td>0 (0)</td></tr></table></td></tr>
<tr><td></td><td></td><td>Downstaged from T3->T2: 25 (58%)
P=0.023 vs TACE
Transplanted: 9 (21%)</td></tr>
<tr><td>cTACE</td><td>35</td><td><table><tr><th></th><th>WHO</th><th>EASL</th></tr><tr><td>CR</td><td>0 (0)</td><td>6 (17)</td></tr><tr><td>PR</td><td>13 (37)</td><td>19 (54)</td></tr><tr><td>SD</td><td>17 (49)</td><td>9 (26)</td></tr></table></td></tr>
</table>

Study	Study Country	Study design	Treatment	Sample Size (n) analysed	Definition	Statistical Analysis	Results n (%)		
							PD	5 (14)	1 (3)
							Median time to WHO PR was 10.9M (95% CI 7.3 -) for TACE and 4.2M (95% CI 3.3-6.9M) for TheraSphere® (p=0.025) Median time to EASL PR was 1.9M (95% CI 1.4-3.3) for TACE and 1.3M (95% CI 1.1 – 2.4) for TheraSphere® (p=0.004) Downstaged from T3->T2: 11 (31%) Transplanted: 11 (26%)		
Moreno-Luna LE *et al.* Cardiovasc Intervent Radiol 2013, 36: 714-723 [46]	USA	Observational Retrospective Case control	TheraSphere®	57	mRECIST	C, F, W,	CR= 7 (12) p=0.17 PR= 22(39) SD= 22 (39) PD= 5 (9) OR= 29 (51) p=1.00 DC= 51 (89) p=0.56		
		Observational Retrospective Case control	cTACE	47			CR= 2 (4) PR= 22 (47) SD= 16 (34) PD= 7 (15) OR= 21 (51) DC= 40 (85)		
Padia SA *et al.* J Vasc Interv Radiol 2017, 28:777-785 [48]	USA	Observational Retrospective Cohort	TheraSphere®	131 for Index tumour 100 for patient overall response	mRECIST	Linear, binary or ordinal LR models	**Index Tumour** CR=121 (92.4%) p<0.001 vs TACE PR=7 (5.3) SD=2 (1.5) PD= 1 (0.8) (unadjusted data) When data was adjusted for baseline characteristics using IPTW, CR P=0.001 vs TACE	**Patient Overall Response** CR= 84 (84.0%) p<0.001 vs TACE PR= 11 (11.0) SD= 2 (2.0) PD= 3 (3.0) (unadjusted data) When data was adjusted for baseline characteristics using	

<table>
<tr><th>Study</th><th>Study Country</th><th>Study design</th><th>Treatment</th><th>Sample Size (n) analysed</th><th>Definition</th><th>Statistical Analysis</th><th colspan="2">Results n (%)</th></tr>
<tr><td rowspan="2"></td><td rowspan="2"></td><td></td><td></td><td></td><td></td><td></td><td colspan="2">IPTW, CR P<0.001 vs TACE</td></tr>
<tr><td>Observational Retrospective Cohort</td><td>TACE: DEB DOX or cTACE:</td><td>103 for Index tumour

77 for patient overall response</td><td>mRECIST</td><td>Linear, binary or ordinal LR models</td><td colspan="2"><u>Index Tumour</u>
CR=76 (73.8)
PR= 19 (18.4)
SD= 5 (4.9)
PD= 3 (2.9)
(unadjusted data)

<u>Patient Overall Response</u>
CR= 45 (58.4)
PR= 20 (26.0)
SD= 6 (7.8)
PD= 6 (7.8)
(unadjusted data)</td></tr>
<tr><td rowspan="3">Padia SA et al. Cardiovasc Intervent Radiol 2015, 38: 913-921 [47]</td><td rowspan="3">USA</td><td rowspan="3">Observational Retrospective Cohort</td><td>TheraSphere®</td><td>6(lesions)</td><td rowspan="3">WHO, EASL</td><td rowspan="3">Mann-Whitney U test (continuous variable), C</td><td colspan="2" rowspan="3">
<table>
<tr><th>WHO n,%</th><th>CR</th><th>PR</th><th>SD</th><th>PD</th><th>OR</th></tr>
<tr><td>TACE</td><td>2(14)</td><td>2(14)</td><td>8(57)</td><td>2(14)</td><td>4(29)</td></tr>
<tr><td>^{90}Y</td><td>0(0)</td><td>2(33)</td><td>1(17)</td><td>3(50)</td><td>2(33)</td></tr>
<tr><th>EASL N,%</th><th>CR</th><th>PR</th><th>SD</th><th>PD</th><th>OR</th></tr>
<tr><td>TACE</td><td>6(43)</td><td>1(7)</td><td>5(36)</td><td>2(14)</td><td>7(50)</td></tr>
<tr><td>^{90}Y</td><td>4(67)</td><td>0(0)</td><td>1(17)</td><td>1(17)</td><td>4(67)</td></tr>
<tr><td colspan="6">No SS between TACE and TARE</td></tr>
</table>
</td></tr>
<tr><td>TACE</td><td>14</td></tr>
<tr><td>Supportive Care</td><td>NR</td></tr>
<tr><td rowspan="2">Salem R et al. Gastroenterol 2011, 140: 497-507 [8]</td><td rowspan="2">USA</td><td rowspan="2">Observational Prospective Cohort</td><td>TheraSphere®</td><td>123</td><td rowspan="2">WHO, EASL Time to response
TTP: from date of first therapy; data censored to curative therapy</td><td rowspan="2">Adjusted P for multiple comparisons</td><td colspan="2">WHO Overall Response Rate: 60/123 (49%)
EASL Overall Response Rate: 88/123 (72%)
WHO Time to response: 6.6M (95% CI:4.2-8.6) p=0.050
EASL time to response: 1.2 (1.1-2.1) p=0.016

13/15 (87%) of patients receiving treatment for bridge to transplant intent (subgroup) were transplanted</td></tr>
<tr><td>cTACE</td><td>122</td><td colspan="2">WHO Overall Response Rate: 44/122 (36%)
EASL Overall Response Rate: 84/122 (69%)

WHO Time to response::10.3M (95% CI 7.7-16)
EASL time to response: 2.2M(95% CI 1.5-3.0)</td></tr>
</table>

Study	Study Country	Study design	Treatment	Sample Size (n) analysed	Definition	Statistical Analysis	Results n (%)
							7/10 (70%) of patients receiving treatment for bridge to transplant intent in this study (subgroup) were transplanted

Key: C – Chi square test; CI – confidence interval; CR – complete response; (c)TACE - (conventional) transarterial chemoembolization; DEBDOX - drug-eluting beads loaded with doxorubicin; EASL - European Association for the Study of the Liver; F – Fischer's Exact test; F/up – follow-up; IPTW - inverse probability of treatment weighting; K – Kaplan-Meier; LR – logistic regression; n – number; M – month; mRECIST – modified RECIST; NR – not reported; PD – progressive disease; PR – partial response; PSM – propensity score matching; RFA – radiofrequency ablation; RCT – randomized controlled trial; SD – stable disease; TARE – transarterial radioembolization; TTP – time to progression; W – Wilcoxon Rank test; WHO – World Health Organization

4.6.2 Non-Comparative Studies Reporting on Response

4.6.2.1 TheraSphere® Treatment in Later Stage Disease

In patients with later stage disease, overall response according to EASL criteria ranged from 40% to 76%, from 21% to 42% using WHO criteria, and from 48% to 66% using RECIST/mRECIST criteria. Rates of overall response in two cohort studies of PVT patients ranged from 70% to 83% using EASL criteria.

Eight non-comparative cohort studies reported on overall response in patients with predominantly later stage HCC after treatment with TheraSphere® (Ali *et al.* 2017; Biederman *et al.* 2015; Biederman *et al.* 2018; Garin *et al.* 2017; Hilgard *et al.* 2010; Lambert *et al.* 2011; Mazzaferro *et al.* 2013; Salem *et al.* 2010) [49-55, 57] (see Table 4-21).

All of these studies reported response after treatment using EASL and/or WHO criteria and/or RECIST/mRECIST criteria. Across these studies, overall response according to EASL criteria ranged from 40% to 76%, from 21% to 42% using WHO criteria, and from 48% to 66% using RECIST/mRECIST criteria.

The overall GRADE quality assessment for this group of studies, and for this outcome is: low quality.[32]

4.6.2.1.1 Subgroup Analysis in PVT Patients

One of these studies also reported an overall response of 37.1% (WHO criteria) in patients with PVT (Mazzaferro *et al.* 2013) [54].

4.6.2.1.2 Studies in PVT Patients

In addition to these studies, two cohort studies reported overall response in patients with PVT (Kulik *et al.* 2008; Pracht *et al.* 2013) [60, 61]. Across these two studies, OR ranged from 70% to 83% using EASL criteria; OR using WHO criteria in Kulik *et al.* (2008) [60] was 42% (see Table 4-21).

Pracht *et al.* (2013) [61] also reported that of the 2 (11%) patients were downstaged to transplantation, 1 (6%) patient received a transplant, and 2 (11%) patients underwent resection.

[32] Using GRADE criteria, all observational studies start with a low initial quality of evidence. The evidence for this outcome was not further downgraded or upgraded.

Table 4-21: Non-Comparative Studies of TheraSphere® in Later Stage Disease: Tumour Response

Study	Study Country	Study design	Treatment	Sample Size (n)	Definition	Statistical Analysis	Results n (%)
Ali R *et al.* Eur J Nucl Med Mol Imaging 2017, 44: 2195-2202 [49]	USA	Observational Retrospective Cohort	TheraSphere®	41	EASL	NR	EASL: CR: 7 (17); PR: 15 (36); SD: 6 (15); PD:13 (32) at least imaging Median time to response: 1.2M (95%CI 0.5-1.9) WHO: CR: 0 (0); PR:14 (34); SD: 17 (42); PD:10 (24) at last imaging Median time to response: 10.5M (95%CI 6.2-14.8)
Biederman DM *et al.* J Vasc Interv Radiol 2015, 26: 1630-1638 [50]	USA	Observational Retrospective Cohort	TheraSphere®	38	mRECIST WHO	NR	<u>mRECIST</u> / <u>WHO</u> CR: 10 (26.3) / 1 (2.6) PR: 11 (28.9) / 7 (18.4) SD: 3 (7.9) / 16 (42.1) PD: 14 (36.8) / 14 (36.8) OR: 21 (55.3) / 8 (21.1) DC: 21 (63.2) / 24 (63.2)
Biederman DM *et al.* Clin Imaging 2018, 47:34-40 [57]	USA	Observational Retrospective Cohort	TheraSphere®	36	mRECIST	NR	CR: 12 (41.4) PD: 9 (31.0) PR: 2 (6.9) OR: 14 (48.2 SD: 6 (20.7) DC: 20 (69.0)
Garin E, *et al.* Liver Int. 2017, 37: 101-110 [52]	France	Consecutive Prospective Cohort	TheraSphere®	80	EASL	K	3 Mo response rate / **EASL- per patient** / **EASL- per lesion** **CR** 10(12.5) 23(17.4) **PR** 51(63.7) 83(62.8) **SD** 14(17.5) 21(15.9) **PD** 4(5) 5(3.9) **<u>LESION Response:</u>** RR at 3M was 80.3% TD was SS higher for responding (353±120Gy) vs nonresponding lesions (171±85Gy) p<0.0001 RR was 91.1% for lesions with TD ≥205Gy vs 5.5% with TD<205Gy, $p<10^{-13}$ **After multivariate analysis, tumour dose remained SS associated with response** **Threshold TD >205 Gy is predictive of TR; p<0.0014**

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td><u>PATIENT RESPONSE:</u>
RR at 3M was 77.5%
TD was SS higher for responding (343±123Gy) vs nonresponding lesions (198±85Gy) p<0.0001</td></tr>
<tr><td>Hilgard P et al.
Hepatology 2010, 52: 1741-1749 [51]</td><td>Germany</td><td>Observational Retrospective Cohort</td><td>TheraSphere®</td><td>76 at 30d post treatment, 62 at 60 and 90 d post treatment</td><td>RECIST (+/- necrosis), WHO (+/- necrosis), EASL
Time to response: from 1st ^{90}Y treatment</td><td>NR</td><td>
<table>
<tr><th>Response post treatment</th><th>30 d (n,%)</th><th>60d (n,%)</th><th>90d (n,%)</th></tr>
<tr><td>RECIST:</td><td></td><td></td><td></td></tr>
<tr><td>CR or PR</td><td>2(3)</td><td>6(10)</td><td>10(16)</td></tr>
<tr><td>SD</td><td>69(90)</td><td>50(80)</td><td>46 (74)</td></tr>
<tr><td>PD</td><td>5(7)</td><td>6(10)</td><td>6(10)</td></tr>
<tr><td>RECIST (+necrosis)</td><td></td><td></td><td></td></tr>
<tr><td>CR</td><td>3(4)</td><td>4(6)</td><td>4(6)</td></tr>
<tr><td>PR</td><td>20(26)</td><td>22(35)</td><td>2(35)</td></tr>
<tr><td>SD</td><td>48(63)/</td><td>30(48)</td><td>30(48)</td></tr>
<tr><td>PD</td><td>5(7)</td><td>6(10)</td><td>6 (10)</td></tr>
<tr><td>WHO</td><td></td><td></td><td></td></tr>
<tr><td>CR or PR</td><td>1(1)</td><td>5(8)</td><td>9(15)</td></tr>
<tr><td>SD</td><td>70(92)</td><td>50(80)</td><td>49(79)</td></tr>
<tr><td>PD</td><td>5(7)</td><td>7(11)</td><td>4(6)</td></tr>
<tr><td>WHO (+necrosis</td><td></td><td></td><td></td></tr>
<tr><td>CR</td><td>3(4)</td><td>5(8)</td><td>2(3)</td></tr>
<tr><td>PR</td><td>19(25)</td><td>18(29)</td><td>23(37)</td></tr>
<tr><td>SD</td><td>49(64)</td><td>32(52)</td><td>33(53)</td></tr>
<tr><td>PD</td><td>5(7)</td><td>7(11)</td><td>4(6)</td></tr>
</table>
</td></tr>
<tr><td>Lambert B et al. Eur J Nucl Mol Imaging 2011, 38: 2117-2124 [53]</td><td>Belgium</td><td>Observational Retrospective Cohort</td><td>TheraSphere®</td><td>20 at median 70d
12 at median 181d</td><td>mRECIST</td><td>NR</td><td>At mean follow up: 73d (33-159):
CR: 3 (15) PD: 4 (20) in 2 PD in untreated lobe
PR: 7 (35) SD: 6 (30)
At mean follow up: 181d (140-287):
CR: 1 (8) PD: 3 (25): 1 PD in treated and un-treated lobe and 1 PD in treated lobe, 1 in untreated
PR: 7 (58) SD: 1 (8)</td></tr>
<tr><td>Mazzaferro V et al.
Hepatology 2013, 57: 1826-1837 [54]</td><td>Italy</td><td>Prospective single arm</td><td>TheraSphere®</td><td>52</td><td>WHO, EASL,</td><td>NR</td><td>EASL: OR: (CR+PR): 21 (40.4); 5 CR (9.6%) of which 3 in PVT, 2 in non-PVT patients. Using WHO or RECIST the number of CR decreased to 4
EASL DCR: (CR+PR+SD): 41 (78.8)

WHO: OR: (CR+PR): 21 (40.4)</td></tr>
</table>

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>WHO:
Without PVT: OR: 8(47%) With PVT: 13(37.1%)
EASL:
Without PVT: OR: 9(52.9) With PVT: 12 (34.3)</td></tr>
<tr><td>Salem R et al.
Gastroenterology 2010, 138: 52-64 [55]</td><td>USA</td><td>Observational Prospective Cohort</td><td>TheraSphere®</td><td>See results</td><td>EASL, WHO</td><td>Descriptive</td><td>
<table>
<tr><th>N,%</th><th>EASL (RR*)</th><th>WHO (RR*)</th></tr>
<tr><td>BCLC B, n=83 (82)</td><td>57(70)</td><td>42(51)</td></tr>
<tr><td>BCLC C, n=107 (99)</td><td>44(44)</td><td>40(40)</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>BCLC C, CP A with PVT 35(34)</td><td>17(50)</td><td>17(50)</td></tr>
<tr><td>BCLC C, CP B with PVT 57(50)</td><td>16(32)</td><td>14(28)</td></tr>
</table>
*RR=responders (CR+PR)
Overall, 32/245 (13.1%) underwent transplantation and 2/245 (0.8%) underwent resection following TheraSphere.</td></tr>
</table>

Key: DC-disease control; C=Chi square test; EASL=European Association for the Study of the Liver; CR= Complete Response; ID=identifier; mRECIST=modified RECIST; n=number; NR=not recorded in publication; OR=objective response; PD= progressive disease; PR=partial response; q= Key: EASL - European Association for the Study of the Liver; CR - Complete Response; DC(R) - Disease control rate (CR+PR+SD); n - number; NR - not recorded in publication; OR - objective response; PD - progressive disease; PR - partial response; SD - stable disease; WHO - World Health Organization

4.6.2.2 TheraSphere® Treatment in Earlier Stage Disease: Radiation Segmentectomy

In patients with earlier stage disease, overall response according to EASL criteria ranged from 67% to 83% (at the last follow-up) and from 46% to 71% (at the last follow-up) using WHO criteria. These results with TheraSphere® are consistent with treatments considered to be curative (resection, ablation or transplantation).

Four non-comparative cohort studies assessed tumour response in patients with earlier stage disease (BCLC A or B) after treatment with TheraSphere® (Lewandowski *et al.* 2018; Riaz *et al.* 2018; Salem *et al.* 2010; Vouche *et al.* 2014) [55, 62-64]. Across these studies, overall response according to EASL criteria ranged from 67% to 83% (at the last follow-up) and overall response using WHO criteria ranged from 46% to 71% (at the last follow-up) after treatment. Vouche *et al.* (2014) [64] reported 86% response using mRECIST criteria (Table 4-22).

Lewandowski *et al.* (2018) [62] demonstrated that 71% patients achieved a radiologic response of whom 16% achieved a complete response using WHO criteria. Using EASL, 90% achieved a radiologic response of whom 59% showed a complete response.

Riaz *et al.* (2018) [63] response data shows that EASL consistently assesses responders at a higher rate than the other assessments as EASL considers tumour enhancement, which is an earlier indicator of tumour response and not considered in WHO or RECIST criteria. This is also demonstrated in the Salem *et al.* (2010) [55] subset of BCLC A patients. In this latter study, overall response was 78% using EASL criteria and 46% using WHO criteria. The authors also reported that 14/48 (29%) of BCLC A patients underwent transplant after treatment.

Vouche *et al.* (2014) [64] showed a CR radiologic response in 47% of patients which correlated well with 52% complete necrosis upon pathologic examination. Another 48% of patients demonstrated 50-99% necrosis of the treated lesion. In this study, TheraSphere® was administered in a segmental fashion. Doses to the segment of >190 Gy (P=0.03) resulted in an increase in complete necrosis (52%) suggesting a potential threshold dose to achieve pathologic response, and demonstrating that local tumour control can occur through radiation segmentectomy.

The overall GRADE quality assessment for this group of studies, and for this outcome is: low quality.[33]

[33]Using GRADE criteria, all observational studies start with a low initial quality of evidence.

Table 4-22: Non-Comparative Studies of TheraSphere® in Earlier Stage Disease: Tumour Response

<table>
<tr><th>Study</th><th>Study Country</th><th>Study design</th><th>Treatment</th><th>Sample Size (n)</th><th>Definition</th><th>Statistical Analysis</th><th>Results n (%)</th></tr>
<tr>
<td>Lewandowski RJ et al. Radiology 2018, 287: 1050-1058 [62]</td>
<td>USA</td>
<td>Observational Retrospective Cohort</td>
<td>TheraSphere®</td>
<td>See results</td>
<td>WHO, EASL</td>
<td>Descriptive OR rates were estimated by considering the patient's best radiologic response during his or her entire follow-up period.</td>
<td>
<table>
<tr><th></th><th colspan="2">1M (n=70)</th><th colspan="2">6M (n=63)</th><th colspan="2">9M (n=42)</th><th colspan="2">12M (n=35)</th></tr>
<tr><th></th><th>EASL</th><th>WHO</th><th>EASL</th><th>WHO</th><th>EASL</th><th>WHO</th><th>EASL</th><th>WHO</th></tr>
<tr><td>CR</td><td>9(13)</td><td>3(4)</td><td>28(42)</td><td>3(5)</td><td>27(64)</td><td>3(8)</td><td>22(63)</td><td>4(11)</td></tr>
<tr><td>PR</td><td>32(46)</td><td>15(21)</td><td>26(42)</td><td>28(44)</td><td>9(21)</td><td>27(64)</td><td>7(20)</td><td>21(60)</td></tr>
<tr><td>SD</td><td>26(37)</td><td>50(71)</td><td>4(6)</td><td>27(43)</td><td>1(3)</td><td>9(21)</td><td>1(3)</td><td>7(20)</td></tr>
<tr><td>PD</td><td>3(4)</td><td>2(3)</td><td>5(8)</td><td>5(8)</td><td>5(12)</td><td>3(7)</td><td>5(14)</td><td>3(9)</td></tr>
</table>
Response at 1M: EASL: 59% WHO: 26%
Response at 6M: EASL: 86% WHO: 49%
Response at 9M: EASL: 85% WHO: 72%
Response at 12M: EASL: 83% WHO: 71%
Best overall response (EASL): 63 (90%) were responders of which 59% were CR, 7 (10%) were non responders
Best overall response (WHO): 50 (71%) were responders of which 16% were CR, 20 (29%) were non responders
</td>
</tr>
<tr>
<td>Riaz A et al. Heptatology 2018, 67: 873-883 [63]</td>
<td>USA</td>
<td>Observational Retrospective Cohort</td>
<td>TheraSphere®</td>
<td>134</td>
<td>WHO,EASL, RECIST 1.1.</td>
<td>NR</td>
<td>
Landmark Analysis: Response (n)
<table>
<tr><th></th><th colspan="2">3M</th><th colspan="2">6M</th><th colspan="2">12M</th></tr>
<tr><th></th><th>R</th><th>NR</th><th>R</th><th>NR</th><th>R</th><th>NR</th></tr>
<tr><td>WHO</td><td>31(23)</td><td>103 (77)</td><td>48 (41)</td><td>68 (86)</td><td>43 (53)</td><td>38 (47)</td></tr>
<tr><td>RECIST 1.1</td><td>28(21)</td><td>106 (79)</td><td>50 (43)</td><td>66 (86)</td><td>43 (53)</td><td>38 (47)</td></tr>
<tr><td>EASL</td><td>83(62)</td><td>51 (38)</td><td>86 (74)</td><td>30 (26)</td><td>54 (67)</td><td>27 (33)</td></tr>
<tr><td colspan="6">R=Responder(CR, PR) NR=non responder (SD, PD)</td></tr>
</table>
</td>
</tr>
<tr>
<td>Salem R et al. Gastroenterology 2010, 138: 52-64 [55]</td>
<td>USA</td>
<td>Observational Prospective Cohort</td>
<td>TheraSphere®</td>
<td>245</td>
<td>WHO, EASL</td>
<td>NR</td>
<td>
<table>
<tr><th>N, %</th><th>EASL (*RR:CR+PR)</th><th>WHO (*RR:CR+PR)</th></tr>
<tr><td>BCLC A n=48(46%)</td><td>36(78)</td><td>21(46)</td></tr>
</table>
*responders rate (CR+PR)
Transplantation:14/48 (29%) of BCLC A patients
Resection: 1/131 (0.8%) BCLC A or B (exact BCLC status NR)
</td>
</tr>
</table>

Vouche M *et al.* Hepatology 2014, 60: 192-201 [64]	USA	NR	TheraSphere®	99	mRECIST	Descriptive	CR= 47 (47) PR= 39 (39) SD= 12 (12) PD= 3 (2.9) Pathology Results: Complete pathologic necrosis: 17/33 (52%) Partial pathologic necrosis: 16/33 (50-99%) all of which showed >90% necrosis Conclusion: radiation segmentectomy resulting in 90-100% pathology necrosis when irradiation exceeded 190 Gy (P=0.03)

Key: CI – confidence interval; CR – complete response; EASL - European Association for the Study of the Liver; F/up – follow-up; Gy – gray (units); IPTW - inverse probability of treatment weighting; n – number; M – month; mRECIST - modified; NR – not reported; OR – objective response; PD – progressive disease; PR – partial response; RECIST - The Response Evaluation Criteria in Solid Tumours; SD – stable disease; WHO – World Health Organization

4.6.2.3 TheraSphere® Treatment in Earlier Stage Disease: Downstaging to Curative Treatment or Bridge to Transplant

In one study using TheraSphere® for downstaging to curative treatment, overall response was 87% according to EASL criteria and 76% using WHO criteria. In another study using TheraSphere® for downstaging in some patients and bridging to transplant in other patients, overall response according mRECIST/WHO criteria was 45%.

When TheraSphere® was specifically used for downstaging to curative intent, downstaging was achieved in 33% to 66% of the patients across three cohort studies. Using TheraSphere® treatment for bridging resulted in a high success rate, ranging from 90% to 100% across three cohort studies.

Six non-comparative cohort studies reported on tumour response in patients treated with TheraSphere® for downstaging or bridging to transplant (Abdelfattah *et al.* 2015; Ibrahim *et al.* 2012; Kulik *et al.* 2006; Kulik *et al.* 2014[34]; Radunz *et al.* 2017; Tohme *et al.* 2013) [65-70] (see Table 4-23). Where reported, these studies included patients in all BCLC stages, with higher proportions of patients with BCLC A or B stage HCC. Abdelfattah *et al.* (2015) [65] reported on nine patients who were successfully transplanted after TheraSphere®, but as the population appears to have been selected by the outcome (i.e. transplant), the usefulness of any response or downstaging data from this study is limited.

Two of these studies reported on tumour response after treatment with TheraSphere® using EASL and/or WHO criteria (Ibrahim *et al.* 2012; Tohme *et al.* 2013) [66, 70]. In one study using TheraSphere® for downstaging to curative treatment, overall response was 87% according to EASL criteria and 76% using WHO criteria (Ibrahim *et al.* 2012) [66] In another study using TheraSphere® for downstaging in some patients, and also bridging to transplant in other patients, overall response according mRECIST/WHO criteria was 45% (Tohme *et al.* 2013)[70].

Kulik *et al.* (2014) [68] reported a decrease in lesion size from a baseline of 28.7mm (6.4-55.9) to 12.2mm (0.0-37.5) at 3 months, and Kulik *et al.* (2006) [67] reported a median reduction in tumour size of 49%.

Where reported, 100% tumour necrosis was observed in 2/8 (25%) of patients in Ibrahim *et al.* (2012) [66], 5/34 (15%) in Kulik *et al.* (2006) [67], 17/40 (43%) in Radunz *et al.* (2017) [69], and 5/20 (25%) in Tohme *et al.* (2013) [70].

In terms of downstaging to curative treatment, 50% of patients in the Ibrahim *et al.* (2012) [66] study were UNOS downstaged from T3 to T2, of which 38% went on to transplantation. In Kulik *et al.* (2006) [67], 3% of patients were downstaged to resection, 32% were downstaged to radiofrequency ablation (RFA), and 56% were downstaged to transplantation; overall 66% fulfilled the intention to be downstaged in this study. In Tohme

[34]Although Kulik *et al.* (2014) also included a TheraSphere® plus sorafenib treatment arm, we have only extracted data from the TheraSphere® arm (as per our inclusion criteria) and thus treated this study as a non-comparative study.

et al. (2013) [70] 33% of patients who received TheraSphere® for downstaging (n=6) were successfully downstaged.

In terms of bridging to transplant, Kulik *et al.* (2006) [67] found that 90% of patients on a transplant list (all within Milan criteria) were successfully bridged to transplant. In Radunz *et al.* (2017) [69], all patients who received TheraSphere® as a bridging treatment remained on the transplant waitlist. In Tohme *et al.* (2013) [70] all patients on a transplant list who were treated with TheraSphere® went on to receive a transplant.

The overall GRADE quality assessment for this group of studies, and for this outcome is: low quality.[35]

4.6.2.3.1 Supplementary Studies Reporting on Downstaging or Bridging to Curative therapy

Several other non-comparative cohort studies have also reported on downstaging to curative therapy (e.g. resection, ablation or transplantation) or transplant data – but as incidental findings (i.e. not as a primary objective or outcome of the study). While we have presented these results in a table below (see Table 3.22), differences between the studies in terms of patient populations and context preclude any comparative or meaningful analysis.

[35] Using GRADE criteria, all observational studies start with a low initial quality of evidence.

Table 4-23: Non-Comparative Studies of TheraSphere® used for Downstaging or Bridge to Transplant: Tumour Response, Downstaging and Transplant

Study	Study Country	Study design	Treatment	Sample Size (n)	Definition	Statistical Analysis	Results n (%)
Abdelfattah MR *et al.* Transplant Proc 2015, 47: 408-411 [65]	Saudi Arabia	Observational Retrospective Cohort	TheraSphere®	Group A[36]: 3	NR	Descriptive	2 patients had UNOS T3 and 1 had UNOS T4 prior to therapy Post therapy, stable mass size with central necrosis in 1 patient and a decrease in the mass size with evidence of necrosis in the other 2 patients All 3 were transplanted
				Group B[37]: 6			5 patients had T2 tumours within Milan and 1 had T3 beyond Milan Stable mass size with central necrosis in 3 patients and a decrease in the mass size with evidence of necrosis in the other 3 patients. All 6 patients were transplanted
Ibrahim, SM, *et al.* Cardiovasc Intervent Radiol. 2012, 35:1094-1101. [66]	USA	Observational Retrospective Cohort	TheraSphere®	8 5 outside Milan criteria (≥T3)	WHO/EASL or development of PVT	Descriptive Statistics	CR: WHO 1 (13), EASL 3 (37) PR: WHO 5 (63), EASL 4 (50) SD: WHO 1 (13), EASL 0 (0) PD: WHO 1 (13), EASL 1 (13)
					Pathologic response		Of 3 explants: 100% necrosis in 2 patients and >50% necrosis in 1 patient 4 patients (50%) were UNOS downstaged from T3 to T2 of which 3 (38%) went on to transplantation

[36] TheraSphere indicated for downstaging
[37] TheraSphere indicated for bridging

Study	Study Country	Study design	Treatment	Sample Size (n)	Definition	Statistical Analysis	Results n (%)
Kulik L *et al.* J Hepatol 2014, 61: 309-317 [68]	USA	Unblinded prospective randomized pilot study	TheraSphere®	10 All on transplant list; all within Milan criteira	mRECIST	Descriptive statistics	**Follow-up** / **Lesion Size (median, range** Baseline: 28.7mm (6.4-55.9) 1 M: 9.5mm (0.0-25.5) 3 M: 12.2mm (0.0-37.5) Last: 0.0mm (0.0-20.2) 9/10 (90%) of patients received a transplant. 1 patient progressed beyond Milan criteria
Kulik, LM *et al.* J Surg Oncol. 2006, 94: 572-86. [67]	USA	Observational Retrospective Cohort	TheraSphere®	34 All T3 requiring downstaging	WHO Time to response=time of treatment to obtaining a PR Time to maximal response=time to treatment to maximal decrease in tumour size	Descriptive Statistics	1/35 (3%) were downstaged to resection 11/34(32%) were downstaged to RFA 19/34 (56%) were downstage to transplantation 23/35 (66%) fulfilled the intention to be downstaged Radiologic and pathologic correlation occurred in 2/7 (29%) of patient with tumour pathology samples Median reduction in tumour size: 49% WHO: 17(50%) had a PR at a median time to PR of 75 days. Median time to maximal response: 120d <u>Tumour Pathology</u> Complete Pathologic Necrosis: 5 (72.5%) >50% necrosis: 2 (28.5%) <50% 0 (0%)
Radunz S *et al.* Ann Transplant 2017, 22: 215-221 [69]	Germany	Observational Retrospective Cohort	TheraSphere®	40 All underwent transplant post TheraSphere®	RECIST using explant pathology	T-test or Mann-Whitney	Complete tumour necrosis: 17 (42.5%) Partial necrosis: 18 (45%) No significant necrosis: 5 (12.5%) Trend towards lower risk of tumour recurrence in patients with complete necrosis After bridging treatment (TheraSphere®) there were no drop outs from the waitlist

Study	Study Country	Study design	Treatment	Sample Size (n)	Definition	Statistical Analysis	Results n (%)
							MELD score before and after radioembolisation were not SS different pre: (9 (range 5–17) vs. post: 10 (range 5–22), p=0.1144)
Tohme S *et al.* J Vasc Interv Radiol 2013, 24: 1632-1639 [70]	USA	Observational Retrospective Cohort	TheraSphere®	20 All on transplant list; 6 of which required downstaging	mRECIST/WHO	C	mRECIST/WHO CR 6 (30) PR 3 (15) SD 7 (35) PD 0 (0) Unknown 4 (20) Mean tumour size before ^{90}Y: 3.37±1.9 cm Mean tumour size before transplant: 1.92±2.0 cm Complete tumour necrosis: 5 (25%); 4 of which had CR on radiology post ^{90}Y 50%-90% necrosis: 6 (30%) <50%: 9 (45%) Of 6 patients who required downstaging, 2 (33%) were successful 20 patients received a transplant in total of which 16 (80%) met the Milan criteria and 4 (20%) did not

Key: C - Chi square test; CPN - complete pathologic necrosis; CR - Complete Response; EASL - European Association for the Study of the Liver; F - Fisher's exact Test, IPTW - inverse probability of treatment weights; K - Kaplan-Meier for univariate survival curves; LR - log-rank test for differences in median and 95% confidence interval (CI); M - months; n - number; OR - Objective Response (CR+PR); PS - propensity score model; PD - Progressive Disease; PR - Partial Response; RFA - radiofrequency ablation; SD - stable disease; SS - statistically significant; UNOS - United Network for Organ Sharing; vs - versus; WHO - World Health Organization

Table 4-24: Additional Incidental Data on Downstaging and/or Transplantation

Study	Therapy	Outcome
Pracht M *et al.* Int J Hepatol 2013, doi: 10.1155/2013/827649 [61]	TheraSphere®	2/18 (11%) patients were downstaged to transplantation eligible; 1 (6%) patient received a transplant; 2 patients (11%) had surgical resection
Ali R *et al.* Eur J Nucl Med Mol Imaging 2017, 44: 2195-2202 [49]	TheraSphere®	4/41 (9.8%) underwent transplantation post therapy
Biederman DM *et al.* J Vasc Interv Radio 2016, 27: 812-821 [36]	TheraSphere®	1 patient was transplanted post therapy (n=69 patients treated with TheraSphere®)
Salem R *et al.* Gastroenterology 2010, 138: 52-64 [55]	TheraSphere®	32/238 (13%) patients underwent transplant and 2 underwent resection post therapy
Hilgard P *et al.* Hepatology 2010, 52: 1741-1749 [51]	TheraSphere®	5/108 (4.6%) were transplanted post therapy
Lambert B *et al.* Eur J Nucl Mol Imaging 2011, 38: 2117-2124 [53]	TheraSphere®	2/29 (6.9%) were transplanted post therapy although 3/29(10%) were successfully downstaged and listed for transplantation
Biederman DM *et al.* Clin Imaging 2018, 47: 34-40 [57]	TheraSphere®	8/55 (15%) were transplanted post therapy
Vouche M *et al.* Hepatology 2014, 60: 192-210 [64]	TheraSphere®	33/102 (32%) transplanted
Vouche M *et al.* J Hepatol 2013, 59: 1029-1036 [75]	TheraSphere®	3/67(5%) resected, 6 (9%) transplanted

Key: ^{90}Y - Yttrium-90; cTACE - Conventional transarterial chemoembolisation; DEBDOX - Drug-eluting beads loaded with doxorubicin; RFA - radiofrequency ablation ; TACE - Transarterial chemoembolisation; UNOS - United Network for Organ Sharing; W - Wilcoxon signed-rank test; w - weeks

4.6.2.4 TheraSphere® Treatment in Earlier Stage Disease: Radiation Lobectomy

Overall response in patients who received a radiation lobectomy with TheraSphere® was high, ranging from 94 to 95% with EASL criteria and 65% with WHO criteria. Hypertrophy in the untreated lobe was noted in most patients with volume changes ranging from 11%-105% in those patients.

Four retrospective cohort studies reported on response in mostly earlier stage disease patients who received a radiation lobectomy with TheraSphere® (Gaba *et al.* 2009; Goebel *et al.* 2017; Gabr *et al.* 2018, Palard *et al.* 2018) [71-74] (see Table 4-25).

Two of these studies reported overall response after treatment with TheraSphere® using EASL and/or WHO criteria (Gaba *et al.* 2009; Palard *et al.* 2018) [72, 74]. Overall response according to EASL criteria ranged from 94% to 95%; Gaba *et al.* (2009) [72] also reported an OR of 65% using WHO criteria. Both Gaba *et al.* 2009 [72] and Gabr *et al.* 2018 [71] reported that all patients experienced disease control.

All of the above studies also reported on reduction of the treated lobe and/hypertrophy of the untreated lobe. Gaba *et al.* (2009) [72] noted a decreased volume of 11 to 75% in treated hepatic lobe and range increase of 11 to 105% in the contralateral untreated lobe. Palard *et al.* (2018) [74] reported a mean maximal decrease of 42% in the treated lobe and a mean maximal increase of 35% in the untreated lobe. Gabr *et al.* (2018) [71] reported 23% contralateral hypertrophy in patients who received radiation lobectomy and 9% in patients who received radiation segmentectomy with TheraSphere® to treat their HCC. Three months post resection, median augmented hypertrophy was 504mL (IQR: 433-664mL) in radiation lobectomy patients and 423 mL (IQR: 263-925mL) in radiation segmentectomy patients.

Goebel *et al.* (2017) [73] presented volume changes, such that the treated lobe decreased from 1094 ml to 713 ml over 9 months ($p<0.05$), and the untreated lobe increased in size from 562 ml to 806 ml.

The overall GRADE quality assessment for this group of studies, and for this outcome is: low quality.[38].

[38] Using GRADE criteria, all observational studies start with a low initial quality of evidence. The evidence for this outcome was not further downgraded or upgraded.

Table 4-25: Non-Comparative Studies of TheraSphere® used in Radiation Lobectomy: Tumour Response

Study	Study Country	Study design	Treatment	Sample Size (n)	Definition	Statistical Analysis	Results n (%)
Gaba *et al.* Ann Surg Oncol 2009, 16: 1587-1596 [72]	USA	Observational Retrospective Cohort	TheraSphere®	17	WHO, RECIST, EASL	NR	<table><tr><th></th><th>WHO</th><th>RECIST</th><th>EASL</th></tr><tr><td>CR</td><td>0 (0)</td><td>0 (0)</td><td>8 (47.1)</td></tr><tr><td>PR</td><td>11 (64.7)</td><td>13 (76.5)</td><td>8 (47.1)</td></tr><tr><td>SD</td><td>6 (35.3)</td><td>4 (23.5)</td><td>1 (5.9)</td></tr><tr><td>PD</td><td>0 (0)</td><td>0 (0)</td><td>0 (0)</td></tr></table> Disease control (DC= CR+PR+SD) was achieved in all patients. Hypertrophy of contralateral lobe volume: range: 11%-105% Reduction in treated lobe volume: 11 to -75% 1 patient underwent resection
Gabr A *et al.* J Vasc Interv Radiol 2018 29: 1502-1510 [71]	USA	Observational Retrospective Cohort	TheraSphere®	31 (Volumetric data on 20 radiation lobectomy patients and 5 radiation segmentectomy patients)	EASL, WHO	Descriptive statistics	<table><tr><th></th><th>EASL</th><th>WHO</th></tr><tr><td>CR</td><td>9 (29)</td><td>0 (0)</td></tr><tr><td>PR</td><td>9 (29)</td><td>8 (26)</td></tr><tr><td>SD</td><td>13(39)</td><td>20 (64)</td></tr><tr><td>PD</td><td>0 (0)</td><td>3 (10)</td></tr></table> All 31 patients underwent resection post TARE and all had tumour DC (CR+PR+SD). Baseline FLR increased from a median of 35% (IQR: 27%-42%) to a median of 45% (IQR: 40%-57%) p<0.001 in patients who received radiation lobectomy. Median FLR hypertrophy was 23.3% (IQR: 10%-48%) Baseline FLR increased from a median of 32% (IQR: 25%-35%) to a median of 34% (IQR: 30%-40.5%) p=0.002 in patients who received radiation segmentectomy. Median FLR hypertrophy was 9% (IQR: 6%-25%) %FLR hypertrophy was significantly higher for radiation lobectomy vs radiation

Study	Study Country	Study design	Treatment	Sample Size (n)	Definition	Statistical Analysis	Results n (%)
							segmentectomy: p=0.037 and in liver remnant volume. P=.77
Goebel *et al.* PLoS One 2017, 12(7): e0181488. [73]	Germany	Observational Retrospective Cohort	TheraSphere®	75	NR	For volume changes: Wilcoxon test or paired t test as appropriate	Median right lobe volume (treated lobe) decreased from 1094ml (433-2737) to 713ml (214-2778) over 9M. Median left lobe volume (contralateral untreated lobe) increased from 562 mL (176-1187 mL) to 806 (274-2373) mL. All changes were SS, p<0.05
Palard *et al.* Eur J Nucl Med Mol Imaging 2018, 45: 392-401 [74]	France	Observational Retrospective Cohort	TheraSphere®	73	EASL	NR	Response rate: (CR+PR: 94.5%. DC rate was 98.6% at 3M after TARE with 1(1.4%) progression and DC rate was 71.2% at 6M with 8(10.9%) patients progressing in the treated liver and 13(17.8) progressing in non-treated liver
							Mean maximal hypertrophy of contralateral lobe was 35.4% ±40.4% at 5.9±3.4M 58(79.5%) had a maximal hypertrophy increase of ≥10% and only 5 (20.5%) had no or minimal hypertrophy <10%). No SS between patients with PVT (39.5±52.4%) or without PVT (32.1±27.1%) Mean maximal atrophy of treated lobe was 41.5±9.8% of the initial volume at 5.9±3.1M post treatment. Only 2(2.7%) patients had 0 or <10% atrophy. CP score, future liver remnant, and healthy injected liver dose were associated with ≥10% maximal hypertrophy

Key: AE - adverse event or side effect; C - Chi square test; Cox - Cox proportional regression model for Hazard ratios; CR - Complete Response; DC - Disease Control (CR+PR+SD); EASL - European Association for the Study of the Liver; F - Fisher's exact Test, FLR - future liver remnant; IPTW - inverse probability of treatment weights; IQR - inter-quartile range; K - Kaplan-Meier for univariate survival curves; LR - log-rank test for differences in median and 95% confidence interval (CI); M - months; ml - millilitres; n - number; NR – not reported; OR - Objective Response (CR+PR); PS - propensity score model; PD - Progressive Disease; PR - Partial Response; PVT - portal vein thrombosis; RECIST - Response Evaluation Criteria in Solid Tumours; SS - statistical significance; TARE – transarterial radioembolization; WHO – World Health Organization; W - Wilcoxon signed-rank test; w - weeks

4.7 HEALTH RELATED QUALITY OF LIFE

QoL for patients faced with a reduced survival expectancy and seeking symptomatic relief is an important consideration when choosing an optimal palliative treatment. Two comparative studies evaluated health related quality of life (QoL) after treatment with TheraSphere® vs. TACE or systemic chemotherapy (cisplatin) in later stage HCC patients. QoL was not adversely affected after treatment with TheraSphere®. Some QoL subscales were significantly improved with TheraSphere® when compared with TACE including social and functional well-being. The study comparing TheraSphere® vs. TACE also used a QoL scale which specifically looked at the QoL parameters most relevant to patients undergoing embolisation (pain, impact of treatment side effects, ability to work, diarrhoea and good appetite) and found that QoL improved with TheraSphere® and worsened with TACE.

Two comparative cohort studies evaluated health related QoL in later stage disease HCC patients[39] after treatment with TheraSphere® (Salem *et al.* 2013; Steel *et al.* 2004) [78, 79] (see Table 4-26). One study mostly included BCLC B or C (62.5%) patients, although 37.6% of patients were BCLC A (Salem *et al.* 2013) [78]. In Steel *et al.* (2004) [79], the majority of patients had later stage HCC.

4.7.1 Comparative Studies Reporting on QoL

No studies were found that compared TheraSphere® with SIR-Spheres®, QuiremSpheres®, bland TAE or DEB-TACE in terms of QoL. A study vs. chemotherapy was identified but this was dated 2004 and considered hepatic infusion of cisplatin which is no longer considered standard of care for HCC.

4.7.1.1 TheraSphere® vs. TACE in Later Stage Disease

One comparative prospective cohort study compared QoL (as assessed by FACT-Hep) after treatment with TheraSphere® vs. TACE at 4 weeks (Salem *et al.* 2013) [78]. No significant difference in overall QoL scores was demonstrated (p=0.05), but patients who received TheraSphere® had significantly improved social well-being (p=0.02) and functional well-being (p=0.03) in comparison with patients who received TACE, despite significantly higher proportions of patients with later stage HCC in the TheraSphere® treatment group. The authors also created an exploratory embolotherapy-specific score (ESS) from FACT-Hep items which captured QoL parameters most relevant to patients undergoing embolisation procedures (pain, bothered by treatment side effects, able to work, diarrhoea and good appetite). This outcome was also significant, with better QoL for patients who received TheraSphere® (adjusted mean change over 4 weeks was 0.63 (0.62) with

[39] In the study by Salem *et al.* (2013), most of the patients who received TheraSphere had BCLC-B and C stage disease (79.3%), so we have considered this to be predominantly later stage disease.

TheraSphere® and -1.84 (0.08) with TACE, p=0.018). GRADE was assessed as: low quality[40]

4.7.1.2 TheraSphere® vs. Chemotherapy in Later Stage Disease

An earlier non-randomised parallel cohort study compared QoL (as assessed by FACT-Hep) after treatment with TheraSphere® with systemic chemotherapy (hepatic infusion of cisplatin) (Steel *et al.* 2004) [79]. The authors reported significantly higher functional well-being (p<0.001) and overall QoL (p<0.001) at 3 months with TheraSphere®, but only functional well-being remained significant at 6 months (p<0.04). GRADE was assessed as: low quality.[41]

Non-comparative studies

No relevant non-comparative studies were identified.

[40] Using GRADE criteria, all observational studies start with a low initial quality of evidence. The evidence for this outcome was not further downgraded or upgraded.
[41] Using GRADE criteria, all observational studies start with a low initial quality of evidence. The evidence for this outcome was not further downgraded or upgraded.

Table 4-26: TheraSphere® Studies that Assessed Quality of Life

Study	Study Country	Study design	Treatment	Sample Size (n)	Definition	Statistical Analysis	Results
Salem R. *et al.* Clinical Gastroenterology and Hepatology 2013, 11:1358-1365 [78]	USA	Prospective comparative cohort	TheraSphere® (120 Gy)	29	The Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep)	Repeated measures linear regression incorporating BCLC stage	Change from baseline (after 4 weeks): Overall QoL 3.88 (2.96) Physical well-being 0.10 (1.00) Social well-being 1.62 (0.93) Emotional well-being -0.10 (0.74) Functional well-being 2.26 (1.29)
			TACE	27			Change from baseline: Overall QoL -3.88 (2.28), p=0.055 Physical well-being -2.09 (1.26), p=0.176 Social well-being -1.02 (0.60, p=0.019 Emotional well-being 0.34 (0.68), p=0.656 Functional well-being -1.00 (0.75), p=0.031
Steel J. *et al.* Pscyho-Oncology 2004, 13: 73-79 [79]	USA	Non-randomised parallel cohort study	TheraSphere® ® (15-150 Gy)	15* (at 3 months) 9 (at 6 months) *as reported	The Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep)	Repeated measures ANOVA	3 months Physical well-being: 20.0 (5.5) Social and family well-being: 22.3 (2.4) Emotional well-being: 15.4 (6.0) Functional well-being: 17.0 (5.3) HCC-or treatment related symptoms: 45.8 (11.1) Overall HR QoL: 74.5 (18.6) 6 months Physical well-being: 12.6 (6.2) Social and family well-being: 18.2 (9.1) Emotional well-being: 7.6 (3.5) Functional well-being: 13.5 (7.3) HCC-or treatment related symptoms: 47.9 (10.5) Overall HR QoL: 47.3 (23.8)
			Cisplatin (125 mg/m^2 every 6 weeks)	13 (at 3 months) 5 (at 6 months)			3 months Physical well-being: 19.0 (3.3) Social and family well-being: 21.7 (3.5) Emotional well-being: 15.4 (4.4) Functional well-being: 14.6 (3.7)

Study	Study Country	Study design	Treatment	Sample Size (n)	Definition	Statistical Analysis	Results
							HCC-or treatment related symptoms: 47.6 (6.3) Overall HR QoL: 76.0 (6.2) 6 months Physical well-being: 12.6 (6.2) Social and family well-being: 18.2 (9.1) Emotional well-being: 7.6 (3.5) Functional well-being: 13.5 (7.3) HCC-or treatment related symptoms:47.9 (10.5) (significance tests were not clear for some comparisons)

Key: ANOVA - analysis of variance; BCLC - Barcelona Clinic Liver Cancer; FACT-Hep - Functional Assessment of Cancer Therapy - Hepatobiliary; Gy - Unit of Gray; HCC - Hepatocellular carcinoma; HR – Hazard ratio; QoL – quality of life; TACE - Transarterial chemoembolisation

Section 5: Adverse events

Overall, the clinical safety data generated from the literature, clinical studies and post-marketing surveillance data confirms an acceptable and reproducible safety profile for TheraSphere® when used according to the manufacturer's instructions. There are no unanswered questions regarding safety, and no new risks have been identified. Given the depth of existing safety information, TheraSphere® can be considered to have an acceptable safety profile.

In the clinical papers reviewed in this submission, the most frequent adverse events were flu-like symptoms such as fatigue, abdominal pain and nausea. Biochemical toxicities were generally low (<10% frequency), although increased AST and ALT, increased bilirubin and hypoalbuminaenia were more frequently observed. The most frequently observed severe adverse event (grade III-IV) was increased bilirubin. These are consistent with the list of adverse events (for all types of patients) included in the investigator's brochure which incorporates post-market surveillance information.

There is a lack of head-to-head evidence comparing TheraSphere® vs. SIR-Spheres® or sorafenib. Broad explorative comparisons of TheraSphere® vs. SIR-Spheres® show that some adverse events are more commonly reported with TheraSphere® and others are more commonly reported with SIR-Spheres®.

There is evidence from a RCT (with an unclear risk of bias) that more patients treated with cTACE experienced grade I-II diarrhoea and hypoalbuminemia compared with TheraSphere®. Data from non-randomised comparative studies generally show higher percentages of patients with abdominal pain, nausea/vomiting, diarrhoea, increased AST/ALT, increased bilirubin and hypoalbuminemia with TACE compared with TheraSphere®, but statistical comparisons were not always consistent across the studies for each of these events. Rates of post-embolisation syndrome were significantly lower in TheraSphere® than in TACE. This difference is explained by the fact that major vessels are not occluded with TheraSphere®, contrary to TACE.

5.1 KNOWN ADVERSE EVENTS ASSOCIATED WITH THERASPHERE®

As reported in an up-to-date investigator's brochure (Feb 2019) [80] based on company-sponsored clinical trials, post-marketing surveillance (PMS) and the published literature, the following device-related or procedure-related adverse events are associated with the use of TheraSphere® (Table 5-1). The majority of the clinical adverse events include flu-like symptoms such as fatigue, abdominal pain and nausea.

Table 5-1: Adverse events frequency of TheraSphere®

Frequency	Description of Adverse Event (per NCI-CTCAE v 3.0)[42]
Common ≥ 10%	Fatigue, pain, nausea, vomiting, anorexia, and laboratory value abnormalities including increased ALP, AST, ALT, bilirubin, hypoalbuminemia, and lymphopenia with no clinical sequellae
Infrequent ≤ 10%	Constipation, heartburn, weight loss, fever, ascites, muscle weakness, variations in creatinine, platelets, haemoglobin, and leukocytes, GI ulcer, dyspnoea, supraventricular arrhythmia, diarrhoea, hypotension, insomnia, rigors/chills, sweating, distension, GI obstruction, hematoma, GI haemorrhage, pleural effusion, hyponatremia, dehydration, allergic reaction, GI other, neurology other
Rare ≤ 1%	Alopecia, bruising, pruritis, rash, hot flashes, taste alteration, haemorrhage, liver dysfunction/failure, radiation hepatitis, radiation pneumonitis, infection, dizziness, mood alteration, sensory neuropathy, somnolence, urine colour change, intraoperative injury, flu-like symptoms, tumour lysis syndrome, thrombosis, metabolic/laboratory abnormalities – neutrophils, hypercalcemia, hyperglycaemia, hyperkalaemia, hypermagnesemia, lipase, lymphatics other, pulmonary other vascular other, death

5.2 POST-MARKET SURVEILLANCE DATA

Post-marketing surveillance data show that the average complaint rate from 01 August 2017 through 31 July 2018 is 0.7%, which is within the acceptable rate of complaints as defined by BTG. BTG defined a quality objective of an acceptable total complaint threshold of 1% based on historical product use, sales and complaints received for TheraSphere®, or less was established. TheraSphere® has a history of clinical use over more than 18 years with an acceptable clinical performance and safety profile.

Of the 107 complaints received during the reporting period, 32 were associated with 88 adverse events. Based on the total number of doses distributed during this review period, the overall adverse event case rate was 0.22%. Of the 88 adverse events reported, 41 events (47%) were considered as serious and 47 events (53%) were considered not to be serious. Of the 41 serious events reported, 12 events were determined to be unrelated to TheraSphere®. Based on the total number of doses distributed during the review period, the overall adverse event rate was 0.60%. During the review period, 12 patient deaths were reported, of which only two were related to TheraSphere®. No new or emerging risks were identified through the risk management and clinical evaluation processes. All individual risks that were categorized as low as reasonably possible by the risk acceptability criteria provided in the TheraSphere® Risk Management Plan were deemed to have benefits that outweigh the risks.

[42] Common terminology criteria for adverse events (CTCAE) – Version 5.0. Published 27 Nov 2017.

5.3 COMPARATIVE STUDIES REPORTING ON ADVERSE EVENTS

5.3.1 TheraSphere® vs. SIR-Spheres® in Later Stage Disease

A recently published systematic review aimed to compare the adverse event profile of TheraSphere® vs. SIR-Spheres® (Kallini *et al.* 2017) [31]. However, the authors did not report data on any head-to-head studies so that their 'comparative' results can only be considered as exploratory. For grade 3 or higher adverse events, Kallini *et al.* (2017) [31] pooled data from the studies and reported that, on average, more patients experienced gastric ulcer, cholecystitis, hepatic encephalopathy, and fatigue in studies of SIR-Spheres® than in studies of TheraSphere®[43]. Larger percentages of patients experienced pleural effusion, ascites, nausea, and abdominal pain in studies of TheraSphere® than in studies of SIR-Spheres®. Again, as direct statistical comparisons could not be made, these results can only be considered as observational.

In addition to this SR, one retrospective cohort study was identified that compared TheraSphere® (n=65) with SIR-Spheres (n=17) (Biederman *et al.* 2016) [36]. The authors reported no significant differences between TheraSphere® and SIR-Spheres® for pain (31% vs. 41%, p=0.56), fatigue (19% vs. 18%, p=1.0), nausea (3% vs. 18%, p=0.06) or anorexia (9% vs. 0%, p=0.34). No other adverse events were presented in this publication.

5.3.2 TheraSphere® vs. TACE in Earlier and Later Stage Disease

One randomised controlled trial (Salem *et al.* 2016) [39], three prospective comparative cohort studies (El Fouly *et al.* 2015; Lewandowski *et al.* 2009: Salem *et al.* 2011) [8, 43, 45], and four retrospective comparative cohort studies (Akinwande *et al.* 2016; Moreno-Luna *et al.* 2013; Padia *et al.* 2015; 2017) [40, 46-48] compared adverse event rates between TheraSphere® and TACE patients (see Table 5-2). The majority of these studies included patients from all HCC stages; three studies only included BCLC A and B patients (El Fouly *et al.* 2015; Salem *et al.* 2016; Lewandowski *et al.* 2009) [39, 43, 45].

We have summarised below any significant differences described in the six studies; for all other adverse events (i.e. not described), no significant differences between treatment groups were demonstrated. All adverse events data are presented in Table 5-2. Broad comparisons across the studies could not be made given that the studies reported results for different adverse event grade categories. The RCT was considered to have an unclear risk of bias[44], and this overall group of studies was considered as GRADE: low quality[45]

[43] We have not presented the averages as reported in Kallini *et al.* (2017) as they pooled potentially heterogeneous studies and did not consider the potential 'weight' of each study.
[44] This study was considered to have an unclear risk of bias because details regarding the method of randomisation and allocation concealment were not reported (although baseline characteristics were balanced). Blinding was not possible and the outcome variable (OS) was objective. It is unclear if there was selective outcome reporting. Outcome data were available for all patients. We note, however, that this study was stopped early.
[45] Using GRADE criteria, all observational studies start with a low initial quality of evidence. The evidence for this outcome was not further downgraded or upgraded.

The RCT (Salem *et al.* 2016) [39] demonstrated that a higher percentage of patients who received cTACE had diarrhoea (grade I-II) (p=0.03), and also hypoalbuminemia (grade I-II) (p<0.001).

Akinwande *et al.* (2016) [40] did not observe a significant difference in rates of adverse events between TheraSphere® and DEBDOX, based on the number of treatments, not patients.

In the study by El Fouly *et al.* (2015) [43], the most commonly reported adverse event was unspecific abdominal pain (grade II-III) which was observed in 83% of cTACE patients compared with 5% in TheraSphere® patients (p<0.001). Grade II-III fatigue and nausea/vomiting were also significantly higher in cTACE patients (p<0.01 and p<0.001, respectively).

Both Moreno-Luna *et al.* (2013) and Padia *et al.* (2017) [46, 48] reported significantly greater fatigue (Grade I-II in the first study and Grade III or above in the second) with TheraSphere® (p=0.003 and p=0.01, respectively). The percentage of patients with Grade III or above pain was significantly higher with TheraSphere® in Padia *et al.* (2017) [48] (adjusted RR: 0.10 [95% CI 0.01 to 0.82], p=0.03), and Grade I fever was lower with cTACE (p=0.02) in Moreno-Luna *et al.* (2013).

Post-embolisation syndrome is a post-inflammatory clinical syndrome defined by fever and right upper quadrant abdominal pain with or without nausea and vomiting. It generally lasts for a couple of days after the procedure. It is important to assess, because post-embolisation syndrome after TACE has been shown to be associated with a worse survival and a two-fold increased risk of death, after adjusting for important confounders (Mason *et al.* 2015) [81]. The study by Padia *et al.* (2015) [47] reported lower grade II or above post-embolisation syndrome in TheraSphere® patients compared with TACE patients (20% vs 47%, p=0.01). Greater percentages of TACE patients had increased AST and ALT levels (grade II or above) (p=0.02 and p=0.002, respectively).

The study by Salem *et al.* (2011) [8] also reported significantly higher percentages of patients with abdominal pain (p<0.001) and diarrhoea (p=0.02) in cTACE patients compared with TheraSphere® patients (all grades). Grade II-IV increased AST/ALT levels were also significantly worse with cTACE (p=0.004).

Lewandowski *et al.* (2009) [45] did not fully report on adverse events, but did state that 60% of the patients treated with TheraSphere® experienced fatigue and transient non-specific flu-like symptoms. With TACE, the most common post-procedure morbidity was postembolisation syndrome, observed in 60% of patients. While lower grade bilirubin toxicity were similar between treatments, grade II/IV was higher with TACE (26% vs. 7%, p value not reported).

Table 5-2: Adverse Events Reported in TheraSphere® vs. TACE Studies

	Akinwande O *et al.*. Anticancer Res 2016, 36: 239-246[46] [40]		El Fouly A.Liver Int 2015, 35: 627-635[47] [43]		Lewandowski RJ, Am J Transplant 2009, 9: 1920-1928 [45]		Moreno-Luna LE. Cardiovasc Intervent Radiol 2013, 36: 714-723[48] [46]		Padia SA. J Vasc Interv Radiol 2017, 28:777-785[49] [48]		Padia SA. Cardiovasc Intervent Radiol 2015, 38: 913-921[50] [47]		Salem R.Gastroenterol 2011, 140: 497-507[51] [8]		Salem R.Gastro-enterology 2016, 151: 1155-1163[52] [39]	
	TheraSphere® (n=117 treatments – not patients)	DEBDOX (n=596 (treatments – not patients)	Thera-Sphere® (n=44)	cTACE 50 mg Adriamycin (n=42)	Thera-Sphere® (n=43)	TACE (n=43)	Thera-Sphere® Target dose of TS=80-150GY (n=61)	cTACE mitomycin-C, doxorubicin (n=55)	Thera-Sphere® Target perfused tissue dose >200Gy (n=132)	TACE: DEB DOX (76%) or cTACE (24%) both 50 mg doxorubicin (n=102)	Thera-Sphere® intended dose 120Gy (n=10)	TACE (n=17)	Thera-Sphere® (n=123)	cTACE 30 mg mitomycin, 30 mg Adriamycin, 100 mg cisplatin (n=122)	TheraSphere® 120Gy (n=24)	cTACE Drug NR (n=19)
Number of adverse events (%)																
Any side effect					60% & non-specific flu-like symptoms	NR	40 (67)	37 (66) NS								
Fatigue	1 (0.9)	1 (0.2)	18 (40)	30 (73) <0.01			28 (46)	11 (20) p=0.003	51 (39)	27 (27) p=0.01	6 (60)	4 (24) NS	68 (55)	47 (38) NS*	21 (88)	12 (63) NS
Abdominal pain			2 (5)	35 (83) <0.001			18 (30)	24 (44) NS			2 (20)	9 (53) NS	18 (15)	46 (38) p<0.001*	7 (29)	10 (53) NS
Chest pain							1 (2)	1 (2) NS								
Pain	5 (4.3)	12 (2)							10 (8)	1 (1) p=0.05						
Nausea/ vomiting	Nausea 3 (2.6)	24 (4)	0 (0)	16 (38) <0.001			15 (25)	13 (24) NS					18 (15)	25 (20) NS	8 (33)	11 (58) NS
Fever							4 (7)	12 (21) p=0.02					10 (8)	2 (2) NS	1 (4)	3 (16) NS
Headache							2 (3)	2 (4) NS								
Diarrhoea													2 (2)	10 (8) p=0.02	4 (21)	24 (0) p=0.03
Post-embolisation syndrome	(0)	3 (0.5)			NR	26 (60)			3 (2)	9 (9) p=0.04 adjusted RR: 3.4	2 (20)	8 (47) p=0.01				

[46] Grade not specified
[47] Grade II-III AE's
[48] All side effects were Grade I except for one patient in the TheraSphere® group who had grade II fatigue and one patient in the TACE group who had grade 3 fever
[49] Side effects ≥ grade 3 within 90 days of treatment were reported in this paper
[50] Side effects ≥ grade 2 were reported in this paper
[51] All grades evaluated; grade II-IV data only for bilirubin and ALT/AST
[52] Grade I-IV AE's

										(95% CI 0.09 to 13.7), p=0.08						
Ascites	0 (0)	1 (0.2)	1 (2)	4 (10) NS					1 (0.8)	1 (1)	2 (20)	3 (18) NS				
Cholecystitis	0 (0)	1 (0.2)	0 (0)	1 (2) NS							0 (0)	0 (0)				
Pneumonitis			0 (0)	1 (2) NS												
GI-ulcer	0 (0)	4 (0.7)	0 (0)	0 (0)			1 (2)	0 (0)	1 (0.8)	0 (0)						
Hepatic abscess							1 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)				
Pleural effusion	1 (0.9)	1 (0.2)									0 (0)	1 (6)				
Leukopenia									6 (5)	5 (5) NS	0 (0)	1 (6)			2 (8)	2 (11) NS
Increased AST									4 (3)	8 (8) NS	0 (0)	7 (41) p=0.02	ALT/AST: 14 (11)	ALT/AST: 36 (29) p=0.004*	5 (21)	9 (48) NS
Increased ALT									2 (2)	3 (3) NS	0 (0)	5 (29) p=0.002			3 (13)	4 (21) NS
Increased total bilirubin			3 (7)	6 (14) NS	Bilirubin toxicity grade 1/II 26 (60%), grade III/IV 3 (7%)	Bilirubin toxicity grade 1/II 26 (60%), grade III/IV 11 (26%)			4 (3)	9 (9) NS	6 (60)	12 (71)	20 (16)	25 (20) NS	8 (33)	11 (58) NS
Hypoalbumaenia			2 (5)	4 (10) NS					3 (2)	3 (3) NS			15 (12)	26 (21) NS	Grade I-II 26 1 (4) Grade II-IV 1 (4)	Grade I-II 11 (58) p<0.001 Grade II-IV 0 (0) NS

Key: *P-value adjusted for multiple comparisons (correction factor n=6 and 5 for clinical and laboratory toxicities respectively; ALT: alanine aminotransferase; AST: aspartate aminotransferase; NR: not reported; NS: not significant

5.3.3 TheraSphere® vs. Sorafenib in Later Stage Disease

No studies have directly compared TheraSphere® with sorafenib. Although a meta-analysis and NMA have been conducted on the efficacy and safety of these treatments [30] safety results were limited. The authors found little overlap in the adverse events reported given the distinct safety profiles of TheraSphere® and sorafenib, thus precluding formal analysis. Where there was overlap, no statistically significant differences between the treatments were demonstrated for grade II-IV albumin, aspartate aminotransferase, alkaline phosphatase, alanine aminotransferase, bilirubin, anorexia (all grades), nausea (all grades), or fatigue (all grades). The authors of the NMA reported, however, that the results had very large confidence intervals so it is uncertain where the true effect may lie.

In general, fewer adverse events were reported in the TheraSphere® studies. The sorafenib studies reported on more systemic AEs not reported in TheraSphere® studies, such as skin conditions.

5.4 NON-COMPARATIVE STUDIES REPORTING ON ADVERSE EVENTS

Grade III-IV adverse events have been extracted from the studies included in this clinical effectiveness section to provide a very broad overview of frequency of adverse events observed. Blank spaces in Table 5-3 below could mean that this outcome was not assessed in a study, or that there were no grade III-IV adverse events for this outcome; this was not always clearly reported. Moreover, although we aimed to report treatment-related adverse events, this was also not always clearly reported.

An overview of 19 non-comparative retrospective or prospective cohort studies shows that increased bilirubin was the most frequently observed severe adverse event.

Table 5-3: Grade III or Above Treatment-Related Adverse Events in Non-Comparative TheraSphere® studies

Reference	Sample Size	Bilirubin	Alkaline phosphatase	Transaminases (ALT/AST)	Lymphopenia	Abdominal pain	Fatigue	Appetite loss/ anorexia	Nausea /vomiting	Diarrhoea	Cholescystitis	Ulceration	Ascites	Other
Abouchaleh J *et al.* Nucl Med 2018, 59: 1042-1048 [58]	CP A: 74 CP B7: 51 CP ≥B8: 60	CP A: 10% CP B: 12% CP≤B: 32%	CP A: 0% CP B: 6% CP≤B: 3%											CP A: albumin: 3% CP B: albumin: 14% CP≤B: albumin: 23%
Biederman, DM *et al.* J Vasc Interv Radiol 2015, 26: 1630-1638 [50]	38	8%		4%										
Biederman *et al.* Clin Imaging, 2018. 47: p. 34-40 [57]	36		11%	ALT: 0%; AST: 3%										Albumin 11%
Garin *et al.* Liver Int, 2017. 37(1): p. 101-110 [52]	80	11%										-		
Gaba *et al.* Ann Surg Oncol 2009, 16: 1587-1596 [72]	17	0% (dos)												
Gabr *et al.* J Vasc Interv Radiol 2018 29: 1502-1510 [71]	31	3%												
Hilgard *et al.* Hepatology, 2010. 52(5): p. 1741-1749 [51]	108	2.8%									1%	-		
Ibrahim *et al.* Cardiovasc Intervent Radiol 2012, 35L1094-1101 [66]	8	13%												

Reference	Sample Size	Bilirubin	Alkaline phosphatase	Transaminases (ALT/AST)	Lymphopenia	Abdominal pain	Fatigue	Appetite loss/ anorexia	Nausea /vomiting	Diarrhoea	Cholescystitis	Ulceration	Ascites	Other
Kokabi *et al.*. Cancer, 2015. 121(13): p. 2164-74 [59]	30	10%	0%	0%		0%	0%							Hepatobiliary toxicity: 0%
Kulik *et al.* J Sug Oncol 2006, 94: 572-586 [67]	35	3%												
Kulik *et al.* Hepatology, 2008. 47(1): p. 71-81 [60]	82					0%								Pleural effusion: 1%, Death 1%
Kulik *et al.* J Hepatol, 2014. 61(2): p. 309-317 [68]	10							10%		20%				
Lambert B *et al.* Eur J Nucl Mol Imaging 2011, 38: 2117-2124 [53]	29 (at 6-12 weeks)	38%											3%	
Lewandowski *et al.* Radiology 2018, 287:1050-1058 [62]	70	1%		AST: 1%										
Mazzaferro *et al.* Hepatology, 2013. 57(5): p. 1826-1837 [54]	52	27%	19%		15%	6%	6%	15%	10%		2%		10%	Liver decompensation 36.5%
Palard *et al.* Eur J Nucl Med Mol Imaging 2018, 45: 392-401 [74]	73 (dos)													Liver toxicities: 4 (6%)
Salem *et al.* Gatroenterology 2010. 138: 52-64 [55]	245	19%												
Vouche *et al.* Hepatology, 2014. **60**(1): p. 192-201 [64]	94 (at 1-3 months)	6%		ALT: 4%; AST: 1%										Lymphocytes 19%

Reference	Sample Size	Bilirubin	Alkaline phosphatase	Transaminases (ALT/AST)	Lymphopenia	Abdominal pain	Fatigue	Appetite loss/ anorexia	Nausea /vomiting	Diarrhoea	Cholescystitis	Ulceration	Ascites	Other
Woodall CE *et al.* J Am Coll Surg 2009, 308: 375-382 [56]	NR													In treated patients with no PVT:25% reported AEs. Grade ≥3: 1 GI bleed, 1 distal aortic dissection secondary to catheter placement In treated patients with PVT: 33% had AEs. No grade ≥3 events

Key: CP – Child Pugh score; AE – adverse event; ALT - Alanine aminotransferase; AST - Aspartate aminotransferase; GI - gastrointestinal; NR – not recorded; PVT – portal vein thrombosis

Section 6: Cost-effectiveness

6.1 COST-EFFECTIVENESS MODELLING METHODS

The overall economic framework considers individuals with unresectable HCC at an early to advanced stage (BCLC A to C) with or without PVT involvement. Per the NICE MTA scoping document, patients are further subcategorised by treatment eligibility:

- Transarterial embolisation eligible (TAE-eligible) patients may be appropriately treated with SIRT, bland embolisation or DEB-TACE. Based on a review of the literature and expert clinical opinion, a number of patients in this group would be expected to be subsequently treated with resection or transplant. In the clinical effectiveness section, this population group was referred to as patients with earlier stage disease (see 3.2.4).
- Transarterial embolisation ineligible (TAE-ineligible) patients may only be appropriately treated with SIRT or established clinical management (including but not limited to target chemotherapy). Based on the literature and expert clinical opinion, very few patients in this group would be expected to be subsequently treated with resection or transplant. Consequently, these treatments are excluded by assumption from the TAE-ineligible care pathway. In the clinical effectiveness section, this population group was referred to as patients with later stage disease (see 3.2.3).

Separate models were constructed for the TAE-eligible and TAE-ineligible populations from the perspective of the NHS and Personal and Social Services (PSS) in England and Wales (see sections 6.1.1 and 6.1.2). The main features of these models are presented in Table 6-1, below.

Table 6-1: Economic analysis features

Feature	Chosen values	Justification
Time horizon	Lifetime (20 years)	To capture all relevant costs and health-related utilities
Cycle length	Four weeks	To align with previous NICE submissions in unresectable HCC [26-28]
Discount rates	3.5% on costs and QALYs	To align with the NICE guide to the methods of technology appraisal [82]
Starting age	65	[83]
Proportion male	75%	[83]

6.1.1 Overview of TAE-Eligible Model

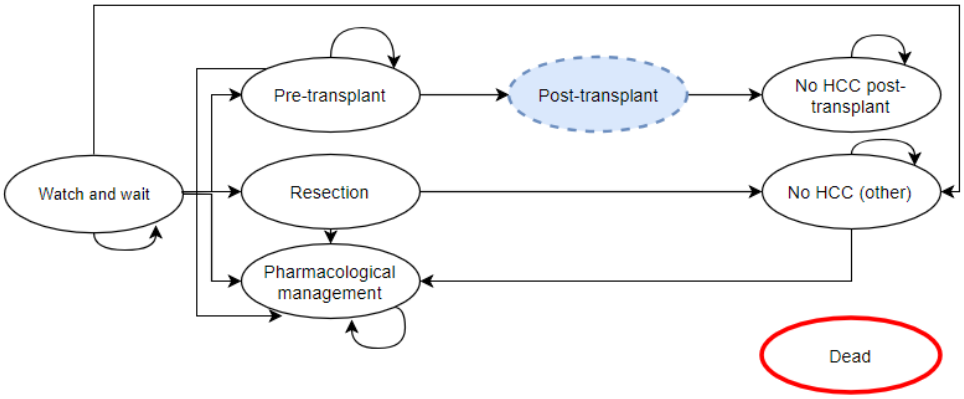
6.1.1.1 Model Structure

A cohort-based Markov model was developed in Microsoft Excel to estimate post-treatment outcomes and costs in the TAE-eligible population. Mutually exclusive health states included in the model are described in detail below, and include:

- Watch and wait
- Pre-transplant
- Post-transplant (a series of three tunnel states)
- No HCC post-transplant
- Resection
- No HCC (other)
- Pharmacological management
- Dead

This model structure is illustrated in Figure 6-1, below.

Figure 6-1: TAE-eligible model structure



*Post-transplant consists of three tunnel states

**The dead state is absorbing such that patients cannot leave it once they have entered.

Patients enter the model in the watch and wait state (i.e. “watchful waiting”) following initial treatment. Patients remain in this state until they:

- Become eligible for transplant, moving on to the pre-transplant state, or
- Become eligible for resection, moving on to the resection state, or
- Enter remission and move on to the no HCC (other) state, or
- Move on to the pharmacological management state due to not entering remission and being ineligible for both liver transplant and resection, or
- Die and move to the dead state

6.1.1.1.1 Transplant pathway

The pre-transplant state captures time when the patients are on the donor organ waiting list. Patients remain in this state until they:

- Receive a transplant, after which they move to the post-transplant state, or
- Experience disease progression or become ineligible for a liver transplant, after which they move to the pharmacological management state, or
- Die and move to the dead state

Upon receiving a transplant, patients move from the pre-transplant state to the first of three post-transplant tunnel states. Patients spend a single cycle in each of the post-transplant states before arriving in the no HCC post-transplant state where they remain until death. There are three tunnel states due to differing resource use between the three states and to enable different mortality rates to be associated with each state (due to complications from the liver transplant).

6.1.1.1.2 Resection pathway

Patients enter the resection state for one cycle after which they move to one of the following states based their resection procedure outcome:

- The resection was successful, and patients move to the No HCC (other) state, or
- The resection was unsuccessful, and patients move to the pharmacological management state, or
- Patients die and move to the dead state.

Patients transition from the no HCC (other) state to the pharmacological management state when HCC recurs, where they remain until death. Patients who do not have a recurrence remain in the no HCC state until death.

6.1.1.1.3 Pharmacological management pathway

Patients enter the pharmacological management pathway where they remain until death. Here, the patients may be in a pre-progressed or a progressed HCC state.

6.1.1.1.4 Key structural assumptions

- Transitions from the no HCC post-transplant state to other alive states do not exist; despite evidence that HCC recurrence exists after a transplant [84], a simplifying assumption has been made that HCC recurrence after a successful liver transplantation is not possible.
- Patients on the transplant pathway may not transition to the resection pathway, and vice versa; it is assumed that salvage transplantation does not occur [85].
- Patients who experience recurrence (transitioning from no HCC (other) to pharmacological management) do not receive further first-line treatment or curative interventions (including SIRT, TACE, bland embolisation, resection or liver transplant)
- A simplifying assumption is made that patients receive only one resection and move on to systemic treatment if it is unsuccessful.
- Patients receive only one transplant.

- Transplants are assumed to be curative; consequently, there is no transition from post-transplant to pharmacological management.
- A half-cycle correction is not applied to one-off costs or utility decrements but is applied to all cyclical costs and utilities.

6.1.1.2 Comparators

The final NICE scope specifies the following comparators (see Appendix F):

- Other SIRTs (SIR-Spheres®; QuiremSpheres®)
- Bland embolisation
- TACE using lipiodol (cTACE)
- Transarterial chemoembolisation using drug-eluting beads (DEB-TACE)

For the comparison versus QuiremSpheres® there is no relevant evidence available in this patient group.

QuiremSpheres® uses a different radionuclide (^{166}Ho) from the other SIRTs. Although also a beta-emitter, it has different pharmacological characteristics [16] and cannot therefore be considered to be equivalent to the ^{90}Y-based products. We were unable to identify any studies of QuiremSpheres in patients with HCC; the only published literature being phase I/II studies in metastatic liver disease from a range of different primary tumours [86] [87]. The intended indication is listed in the QuiremSpheres® pack insert as: "[it] is indicated for the treatment of unresectable liver tumours…" but it is unclear whether this includes HCC, given that the extrapolation of data from metastatic disease to HCC is open to question.

However, despite these limitations, for modelling purposes it was assumed at QuiremSpheres® was equivalent to other SIRTs despite the use of a different nucleotide and an overall absence of clinical data relating to patients with HCC.

6.1.1.3 State Occupancy

Patient movement between health states is determined by a set of fixed transition matrices (see Appendix G). The distribution of patients leaving the initial watch and wait state differs between treatments. Beyond this, transition probabilities are assumed to be equivalent across all treatment cohorts.

6.1.1.3.1 Departing the watch and wait state

The probability of remaining in watch and wait between cycles was derived from a published median time to downstaging. This study by Lewandowski *et al.* (2009) [45] was carried out in a population of unresectable HCC patients who did not meet the Milan criteria at presentation, and were subsequently treated with either TheraSphere® or cTACE [45]. Downstaging was defined as a change in UNOS status from T3 to T2. The median time (3.1 months) was used first to derive an exponential rate for the cycle, which was then converted into a probability. To facilitate this derivation it was assumed that the median time to

downstaging is representative of the median time spent in monitoring (i.e. in watch and wait), and so patients who are not successfully downstaged transition out of watch and wait at the same rate as those who are. It is also assumed that monitoring time is consistent across all treatments.

In the base case it was imposed that all patients who are downstaged go on to the transplant wait list, with none of the cohort referred for resection. This simplifying assumption is supported by the reported treatment pathways in patients who have been downstaged, where very few are resected in favour of transplant [45, 55]. Patients who are not successfully downstaged to transplant transition instead to pharmacological management, or to the dead state. The transition probabilities from watch and wait are populated accordingly.

Lewandowski *et al.* (2009) reported a significantly (p=0.023) increased likelihood of downstaging from TheraSphere® treatment (58% down-staged) compared to cTACE (31% down-staged) [45]. These probabilities are applied to the proportion of the cohort leaving watch and wait in each cycle to determine the transition probabilities to pre-transplant and to pharmacological management. The derived cycle probabilities for cTACE were assumed to also hold for DEB-TACE and bland embolisation due to a lack of evidence. Similarly, the values for SIR-Spheres® and QuiremSpheres® were assumed to be the same as the derived values for TheraSphere®, again due to a lack of published evidence for this parameter.

6.1.1.3.2 Liver transplant

From the pre-transplant state, which represents a wait list, the transition probabilities are informed by the median wait time for a liver transplant in the UK, reportedly 130 days [88]. This wait time is not specific to an indication of HCC. The probability of transitioning from pre-transplant to pharmacological management, in the case that a patient becomes ineligible for transplant whilst waiting, is informed by clinical advice applied as a ratio against the transition to transplant (16 cases of leaving the wait list due to disease progression, for every 103 transplants) (National Audit for Liver Transplant).

6.1.1.3.3 Others

All other transition probabilities are assumed due to data paucity or, in the case of tunnel states and absorbing states, are populated suitably according to the defined pathways of the model.

6.1.1.4 Mortality

General population all-cause mortality is included in the model to capture the background number of deaths, based on life tables for England and Wales [89]. Age and gender stratified rates are used, such that the rates change as the modelled cohort ages. The patient cohort enter the model at age 65, reflecting the patient population described in Section 6.1. The prevalence of HCC is higher in males and this imbalance is incorporated in the model so the mortality rates are based on a 75:25 split of males to females [17].

There is an absolute mortality rate associated with each health state in the model, summarised below in Table 6-2. To ensure that background mortality is taken into account as the cohort ages, the total mortality rate for a patient at any time is the maximum of the health state mortality rate and their all-cause background mortality.

Due to lack of data, the watch and wait mortality rate was assumed to be the same as the pre-transplant mortality rate, as described below.

The pre-transplant mortality value was based on NHS data where a cohort of 2,706 patients with HCC were on the waiting list for an average of 130 days [88], with up to 18% of patients dying whilst on the liver transplant waiting list [29]. From this the absolute 4-week mortality rate was derived and the maximum of this rate and the background mortality rate was applied to each cycle. This ensured inclusion of the background mortality rate if it exceeded the absolute mortality rate.

The pharmacological management mortality value was based on the median overall survival of BSC patients (34.4 weeks) from the NICE sorafenib submission [26]. A value for BSC was used so as not to bring the benefit of a particular HCC treatment into the model, as patients in the pharmacological management health state would be on different treatments. The absolute mortality rate was derived from the median OS, assuming an exponential distribution and the maximum out of this rate and the background mortality rate was applied to each cycle.

The resection value was based on information in Bellavance *et al.* [90], where a cohort of 245 patients with HCC were followed up for a period of 30 days and four deaths were observed. From this the absolute 4-week mortality rate was derived and the maximum of this rate and the background mortality rate was applied to each cycle.

The post-transplant (1 month) mortality value was based on information in Bellavance *et al.* [90], where a cohort of 134 patients with HCC were followed up for a period of 30 days after transplant and two deaths were observed. From this the absolute 4-week mortality was derived and the maximum of this rate and the background mortality rate was applied to each cycle. The absolute mortality rates for the two further post-transplant tunnel states were assumed to take the same value as the first.

The post-transplant no HCC health state value was based on NHS 5-year survival rates following transplantation [88] where a cohort of 1,854 patients who had a liver transplant were followed up for a period of five years and 227 deaths were observed. From this, the absolute 4-week mortality rates were derived. Although the NHS data is for all liver transplant patients, with it being unknown if they were initially downstaged, a systematic review conducted by Gordon-Weeks *et al.* (2011) [29] assessed the evidence on HCC tumour downstaging before liver transplantation. Patients who had a liver transplant after being downstaged had a similar survival to those who initially met the criteria for a liver transplant (without having to be downstaged). This justifies our assumption that the mortality rates for a downstaged population can be assumed equivalent to a population who were not originally downstaged.

The no HCC other health state was associated with an absolute mortality rate of zero, as these patients would only have all-cause mortality and would not have the associated risks of a liver transplant long-term. Patients occupying this state do not have active disease.

Table 6-2: Absolute mortality values (per cycle)

Health State	Absolute mortality rate	Source
Watch and wait	3.88%	Assumed the same as pre-transplant
Pre-transplant	3.88%	[29, 88]
Pharmacological management	7.74%	[26]
Post-transplant 1	1.39%	[90]
Post-transplant 2	1.39%	[90]
Post-transplant 3	1.39%	[90]
No HCC (post-transplant)	0.29%	[88]
Resection	1.52%	[90]
Other no HCC	0.00%	--

6.1.1.5 Remaining inputs in the TAE-Eligible economic model

See 6.1.5, 6.1.6 and 6.1.4 for resource use, costs and health-related QoL data used in the TAE-eligible economic model.

6.1.1.6 PVT subgroup

The EASL guidelines state that portal invasion is part of the classification criteria for BCLC-C patients but not A or B [91]. Therefore, it is not necessary to analyse PVT patients in the TAE-eligible model as they do not fit the patient population.

6.1.2 Overview of TAE-ineligible model

6.1.2.1 Model structure

A partitioned survival model was developed in Microsoft Excel to determine the cost-effectiveness of TheraSphere® in the treatment of unresectable HCC, over a lifetime horizon. This type of model has been used in previous NICE appraisals for HCC [26-28, 92].

This model analyses the population who are TAE-ineligible. There are three mutually exclusive health states: alive and progression-free (PF), alive and post-progression (PP) and dead (see Figure 6-2). The dead state is absorbing such that patients cannot leave it once they have entered. These health states allow the model to capture the progressive nature of HCC.

Patients remain in the PF state until either disease progression or death. The proportion of patients in each state changes over time, as determined by the treatment-dependent TTP and OS curves. The TTP curve determines the number of patients in the PF state, the OS

curve determines the number of patients in the death state and the difference between the two curves determines the number of patients in the PP state (see Figure 6-3).

Figure 6-2: TAE-ineligible model structure

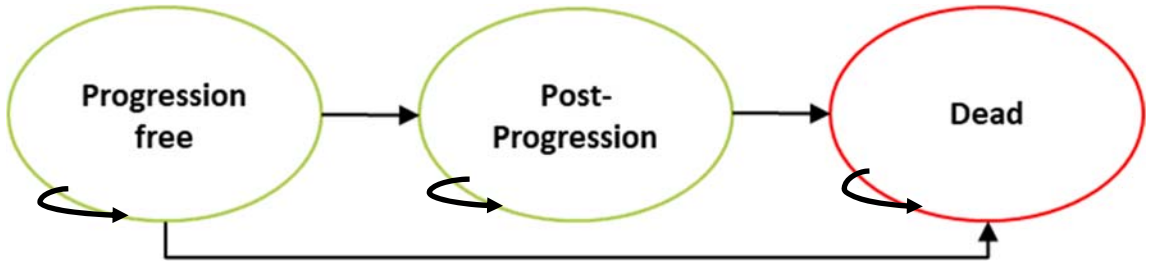
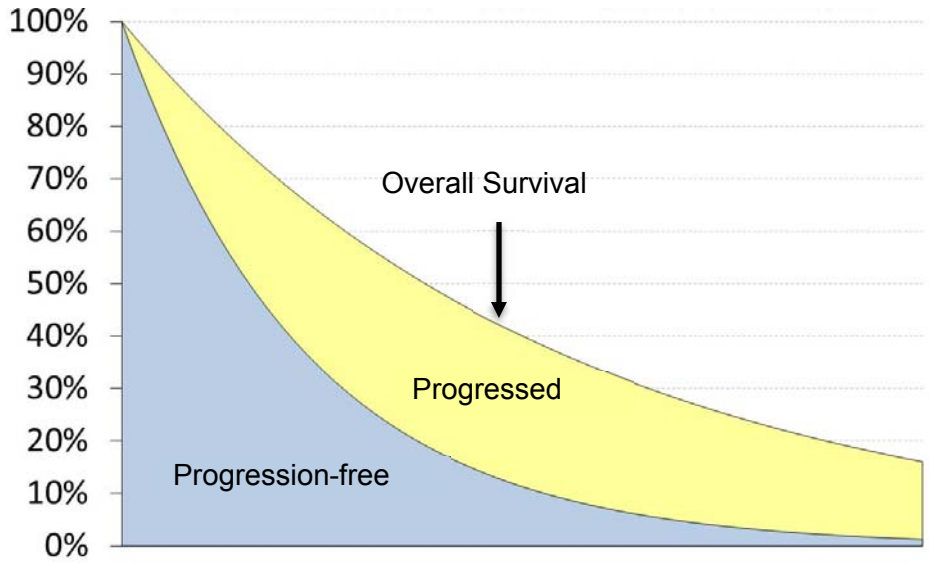


Figure 6-3: (Illustrative) OS and TTP



6.1.2.1.1 SIRT arms TheraSphere®, SIR-Spheres® and QuiremSpheres

Patients receive treatment in the first cycle of the model, whilst in the PF health state. The SIRT treatments include a work-up (described in Appendix H) and a one-time treatment cost.

SIRT patients then go on to receive further treatment from the second cycle, which may consist of systemic therapy or BSC.

6.1.2.1.2 Systemic therapy arms (sorafenib, lenvatinib, regorafenib)

Patients received the same therapy from the first cycle until disease progression (e.g. patients in the sorafenib arm continue on sorafenib and patients in the lenvatinib arm continue on lenvatinib). When the disease progresses, patients move to the PP state and stop active therapy (but continue receiving medical management and palliative care) until death.

6.1.2.2 Comparators

The comparators in this model are those described in the final NICE MTA scope (see Appendix F), whereby sorafenib, lenvatinib and regorafenib have been included as target chemotherapies, being the three recommended treatments for unresectable, advanced HCC.

6.1.2.3 State occupancy (TheraSphere®)

Individual patient-level data (IPD) was recreated from a published source [54]. The source chosen was a Phase 2 study which includes both OS and TTP data for the same patient population (patients with intermediate to advanced HCC who are not candidates for TAE, TACE or DEB-TACE due to PVT). An algorithm originally published by Guyot *et al.* (2012) [93] was implemented in the statistical package R in order to reconstruct the data. Further detail can be found in Appendix I.

6.1.2.3.1 Overall survival

The parametric overall survival curves produced in R were recreated within the economic model using the regression coefficients estimated for six parametric functions (Exponential, Weibull, gompertz, log-normal, log-logistic and generalised gamma) [94].

The resulting survival curve was then used to estimate the number of patients in the dead health state, as described previously. The distribution selected was that which was most clinically plausible, whilst also taking statistical fit into consideration. The AIC and BIC values are presented in Appendix I.

Despite log-logistic and log-normal producing the best statistical fit, a Weibull distribution was used due to being more clinically plausible. As log-logistic and log-normal curves have longer tails, they predict a greater chance of survival and a small proportion of patients will never die in the model which is implausible. This is shown in Figure I1 in Appendix I. Additionally, there was little difference between the AIC and BIC values in these distributions (see Table I1 in Appendix I).

6.1.2.3.2 Time to Progression

The parametric TTP curves produced in R were recreated using the same methods as used for the OS curves, described in 6.1.2.3.1 above. The resulting survival curve was then used to estimate the number of patients in the PF state, with the difference between the TTP and OS curves determining the number of patients in the PP state.

The AIC and BIC values for the fitted parametric functions are presented in Appendix I. The exponential distribution was selected for the TTP curves. Although not the statistically best fit, this was found to be more clinically plausible than the log-logistic, log normal and generalised gamma extrapolations. This is shown in Figure I2 in Appendix I.

6.1.2.3.3 Quantifying the relative efficacy of the comparators

In order to generate survival curves for the comparators, hazard ratios were applied to the baseline TheraSphere® TTP and OS parametric curves.

6.1.2.3.4 OS hazard ratios

The hazard ratios applied to the model for each comparator are summarised in Table 6-3. A NMA conducted by Precision [30] (see Appendix J for methodology) informed the values for SIR-Spheres® and sorafenib (see Table H3 in Appendix K). The values generated in the NMA and used in the economic model were those for a BCLC-C HCC population, which is a close match to the patient population in the economic model (no higher quality data was found, as is described in 4.4). As the NMA presented hazard ratios for TheraSphere®, rather than sorafenib or SIR-Spheres®, the ratios were inverted to the values shown in Table 6-3. Due to lack of data for QuiremSpheres®, the hazard ratio was assumed to be the same as that for SIR-Spheres®, due to it being a SIRT. Similarly, in the absence of specific data for lenvatinib and regorafenib, the hazard ratios have been assumed to be equivalent to sorafenib, on the basis that all are VEGF-TKIs. It should be borne in mind, however, that specific studies in this patient group are currently lacking, so any conclusions should be regarded as exploratory.

Table 6-3: Hazard ratios

Comparators	OS	Source
SIR-Spheres®	1.72	NMA [30]
QuiremSpheres®	1.72	Assumption
Sorafenib	1.59	NMA [30]
Lenvatinib	1.59	Assumption
Regorafenib	1.59	Assumption

6.1.2.3.5 Time to progression hazard ratios

As highlighted in Section 4.5 no data has been found in an NMA for TTP hazard ratios. In absence of any TTP relative efficacy estimates, a simple heuristic was used to link TheraSphere® and all comparators. It was assumed that the proportional hazard assumption held, and that TTP for all interventions would follow an exponential distribution. To calculate hazard ratios, median TTP estimates were sourced from the literature. The sources can be found in Appendix L. When more than one value was found, a weighted average was calculated. Due to the lack of data for QuiremSpheres®, the value has been assumed equivalent to SIR-Spheres®. From the average median TTP estimates, the 4-weekly constant hazard rates were calculated to produce a rate per cycle. Indicative hazard ratios were then generated (see Table 6-4).

Table 6-4: Derivation of TTP Hazard ratios

Comparators	Median TTP	Hazard rate	Hazard ratio	Source
TheraSphere®	11 months	0.06	N/A	[54]
SIR-Spheres®	3 months	0.23	3.67	Calculated
QuiremSpheres®	3 months	0.23	3.67	Assumption

Sorafenib	3.89 months	0.18	2.83	Calculated
Lenvatinib	8.9 months	0.08	1.24	Calculated
Regorafenib	3.2 months	0.22	3.44	Calculated

6.1.2.4 PVT subgroup

A subgroup analysis of the TAE-ineligible PVT subgroup was not undertaken because the ICERs are unlikely to be substantially different from the ICERs in the TAE-ineligible model.

First, based on our understanding of the care pathways, relative treatment costs should be unaffected by the presence or absence of PVT (although total costs could differ). Second, the evidence reviewed above suggests that relative treatment effects on OS and PFS may be largely independent of PVT involvement:

- The OS hazard ratio on the TAE-ineligible model (1.72, Table 6.3) is similar to OS hazard ratios reported in the PVT subpopulation. Specifically, OS hazard ratios for TheraSphere® vs SIR-Spheres® in patients with lobar PVT are 2.1 ([95% CI 1.1 to 4.3], p=0.027) and 2.7 in patients with main PVT ([95% CI 1.1 to 6.4], p=0.024) (Biederman *et al.* 2016) [27].
- PVT status appears to not impact OS among patients treated with TheraSphere® (Salem *et al.* [55])
- PVT did not significantly impact OS in cohorts of mixed HCC patients by Hilgard (n=108, p=0.96) [51] and Mazzaferro *et al.* (n=52, p=not reported) [54].
- The NMA comparing TheraSphere® with sorafenib in non-Asian patients found that "portal vein thrombosis (PVT) did not substantially change the estimates of the relative treatment effect" [54]. As part of the meta-analysis of the impact of treatment on OS, a meta-regression was undertaken to explore how the relative treatment effects varied by key subgroups, including PVT [30]. Relative to TheraSphere®, the hazard ratios for SIR-Spheres®, sorafenib and no treatment were very similar in the core analysis, patients with BCLC-C HCC and those with PVT (values reported in Table K3, Appendix K). While no formal test of statistical significance was undertaken, there is a large overlap in all credible intervals regardless of whether a fixed or random effect model is used. Hence, this study is strongly supportive of the statement that PVT is not a treatment effect modifier.
- One of the findings of the SARAH study was that location of portal vein invasion (main vein or other) was also not a treatment effect modifier [95].
- A Phase III RCT studying sorafenib in non-Asian patients also showed no difference in OS in patients with and without PVT [96].

We are unaware of any studies comparing TheraSphere® with lenvatinib, regorafenib or QuiremSpheres® in the PVT subpopulation.

It is noted that there is some clinical opinion that TheraSphere® may be relatively better at treating PVT patients. Secondly, a paper has shown TheraSphere® to be effective in PVT patients (though only 30 patients were enrolled in this study) [59]. However, higher quality

evidence (in the studies mentioned above) suggests PVT is likely to be neither a baseline risk nor treatment effect modifier once other clinical variables are accounted for. Therefore, we have not presented results in this submission. However, results of any subgroup analysis of PVT patients would be expected to show equivalent if not superior cost-effectiveness of TheraSphere® compared to the base case, based on the evidence summarised above.

6.1.3 Treatment-related adverse events (both patient populations)

Grade 3 and 4 treatment related adverse events (TRAEs) are included in both models to represent those events that are likely to have a substantial negative effect on QoL. For SIRT, the adverse event data were sourced from a systematic review comparing TheraSphere® and SIR-Spheres® adverse events, as described in 5.3.3 [31], with event rates for QuiremSpheres® assumed to be the same as SIR-Spheres® due to lack of published data. In line with multiple previous submissions to NICE, we have only included severe TRAEs that occurred in more than 5% of patients in at least one arm where two intervention's rates come from one source into the model(s).

The relevant TRAEs and corresponding rates arising from systemic therapies were informed by the NICE submissions for both lenvatinib (TA551 [27]) and regorafenib (TA555 [28]), and so have previously been validated.

Rates of TRAEs for cTACE and DEB-TACE were sourced from an RCT of DEB-TACE versus cTACE in HCC [97]. This RCT is not described in the clinical section of the dossier as it does not compare with TheraSphere®. However, when compared to the studies described in 5.3.2, as an RCT it contains higher quality data and, therefore, has been used in the economic model. Adverse event rates for bland embolisation have been sourced from a further RCT of TACE versus TAE for HCC patients [98].

Table 6-5: Adverse event rates (grade 3/4) used in both models

Adverse Events	TheraSphere® [31]	SIR-Spheres® [31]	Quirem Spheres® (assumed)**	Sorafenib [27]	Lenvatinib [27]	Regorafenib [28]	cTACE [97]	DEB-TACE [97]	Bland embolisation [98]
Aspartate aminotransferase increase	0.0%*	0.0%*	0.0%	8.0%	5.0%	16.0%	0.0%*	0.0%*	0.0%
Proteinuria	0.0%*	0.0%*	0.0%	1.7%	5.7%	0.0%	0.0%*	0.0%*	0.0%
Blood bilirubin increase	0.0%*	0.0%*	0.0%	4.8%	6.5%	11.0%	0.0%*	0.0%*	16.0%
Diarrhoea	0.0%*	0.0%*	0.0%	4.2%	4.2%	0.0%	0.0%*	0.0%*	0.0%
Fatigue	1.9%	2.3%	2.3%	3.6%	3.8%	8.0%	0.0%	0.0%	8.0%
Gamma-glutamyl transferase increase	0.0%*	0.0%*	0.0%	4.0%	5.5%	0.0%	0.0%*	0.0%*	26.0%
Hypertension	0.0%*	0.0%*	0.0%	14.3%	23.3%	25.0%	0.0%*	0.0%*	0.0%
Weight decrease	0.0%*	0.0%*	0.0%	2.9%	7.6%	0.0%	0.0%*	0.0%*	0.0%
Platelet count decrease	0.0%*	0.0%*	0.0%	3.4%	5.5%	0.0%	0.0%*	0.0%*	0.0%
Palmar-plantar erythrodysesthesia syndrome	0.0%*	0.0%*	0.0%	11.4%	2.9%	16.0%	0.0%*	0.0%*	0.0%
Ascites	6.1%	2.3%	2.3%	0.0%*	0.0%*	5.0%	0.0%*	0.0%*	0.0%
Cholecystitis	1.9%	5.0%	5.0%	0.0%*	0.0%*	0.0%*	0.0%	1.1%	0.0%
Hepatic encephalopathy	2.8%	8.0%	8.0%	0.0%*	0.0%*	0.0%*	0.0%*	0.0%*	0.0%
Post-procedural pain	1.9%	1.2%	1.2%	0.0%*	0.0%*	0.0%*	18.2%	0.0%*	21.0%

*These adverse events were not specifically recorded in the papers and, therefore, 0% is assumed.

**Due to lack of data, adverse event rates for QuiremSpheres® have been assumed the same as SIR-Sphere

6.1.4 Health-related quality of life

6.1.4.1 Population norms

Gender adjusted norms from Kind *et al.* [99] were applied to the model. These allow for the utility values at cycle 0 of the model to match the utilities of the age of the population entering the model (assuming a common starting age (65 years) for both the TAE-eligible and TAE-ineligible models). Decrements were then subtracted from this value to obtain the utility values for each health state at each cycle, as explained in the sections below.

6.1.4.2 TAE-eligible

Utility decrements were assigned to each health state within the model. For each cycle in the relevant health state, the baseline utility value for each health state was calculated by subtracting the decrement from the age and gender adjusted norms from Kind *et al.* [99].

The absolute utility values and decrements are presented in Table 6-6. The absolute values for all states, with the exception of the post-transplant tunnel states and the no HCC other health state, were assumed to be the same as that for pre-progressed HCC as informed by the NICE lenvatinib submission [27]. This assumption has been validated by expert opinion. There are alternative utility values available for pre- and post-liver transplant (0.53 for patients on the waiting list, 0.62 for patients three months post-transplant and 0.73 at one-year post-transplant - Ratcliffe *et al.* [100]), however, as these values are taken from a population mainly made up of patients with alcoholic liver disease they do not closely match our patient population. Secondly, as the TAE-ineligible model uses the lenvatinib pre-progressed HCC utility value for the pre-progressed health state (where the patients are likely in a more advanced state of disease), it would appear inconsistent to use lower utility values for the TAE-eligible model. However, the Ratcliffe *et al.* utility values will be run through a scenario analysis (see 6.1.7.26.2.3) to see the impact on the model.

The utility applied to the pharmacological management state is calculated by taking an average of the pre-progressed and progressed HCC health states from the NICE lenvatinib submission [27], due to this state being made up of 50% pre-progressed and 50% progressed HCC patients.

Table 6-6: Utility values used in the TAE-eligible model

Health State	Absolute Utility	Source	Utility decrement
Watch & wait	0.75	Assumption from [27]	0.25
Pre-transplant	0.75	Assumption from [27]	0.25
Post-transplant 1	0.69	[101]	0.31
Post-transplant 2	0.69	[101]	0.31
Post-transplant 3	0.69	[101]	0.31
No HCC post-transplant	0.75	Assumption from [27]	0.25
Resection	0.75	Assumption from [27]	0.25
No HCC other	Population norm	[99]	0.00
Pharmacological management	0.72	Calculated from [27]	0.29

*The ‘no HCC other’ health state matches the general population norms

6.1.4.3 TAE-ineligible

Utility decrements were assigned to each health state within the model. These were derived from the absolute utility values used for the PF and PP health states in the lenvatinib NICE submission model [27] (by subtracting them from one) and are presented in Table 6-7. For each cycle in the relevant health state, the baseline utility value was calculated as stated above.

The small difference between the two health state utilities is said to reflect the data produced from the REFLECT trial in the lenvatinib submission [27]. The values are not dissimilar to values used in the regorafenib and sorafenib NICE submissions [26, 28]. However, it is likely that the utility values applied to the model may not accurately reflect the HRQoL during the progressed health state (in particular towards the end of life). Therefore, alternative utilities were explored in a scenario analysis (see 6.1.7.2).

Table 6-7: Utility values used in the TAE-ineligible sub-model

	Absolute utility	Source	Utility decrement
Progression-free	0.75	Lenvatinib NICE submission [27]	0.26
Progressed	0.68	Lenvatinib NICE submission [27]	0.32

As per previous oncology submissions, one assumed utility decrement of 0.014 was associated with each adverse event which was incorporated in to the first cycle only.

6.1.5 Resource use

6.1.5.1 Treatments

The average number of SIRT treatments per patient was clinically-informed for TheraSphere® and assumed to be the equal for the other SIRTs. Each patient in the model has an average of 1.2 SIRT treatments which is applied to the first cycle only, with one work-up (assessment) per patient. An assumption has been made that only patients who are eligible for SIRT enter the model. The number of SIRT treatments has been clinically validated for a UK population. Despite published papers showing a higher average number of SIRT treatments, these do not come from a UK population [55]. Details of the work-up can be found in Appendix H.

In the TAE-eligible model, every patient in the cTACE and bland embolisation arms have three initial treatments in their respective arms, applied to the first cycle of the model, whilst patients in the DEB-TACE arm have 1.5. In practice, repeat procedures may be spread over multiple cycles, however, a simplifying assumption has been made that all are applied to the first cycle of the model. The number of treatments, and the number of vials per treatment, was informed by clinician input.

The dosing for systemic therapy (sorafenib, lenvatinib and regorafenib) were based on recommended doses for HCC patients, from their respective Summary of Product Characteristics (SmPC) [102-104], and are summarised in Appendix M.

In the TAE-ineligible population, after the initial SIRT treatment (TheraSphere®, SIR-Spheres® or QuiremSpheres®), patients in the SIRT arms are assumed to proceed to start systemic therapy or BSC. The proportion of patients moving on to each therapy is presented in Table 6-8. Due to absence of data, these are based on assumptions. It is assumed that the majority of individuals will continue on systemic therapy to maximise PFS. A proportion of patients may decide they wish to have no further treatment or are ineligible for systemic therapies.

In the TAE-eligible population, when patients move into the pharmacological management health state, they receive the same treatments as shown in Table 6-8. However, as they stay in this state until death, at any given point in time, the health state includes individuals who could be classified as either pre- or post-progressed. In absence of data it was assumed, for simplicity, that the distribution of patients across these two categories is constant and equal (i.e. 50% in each). Therefore, more patients in this health state will be on BSC, as patients in a progressed state would come off of active treatment [91].

Table 6-8: Proportion of patients on each treatment after SIRT treatment (TAE-ineligible population) or in the pharmacological health state (TAE-eligible population)

Treatment	TAE-ineligible population	TAE-eligible population
Sorafenib	33%	16.5%
Lenvatinib	0%	0%
Regorafenib	0%	0%
Best supportive care	67%	83.5%

6.1.5.2 Drug administration

Following recommendations from the NICE submission for lenvatinib, systemic treatment should be initiated and supervised by a health care professional [27]. This was assumed to occur in an outpatient setting and is captured in the resource use described in 6.1.5.3. Administration involved in SIRT therapy is captured in the work up assessment (see Appendix H) and the HRG code for the embolisation procedure (see Appendix N).

6.1.5.3 Health state resources

6.1.5.3.1 TAE-eligible model

Due to an absence of evidence from published literature for resource use for the TAE-eligible health states, expert opinion was sought from clinicians at the Christie Hospital, Manchester. These are presented in Appendix M. The frequency of resource use in the pharmacological management health state was assumed the same as the weighted average of the pre- and post- progressed

6.1.5.3.2 TAE-ineligible model

In the absence of evidence from published literature for TheraSphere®, estimates of resource use the PF and PP health states in the TAE-ineligible model were based on a resource use survey commissioned by the manufacturer of sorafenib, presented in TA189 [92]. The costs were updated in TA474 [26] (the 2016 reconsideration of sorafenib), however, resource use was not provided directly in the new submission. Due to the substantial cost differences between the two surveys and without being able to compare resources, new unit costs taken from published, national sources were applied to the presented resource use estimates for the original survey only. Appendix M presents the resources used in the model and the proportion of patients they were applied to.

6.1.6 Costs

6.1.6.1 Summary of unit costs

A summary of unit costs contained in both models are presented in Appendix N. The SIRT work-up cost was informed by a micro-costing conducted by Christie Hospital (see Appendix H).

6.1.6.2 Pre-treatment assessment and procedure costs

Patients undergoing SIRT treatment have a series of assessment tests (a work-up) before the procedure in an outpatient appointment. This is a one-off cost applied to the first cycle of each model. The one-off costs for TACE and bland embolisation are presented in Table 6-9 and are applied to the first cycle of the TAE-eligible model.

No procedure costs were associated with the systemic therapies in the TAE-ineligible model due to being oral drugs.

The TAE-eligible model also includes liver transplant and liver resection procedures. These costs are presented in Table 6-9. The cost of transplant work-up is applied as a one-off cost, to patients entering the pre-transplant state. The cost of the transplant is applied to the first post-transplant tunnel state, which patients occupy for only one cycle. This ensures that patients who die on the wait-list accrue the cost of work-up but not the procedural cost.

The cost of resection is applied to every patient who moves into the resection state. The patient stays in this state for only one cycle.

Table 6-9: Summary of procedure costs used in the model

Procedure	Cost
cTACE plus procedure (average 3 procedures)	£9,120
DEB-TACE plus procedure (average 1.5 procedures)	£5,174
Bland beads plus procedure (average 3 procedures)	£8,730
SIRT (work up and procedure) (average 1.2 procedures, 1 work up)	£13,583
Liver transplant procedure and work up	£17,340

Resection procedure	£4,994

6.1.6.3 Administration cycle costs

Systemic treatment should be initiated and supervised by a health care professional [27]. This was assumed to occur in an outpatient setting and these costs are captured in the health state costs. After initiation it was assumed that lenvatinib, sorafenib and regorafenib would not be associated with administration costs and that patients would orally self-administer all products.

The SIRT administration costs are captured in the assessment and procedure costs for SIRT and are applied to the first cycle only.

The administration costs for cTACE, DEB-TACE and bland bead treatments are captured in the procedure cost described above (HRG code YR57Z).

6.1.6.4 Heath state cycle costs

The health state cycle costs for the TAE-eligible and TAE-ineligible model are summarised in Table 6-10 and Table 6-11. Please see Appendix N for broken down costs and Appendix N for resource use.

Table 6-10: Health state cycle costs TAE-eligible population

Item	SIRT
Total watch and wait	£539.16
Total pre-transplant	£577.42
Total post-transplant 0-1	£971.71
Total post-transplant 1-2	£1049.22
Total post-transplant 2-3	£516.42
No HCC post-transplant	£502.49
Resection	£345.07
No HCC other	£306.50
Pharmacological management	£1308.57

Table 6-11: Health state cycle costs TAE-ineligible population

Item	Cost per cycle progression free	Cost per cycle progressed
Physician visits	£222.54	£257.17
Laboratory tests	£58.61	£13.00
Radiological tests	£35.53	£46.13
Hospitalisation	£130.99	£341.70
Hospital follow-ups	£179.63	£341.40
Total cycle costs	**£627.31**	**£999.40**

6.1.6.5 Treatment-related adverse event cycle costs

The weighted average cost of adverse events was applied to the first cycle only and is presented for each treatment in Table 6-12.

Table 6-12: Treatment-related adverse event costs

Treatment	Total adverse event cost
TheraSphere®	£88.65
SIR-Spheres®	£111.33
QuiremSpheres®	£111.33
cTACE	£112.07
DEB-TACE	£5.59
TAE	£483.88
Sorafenib	£384.15
Lenvatinib	£502.93
Regorafenib	£559.69

6.1.6.6 Additional costs

Additional costs considered in the analysis included those for end of life care and one-off post progression costs.

The one-off progression costs for individuals in the TAE-ineligible model were sourced from the regorafenib NICE submission [28], originally coming from the sorafenib physician survey, which was directly transferable to regorafenib. In the model, all patients, after initial treatment of SIRT, are moved on to a weighted average cost of the systemic therapies or BSC. For the systemic therapies, patients remain on the same intervention until disease progression. It was assumed that the same one-off post-progression cost can be applied to all interventions at the point of progression.

Table 6-13: One-off post progression costs

Item	Mean cycle cost	Source
Laboratory tests	£82.86	Regorafenib NICE submission [28]
Radiological tests	£12.46	
Total	**£95.32**	

The cost for end of life care was taken from a 2014 report which estimated costs in the last 3 months of life with a cancer diagnosis. The total figure was inflated from 2010/11 to 2017/18 prices using the inflation factors from the HCHS Pay and Prices Index [105]. This produced a figure of £8,191. This cost was applied to patient deaths in both models.

6.1.7 Sensitivity analysis

6.1.7.1 Probabilistic sensitivity analysis (PSA)

PSA was performed to account for multivariate and stochastic uncertainty in the model. A PSA was undertaken with 1,000 model simulations. See Table 6-14 for a summary of distributions used in the models. Probability distributions were based on sampling error estimates from data sources, such as confidence intervals. In the absence of data on the variability around the sampling distribution of mean values, the standard error was assumed equal to 10% of the mean.

Table 6-14: PSA summary of distributions used in both the TAE-eligible and TAE-ineligible model

Parameter group	Distribution	Source
Costs	Gamma	[106]
Resource use	Beta	
Absolute utilities	Beta	
Transition probabilities	Dirichlet	
Relative risk	Lognormal	

6.1.7.2 Scenarios

TAE-eligible model

The following scenarios were explored to observe the effect on the cost-effectiveness of TheraSphere®:

1. 50% discount on TheraSphere® cost
2. TheraSphere® treatment free when more than one treatment needed
3. 50% of downstaged patients transition to resection rather than transplant
4. Removal of SIRT work-up costs
5. Alternative utility values
6. Alternate downstaging rates for SIRT
7. Alternate post-transplant mortality rates

TAE-ineligible model

The following scenarios were explored to observe the effect on the cost-effectiveness of TheraSphere®:

1. 50% discount on TheraSphere®
2. TheraSphere® treatment free when more than one treatment needed
3. Sorafenib not offered as a second-line treatment (replaced by BSC)
4. Alternative utility values for progressed HCC
5. Altering the OS HR by 50%
6. HR including Asian studies
7. Removal of SIRT work-up costs

6.2 COST-EFFECTIVENESS MODEL RESULTS

6.2.1 Base case results (TAE-Eligible)

Table 6-15 presents the raw, unranked model outputs. Table 6-16 presents the model outputs ranked by cost outputs. All three SIRTs and DEB-TACE are the only treatments on the frontier (Figure 6-4), with the remaining treatments being extended dominated (cTACE and bland embolisation). The ICER for TheraSphere® compared to the next treatment on the frontier is approximately £24,600 per QALY gained.

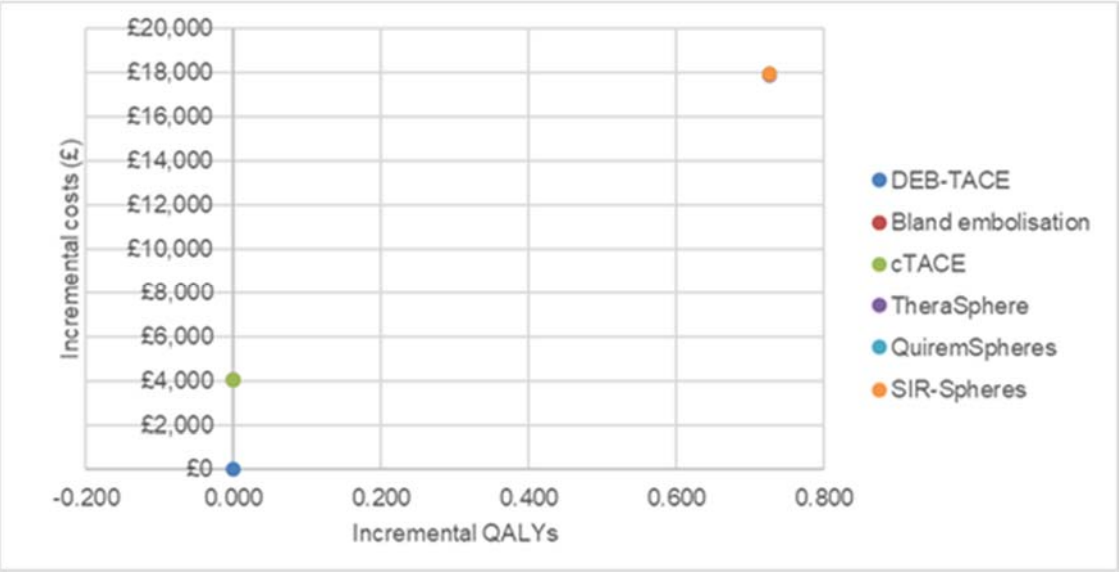
Table 6-15: TAE-eligible – Raw model outputs (unranked)

Treatment	Costs	QALYs
TheraSphere®	£57,338	2.119
QuiremSpheres®	£57,361	2.119
SIR-Spheres®	£57,361	2.119
cTACE	£43,488	1.393
DEB-TACE	£39,435	1.393
Bland embolisation	£43,470	1.392

Table 6-16: TAE-eligible – Results ranked by incremental cost model outputs

Treatment	Δ Costs	Δ QALYs	ICER
SIR-Spheres®	£17,925	0.726	£24,647
QuiremSpheres®	£17,925	0.726	£24,647
TheraSphere®	£17,903	0.726	£24,647
cTACE	£4,053	0.000	Dominated
Bland embolisation	£4,035	-0.001	Dominated
DEB-TACE	£0	0.000	Referent

Figure 6-4: TAE-eligible – Cost-effectiveness frontier



Note: TheraSphere®, QuiremSpheres® and SIR-Spheres® are all equivalent and overlap on the frontier. cTACE and DEB-TACE also overlap.

6.2.2 Base case results (TAE-Ineligible)

Table 6-17 presents the raw, unranked model outputs.
Table 6-18 presents the results ranked by cost outputs. TheraSphere® and regorafenib are the only treatments on the frontier.), with the remaining treatments being dominated (Lenvatinib, SIR-Spheres® and QuiremSpheres®) or extended dominated (sorafenib). The ICER for TheraSphere® compared to the next treatment on the frontier is approximately £64,700 per QALY gained.

As can be seen from Table 6-17 below, the median life expectancy in the absence of TheraSphere® is approximately 1 year. In the presence of TheraSphere® this increases to 1.44 years; a gain of approximately 6 months of OS. As noted earlier in this dossier, the number of English patients with HCC at any time is 4,925, of which 36% are "advanced" and hence assumed to be no longer eligible for TAE. Hence, the size of the England/ Wales TAE-eligible population is 1,773 individuals.

Overall, these results indicate that the NICE end of life criteria should be applied when assessing the cost-effectiveness of TheraSphere® in this patient population. TheraSphere® is over the end of life cost-effectiveness threshold (£50,000 per QALY gained).

Table 6-17: TAE-ineligible – Raw model outputs (unranked)

Treatment	Costs	QALYs	LYG (undisc)
TheraSphere®	£50,921	0.715	1.443
QuiremSpheres®	£38,205	0.489	1.036
SIR-Spheres®	£38,205	0.489	1.036
Sorafenib	£39,823	0.518	1.09
Lenvatinib	£63,085	0.548	1.09
Regorafenib	£37,885	0.514	1.09

Table 6-18: TAE-ineligible – Results ranked by incremental cost model outputs

Treatment	Δ Costs	Δ QALYs	ICER
Lenvatinib	£25,201	0.034	Dominated
TheraSphere®	£13,037	0.202	£64,693
Sorafenib	£1,938	0.005	Ext dominated
QuiremSpheres®	£320	-0.024	Dominated
SIR-Spheres®	£320	-0.024	Dominated
Regorafenib	£0	0.000	Referent

Figure 6-5: TAE-ineligible - Cost-effectiveness frontier

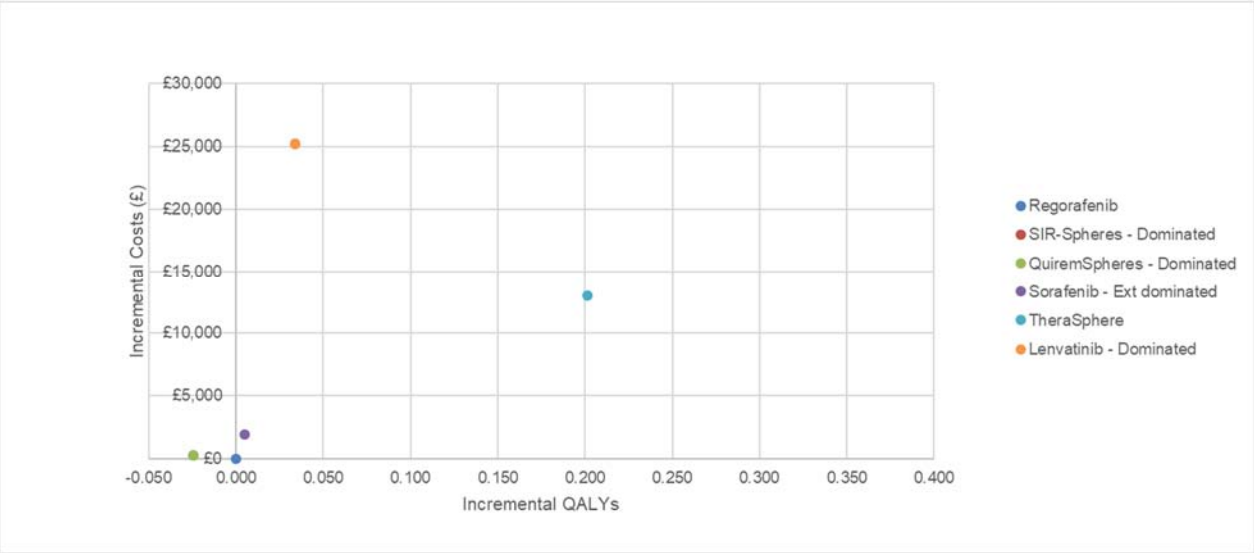


Table 6-19 presents a breakdown of costs. Both lenvatinib and TheraSphere® have higher resource and treatment costs in the PF state than PD state.

Table 6-19: Cost-breakdown by intervention

Intervention	Pre-progressed	Progressed	Treatment pre-progression	Treatment progressed	One-off progression costs
TheraSphere®	£9,215	£3,459	£30,319	£0	£52
QuiremSpheres®	£3,081	£8,250	£18,786	£0	£81
SIR-Spheres®	£3,081	£8,250	£18,786	£0	£81
Sorafenib	£3,814	£7,739	£19,928	£0	£77
Lenvatinib	£7,370	£2,073	£45,200	£0	£59
Regorafenib	£3,245	£8,644	£17,474	£0	£80

6.2.3 Merged ICER

An ICER of £64,693 in the TAE-ineligible population and an ICER of £24,647 in the TAE-eligible population is presented above. Based on the patient pathways in HCC in the UK, 15% of patients are treated as intermediate stage patients and 36% are treated as advanced HCC patients [107]. Therefore, 70.6% of the total patients in both models enter the TAE-ineligible model, and 29.3% of patients enter the TAE-eligible model. This gives a weighted average ICER of £52,894.

6.2.4 PSA results

The results for the PSA analysis are displayed in Appendix O.

6.2.5 Scenarios

The results to the scenarios described in 6.1.7.2 are displayed in Appendix P and Q. These are summarised in.Table 6-20: Results of scenario analyses

Table 6-20: Results of scenario analyses

Scenario	ICER
TAE-eligible scenarios (base case ICER = £24,647)	
50% discount on TheraSphere®	£18,039
TheraSphere® treatment free when more than one treatment needed	£21,676
50% of downstaged patients transition to resection rather than transplant	£31,112
Removal of SIRT work-up costs	£23,773
Alternative utility values	£25,003
Alternate downstaging rates for SIRT (relative efficacy of SIRT decreased vs. TACE/bland embolisation)	£38,203
Alternate downstaging rates for SIRT (relative efficacy of SIRT increased vs. TACE/bland embolisation)	£20,561
Alternate post-transplant mortality rates (increased)	£26,744
TAE-ineligible scenarios (base case ICER = £64,693)	
50% discount on TheraSphere® cost	£40,873
Sorafenib not offered as a second-line treatment (replaced by BSC)	£5,288
TheraSphere® treatment free when more than one treatment needed	£56,753
Alternative utility values	£47,832
Altering the OS HR by 50% (increase by 50%)	£52,197
Altering the OS HR by 50% (decrease by 50%)	Dominated
HR including Asian studies	£57,702
Removal of SIRT work-up costs	£62,370

Section 7: Summary and Conclusions

7.1 DISEASE BACKGROUND AND MANAGEMENT OPTIONS

HCC is a heterogeneous cancer with complex aetiology. HCC is primarily a disease of older people, therefore HCC is often accompanied by co-morbidities together with the causal underlying liver disease. These factors make the treatment of HCC uniquely challenging amongst cancers (Villaneuva *et al.* 2008, Vogel *et al*, 2019) [22, 23].

The aim of treatment in HCC is to increase survival while maintaining QoL. There are a number of potentially useful treatment options which are broadly divided into curative treatment for early stage disease (surgical liver resection, liver transplantation and local destructive methods such as radiofrequency ablation or microwave ablation) and palliative treatment for later stage disease (interventional procedures such as SIRT, TAE, TACE/DEB-TACE and systemic chemotherapy such as sorafenib) [23].

Treatment for HCC should be individualised to each patient to ensure optimal outcomes. Careful selection of candidates for each treatment option and the expert application of these treatments is essential (Forner *et al.* 2018) [21].
Over the last 15 years, numerous prospective and retrospective studies using TheraSphere® to treat HCC have been published, establishing a broad body of evidence in which to place TheraSphere® within the treatment pathway.

7.2 CLINICAL EFFECTIVENESS FOR THERASPHERE®

Comparative evidence is available for TheraSphere® vs. SIR-Spheres® (three studies and one network meta-analysis [NMA]), TACE (13 studies including three with DEB-DOX and two which also included DEB-DOX) and sorafenib (one NMA). There is no comparative evidence against QuiremSpheres® or bland TAE.

Non-comparative evidence provides supportive evidence of the value of TheraSphere® in later stage disease when used as a palliative treatment and in early stage disease (including radiation lobectomy, downstaging disease and use as locoregional tumour control in patients on the transplant list).

It is challenging to compare data across studies due to differences in study design and reporting (patient populations, reporting styles e.g. by BCLC type or PVT status, prior and subsequent treatment, concomitant treatment, dosing).

7.2.1 Later Stage HCC

Comparative studies of TheraSphere® vs. SIR-Spheres® reveal that outcomes are improved with TheraSphere® or comparable to those with SIR-Spheres® in later stage disease. In an NMA comparing TheraSphere® and SIR-Spheres®, TheraSphere® was non-inferior to SIR-

Spheres® with [redacted]-year survival of approximately [redacted] vs. [redacted]. Patients with PVT have improved outcomes with TheraSphere® vs. SIR-Spheres. This may be in part due to the physical, radioactivity and embolic differences which hinder the effective treatment of PVT patients with SIR-Spheres®. TheraSphere® is an effective alternative treatment to SIR-Spheres®, particularly in patients with PVT. There are no comparative studies of TheraSphere® vs. QuiremSpheres.

Comparative studies vs. TACE demonstrate broadly improved or comparable outcomes with TheraSphere®. DEB-TACE has shown improved outcomes (OS and PFS) against TheraSphere® in one study, although DEB-TACE in patients with PVT had comparable results to TheraSphere®. TheraSphere® is an effective alternative treatment to TACE, particularly in patients with PVT for whom TACE is unsuitable, patients unable to tolerate TACe, those who have failed previous TACE or whose vasculature has changed as a result of prior treatments and are now unsuitable for TACE.

There are no head-to-head studies comparing TheraSphere® vs. sorafenib, however an NMA intended to demonstrate non-inferiority, showed TheraSphere® was a non-inferior treatment to sorafenib for OS. Approximate survival at [redacted] years was [redacted] with TheraSphere® and [redacted] with sorafenib. There is no comparable data for PFS or response vs sorafenib. TheraSphere® has the added benefits that it does not have dose-limiting systemic side effects, does not require lifetime twice daily dosing (sorafenib Package Insert 2017) [103] and does not induce treatment resistance seen with sorafenib (Mendez-Blanco *et al.* 2018) [108].

Non-comparative evidence suggests that TheraSphere® is an effective locoregional therapy for palliative care in later stage disease. Across nine cohort studies, median OS ranged from 12.3 to 22.1 months. In patients with PVT, median OS was shorter (3.2 months to 14.3 months) and main PVT had poorer outcomes than other PVT locations.

PVT is relatively common in HCC [109], around 10% to 40% of HCC patients have PVT at diagnosis rising to 35% to 44% at the time of death. PVT is a negative prognostic factor and patients with PVT are more likely to have metastatic disease at diagnosis, have fewer therapeutic options and have shortened OS compared to patients without PVT. In patients with PVT treated with supportive care, studies have reported OS ranging from 2 to 4 months, compared to 10 to 24 months in HCC patients without PVT. Thrombus involving the main portal vein is a worse prognostic factor than thrombus involving a branch portal vein. There is evidence that TheraSphere® is an effective treatment option in this patient group.

7.2.2 Early Stage HCC

In early stage disease TheraSphere® can be used as a potentially curative treatment in patients with small tumours not suitable for other curative treatments (radiation segmentectomy), used as lobar treatment for patients who have insufficient remaining normal tissue to undergo other curative treatments (radiation lobectomy), used to

downstage disease in order that patients can undergo resection or ablation or used as locoregional tumour control in patients on the transplant list.
There are no comparative studies of TheraSphere® vs. the other SIRT products in early disease. However, four studies compared TheraSphere® with TACE in earlier stage disease and demonstrated longer time to progression with TheraSphere® and comparable results in terms of OS and response rate. The delay in disease progression with TheraSphere® may offer an advantage in patients awaiting transplant. Being treated with TheraSphere® could increase a patient's chance of staying on the waiting list for a transplant while decreasing the chance of progression - and follows current NHS transplant guidelines to consider locoregional therapy in all transplant list patients.

A retrospective cohort study by Lewandowski *et al.* (2018) [62] in 70 patients with preserved liver function and single tumours ≤5 cm achieved median OS of 6.7 years with TheraSphere® radiation segmentectomy. This is comparable to outcomes reported with other curative treatments. A similar study by Vouche *et al.* (2014) [64] in 102 patients with single tumours (median 3 cm) and not amenable to resection or ablation, achieved median OS of 4.5 years with TheraSphere® radiation segmentectomy. One-third of patients went onto receive a liver transplant. Two other studies provide additional supportive evidence.

For some patients, liver resection may not be a curative option due to insufficient remaining normal functioning liver post resection or 'future liver remnant' (FLR). For patients with inadequate FLR, unilobar disease and with otherwise good liver function TheraSphere® administered to the diseased lobe can cause hypertrophy in the contralateral lobe (radiation lobectomy). This volumetric increase in normal parenchyma makes curative resection an option in some patients. Radiation lobectomy offers the advantage over other treatments used to effect hypertrophy (e.g. portal vein embolisation) of not only increasing normal tissue volume but simultaneously treating tumours locally. Three studies provide evidence for TheraSphere® as radiation lobectomy, with mean OS of 31 months in one study, median OS of 36.6 months in another and median OS had not yet been reached in the other. The studies reviewed demonstrated hypertrophy in a vast majority of patients with increases of up to 105% noted in these patients. Overall tumour response in patients who received a radiation lobectomy with TheraSphere® was high, ranging from 94% to 95% with EASL criteria and 65% with WHO criteria.

Six cohort studies assessed TheraSphere® for downstaging disease and/or locoregional control to maintain patient's status on the transplant list. Survival varied from around 2 to 4 years pre-transplant depending on the study with longer survival post-transplant. When TheraSphere® was specifically used for downstaging to curative intent, downstaging was achieved in 33% to 66% of patients across three cohort studies. Using TheraSphere® treatment for bridging resulted in a high success rate, ranging from 90% to 100% across three cohort studies.

7.2.3 Health-related Quality of life

HRQoL for patients faced with a reduced survival expectancy and seeking symptomatic relief is an important consideration when choosing palliative treatment. Two comparative

studies evaluated health related quality of life (QoL) after treatment with TheraSphere® vs. TACE or systemic chemotherapy (cisplatin, now longer standard of care) in later stage HCC patients. QoL was not adversely affected after treatment with TheraSphere®. Some QoL subscales were significantly improved with TheraSphere® when compared with TACE including social and functional well-being. The study comparing TheraSphere® vs. TACE also assessed QoL parameters most relevant to patients undergoing embolisation (pain, impact of treatment side effects, ability to work, diarrhoea and good appetite) and found that QoL improved with TheraSphere® and worsened with TACE.

7.2.4 Adverse events

Overall, the clinical safety data generated from the literature, clinical studies, and post-marketing surveillance data confirms an acceptable and reproducible safety profile for TheraSphere® when used according to the manufacturer's instructions. There are no unanswered questions regarding safety and no new risks have been identified. Given the depth of existing safety information, TheraSphere® can be considered to have an acceptable safety profile.

In the clinical papers reviewed in this submission, the most frequent adverse events were flu-like symptoms such as fatigue, abdominal pain and nausea.

The lack of head-to-head evidence comparing TheraSphere® vs. SIR-Spheres® or sorafenib mean that meaningful comparisons are difficult to make. However, evidence from a RCT suggests that patients receiving TACE may be more likely to experience diarrhoea and hypoalbuminemia than those receiving TheraSphere®. It should be noted that rates of post-embolisation syndrome were significantly lower with TheraSphere® than with TACE. This is a key benefit with TheraSphere® since post-embolisation syndrome after TACE has been shown to be associated with a worse survival and a two-fold increased risk of death, even after adjusting for important confounders [81].

7.2.5 Limitations

The data are limited by the quality; most studies are retrospective or prospective cohort studies. As a result, these studies were collectively considered to present low quality evidence.

The paucity of head-to-head studies mean that it is challenging to compare TheraSphere® with other agents for HCC. We have gathered together the existing comparative and non-comparative evidence for TheraSphere®, however, it is difficult to compare data across studies due to differences in patient population, baseline disease status, concurrent/prior and subsequent treatments and outcomes measured. Our aim was to provide a comprehensive review of the evidence for TheraSphere® and present the evidence in an easy to read fashion.

We have divided the data into later stage disease and earlier stage disease, however, some of the evidence is from mixed populations. The distinction is largely arbitrary since patients

may be initially treated with curative intent but their treatment may actually be palliative and *visa versa*.

7.3 COST-EFFECTIVENESS FOR THERASPHERE®

7.3.1 TAE-eligible population (patients with earlier stage disease)

In the TAE-eligible population, TheraSphere® produces a QALY gain equivalent to other SIRT treatments and superior to cTACE, DEB-TACE and bland embolisation. The costs associated with TheraSphere® are lower than that of the other SIRTs but this difference is nominal. Thus, in this population, the three SIRT treatments carry very similar costs and benefits and share an ICER of approximately £24,600 when the price of treatment is £8,000. All other treatments are dominated.

The assumption of equivalent efficacy between SIRT treatments is a conservative one, made due to data paucity in this population. If the relative survival benefit of TheraSphere® that is seen in the TAE-ineligible population extends to this population, then the economic evaluation would find QuiremSpheres® and SIR-Spheres® to be dominated by TheraSphere®.

7.3.2 TAE-ineligible population (patients with later stage disease)

In the TAE-ineligible population, TheraSphere® was found to be the most costly treatment option as well as the most beneficial in terms of QALYs gained. The ICER for TheraSphere® is approximately £64,700/QALY, with all other treatments dominated or extended dominated. The reason why TheraSphere® appears to be more expensive than the other SIRTs in this population is partly as a result of improved efficacy which maintains patients in a pre-progressed health state for a longer period, incurring costs associated with the health state.

We believe TheraSphere® treatment meets NICE's end of life criteria (i.e. extending life expectancy compared to current therapy, in patients with a disease with a short life expectancy; and indicated for a small patient population). Firstly, as reported above, there is evidence to suggest TheraSphere® improves OS in patients with advanced stage HCC compared with some other palliative treatments. Secondly, the prognosis of HCC is poor, with median OS for patients with advanced HCC of <1 year (4 to 8 months with BSC; 6 to 11 months with sorafenib and 7.8 months with regorafenib [2, 15]). Lastly, this treatment group is indicated for a fairly small patient group. If 51% of patients are typically classified as having intermediate or advanced stage HCC [107], and 4,925 are diagnosed with the disease per year [20], approximately 2,511 patients would be indicated to receive TheraSphere®.

Notably, in a scenario where no costs of second-line treatment with sorafenib are incurred, the ICER of TheraSphere® falls to approximately £5,300/QALY. As NICE has noted in multiple appraisals, there are situations where companion products, unrelated to the

intervention being assessed, force the ICER above an acceptable value. The cost of sorafenib in pre-progressed patients is a key driver of the results.

7.4 CONCLUSIONS

Overall, the clinical effectiveness and safety evidence demonstrates that TheraSphere® is effective and safe in the treatment of earlier and later stage HCC. Although there is high variability in the results between studies, this is likely to be due to a number of confounding factors. Nevertheless, there is clear evidence to suggest that TheraSphere® can be used to make curative options available for some patients who would otherwise not have that option and has similar or better outcomes to other recommended therapies, such as TACE, in the palliative setting.

We acknowledge that the data are limited by the fact that most of the studies are retrospective or prospective cohort studies. As a result, these studies were collectively considered to present low quality evidence. Despite these limitations, the extensive body of studies and consistent results supporting the use of TheraSphere® in the palliative and curative intent settings, provides evidence that TheraSphere® can be used as an alternative to well accepted therapies included in staging algorithms.

TheraSphere® is likely to be a cost-effective treatment at the listed price of £8,000 for patients who may be downstaged to curative treatments. TheraSphere® may also be a cost-effective treatment for later stage, unresectable HCC in certain scenarios, if considered to meet NICE end of life criteria. When the two sub populations are considered collectively (i.e. TAE-eligible and TAE-ineligible), TheraSphere® has a merged ICER of approximately £52,900/QALY.

References

1. Kennedy A, Nag S, Salem R, Murthy R, McEwan AJ, Nutting C*, et al.* Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: A consensus panel report from the Radioembolization Brachytherapy Oncology Consortium. Int J Radiat Oncol Biol Phys. 2007;68(1):13-23.
2. Merkel C, Montagnese S, Amodio P. Functional anatomy of liver circulation. In: Keiding S, Sorensen M, editors. Functional Molecular Imaging In Hepatology. Sharjah, UAE: Bentham Books; 2012.
3. Pellerin O, Lin MD, Bhagat N, Shao WB, Geschwind JF. Can C-arm cone-beam CT detect a micro-embolic effect after TheraSphere radioembolization of neuroendocrine and carcinoid liver metastasis? Cancer Biother Radio. 2013;28(6):459-65.
4. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET*, et al.* Toxicity and response criteria of the eastern cooperative oncology group. Am J Clin Oncol. 1982;5(6):649-55.
5. BTG PLC International. Package Insert Rev8: TheraSphere Yttrium-90 Glass Microspheres. London: BTG International; [cited 18 April 2019]. Available from: https://btgplc.com/BTG/media/TheraSphere-Documents/PDF/10093509-Rev8_English-searchable.pdf.
6. Harrison L, Blackwell K. Hypoxia and anemia: factors in decreased sensitivity to radiation therapy and chemotherapy? Oncologist. 2004;9 Suppl 5:31-40.
7. Fournier LS, Oudard S, Thiam R, Trinquart L, Banu E, Medioni J*, et al.* Metastatic renal carcinoma: evaluation of antiangiogenic therapy with dynamic contrast-enhanced CT. Radiology. 2010;256(2):511-8.
8. Salem R, Lewandowski RJ, Kulik L, Wang E, Riaz A, Ryu RK*, et al.* Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology. 2011;140(2):497-507 e2.
9. National Institute for Health and Care Excellence. SIR-spheres for treating inoperable hepatocellular carcinoma. Medtech innovation briefing [MIB63]. London: National Institute for Health and Care Excellence; 2016. Available from: https://www.nice.org.uk/advice/mib63/resources/sirspheres-for-treating-inoperable-hepatocellular-carcinoma-pdf-63499285313989.
10. Acuff S, Whittle B, Osborne D. Comparison of workflow efficiency and technologist radiation exposure when using TheraSphere and SIR-Sphere Y90 microspheres for liver cancer therapy. J Nucl Med. 2016;57:2717.
11. BTG PLC International. ALARA and radiation safety (internal document). Ottawa: BTG PLC International; 2015.
12. BTG PLC International. Radiation exposure garin sales aide US (internal document). BTG PLC International: BTG PLC International; 2016.
13. Laffont S, Rolland Y, Ardisson V, Edeline J, Pracht M, Le Sourd S*, et al.* Occupational radiation exposure of medical staff performing (9)(0)Y-loaded microsphere radioembolization. Eur J Nucl Med Mol Imaging. 2016;43(5):824-31.

14. Garin E, Laffont S, Rolland Y, Olivie D, Lecloirec J, Herry JY, *et al.* Safe radiation exposure of medical personnel by using simple methods of radioprotection while administering I-131-lipiodol therapy for hepatocellular carcinoma. Nucl Med Commun. 2003;24(6):671-78.
15. Sirtex Medical Limited. Package insert - Sirtex SIR-Spheres Y-90 resin microspheres (Yttrium-90 microspheres). Woburn: Sirtex Medical Inc.; 2019. [cited 21 May 2019]. Available from: https://www.sirtex.com/media/155126/ssl-us-13.pdf.
16. Quirem Medical. Package insert (IFU) QuiremSpheres® LS-1101-10.04. Netherlands: Quirem Medical; 2018. Last updated 2018. [cited 21 May 2019]. Available from: https://www.quirem.com/wp-content/uploads/delightful-downloads/2019/02/LS-1101-10_04-IFU-QuiremSpheres-Multilanguage.pdf.
17. Cancer Research UK. Liver cancer incidence statistics. Oxford: Cancer Research UK; 2015. Last updated January 2018. [cited March 2019]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/liver-cancer/incidence#heading-Zero.
18. Nordenstedt H, White DL, El-Serag HB. The changing pattern of epidemiology in hepatocellular carcinoma. Dig Liver Dis. 2010;42 Suppl 3:S206-14.
19. El-Serag HB. Epidemiology of hepatocellular carcinoma in USA. Hepatol Res. 2007;37 Suppl 2:S88-94.
20. Office for National Statistics. Cancer registration statistics, England: 2016. London: Office for National Statistics; 2018. [cited 17 April 2019]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/final2016.
21. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018;391(10127):1301-14.
22. Villanueva A, Toffanin S, Llovet JM. Linking molecular classification of hepatocellular carcinoma and personalized medicine: preliminary steps. Curr Opin Oncol. 2008;20(4):444-53.
23. Vogel A, Cervantes A, Chau I, Daniele B, Llovet JM, Meyer T, *et al.* Hepatocellular carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019
24. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet. 2003;362(9399):1907-17.
25. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, *et al.* Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378-90.
26. National Institute for Health and Care Excellence. Sorafenib for advanced hepatocellular carcinoma (cancer drugs fund reconsideration of TA189). London: National Institute for Health and Care Excellence; 2016. Available from: https://www.nice.org.uk/guidance/ta474/documents/final-appraisal-determination-document.
27. National Institute for Health and Care Excellence. Lenvatinib for advanced, unresectable, untreated hepatocellular carcinoma [ID1089]. London: National Institute for Health and Care Excellence; 2018.
28. National Institute for Health and Care Excellence. Regorafenib for previously treated unresectable hepatocellular carcinoma [ID991]. London: National Institute for Health and Care Excellence; 2017. Available from: https://www.nice.org.uk/guidance/ta514.
29. NHS England. Schedule 2 - The services. Liver transplantation service (adults). Service specification 170003/S. Redditch: NHS England; 2017. Available from: https://www.england.nhs.uk/wp-content/uploads/2017/04/liver-transplantation-service-adults.pdf.

30. Precision Xtract. A network meta-analysis to compare the efficacy and safety of TheraSphere® and sorafenib for the treatment of unresectable hepatocellular carcinoma. Final technical report to BTG International. Precision Xtract; 2018.
31. Kallini JR, Gabr A, Thorlund K, Balijepalli C, Ayres D, Kanters S, *et al.* Comparison of the adverse event profile of TheraSphere((R)) with SIR-Spheres((R)) for the treatment of unresectable hepatocellular carcinoma: a systematic review. Cardiovasc Intervent Radiol. 2017;40(7):1033-43.
32. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, *et al.* Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009;10(1):25-34.
33. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19(3):329-38.
34. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. Chichester: Wiley-Blackwell; 2008.
35. Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, *et al.* Interpreting results and drawing conclusions. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. Chichester: Wiley-Blackwell; 2008. p. 359-87.
36. Biederman DM, Titano JJ, Tabori NE, Pierobon ES, Alshebeeb K, Schwartz M, *et al.* Outcomes of radioembolization in the treatment of hepatocellular carcinoma with portal vein invasion: resin versus glass microspheres. J Vasc Interv Radiol. 2016;27(6):812-21 e2.
37. Bhangoo MS, Karnani DR, Hein PN, Giap H, Knowles H, Issa C, *et al.* Radioembolization with Yttrium-90 microspheres for patients with unresectable hepatocellular carcinoma. J Gastrointest Oncol 2015;6(5):469-78.
38. Van Der Gucht A, Jreige M, Denys A, Blanc-Durand P, Boubaker A, Pomoni A, *et al.* Resin versus glass microspheres for (90)Y transarterial radioembolization: comparing survival in unresectable hepatocellular carcinoma using pretreatment partition model dosimetry. J Nucl Med. 2017;58(8):1334-40.
39. Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, *et al.* Y90 radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology. 2016;151(6):1155-63 e2.
40. Akinwande O, Philips P, Scoggins C, Martin RC. Radioembolization versus chemoembolization (DEBDOX) for the treatment of unresectable hepatocellular carcinoma: a propensity matched study. Anticancer Res. 2016;36(1):239-46.
41. Biederman DM, Titano JJ, Korff RA, Fischman AM, Patel RS, Nowakowski FS, *et al.* Radiation segmentectomy versus selective chemoembolization in the treatment of early-stage hepatocellular carcinoma. J Vasc Interv Radiol. 2018;29(1):30-37 e2.
42. Carr BI, Kondragunta V, Buch SC, Branch RA. Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma: a two-cohort study. Cancer. 2010;116(5):1305-14.
43. El Fouly A, Ertle J, El Dorry A, Shaker MK, Dechene A, Abdella H, *et al.* In intermediate stage hepatocellular carcinoma: radioembolization with yttrium 90 or chemoembolization? Liver Int. 2015;35(2):627-35.
44. Gabr A, Abouchaleh N, Ali R, Vouche M, Atassi R, Memon K, *et al.* Comparative study of post-transplant outcomes in hepatocellular carcinoma patients treated with chemoembolization or radioembolization. Eur J Radiol. 2017;93:100-06.
45. Lewandowski RJ, Kulik LM, Riaz A, Senthilnathan S, Mulcahy MF, Ryu RK, *et al.* A comparative analysis of transarterial downstaging for hepatocellular carcinoma: chemoembolization versus radioembolization. Am J Transplant. 2009;9(8):1920-8.

46. Moreno-Luna LE, Yang JD, Sanchez W, Paz-Fumagalli R, Harnois DM, Mettler TA, *et al*. Efficacy and safety of transarterial radioembolization versus chemoembolization in patients with hepatocellular carcinoma. Cardiovasc Intervent Radiol. 2013;36(3):714-23.
47. Padia SA, Chewning RH, Kogut MJ, Ingraham CR, Johnson GE, Bhattacharya R, *et al*. Outcomes of locoregional tumor therapy for patients with hepatocellular carcinoma and transjugular intrahepatic portosystemic shunts. Cardiovasc Intervent Radiol. 2015;38(4):913-21.
48. Padia SA, Johnson GE, Horton KJ, Ingraham CR, Kogut MJ, Kwan S, *et al*. Segmental Yttrium-90 radioembolization versus segmental chemoembolization for localized hepatocellular carcinoma: results of a single-center, retrospective, propensity score-matched study. J Vasc Interv Radiol. 2017;28(6):777-85 e1.
49. Ali R, Riaz A, Gabr A, Abouchaleh N, Mora R, Al Asadi A, *et al*. Clinical outcomes of Y90 radioembolization for recurrent hepatocellular carcinoma following curative resection. Eur J Nucl Med Mol Imaging. 2017;44(13):2195-202.
50. Biederman DM, Titano JJ, Lee KM, Pierobon ES, Schwartz M, Facciuto ME, *et al*. Yttrium-90 glass-based microsphere radioembolization in the treatment of hepatocellular carcinoma secondary to the hepatitis B virus: safety, efficacy, and survival. J Vasc Interv Radiol. 2015;26(11):1630-8.
51. Hilgard P, Hamami M, Fouly AE, Scherag A, Muller S, Ertle J, *et al*. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. Hepatology. 2010;52(5):1741-9.
52. Garin E, Rolland Y, Pracht M, Le Sourd S, Laffont S, Mesbah H, *et al*. High impact of macroaggregated albumin ‐ based tumour dose on response and overall survival in hepatocellular carcinoma patients treated with 90Y ‐ loaded glass microsphere radioembolization. Liver Int. 2017;37(1):101-10.
53. Lambert B, Sturm E, Mertens J, Oltenfreiter R, Smeets P, Troisi R, *et al*. Intra-arterial treatment with (9)(0)Y microspheres for hepatocellular carcinoma: 4 years experience at the Ghent university hospital. Eur J Nucl Med Mol Imaging. 2011;38(12):2117-24.
54. Mazzaferro V, Sposito C, Bhoori S, Romito R, Chiesa C, Morosi C, *et al*. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. Hepatology. 2013;57(5):1826-37.
55. Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, *et al*. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology. 2010;138(1):52-64.
56. Woodall CE, Scoggins CR, Ellis SF, Tatum CM, Hahl MJ, Ravindra KV, *et al*. Is selective internal radioembolization safe and effective for patients with inoperable hepatocellular carcinoma and venous thrombosis? J Am Coll Surg. 2009;208(3):375-82.
57. Biederman DM, Posham R, Durrani RJ, Titano JJ, Patel RS, Tabori NE, *et al*. Outcomes of radioembolization for unresectable hepatocellular carcinoma in patients with marginal functional hepatic reserve. Clin Imaging. 2018;47:34-40.
58. Abouchaleh N, Gabr A, Ali R, Al Asadi A, Mora RA, Kallini JR, *et al*. 90Y radioembolization for locally advanced hepatocellular carcinoma with portal vein thrombosis: long-term outcomes in a 185-patient cohort. J Nucl Med. 2018;59(7):1042-48.
59. Kokabi N, Camacho JC, Xing M, El-Rayes BF, Spivey JR, Knechtle SJ, *et al*. Open-label prospective study of the safety and efficacy of glass-based yttrium 90 radioembolization for infiltrative hepatocellular carcinoma with portal vein thrombosis. Cancer. 2015;121(13):2164-74.

60. Kulik LM, Carr BI, Mulcahy MF, Lewandowski RJ, Atassi B, Ryu RK*, et al.* Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. Hepatology. 2008;47(1):71-81.
61. Pracht M, Edeline J, Lenoir L, Latournerie M, Mesbah H, Audrain O*, et al.* Lobar hepatocellular carcinoma with ipsilateral portal vein tumor thrombosis treated with yttrium-90 glass microsphere radioembolization: preliminary results. Int J Hepatol. 2013;2013:827649.
62. Lewandowski RJ, Gabr A, Abouchaleh N, Ali R, Al Asadi A, Mora RA*, et al.* Radiation segmentectomy: potential curative therapy for early hepatocellular carcinoma. Radiology. 2018;287(3):1050-58.
63. Riaz A, Gabr A, Abouchaleh N, Ali R, Al Asadi A, Mora R*, et al.* Radioembolization for hepatocellular carcinoma: Statistical confirmation of improved survival in responders by landmark analyses. Hepatology. 2018;67(3):873-83.
64. Vouche M, Habib A, Ward TJ, Kim E, Kulik L, Ganger D*, et al.* Unresectable solitary hepatocellular carcinoma not amenable to radiofrequency ablation: multicenter radiology-pathology correlation and survival of radiation segmentectomy. Hepatology. 2014;60(1):192-201.
65. Abdelfattah M, Al-Sebayel M, Broering D, Alsuhaibani H. Radioembolization using yttrium-90 microspheres as bridging and downstaging treatment for unresectable hepatocellular carcinoma before liver transplantation: initial single-center experience. Transplant Proc. 2015;47(2):408-11.
66. Ibrahim SM, Kulik L, Baker T, Ryu RK, Mulcahy MF, Abecassis M*, et al.* Treating and downstaging hepatocellular carcinoma in the caudate lobe with yttrium-90 radioembolization. Cardiovasc Intervent Radiol. 2012;35(5):1094-101.
67. Kulik LM, Atassi B, van Holsbeeck L, Souman T, Lewandowski RJ, Mulcahy MF*, et al.* Yttrium-90 microspheres (TheraSphere) treatment of unresectable hepatocellular carcinoma: downstaging to resection, RFA and bridge to transplantation. J Surg Oncol. 2006;94(7):572-86.
68. Kulik L, Vouche M, Koppe S, Lewandowski RJ, Mulcahy MF, Ganger D*, et al.* Prospective randomized pilot study of Y90+/-sorafenib as bridge to transplantation in hepatocellular carcinoma. J Hepatol. 2014;61(2):309-17.
69. Radunz S, Treckmann J, Baba HA, Best J, Muller S, Theysohn JM*, et al.* Long-term outcome after liver transplantation for hepatocellular carcinoma following Yttrium-90 radioembolization bridging treatment. Ann Transplant. 2017;22:215-21.
70. Tohme S, Sukato D, Chen HW, Amesur N, Zajko AB, Humar A*, et al.* Yttrium-90 radioembolization as a bridge to liver transplantation: a single-institution experience. J Vasc Interv Radiol. 2013;24(11):1632-8.
71. Gabr A, Abouchaleh N, Ali R, Baker T, Caicedo J, Katariya N*, et al.* Outcomes of surgical resection after radioembolization for hepatocellular carcinoma. J Vasc Interv Radiol. 2018;29(11):1502-10 e1.
72. Gaba RC, Lewandowski RJ, Kulik LM, Riaz A, Ibrahim SM, Mulcahy MF*, et al.* Radiation lobectomy: preliminary findings of hepatic volumetric response to lobar yttrium-90 radioembolization. Ann Surg Oncol. 2009;16(6):1587-96.
73. Goebel J, Sulke M, Lazik-Palm A, Goebel T, Dechene A, Bellendorf A*, et al.* Factors associated with contralateral liver hypertrophy after unilateral radioembolization for hepatocellular carcinoma. PLoS ONE. 2017;12(7):e0181488.

74. Palard X, Edeline J, Rolland Y, Le Sourd S, Pracht M, Laffont S, *et al.* Dosimetric parameters predicting contralateral liver hypertrophy after unilobar radioembolization of hepatocellular carcinoma. Eur J Nucl Med Mol Imaging. 2018;45(3):392-401.
75. Vouche M, Lewandowski RJ, Atassi R, Memon K, Gates VL, Ryu RK, *et al.* Radiation lobectomy: time-dependent analysis of future liver remnant volume in unresectable liver cancer as a bridge to resection. J Hepatol. 2013;59(5):1029-36.
76. Tandon P, Garcia-Tsao G. Prognostic indicators in hepatocellular carcinoma: a systematic review of 72 studies. Liver Int. 2009;29(4):502-10.
77. Lewandowski RJ, Geschwind JF, Liapi E, Salem R. Transcatheter intraarterial therapies: rationale and overview. Radiology. 2011;259(3):641-57.
78. Salem R, Gilbertsen M, Butt Z, Memon K, Vouche M, Hickey R, *et al.* Increased quality of life among hepatocellular carcinoma patients treated with radioembolization, compared with chemoembolization. Clin Gastroenterol Hepatol. 2013;11(10):1358-65 e1.
79. Steel J, Baum A, Carr B. Quality of life in patients diagnosed with primary hepatocellular carcinoma: hepatic arterial infusion of cisplatin versus 90-Yttrium microspheres (Therasphere). Psychooncology. 2004;13(2):73-9.
80. BTG PLC International. Investigator's brochure therasphere™ yttrium-90 glass microsphere system (TheraSphere-IB-6.1). Surrey: BTG PLC International; 11 February 2019.
81. Mason MC, Massarweh NN, Salami A, Sultenfuss MA, Anaya DA. Post-embolization syndrome as an early predictor of overall survival after transarterial chemoembolization for hepatocellular carcinoma. HPB. 2015;17(12):1137-44.
82. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Process and methods [PMG9]. London: National Institute for Health and Care Excellence; April 2013. Available from: https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781.
83. Salem R, Gabr A, Riaz A, Mora R, Ali R, Abecassis M, *et al.* Institutional decision to adopt Y90 as primary treatment for hepatocellular carcinoma informed by a 1,000-patient 15-year experience. Hepatology. 2018;68(4):1429-40.
84. Fernandez-Sevilla E, Allard MA, Selten J, Golse N, Vibert E, Sa Cunha A, *et al.* Recurrence of hepatocellular carcinoma after liver transplantation: Is there a place for resection? Liver Transpl. 2017;23(4):440-47.
85. Li HY, Wei YG, Yan LN, Li B. Salvage liver transplantation in the treatment of hepatocellular carcinoma: a meta-analysis. World J Gastroenterol. 2012;18(19):2415-22.
86. Smits ML, Nijsen JF, van den Bosch MA, Lam MG, Vente MA, Mali WP, *et al.* Holmium-166 radioembolisation in patients with unresectable, chemorefractory liver metastases (HEPAR trial): a phase 1, dose-escalation study. Lancet Oncol. 2012;13(10):1025-34.
87. Prince JF, van den Bosch M, Nijsen JFW, Smits MLJ, van den Hoven AF, Nikolakopoulos S, *et al.* Efficacy of radioembolization with (166)ho-microspheres in salvage patients with liver metastases: a phase 2 study. J Nucl Med. 2018;59(4):582-88.
88. NHS Blood and Transplant. Organ donation and transplantation. Activity report 2017/18. Cambridge: NHS Blood and Transplant; 2018. Available from: https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/12300/transplant-activity-report-2017-2018.pdf.
89. Office for National Statistics. National life tables: England and Wales. London: Office for National Statistics; 2018. Last updated September 2018. [cited 18 April 2019]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandandwalesreferencetables.

90. Bellavance EC, Lumpkins KM, Mentha G, Marques HP, Capussotti L, Pulitano C, *et al.* Surgical management of early-stage hepatocellular carcinoma: resection or transplantation? J Gastrointest Surg. 2008;12(10):1699-708.
91. EASL. EASL clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2018;69:182-236.
92. Bayer Healthcare. Single technology appraisal (STA) of sorafenib (Nexavar•) for the treatment of hepatocellular carcinoma (HCC). London: Bayer Healthcare; 14 January 2009. Available from: https://www.nice.org.uk/guidance/ta189/documents/bayer-appendices2.
93. Guyot P, Ades A, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published kaplan-meier survival curves. BMC Med Res Methodol. 2012;12(1):9.
94. Latimer N. NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. Sheffield: NICE Decision Support Unit; 2011. Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf.
95. Vilgrain V, Pereira H, Assenat E, Guiu B, Ilonca AD, Pageaux GP, *et al.* Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. Lancet Oncol. 2017;18(12):1624-36.
96. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, *et al.* Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378-90.
97. Golfieri R, Giampalma E, Renzulli M, Cioni R, Bargellini I, Bartolozzi C, *et al.* Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer. 2014;111(2):255-64.
98. Meyer T, Kirkwood A, Roughton M, Beare S, Tsochatzis E, Yu D, *et al.* A randomised phase II/III trial of 3-weekly cisplatin-based sequential transarterial chemoembolisation vs embolisation alone for hepatocellular carcinoma. Br J Cancer. 2013;108(6):1252-9.
99. Kind P, Hardman G, Macran S. UK population norms for EQ-5D. York: Centre for Health Economics; 1999. 1-8.
100. Ratcliffe J, Longworth L, Young T, Bryan S, Burroughs A, Buxton M. Assessing health-related quality of life pre- and post-liver transplantation: a prospective multicenter study. Liver Transpl. 2002;8(3):263-70.
101. Lim KC, Wang VW, Siddiqui FJ, Shi L, Chan ES, Oh HC, *et al.* Cost-effectiveness analysis of liver resection versus transplantation for early hepatocellular carcinoma within the Milan criteria. Hepatology. 2015;61(1):227-37.
102. Eisai Ltd. Summary of product characteristics. LENVIMA 4 mg hard capsules. Leatherhead: electronic Medicines Compendium; 2019. Last updated 20 Feb 2019. [cited 18 April 2019]. Available from: https://www.medicines.org.uk/emc/product/6840/smpc.
103. Bayer plc. Summary of product characteristics. Nexavar 200mg film-coated tablets. Leatherhead: electronic Medicines Compendium; 2018. Last updated 5 July 2018. [cited 18 April 2019]. Available from: https://www.medicines.org.uk/emc/product/226/smpc.
104. Bayer plc. Summary of product characteristics. Stivarga 40 mg film-coated tablets. . Leatherhead: electronic Medicines Company; 2018. Last updated 6 September 2018. [cited 18 April 2019]. Available from: https://www.medicines.org.uk/emc/product/1263/smpc.
105. Personal Social Services Research Unit (PSSRU). Unit costs of health and social care 2018. Canterbury: Personal Social Services Research Unit; 2018. Available from: https://kar.kent.ac.uk/70995/1/Unit%20Costs%202018%20-%20FINAL%20with%20bookmarks%20and%20covers%20%282%29.pdf.

106. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation. Oxford: Oxford University Press; 2006.
107. BTG PLC International (MDoutlook). Understanding patient pathways in HCC for Europe (EU5) United Kingdom (internal). MDoutlook L; 2015.
108. Mendez-Blanco C, Fondevila F, Garcia-Palomo A, Gonzalez-Gallego J, Mauriz JL. Sorafenib resistance in hepatocarcinoma: role of hypoxia-inducible factors. Exp Mol Med. 2018;50(10):134.
109. Quirk M, Kim YH, Saab S, Lee EW. Management of hepatocellular carcinoma with portal vein thrombosis. World J Gastroenterol. 2015;21(12):3462-71.

NICE Multiple Technology Appraisal ID1276

Selective internal radiation therapies for treating hepatocellular carcinoma

SIRTEX Medical

Company evidence submission

SIR-Spheres Y-90 resin microspheres

28th May 2019 (updated 11th July 2019)

REDACTED

Contents

Tables

Figures

Abbreviations

Acronym	Definition
AE	Adverse event
A&E	Accident and emergency department
AFP	Alpha-fetoprotein
AIC	Akaike information criteria
ALBI	Albumin-bilirubin grade
ALT	Alanine transferase
AST	Aspartate transferase
BCLC	Barcelona clinic liver cancer staging
BD	Twice daily
BIC	Bayesian information criteria
BSA	Body surface area
BSC	Best supportive care
BUN	Blood urea and nitrogen
CEAC	Cost-effectiveness acceptability curve
CIRT	CIRSE Registry for SIR-Spheres Therapy
CMA	Cost-minimisation analysis
coeff	Coefficient
CR	Complete response
CT	Computed tomography
cTACE	Conventional transarterial chemoembolisation
DEBDOX	Drug eluting beads of doxorubicin
DEB-TACE	Drug-eluting bead- transarterial chemoembolisation
(DEB-)TACE	Transarterial chemoembolisation using either conventional administration or drug eluting beads
DIC	Deviance information criteria
DLHCC	Hepatocellular carcinoma with diseased liver
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EASL	European Association for the Study of the Liver
ECOG	Eastern Cooperative Oncology Group
EHD	Extrahepatic disease
EHS	Extrahepatic spread
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
exp	Exponential
FACT-G	Functional Assessment of Cancer Therapy - General
FBC	Full blood count
gen	Generalised
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
INB	Incremental net benefit
INR	International normalised ratio
IPTW	Inverse probability of treatment weighting
IQR	Interquartile range
ISPOR-SMDM	International Society for Pharmacoeconomics and Outcomes Research- Society for Medical Decision Making
ITT	Intention-to-treat

KM	Kaplan-Meier
KOL	Key opinion leader
LCI	Lower confidence interval
LYG	Life-years gained
LTX	Liver transplant
MAIC	Matched adjusted indirect comparison
MCMC	Markov chain Monte Carlo
MIRD	Medical Internal Radiation Dose
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	Magnetic resonance imaging
MVI	Macroscopic vascular invasion
NASH	Non-alcoholic steatohepatitis
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NLHCC	Hepatocellular carcinoma with normal liver
NMA	Network meta-analysis
NR	Not reported
ORR	Objective response rate
OS	Overall survival
PCEI	Percutaneous ethanol infusion
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PP	Per-protocol
PR	Partial response
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PVA	Polyvinyl alcohol
PVI	Portal vein involvement
PVT	Portal vein thrombosis
PVTT	Portal vein tumour thrombosis
QALY	Quality-adjusted life-year
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	Radiofrequency ablation
SAE	Serious adverse events
SBRT	Stereotactic body radiotherapy
SD	Stable disease OR standard deviation
SE	Standard error
SEER	Surveillance, Epidemiology and End Results
SIR-Spheres	SIR-Spheres® Y-90 resin microspheres
SIRT	Selective internal radiation therapy
SLR	Systematic literature review
SPECT/ CT	Single-photon emission computed tomography
TA	Technology appraisal
TACE	Transarterial chemoembolisation
TAE	Transarterial embolisation
TARE	Transarterial radioembolisation
^{99m}Tc-MAA	99m-Technetium macroaggregated albumin
TEAE	Treatment-emergent adverse events, treatment-related adverse events
TNM	Tumour node metastasis
TTD	Time to treatment discontinuation

TTO	Time trade-off
TTP	Time to progression
TTUP	Time to untreatable progression
TTV	Total tumour volume
UCI	Upper confidence interval
vs	Versus
WHO	World Health Organization

Classifications

Classification	Definition
BCLC stage (1)	Very early stage 0: single <2 cm tumour, preserved liver function, performance status (PS) 0 Early stage A: single or 2-3 nodules < 3cm, preserved liver function, PS 0 Intermediate stage B: multinodular, unresectable, preserved liver function, PS 0 Advanced stage C: portal invasion/ extrahepatic spread, preserved liver function, PS 1-2 Terminal stage D: non-transplantable, end-stage liver function, PS 3-4
Child-Pugh grade (2)	A: bilirubin <34 µmol/L, albumin >35 g/L, no ascites, no encephalopathy, nutritional status good B: bilirubin 34-51 µmol/L, albumin 30-35 g/L, controlled ascites, minimal encephalopathy, nutritional status fair C: bilirubin >51 µmol/L, albumin <30 g/L, refractory ascites, advanced encephalopathy, nutritional status poor
Portal Vein Thrombosis (3)	Macrovascular: thrombosis in the main portal vein or its branches, hepatic veins or their branches or inferior vena cava in the liver Microvascular: thrombosis in smaller hepatic vessels

Executive summary

SIR-Spheres® Y-90 resin microspheres (SIR-Spheres) have a marketing authorisation for all unresectable, primary or secondary liver tumours. This submission focuses on subpopulations within the marketing authorisation:

- **[Population 1 – TACE-eligible].** People with unresectable early (BCLC stage A), intermediate stage (BCLC stage B) or advanced HCC (BCLC stage C), for whom transarterial chemoembolisation therapies (TACE, DEB-TACE) are appropriate.

- **[Population 2 – TACE-ineligible].** People with unresectable intermediate stage (BCLC stage B) or advanced HCC (BCLC stage C), for whom any transarterial embolisation are inappropriate, with or without portal vein thrombosis/involvement, without extrahepatic disease, with a tumour burden ≤25% and a preserved liver function (ALBI grade 1).

SIR-Spheres consist of sterile, single-use, resin microspheres containing yttrium-90, used for selective internal radiation therapy (SIRT). SIRT delivers radiation therapy by intra-arterial infusion to the liver tumour, minimising radiation exposure to the non-tumoural liver tissue.

HCC is a complex disease with a high prevalence of chronic liver disease in affected patients. This increases morbidity and mortality risk, worsens quality of life, adds to caregiver burden and means that patients with otherwise treatable tumours may not be able to tolerate potentially curative interventions. Approximately 80% of patients in the UK present with intermediate or advanced: these patients, and those who have failed prior treatment with a curative intent, are considered as having unresectable HCC. The submission focuses on patients with unresectable HCC, who have a poor survival prognosis and limited treatment options.

Recommended treatments for patients with unresectable HCC are generally restricted to transarterial chemoembolisation (TACE), either conventional (cTACE) or using drug-eluting beads (DEB-TACE). For patients ineligible for TACE, treatment options are restricted to systemic therapy. While TACE and systemic therapy offer active treatment options to patients for whom best supportive care was the only management option prior to their introduction, they do not always meet therapeutic goals in unresectable HCC, which are to slow progression of disease, prolong survival and improve patient health-related quality of life (HRQL).

TACE has generally, but not consistently, been shown to be effective in intermediate-stage (BCLC stage B) HCC, although this includes a particularly heterogeneous group of patients and guidelines acknowledge that there is a need to sub-divide this population further to better predict outcomes. TACE requires multiple administrations, typically 3 to 4 per patient, each one requiring a hospital stay of 3 to 6 days, and causes considerable pain, with a risk of post-embolisation syndrome and impaired quality of life.

Sorafenib is an established therapy for patients not suitable for TACE and is taken orally until progression or unacceptable toxicity occurs. Adverse events of sorafenib impair patients' HRQL, incur ongoing healthcare costs, and lead to approximately one-third of patients discontinuing treatment early. **Lenvatinib,** recently recommended by NICE, has similar efficacy and tolerability to sorafenib due to its similar mechanism of action. Down-staging from sorafenib or lenvatinib to potentially curative treatments is extremely rare in clinical practice, so these are considered palliative treatment options.

There is therefore a considerable unmet need in patients with unresectable HCC. SIRT has the potential to benefit patients and add value in these populations. Recent EASL guidelines have concluded that the subgroup of patients who are most likely to benefit from SIRT needs to be defined.

[Population 2 – TACE-ineligible]. In this submission, the **target population for SIR-Spheres**, which is used for the base-case analysis, has been identified based on the literature and clinical expert opinion as follows:

- **Patients with a low tumour burden (defined as a tumour involvement ≤25% of the liver volume).** This selects patients who are most likely to have tumours that are suitable for SIRT and in which a tumoricidal radiation dose can be attained without exposing non-tumoural tissue.
- **Patients with a well-preserved liver function (defined as an albumin-bilirubin [ALBI] grade of 1).** This selects patients who are most likely to tolerate locoregional therapies such as SIRT.

The efficacy and tolerability of SIR-Spheres in patients who are ineligible for TACE was compared with sorafenib in two Phase III randomised controlled trials (RCTs). The SARAH trial recruited 459 patients with locally advanced or recurrent HCC in France, and the SIRveNIB trial recruited 360 patients with locally advanced HCC in Asia. The SARAH trial was initiated in 2009 and reflected clinical practice at the time, in that the population recruited was broader than the population who would now be considered suitable for SIRT. In particular, the trial included patients with poor liver function and extensive tumour burden, which are associated with very poor prognosis. This submission is based on a subgroup of participants from the SARAH study with low tumour burden and well-preserved liver function, considered by clinicians as good candidates for SIR-Spheres. The Asian population of the SIRveNIB trial was not considered to be representative of the UK population with HCC so data from this study have not been used in the economic model, although headline results of this trial were similar to the SARAH trial.

The intention to treat population (ITT) of the SARAH study showed no statistically significant difference in overall survival (OS), the primary outcome measure, between SIR-Spheres and sorafenib (hazard ratio [HR] 1.15, 95% CI 0.94 to 1.41, p=0.18). However, 22% of patients randomised to SIR-Spheres did not receive this treatment, only 49% of whom received sorafenib instead. Further, 5.1% of patients randomised to SIR-Spheres were down-staged and as such became eligible for potentially curative treatments, compared with 1.4% of the sorafenib group. Most of these patients were alive and censored at the end of the trial: the SARAH trial analyses, which assume uninformative censoring, are therefore likely to underestimate OS for these patients. SIR-Spheres were well-tolerated, with significantly fewer overall or grade 3+ adverse events than with sorafenib. This translated into a **HRQL benefit for SIR-Spheres** compared to sorafenib, as measured by the global health status sub-score of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), which was significantly better in the SIR-Spheres arm than in the sorafenib arm (group effect p=0.0447, time effect p<0.0001)

In a multivariate Cox regression, the interaction effect between treatment and the combination of a **tumour burden ≤25% and an ALBI grade of 1** was 0.609 (95% CI: 0.344 to 1.079, p=0.089) indicating **that SIRT was relatively more effective in this target subgroup.** For patients with a tumour burden ≤25% and ALBI grade 1, median OS was 21.9 months with SIR-Spheres versus 17.0 months with sorafenib (HR 0.73, 95%CI 0.44 to 1.21, p=0.22) and HR for progression-free survival (PFS) was 0.65 (95%CI 0.41 to 1.02, p=0.06). In this subgroup, 92% of patients who were randomised to SIR-Spheres had received this treatment and 14% were down-staged to potentially curative therapy, versus 2% of patients randomised to sorafenib.

The SARAH trial was supplemented by a **network meta-analysis** (NMA) based on a systematic literature review, which included an additional RCT that compared sorafenib with lenvatinib (the REFLECT trial). No RCTs were identified of the other interventions (TheraSphere and QuiremSpheres) in this population, and no assumptions can be made regarding their efficacy and safety in this population.

A de novo economic model was developed to determine the cost-effectiveness of SIR-Spheres compared with sorafenib in TACE-ineligible patients with or without portal vein involvement, without extrahepatic disease, with a tumour burden ≤25% and ALBI grade 1 (the base case). ITT and other populations were included as

sensitivity analyses. Lenvatinib was included as a comparator in a scenario analysis as multiple assumptions had to be made, and regorafenib was included as a subsequent treatment, in line with NICE guidance. The model used a partitioned survival approach. Subsequent potentially curative therapy was included in the model with a separate OS curve for patients with HCC successfully down-staged by their initial treatment, applied from 16 months onwards. Efficacy data were taken from the SARAH trial and extrapolated using parametric survival models. Utility values were mapped from EORTC QLQ-C30 scores from the SARAH trial, resource use was based on the SARAH trial discontinuation for sorafenib, registries and two surveys of expert opinion, with unit costs applied as recommended by NICE. Costs of grade 3 and 4 adverse events that affected ≥5% of patients were included in the model. Deterministic and probabilistic sensitivity analyses explored uncertainty in the model parameters and scenario analyses tested the model's robustness for structural uncertainties.

In the discounted base-case analysis, SIR-Spheres led to 2.637 life-years gained and 1.982 QALYs compared with 1.890 life-years gained and 1.381 QALYs with sorafenib. Discounted total costs were £29,143 for SIR-Spheres compared with £30,927 for sorafenib. **SIR-Spheres resulted in higher efficacy and lower costs, dominating sorafenib** with an incremental net benefit of £13,801 for SIR-Spheres. Probabilistic sensitivity analyses showed that there was a **95% probability of SIR-Spheres being cost-effective at a willingness-to-pay threshold of £20,000/QALY** gained. SIR-Spheres remained dominant with most of the changes tested in scenario analyses. When the cost of sorafenib was reduced by 20-40%, as could be the case with a patient access scheme, SIR-Spheres were cost-effective with an incremental cost-effectiveness ratio of up to £5,443/QALY gained. SIR-Spheres remained cost-effective when considering the overall ITT population of the SARAH trial, with markedly lower costs (-£6,142) and a small reduction in QALYs (-0.105). The ICER of sorafenib vs. SIR-Spheres was £58,763 per QALY in this scenario.

[Population 1 – TACE-eligible]. A systematic literature review was conducted for **patients who are eligible for TACE**. This found 2 RCTs of SIR-Spheres versus DEB-TACE and cTACE. One small Phase IV RCT found no significant difference in OS and PFS in 25 patients treated with either SIR-Spheres or DEB-TACE, but this study did not assess quality of life or adverse events. A second small Phase II RCT found similar OS, PFS and time to progression (TTP) with SIR-Spheres and DEB-TACE that compared SIR-Spheres with cTACE.

The systematic literature review identified one small (n=45) RCT for TheraSphere versus cTACE and two RCTs that compared cTACE with DEB-TACE. All but one trial could be included in a network meta-analysis. The trials formed a connected network of evidence, but this was underpinned with small studies and resulted in important uncertainty around the comparative effectiveness of each intervention and comparator. In addition, no suitable data could be found to conduct a matched adjusted indirect comparison for SIR-Spheres and these comparators. **No assumptions of comparable efficacy** could therefore be made. A cost minimisation analysis (CMA) was developed for SIR-Spheres in this TACE-eligible population. This found that **SIR-Spheres had comparable costs to TACE and lower costs than TheraSphere** depending on the data source used.

Important differences exist between the different interventions that can affect patient experiences and healthcare resource use. SIR-Spheres can be administered to both lobes of the liver during the same procedure, unlike TheraSphere or TACE, which reduces the burden of administration on the patient. SIR-Spheres do not cause post-embolic syndrome so are better tolerated than TACE with a shorter duration of hospital stay. SIR-Spheres can be administered to patients as a day-case procedure, and this is being introduced in some UK centres. Adverse events of SIR-Spheres are generally short-term, unlike systemic therapy, which can cause adverse events for the duration of therapy and result in impaired quality of life and greater costs.

In conclusion, **SIR-Spheres are dominant and cost-effective when compared with sorafenib** in patients who are not eligible for TACE, have a low tumour burden and good liver function. In patients who are eligible for TACE, SIR-Spheres is an alternative to TACE with reduced patient burden. Crucially, **SIR-Spheres offer patients with unresectable HCC a chance of being down-staged to receive potentially curative therapy**.

1 Decision problem

SIR-Spheres® Y-90 resin microspheres (SIR-Spheres) has a marketing authorisation (CE mark) for all unresectable, primary or secondary liver tumours. Secondary liver tumours are metastases to the liver of any primary tumour, including metastatic colorectal cancer, breast cancer or neuroendocrine tumours, among other aetiologies. Primary tumours include hepatocellular carcinoma (HCC), cholangiocarcinoma and other rare forms of primary liver cancer.

This submission focuses only on HCC. HCC covers a broad population. The staging system most commonly used for HCC is the Barcelona Clinic Liver Cancer (BCLC) system, recommended by clinical guidelines to stratify patients into five groups which have major differences in terms of prognostic and available treatment options, from very early to terminal HCC.

Patients with very early and early stage HCC (BCLC stages 0-A) may receive curative therapy, including liver transplantation, tumour resection or ablation. These patients are classified as having resectable HCC.

Patients not considered suitable for curative therapy are considered as having unresectable HCC, whether at the early, intermediate or advanced stage (BCLC stages A-C). These patients receive loco-regional treatment such as transarterial embolisation (TAE) or chemoembolisation (TACE), whether using lipiodol or other embolic agents and drugs (e.g. DEB-TACE): although TAE and TACE are considered palliative in nature, down-staging to subsequent curative therapy remains a possible treatment strategy for some patients.

Patients not considered suitable for TAE or TACE receive first-line targeted chemotherapy, including sorafenib and lenvatinib. Patients may be considered unsuitable for TAE or TACE in UK clinical practice because they have portal vein thrombosis/involvement, extrahepatic metastases, a degraded performance status or because their liver tumours are not responding to TAE or TACE. Switching from loco-regional treatment options to systemic therapy marks a negative prognostic evolution, as sorafenib and lenvatinib are considered palliative treatments. Down-staging to subsequent curative therapy is extremely rare and is not a recognised strategy after systemic therapy.

Within the broader indication of unresectable HCC, this submission focuses on 2 specific parts of the marketing authorisation, due to the above differences in survival prognosis and available treatment options, and to reflect treatment allocation in UK clinical practice:

- **[Population 1 – TACE-eligible].** People with unresectable early (BCLC stage A), intermediate stage (BCLC stage B) or advanced HCC (BCLC stage C), for whom transarterial chemoembolisation therapies (TACE, DEB-TACE) are appropriate.

- **[Population 2 – TACE-ineligible].** People with unresectable intermediate stage (BCLC stage B) or advanced HCC (BCLC stage C), for whom any transarterial embolisation are inappropriate, with or without portal vein thrombosis/involvement, without extrahepatic disease, with a tumour burden ≤25% and a preserved liver function (ALBI grade 1).

The proposed indications are sub-populations within the marketing authorisation because:

- TACE-eligible patients will predominantly have intermediate-stage HCC (BCLC stage B), but this can include early or advanced stages (BCLC stages A-C).
- TACE-ineligible patients will predominantly have advanced HCC (BCLC stage C), but this can include intermediate-stage HCC (BCLC stage B). Patients with early stage HCC (BCLC stage A) are normally considered TACE-eligible.

- The two populations have a different prognosis. The overall survival of TACE-eligible patients is expected to be ≥2.5 years compared to ≥10 months for TACE-ineligible patients receiving systemic therapy (1).
- Treatment options are different for each population, resulting in different comparators being appropriate for the decision problem (4). Clinicians have confirmed this reflects treatment allocation in the UK which can deviate from the BCLC staging system (5).
- Patients with portal vein thrombosis/involvement are normally considered TACE-ineligible and these characteristics are therefore not described in relation to the TACE-eligible population. SIRT can be used in patients with or without portal vein thrombosis/involvement. Phase III randomised trials of SIR-Spheres have included patients with or without portal vein thrombosis/involvement (6, 7).
- Patients with extrahepatic disease are normally considered TACE-ineligible. SIRT would not be used in patients with extrahepatic disease, as this is a liver-directed treatment option. Phase III randomised trials of SIR-Spheres have excluded patients with extrahepatic disease (6, 7).
- Clinicians in the UK consider SIR-Spheres to be an appropriate treatment option in TACE-ineligible patients with a relatively low tumour burden and a well-preserved liver function (8). In this submission, low tumour burden is defined as a tumour involvement ≤25% of the total liver volume, and a well-preserved function is defined as an ALBI grade of 1. This subgroup of TACE-ineligible patients is considered in the base case of this submission. Available evidence for TACE-eligible patients did not allow for further stratification into subgroups (section 8.1.1, page 85).
- SIR-Spheres are cost-effective in these clinically relevant populations (section 7.2.7 page 71).

Differences between the final scope issued by NICE and the decision problem addressed in this submission are summarised in Table 1.

Table 1. Decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with unresectable early (BCLC stage A), intermediate-stage (BCLC stage B) and advanced (BCLC stage C) HCC (with or without portal vein thrombosis/involvement).	**[Population 1 – TACE-eligible].** People with unresectable early (BCLC stage A), intermediate stage (BCLC stage B) or advanced HCC (BCLC stage C), for whom transarterial chemoembolisation therapies (TACE, DEB-TACE) are appropriate.	TACE-eligible patients have a distinct, better prognosis and different treatment options than patients in population 2 (overall survival ≥2.5 years). The BCLC staging system was not used to stratify the two populations because: (a) Intermediate and advanced stages include heterogeneous populations, for whom different treatment options are appropriate; (b) Treatment decision is not fully adhering to the BCLC staging system in UK practice.
		[Population 2 – TACE-ineligible]. People with unresectable intermediate stage (BCLC stage B) or advanced HCC (BCLC stage C), for whom any transarterial embolisation are inappropriate, with or without portal vein thrombosis/involvement, without extrahepatic disease.	TACE-ineligible patients have a distinct, poorer prognosis than patients in population 1 (overall survival ≥10 months). These patients receive systemic therapy in UK clinical practice. This population can include patients with or without portal vein thrombosis. Patients with extrahepatic disease are not appropriate candidates for SIRT, which is a liver-directed therapy.
Intervention(s)	SIR-Spheres® Y-90 resin microspheres, TheraSphere, QuiremSpheres	**[Population 1 – TACE-eligible].** People with unresectable early (BCLC stage A), intermediate stage (BCLC stage B) or advanced HCC (BCLC stage C), for whom transarterial chemoembolisation therapies (TACE, DEB-TACE) are appropriate: • SIR-Spheres® Y-90 resin microspheres • TheraSphere	QuiremSpheres are excluded because no evidence was identified for the efficacy or safety of this intervention.
		[Population 2 – TACE-ineligible]. People with unresectable intermediate stage (BCLC stage B) or advanced HCC (BCLC stage C), for whom any transarterial embolisation are inappropriate, with or without portal vein thrombosis/involvement, without extrahepatic disease: • SIR-Spheres® Y-90 resin microspheres	TheraSphere and QuiremSpheres are excluded because no evidence was identified for the efficacy or safety of these interventions.

Comparator(s)	Unresectable HCC: • The interventions will be compared with each other: • Transarterial embolisation (TAE) • Conventional transarterial chemoembolisation using lipiodol (TACE) • Transarterial chemoembolisation using drug-eluting beads (DEB-TACE) (doxorubicin and cisplatin do not currently have a marketing authorisation in the UK for HCC).	**[Population 1 – TACE-eligible].** People with unresectable early (BCLC stage A), intermediate stage (BCLC stage B) or advanced HCC (BCLC stage C), for whom transarterial chemoembolisation therapies (TACE, DEB-TACE) are appropriate: • The interventions will be compared with each other: • Conventional transarterial chemoembolisation using lipiodol (TACE) • Transarterial chemoembolisation using drug-eluting beads (DEB-TACE) (doxorubicin and cisplatin do not currently have a marketing authorisation in the UK for HCC).	TAE is excluded because no studies were identified that allowed a network meta-analysis of this comparator versus SIR-Spheres in equivalent populations.
	For people for whom any transarterial embolisation are inappropriate: • Established clinical management without SIRT (including but not limited to target chemotherapy).	**[Population 2 – TACE-ineligible].** People with unresectable intermediate stage (BCLC stage B) or advanced HCC (BCLC stage C), for whom any transarterial embolisation are inappropriate, with or without portal vein thrombosis/involvement, without extrahepatic disease: • Systemic therapy (sorafenib, lenvatinib)	Best supportive care is excluded as a comparator because it is reserved for patients who are not fit for any active treatment. Established clinical management is limited to systemic therapy with sorafenib or lenvatinib in UK clinical practice. Regorafenib is excluded as a comparator because it is only recommended in the UK for second-line systemic therapy. However, regorafenib has been included only as a subsequent treatment option.
Outcomes	• Overall survival • Progression-free survival • Time-to-progression • Response rates • Rates of liver transplantation or resection • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Time-to-progression • Response rates • Rates of liver transplantation or resection • Adverse effects of treatment • Health-related quality of life • Time on treatment/ number of treatments	Time on treatment/number of treatments are added as an outcome because this can affect the relative costs and effectiveness of the interventions and comparators: (a) The SIRT interventions have different administration methods, which can result in multiple treatment sessions being necessary for a complete administration. (b) TACE is usually administered in multiple sessions (c) Sorafenib and lenvatinib are usually administered until progression.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical	**[Population 1 – TACE-eligible].** People with unresectable early (BCLC stage A), intermediate stage (BCLC stage B) or advanced HCC (BCLC stage C), for whom transarterial chemoembolisation therapies (TACE, DEB-TACE) are appropriate: • Cost-minimisation model	The available clinical evidence was insufficient to develop a cost-effectiveness model. There was important uncertainty on the relative effectiveness of the interventions and the comparators in terms of overall survival (Section 8.1.2). No evidence was available in terms of progression-free survival. Costs of the interventions and comparators are compared.

	and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. The economic modelling should include the costs associated with any work-up phase to identify patients that are not likely to benefit from SIRT. A sensitivity analysis should be provided without the cost of the work-up phase. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the comparator technologies will be taken into account.	**[Population 2 – TACE-ineligible].** People with unresectable intermediate stage (BCLC stage B) or advanced HCC (BCLC stage C), for whom any transarterial embolisation are inappropriate, with or without portal vein thrombosis/involvement, without extrahepatic disease: • Decision-analytic cost-utility model with Monte Carlo simulation, developed in accordance with the NICE reference case • NHS and PSS perspective • 3.5% discount rate for costs and QALYs • Scenario analyses to test the sensitivity of the model to changes in structural assumptions of the model • One-way and two-way sensitivity analyses around key parameter values	This model complies with the reference case.
Other considerations	Guidance will only be issued in accordance with the CE marking. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the CE marking.	Guidance will only be issued in accordance with the CE marking. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the CE marking.	No changes.
	If the evidence allows the following subgroups will be considered:	The following subgroups will be considered in **Population 2 – TACE-ineligible**, for people for whom any transarterial embolisation are inappropriate:	Subgroups were only considered in **Population 2 – TACE-ineligible**, in which the clinical evidence allowed this. Available clinical evidence did not allow for stratification into subgroups in **Population 1 – TACE-eligible.** for people for whom transarterial chemoembolisation therapies (TACE, DEB-TACE) are appropriate (Section 8.1).
	• People with unresectable HCC for whom treatments for down-staging to resection or transplantation or as a bridge to	*Removed as a subgroup analysis.*	People for whom treatments for down-staging to resection or transplantation or as a bridge to transplantation are considered appropriate treatment options are excluded from subgroup analyses because:

	transplantation are considered appropriate treatment options		(a) Patients suitable for down-staging to resection or transplantation do not constitute a clinically identifiable subgroup at presentation. All patients enrolled in the Phase III SARAH trial of SIRT versus sorafenib had unresectable HCC at presentation, however 5-12% patients receiving SIRT have been down-staged to receive liver transplantation, tumour resection or ablation (6). (b) Patients suitable for bridge to transplantation should be considered as having resectable HCC (1, 9) and should therefore be excluded from the decision problem.
	Not applicable.	• Patients with a tumour burden ≤25% and a preserved liver function (ALBI grade 1), as a base case for the submission.	Clinical guidelines (1, 9) have recommended tumour burden and liver function as key factors in the clinical decision-making for loco-regional therapy, including SIRT. These affect the relative clinical effectiveness and cost-effectiveness of SIR-Spheres compared to sorafenib, due to differences in the mode of action between SIRT and systemic therapy. UK clinicians have reported that patients in the subgroup are appropriate candidates for SIR-Spheres (8)
	• People with unresectable HCC with portal vein thrombosis/involvement.	• People with unresectable HCC with portal vein thrombosis/involvement.	No changes.

2 Intervention

2.1 SIR-Spheres description and mode of action

SIR-Spheres® Y-90 resin microspheres consist of sterile, single-use, resin microspheres containing yttrium-90 that are supplied as 3 GBq yttrium-90 per vial in 5 mL water for injection in a lead-shielded shipping vial. Each vial contains 40 to 80 million microspheres, ranging from 20 to 60 micrometres in diameter (median diameter 32.5 micrometres). The maximum range of beta emission in tissue is 11 mm with a mean of 2.5 mm. Other characteristics of the product are summarised in Table 2, page 20.

Figure 1. V-vial, source vial and lead-shielded shipping vial for SIR-Spheres

Mode of action

Liver tumours receive most of their blood supply from the hepatic artery; in contrast, normal liver parenchyma receives most of its blood supply from the portal vein. Liver tumours also have greater microvascular density than the surrounding liver parenchyma (10). Selective internal radiation therapy (SIRT), also known as radioembolisation or transarterial radioembolisation (TARE) utilises the unique opportunity arising from these differences in vascular supplies and microvascular densities to selectively deliver radiation therapy to the liver tumour, minimising radiation exposure to non-malignant liver tissue.

During the procedure, SIR-Spheres are infused slowly into the hepatic artery at the site of the tumour using a flexible catheter passed through the femoral artery. SIR-Spheres travel in the bloodstream into the microvasculature of the tumour, becoming lodged in the arterioles around the tumour rim, from where they release beta radiation that kills tumour cells. The half-life of 64.1 hours means that 94% of the radiation is released over 11 days (11). The tumour cells are killed by the radiation alone, with minimal embolic effect, meaning that SIR-Spheres can be safely used in patients with portal vein thrombosis (1, 12).

Table 2. Technology being appraised

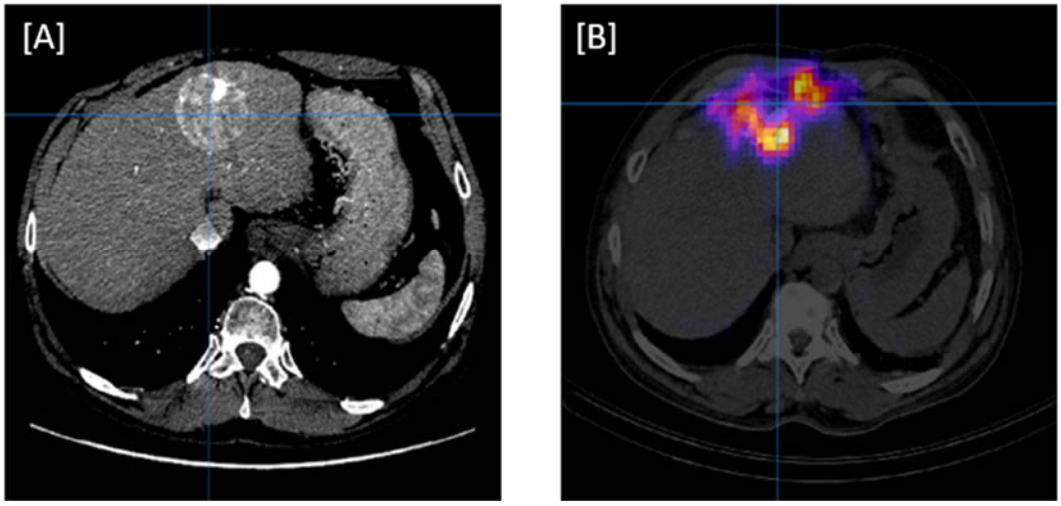
UK approved name and brand name	SIR-Spheres® Y-90 resin microspheres (Yttrium-90 resin microspheres)
Mechanism of action	SIR-Spheres yttrium-90 (Y-90) resin microspheres become lodged in the arterioles around the growing rim of the liver tumour where they emit beta-radiation with a mean energy of 0.93 MeV over a mean range of 2.5 mm. The half-life of 64.1 hours means that 94% of the radiation is delivered in 11 days (Sir-Spheres Package insert HCC)(11). The anti-tumour effect is not via embolisation but is purely due to radiation (1, 12, 13).
Marketing authorisation/CE mark status	SIR-Spheres has received a CE mark as an active implantable medical device in October 2002. The CE mark covers the microspheres, delivery system and v-vial.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	SIR-Spheres are indicated for the treatment of advanced inoperable liver cancer. SIR-Spheres are contraindicated in patients who have had previous external beam radiotherapy to the liver; ascites or clinical liver failure; markedly abnormal liver function tests; >20% lung shunting of hepatic artery blood flow; pre-assessment angiogram that demonstrates abnormal vascular anatomy that would result in significant reflux of hepatic arterial blood to the stomach, pancreas or bowel; been treated with capecitabine within the two previous months, or who will be treated with capecitabine at any time following treatment with SIR-Spheres microspheres.
Method of administration and dosage	SIR-Spheres are provided in a vial containing 3GBq of yttrium-90 with 5 mL water for injection shipped in a 6.4 mm thick lead pot. They are implanted into hepatic tumours via the common, right or left hepatic artery using a catheter in the femoral artery or implanted port in the hepatic artery under X-ray guidance. Individual dosing is determined either by a body surface area (BSA) model using the patient's height and weight and the tumour burden, or by a partition model based on maximum safe doses to the liver parenchyma or lung. Administered activities are usually between 1.3 and 3.0 GBq (11).
Additional tests or investigations	SIR-Spheres are administered after an initial work-up with hepatic angiography and 99mTc-macroaggregated albumin [MAA]-SPECT/CT scan has determined suitable predicted dosimetry, tumour vascularity and lung shunting, and liver function tests have shown adequate liver function (11).
List price and average cost of a course of treatment	List price: £8,000. Patients receiving SIR-Spheres will undergo a work-up and a treatment procedure, performed as separate hospital admissions, classified in HRG code YR57Z. Total average cost of a full course of treatment is estimated at £13,239 in the economic model (section 7.2.4.1.1, page 63)
Patient access scheme (if applicable)	N/A

Patient selection

Patients considered for SIRT undergo a work-up. This is used both to confirm eligibility of the patient for the SIRT procedure, and to plan the administration of this procedure. This applies to all patients considered for SIR-Spheres, across the two populations defined in the decision problem (Section 1). The processes of patient selection and calculation of the individual dose and activity are crucial to maximise the likely benefit and minimise toxicity of the treatment. Work-up prior to administration of SIR-Spheres takes approximately one hour and determines patient eligibility, based on the following criteria (11):

- tumour vascularity determined by hepatic angiogram;
- lung shunting (the proportion of microspheres likely to reach the lung tissue via the liver vasculature), shunting to the stomach or duodenum, and uptake of a surrogate marker for the microspheres by tumours in the liver. These are determined with a ^{99m}Tc-macroaggregated albumin [MAA]-SPECT/CT scan – images reproduced in Figure 2, page 21;
- residual liver function (such as serum bilirubin <3 mg/dL (14) or ALBI grade 1); and
- disease spread and portal vein involvement, determined by X-ray, CT scan, ultrasound and bone scans.

Figure 2. Baseline CT and pre-treatment SPECT/CT imaging



[A] Baseline CT scan showing a large solitary tumour; [B] Pre-treatment SPECT/CT showing appropriate tumour uptake of ^{99m}Tc-MAA. Source: Hermann et al. 2018 (15)

Calculation of dose and activity

The amount of radioactivity ("activity") of yttrium-90, expressed in GBq, is determined for each patient using approved activity calculation methods. A typical treatment with SIR-Spheres consists of infusing 1.4 to 2.0 GBq of activity, equivalent to 30 to 40 million resin microspheres at calibration time, into the hepatic artery or arteries supplying the target tumour(s). Activity calculation is performed as part of the work-up.

In the UK, the dose delivered to the patient's liver is usually calculated through the BSA method, which adjusts the amount of administered activity according to the size and weight of the patient and the volume of the tumour compared to the target lobe and total liver. Alternatively, the partition method is used, which calculates the maximum activity that will not exceed safe radiation doses to the normal liver and lung (11).

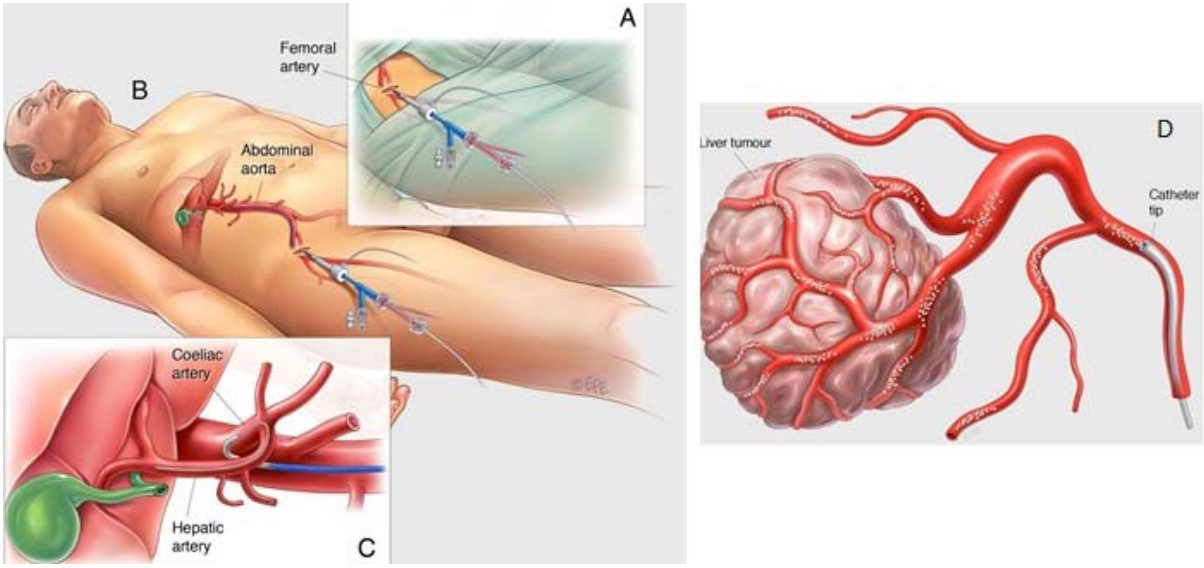
Treatment administration

The procedure is usually performed under sedation and local anaesthetic by a specially trained interventional radiologist, and intravenous analgesia may be needed. It takes approximately 1 hour and is carried out under X-ray guidance. SIR-Spheres are useable for up to 24 hours after calibration (16).

As depicted in Figure 3, page 22, the radiologist makes a small incision into the femoral artery near the groin (A). A micro catheter is then guided through the femoral artery to a pre-specified site in the hepatic artery (identified as part of pre-treatment planning) (B). SIR-Spheres are administered through this catheter (C), from where they travel directly to the tumour microvasculature (D). During the procedure, a syringe containing contrast medium is connected to the delivery system, allowing intermittent contrast medium injection to maintain forward flow throughout and to allow the clinician to track the distribution of the microspheres.

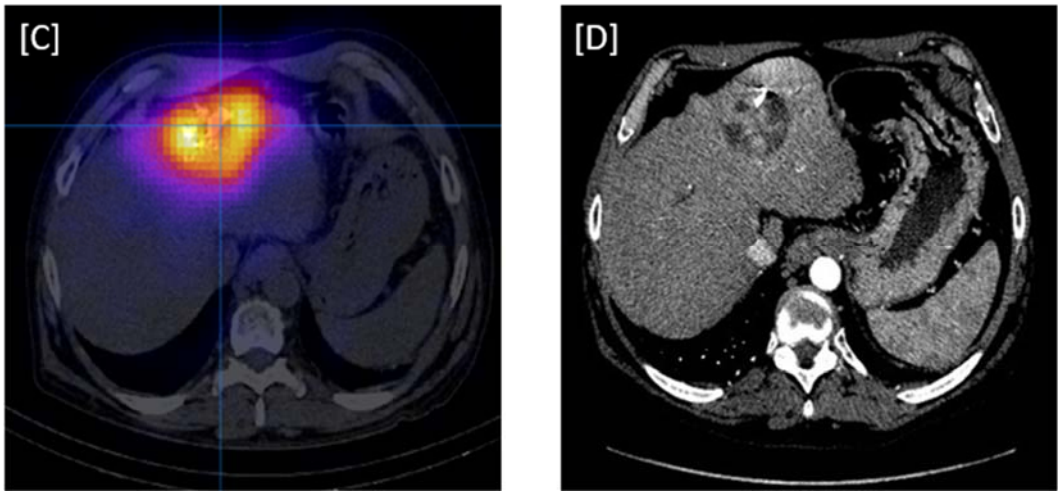
It is recommended that within 24 hours of administration, a SPECT/CT scan (which detects the Bremsstrahlung radiation from the Y-90) or positron emission tomography (PET) scan is performed to confirm that placement of SIR-Spheres Y-90 resin microspheres is confined to the liver. Post-treatment SPECT/CT images are reproduced in Figure 4, page 22.

Figure 3. Administration of SIRT using SIR-Spheres Y-90 resin microspheres



Key: SIRT, selective internal radiation therapy; Y-90, yttrium-90.

Figure 4. Post-treatment SPECT/CT imaging and response assessment



[C] Post-treatment ^{90}Y SPECT/CT showing tumour uptake of SIR-Spheres
[D] 6-month follow-up CT showing disease control per RECIST. Source: Hermann et al. 2018 (15)

Traditionally, workup and administration would be scheduled as separate appointments 1-2 weeks apart; however, practice may evolve with increased experience to a single appointment for both procedures in the future (17). Furthermore, clinicians in the UK have reported increasing use of a transradial vascular approach instead of the transfemoral approach, allowing for patients to receive outpatient care. Both evolutions could reduce the delay in receiving the treatment and minimise costs to the patient and healthcare providers.

SIRT normally uses existing personnel, skills, equipment and physical infrastructure, as all investigations and procedures associated with SIR-Spheres Y-90 resin microspheres are used in routine clinical practice and covered by standard PbR tariffs.

Dedicated accessories are provided by Sirtex to meet the general principles of radiation safety and to assist in the handling of SIR-Spheres Y-90 resin microspheres. Directions for the use of the SIR-Spheres Delivery Set are included with the device and users are required to undergo a full training and evaluation program, including proctor-supervised cases, before being certified by Sirtex for routine use of SIR-Spheres (18).

2.2 *Other SIRT technologies*

Although clinical guidelines do not currently differentiate between different types of SIRT (1, 9), there are some important differences that can affect the patient experience and healthcare resource use when using SIR-Spheres, TheraSphere or QuiremSpheres. These are presented in Table 3 and described in more detail below.

Table 3. Differences between SIRT technologies

	SIR-Spheres Y-90 resin microspheres	**TheraSphere**	**QuiremSpheres**
Manufacturer	Sirtex Medical	BTG	Quirem Medical / Terumo
Differences in characteristics affecting the clinical effectiveness or safety of SIRT			
Isotope	Yttrium-90 Half-life: 64.1 hours β^- emission: ~100% E_{max} : 2.28 MeV E_{avg} : 0.933 MeV γ emission: none	Yttrium-90 Half-life: 64.1 hours β^- emission: ~100% E_{max} : 2.28 MeV E_{avg} : 0.933 MeV γ emission: none	Holmium-166 Half-life: 26.8 hours β^- emission: 93.4% E_{max} : 1.77 MeV (48.7%) 1.86 MeV (50.0%) E_{avg}: 0.665 MeV γ emission: 6.7% E_{avg}: 81 keV
Material	Resin	Glass	Poly-L-lactic acid
Radioactivity per micro-sphere at calibration time	50 Bq	2 500 Bq	450 Bq
Number of microspheres in a 3 GBq total dose	40-80 million	1.2 million	Estimated at 6.7 million
Administration procedure	Controlled, pulsatile infusion with contrast material under X-ray guidance	One-off complete injection without X-ray guidance	Controlled, pulsatile infusion under MRI guidance
Work-up imaging procedure	Uptake of ^{99m}Tc-MAA under SPECT/CT scan	Uptake of ^{99m}Tc-MAA under SPECT/CT scan	Uptake of a non-therapeutic dose of Ho-166 microspheres
Dose calculation method	BSA or partition model, validated in Phase III randomised trials	MIRD model, no validation in Phase III randomised trials	MIRD model, no validation in Phase III randomised trials
Impact on clinical effectiveness or safety	**Due to the differences between SIRT devices, this submission only presents SIR-Spheres in the base case analysis, equal efficacy or safety are not assumed in any of the economic models in this submission.**		
Differences in characteristics affecting the resource use for SIRT			
Treatment strategy for patients with bi-lobar disease	Single session, whole-liver treatment with multiple injections points	Sequential lobar treatment in two separate admissions	No information available
Dose preparation flexibility	Source vial can be divided in different v-vials for injection in different points of hepatic arterial network	Source vial cannot be divided, multiple injections require multiple doses	No information available
Impact on resource use	**Most patients will receive treatment using a single vial of SIR-Spheres, as opposed to TheraSphere requiring a vial for each injection and each treated lobe. This will result in additional costs for patients requiring more than one injection, in case of a large tumour having multiple arterial afferences, or multiple tumours spread in both liver lobes (bi-lobar disease). This is reflected in a lower number of procedures per patient being observed for SIR-Spheres vs. TheraSphere and being used in the cost minimisation model provided for Population 1 – TACE-eligible patients.**		

Differences in administration procedures affecting the clinical effectiveness or safety of SIRT

SIR-Spheres are infused with intermittent injection of contrast medium to confirm forward flow throughout the procedure and to allow the clinician to track the distribution of the microspheres. This results in the ability to interrupt the infusion of SIR-Spheres should the contrast medium show that too much of the dose is being delivered to non-target healthy gastrointestinal tissues, for example due to retrograde blood flow.

TheraSphere or QuiremSpheres are not infused with contrast medium (19, 20). This is particularly important because non-target deposition of SIRT microspheres can be associated with severe complications, and the interventional radiologist is unlikely to be able to detect that the shunting of TheraSphere is occurring in adequate time to stop the infusion (11, 19, 20).

Differences in dosage affecting the clinical effectiveness or safety of SIRT

Despite carrying the same radioactive isotope yttrium-90, SIR-Spheres and TheraSphere cannot be considered equivalent due to differences in both dosage and administration methods. The average radioactivity per microsphere at the time of calibration varies by 50-fold between the two devices: 50 Bq per microsphere for SIR-Spheres versus 2,500 Bq for TheraSphere (21). Due to the lower activity per microsphere, a typical treatment using SIR-Spheres is performed with approximately 10-15 times more microspheres than a treatment with TheraSphere (21).

This can affect patient outcomes, because the aim of SIRT is to provide sufficiently uniform, tumouricidal doses of radiation to target tumours, while minimising exposure of non-tumoral tissue. Distribution of SIRT microspheres in tumour and liver tissue is guided by blood flow and therefore presents a degree of heterogeneity (21, 22). A higher number of injected microspheres will increase the homogeneity of the radiation dose delivered to the tumour (22): conversely, a lower microsphere density in the treated tissue may cause a greater fraction of tumour to receive a lower absorbed dose (22).

Because of this risk, higher amounts of injected radioactivity (21) and of tumour-absorbed dose (22, 23) are recommended for the administration of TheraSphere compared to SIR-Spheres, such that a tumoricidal dose can be attained in tumour regions receiving less of the injected TheraSphere microspheres. This is reflected in specific dose calculation methods being used for each device, per their licensed instructions for use: both QuiremSpheres and TheraSphere are using the Medical Internal Radiation Dose (MIRD) model, which has not been validated in Phase III trials to date.

These differences between SIR-Spheres and TheraSphere may result in different outcomes of SIRT using either device, both in terms of effectiveness and safety, because increased injected radioactivity and radiation dose to the non-tumoural liver parenchyma are associated with increased risks of liver complications of SIRT (14, 23). Due to this and to the considerable differences in the quantity and quality of evidence supporting SIRT devices, equal efficacy cannot be assumed between these devices.

Differences in number of procedures, healthcare resources utilisation and patient burden

Differences in the administration procedures for both devices can also affect the patient experience and impact the use of healthcare resources. SIR-Spheres can be administered to both lobes of the liver in one session, as seen in clinical trials and registry studies (7, 24, 25). This is because the source vial for this product can be prepared into multiple v-vials for administration in different hepatic arteries of a single patient, each feeding different tumoural regions.

In contrast, TheraSphere vials cannot be split, and one vial is required for each injection. This will result in additional resource use, with an increased number of vials being required. For patients with bi-lobar disease,

this implies that TheraSphere can only be administered in one lobe per session (19) and that whole-liver treatment requires two sequential hospital admissions.

This results in a higher number of treatment sessions per patient for TheraSphere versus SIR-Spheres, when comparing the largest published observational studies on each SIRT technology (26, 27). The majority (95.9%) of patients in the ENRY register who received whole-liver treatments with SIR-Spheres had this as a single session through one or more injections (26). In total 93.2% of patients received a single treatment, with a mean of 1.08 treatments per patient. In contrast, a published analysis of 1,000 patients who received SIRT with TheraSphere reported a median 1, mean 1.58 and range of 1 to 8 treatments per patient (27): this may be explained by the administration method for TheraSphere, using only segmental or lobar injections (i.e. no whole-liver, single-session treatment is possible). This is supported by a recent audit of patients receiving SIRT at a specialist centre in England, which found that patients received a mean of [redacted] treatments with SIR-Spheres vs. [redacted] treatments with TheraSphere (28).

The differences between average numbers of treatments per patients are reflected in the economic model developed for the TACE-eligible patient population (Population 1), in which TheraSphere is considered a comparator.

3 Epidemiology

HCC is a cancer composed of malignant hepatocytes, developing in the liver parenchyma. HCC is the predominant histology of primary liver cancer, accounting for 50% of all cases in the UK (29). There were an estimated 7,618 new cases of liver cancer in the UK in 2018, an age-standardised rate of 5.1 per 100,000 and accounting for 1.7% of all new cancer diagnoses that year (30). The incidence and mortality of HCC are projected to increase over the next 20 years (29).

Liver cancer disproportionately affects men and the most deprived adults of either gender in the UK, with age-standardised incidence in 2006 to 2010 of 4.7 per 100,000 for men and 2.4/100,000 for women in the least deprived quintile, compared with 9.7/100,000 for men and 4.2/100,000 for women in the most deprived quintile (29).

Liver cancer also disproportionately affects older adults, with an age-standardised incidence of 52.2/100,000 adults aged 80+ years in the UK in 2013-15 compared with 36.5/100,000 in those aged 70 to 79 and 19.8/100,000 in those aged 60 to 69 years (29).

4 HCC: a complex disease

The presentation and management of HCC are complex because of the interaction between two aspects of the disease: impaired liver function and cancer.

4.1 Underlying liver disease

The liver is the largest internal organ of the body and receives 25% of total cardiac output at rest (more than any other organ). It is estimated that the liver performs over 500 different critical functions (31-33). Hepatocytes make up approximately 80% of the liver's mass and are the chief functional cells of the liver, performing several crucial metabolic, endocrine and secretory processes, including detoxification, metabolism and storage of nutrients, protein synthesis and production of biochemicals necessary for digestion (bile)(31, 34).

The majority of HCC occurs in patients with underlying liver disease, mostly as a result of hepatitis B or C virus (HBV or HCV) infection or alcohol abuse (35). In Western Europe, 32% of HCC cases are secondary to alcohol

abuse, 13% to chronic HBV infection, 44% to chronic HCV infection and 10% due to other causes (1), all of which damage hepatocytes resulting in impaired liver function. Patients with chronic liver disease have sustained hepatic inflammation, fibrosis, and aberrant hepatocyte regeneration (35).

Considering the critical role of the liver, patients with liver disease can experience significant physical burden independently from the risk of mortality induced by the progression of liver cancer. People with compensated cirrhosis (severe scarring of the liver but with enough healthy cells for the liver to perform all normal functions) can develop decompensation of liver function (where the liver is not capable of performing all normal functions) with symptoms including ascites, peripheral oedema, encephalopathy and jaundice. In addition, patients with cirrhosis often have a condition called portal hypertension that can result in the development of oesophageal varices. The latter may result in haemorrhage, which can be further complicated by the decompensation of liver function (36-38). People with chronic, decompensated liver function have a very poor prognosis and receive best supportive care in clinical practice. Underlying liver disease is associated with an independent risk of mortality, separate from liver cancer in terms of progression and treatment; consequently, the overall prognosis for HCC is very poor (35).

Several scores and classifications have been proposed to describe liver function such as the Model for End-Stage Liver Disease (MELD) score, calculated based on serum bilirubin, serum creatinine, and the international normalized ratio for prothrombin time (INR), or the Child-Pugh score, based on liver function tests and clinical symptoms of liver failure. The Child-Pugh score is the most commonly used system used for classification of liver function in UK clinical practice, however this system has been criticised for including subjective assessments of liver failure (1). Clinicians have also stated that this system may not be sensitive enough to identify sub-clinical signs of liver failure, among Child-Pugh A patients (those considered to have the best prognosis) (39). The albumin-bilirubin (ALBI grade) has been validated by clinical guidelines as an alternative measure of liver function which allows subgrouping of Child-Pugh A patients (1).

4.2 *Liver cancer*

The inflammation, fibrosis and aberrant hepatocyte regeneration observed in patients with chronic liver disease can cause cirrhosis and a series of genetic and epigenetic alterations that can culminate in the formation of pre-cancerous nodules. Additional molecular alterations provide these abnormal cells with the capacity to proliferate and invade surrounding tissue, completing the transition to full-blown HCC. HCC can also arise in patients who have chronic liver disease but do not have established cirrhosis or marked inflammation (e.g., patients with HBV infection) (35).

HCC is a severe health condition with poor prognosis. Primary liver cancer accounted for 6,836 deaths in the UK in 2018, or 3.8% of all cancer deaths that year (30), a figure close to the incidence of primary liver cancer the same year and reflecting the severity of this disease. In addition to the poor survival prognosis, HCC has a significant impact on patients' well-being. At diagnosis, common physical symptoms of HCC include hepatomegaly, abdominal pain and weight loss (this symptom triad is observed in 90–95% of patients) (36-38). Alongside this physical burden, HCC can markedly affect the psychological well-being of patients; patients with HCC were reported to have the third highest level of psychological distress or depression in a survey across patients with 14 cancer types (36, 40). Formal assessment of health-related quality of life (HRQL) demonstrates a statistically significant and clinically meaningful reduction in HRQL of patients with HCC compared with generally healthy people, people with chronic liver disease/cirrhosis and people with heterogeneous cancer (41). HRQL is shown to decrease with advancing stage disease; in addition to the progressive symptom burden, this is likely related to worsening prognosis and treatment modalities (41, 42).

As well as the direct burden on patients, HCC poses a significant burden to carers, health services and wider society. Almost half (45%) of all patients with chronic liver disease receive help from an informal carer who

themselves can experience deteriorating mental health and a substantial negative impact on daily activity as a result of care provision (43). The economic burden of HCC is mainly driven by direct costs to health services, specifically hospitalisation costs (44). Productivity loss of patients and carers can add to the economic burden of this disease, with HCC associated with a productivity loss of 1.5–2.8 days/patient/month depending on aetiology (44).

Many treatments for HCC, whilst potentially effective in treating the cancer, have the potential to have a detrimental effect on the background liver function and may themselves contribute to decompensation (notably for surgery and TACE) (1).

4.3 *Staging*

The most commonly adopted staging system for the classification and management of patients with HCC is the Barcelona Clinic Liver Cancer (BCLC) staging system, summarised in Table 4. This incorporates measures of tumour burden, similar to the Tumour-Node-Metastasis (TNM) system used with other solid tumours. However, use of TNM system alone is considered inadequate because it does not include measures of liver function or performance status (1).

Table 4. BCLC staging system

Stage	Description	Tumour burden	Liver function	Performance status
0	Very early HCC	Single nodule <2cm in diameter	Child–Pugh A	ECOG 0
A	Early HCC	Single nodule or up to 3 nodules <3cm in diameter	Child–Pugh A or B	ECOG 0
B	Intermediate HCC	Multiple nodules	Child–Pugh A or B	ECOG 0
C	Advanced HCC	Macrovascular invasion (*portal vein involvement*) and/or extrahepatic spread (lymph nodes or other organs)	Child–Pugh A or B	ECOG 1–2
D	End-stage HCC	-	Child–Pugh C	ECOG >2

Key: BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma.
Source: Forner et al. 2010, Llovet et al.2003 (45, 46).

5 Available treatment options

For patients with early stage HCC, there is the potential for long-term survival with liver transplantation or removal of tumours through surgical resection or local ablation. Clinical guidelines are therefore unanimous in their recommendation for first-line treatment with liver transplantation or tumour removal when proper indications are met (1, 9, 47).

Most patients with HCC in the UK (~80%) are however not amenable to potentially curative therapy at presentation, with 22% presenting with intermediate (BCLC B), 25% with advanced (BCLC C) and 33% with end-stage disease (BCLC D) in 2014 (48). Over half of all patients undergoing surgical resection or local ablation also experience local or distant disease recurrence within 5 years (49-59).

For patients with unresectable HCC who are not amenable to potentially curative therapy, recommended treatment options are generally restricted to transarterial chemoembolisation (TACE) or systemic therapy, of which sorafenib is the most established in current practice (1, 9, 47). Which of these treatments is more suitable is determined on assessment of multiple disease characteristics, with the BCLC staging system commonly recommended for treatment allocation decisions.

It is important to acknowledge that there is notable heterogeneity across patients within the same BCLC stage, which may result in "treatment stage migration" (1): clinical guidelines recognise that a proportion of patients in a given BCLC stage do not fulfil all criteria for recommended treatment allocation and should be offered other therapies.

While TACE and sorafenib offer active treatment options to patients for whom best supportive care was the only management option prior to their introduction, they do have a number of limitations such that they do not always meet therapeutic goals in unresectable HCC, which are to slow progression of disease, prolong survival and improve patient HRQL.

In the next sections we provide more detail on the following treatments:

- TACE: including conventional TACE and TACE using embolic drug-eluting beads;
- Systemic therapy, including sorafenib and lenvatinib.

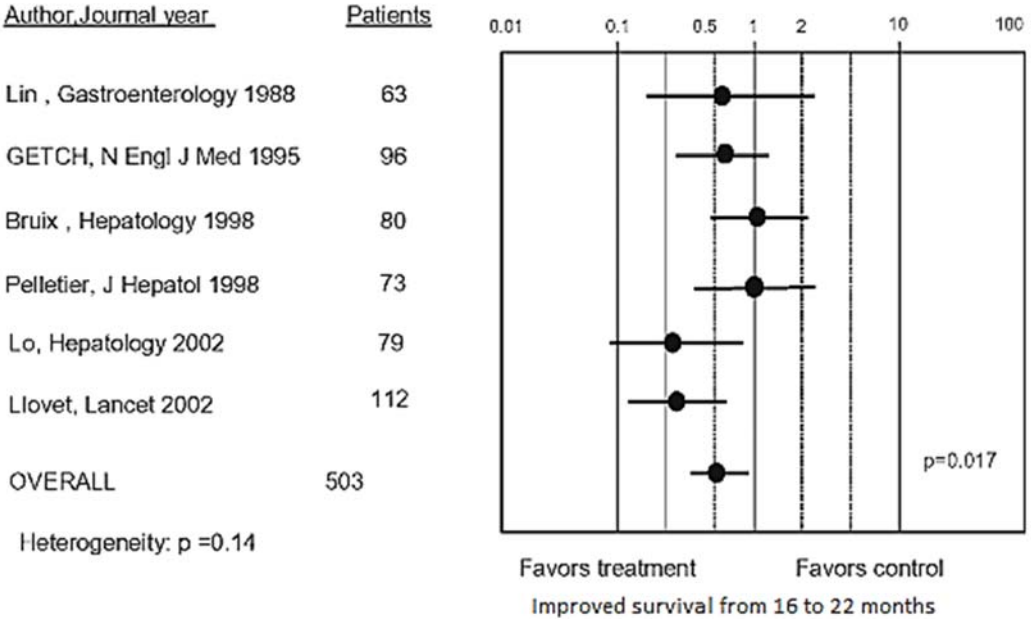
5.1 *Transarterial chemoembolisation*

Two main procedures are covered under the generic denomination of TACE: conventional TACE (cTACE) and TACE using embolic drug-eluting beads (DEB-TACE). Conventional TACE involves the intra-arterial injection of a chemotherapeutic emulsion followed by embolisation of the blood vessel with an embolic agent to achieve a cytotoxic effect enhanced by ischaemia (60, 61). Several chemotherapy agents have been used for cTACE, but the most commonly used are doxorubicin and cisplatin. There are also several embolic agents available, including gelatine sponges, polyvinyl alcohol (PVA) particles and microspheres. In more recent years, the introduction of embolic drug-eluting beads has offered a more consistent approach to TACE with better repeatability (60).

While TACE in general has been uniformly adopted in clinical practice, its therapeutic efficacy for HCC is still a matter of clinical debate, with the Cochrane Group reporting an "absence of evidence of TACE having a beneficial effect on survival in participants with unresectable HCC"(62). While several biases in the Cochrane investigation diminish its impact, and many clinical studies do report tumour necrosis with TACE in HCC, response rates markedly vary (ranging from 15 to 60%), and a positive correlation between tumour necrosis and long-term benefit is not consistently observed (61).

One of the largest randomised controlled trials (RCT) investigating the use of TACE for patients with early or intermediate stage HCC (BCLC Stages A/B) not suitable for potentially curative therapy is the Phase II PRECISION V trial, which compared cTACE with DEB-TACE (both doxorubicin-based)(63). In the primary efficacy analysis, DEB-TACE was not shown to be superior to cTACE as measured through tumour response (p=0.11); similar rates of complete response (27% vs 22%), objective response (52% vs 44%) and disease control (63% vs 52%) were observed in both groups (DEB-TACE vs cTACE) (63). This study did not collect survival data, but an associated study in a smaller patient group in Italy (Precision Italia) similarly failed to meet the primary hypothesis of a superior 2-year survival benefit with DEB-TACE compared with cTACE (57% vs 55%; p=0.949)(64). However, a naïve crude comparison of these data with survival estimates for patients with BCLC Stage B HCC does suggest a survival benefit with TACE compared to no treatment, as reported in a meta-analysis of early trials of transarterial embolisation (TAE) or TACE versus conventional management, depicted in Figure 5. A more recent analyses that compared survival of Stage I/II unresectable HCC patients treated with DEB-TACE to survival of a matched population from the Surveillance, Epidemiology and End Results (SEER) database managed with best supportive care (no active treatment) reported a significant improvement in overall survival (OS) with DEB-TACE treatment: 28.9 versus 10.0 months; p<0.0001 (65).

Figure 5. Meta-analysis of RCTs comparing 2-year OS with TAE/TACE vs conservative management



Key: RCT, randomised controlled trial; TACE, transarterial chemoembolisation; TAE, transarterial embolisation. Source: Bruix et al. 2004 (66)

While there is inconsistency in the TACE data, supporting the conclusions of the Cochrane Group, this appears in part to be attributed to the exact technique adopted, but is also likely to be heavily influenced by differences in the disease characteristics of patients undergoing treatment. Patients with intermediate stage HCC (BCLC Stage B) are a significantly heterogeneous group, and median survival estimates range from 16-40 months depending on their suitability for treatment (1). To give some granularity to the BCLC staging system, several sub-classification tools for BCLC Stage B disease have been proposed (66). None of these tools have been uniformly adopted but all have a commonality in that they generally assess liver function and tumour burden; this is applied during patient assessment for treatment eligibility in clinical practice.

Specific characteristics associated with negative survival outcomes with TACE are summarised in Table 5. In general, patients with lobar disease, ≤5 nodules and low tumour volume (with no macrovascular invasion) are considered 'ideal' candidates for TACE, and those with bi-lobar disease, >5 nodules, high tumour volume (bulky disease) and portal vein tumour thrombosis (PVTT) are considered 'poor' candidates (67, 68). Of patients considered poor candidates for TACE, some may "stage migrate" to treatment with sorafenib; others may still be treated with TACE in the absence of a better option in the opinion of the treating physician but with limited expectation of a good response (8).

Table 5. Characteristics associated with negative survival outcomes with TACE

Patient characteristics	Disease characteristics	Treatment characteristics
• Child–Pugh C or B • Presence of ascites • AFP ≥400ng/mL • Bilirubin >30mg/L • WHO PS 1-4	• ≥3 liver lesions • Tumour ≥5cm • Multi-nodular or diffuse • Bi-lobar tumour • Extrahepatic spread • PVTT	• Multiple treatment sessions • Lobar embolisation (compared with super selective embolisation)

Key: AFP, alpha-fetoprotein; PS, performance status; PVTT, portal vein tumour thrombosis; TACE, transarterial chemoembolisation; WHO, World Health Organization. Source: Raoul et al. 2011(69).

Alongside the limitation of a consistent therapeutic efficacy profile, TACE is also associated with important safety concerns. Embolisation can cause considerable pain and discomfort immediately after the procedure with post-embolisation syndrome, consisting of transient fever and abdominal pain, reported in approximately 80% of patients with unresectable HCC undergoing TAE/TACE (62). Elevated hepatic transaminases typically accompany post-embolisation syndrome. There are also numerous, less common but severe AEs that have been associated with TACE treatment, including acute renal failure, acute gastroduodenal ulcerations, ascites, encephalopathy, transient liver failure, cholecystitis, bacteraemia and administration site bleeding (62). DEB-TACE is thought to have an improved safety profile compared to cTACE, but no significant differences in serious adverse events (SAE) related to study-treatment are observed in key trials; however, there does appear to be some improvement in post-procedural pain and chemotherapy-related AEs with DEB-TACE (63, 64). In addition, the use of selective TACE to maximise the amount of the chemotherapeutic dose directed to the tumour (and thus minimise the amount of the chemotherapeutic agent that could damage the normal liver tissue) can reduce the risk of AEs (61).

These safety concerns, particularly pain/discomfort and potential liver decompensation, could have a detrimental impact on the patient's quality of life. Indeed, formal assessment of HRQL of patients with HCC treated with TACE in clinical trials demonstrates a reduction in patient HRQL immediately after treatment (40, 70-72). In an international survey of patients with HCC, conducted with 256 patients across 13 countries, including the UK, TACE was the most frequently reported later-stage treatment reported by patients (43%, n=111). Patients were asked to specify which treatment throughout their patient journey they found the most challenging, excluding surgery, in terms of impact on their quality of life. Out of those patients who answered this question, 37% thought that TACE was the most challenging (73).

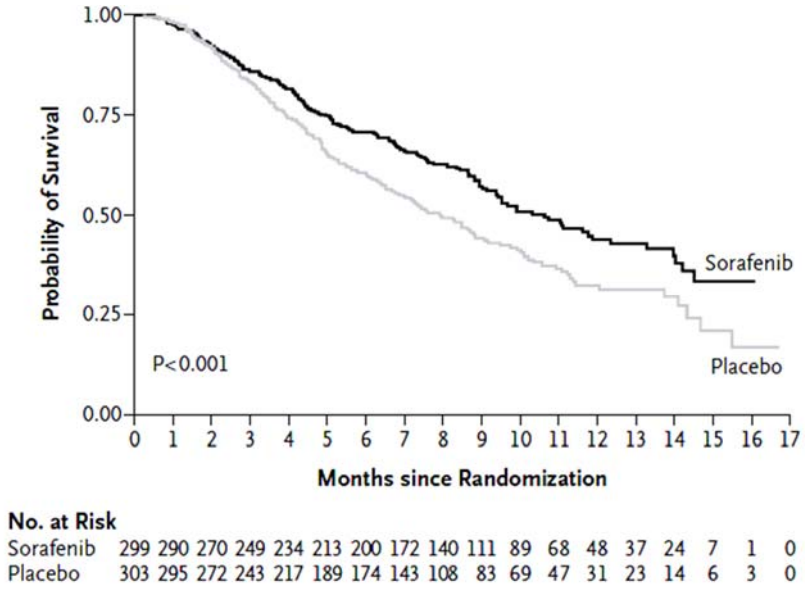
One important factor of TACE identified as a potential influence on patient HRQL is the number of interventions required. While the optimal frequency of therapy is a topic of clinical debate (with some physicians performing TACE at regular, predefined, intervals and others performing TACE 'on demand' according to tumour response), TACE is not a one-off treatment and multiple interventions are required. Patients with bi-lobar disease may have an even greater number of interventions as they often require separate TACE treatments per lobe. The average number of TACE interventions per patient is estimated at 3–4, with each session requiring a hospital stay of 3–6 days (64, 74-78). A recent audit of [redacted] patients receiving TACE found that the mean number of treatments per patient was [redacted]. However, [redacted] patients [redacted] received 10 or more TACE treatments, and [redacted] patients [redacted] received 5 or more TACE treatments (18). While the literature is highly varied regarding absolute values, this administration and adverse event (AE) management burden generates significant costs to the health service. Furthermore, repeat TACE procedures can result in arteriopathy, or very rarely vascular dissection: this was evidenced in the study of Pitton et al. 2015, in which vascular disease such including stenoses and occlusions were correlated with the number of TACE procedures received by the patient (78). These events can limit the scope for further intra-arterial treatment.

5.2 *Systemic therapy*

5.2.1 Sorafenib

Sorafenib is a multi-kinase inhibitor that induces tumour necrosis through anti-growth and anti-angiogenesis mechanisms. Available in tablet form, sorafenib is self-administered twice daily and treatment is continued if clinical benefit is observed or until unacceptable toxicity. In the regulatory Phase III RCT, SHARP, sorafenib demonstrated a significant survival benefit in previously untreated patients with advanced HCC compared with placebo, as demonstrated in Figure 6.

Figure 6. Kaplan-Meier plot of OS in the SHARP trial



Source: Llovet et al. 2008 (79).

Patients receiving systemic therapy with sorafenib usually experience disease progression due to tumour escape and resistance mechanisms commonly associated with anti-angiogenic treatments (80). More concerning is that approximately one third of patients discontinue sorafenib treatment due to unacceptable toxicity; dose reductions and dose interruptions due to AEs are also common, and investigation of titrated dosing showed no improvement with such a regimen (37, 79, 81, 82). In the SHARP trial, approximately a quarter of patients (24%) in the sorafenib group did not receive the prescribed daily dose of treatment. While the overall incidence of treatment-emergent adverse events (TEAE) was similar between treatment groups of SHARP, the rate of Grade 3–4 TEAEs was significantly greater in patients treated with sorafenib (45% vs 32%; p=0.04) (79). The most common toxicities associated with sorafenib use in HCC are gastrointestinal, constitutional and dermatological in nature; diarrhoea, fatigue, abdominal pain, hand-foot skin reaction (HFSR) and rash/desquamation commonly occur and regularly require medical management (83).

These events can be severe and are often continuous; for example, fatigue anecdotally can last for up to 6 months (although it can be difficult to separate disease-related and treatment-related fatigue in HCC) and diarrhoea is experienced 2–3 days a week (83). Management of such events can result in significant costs to health services. Important SAEs reported in the SHARP trial also included liver dysfunction (7%), cardiac ischaemia/infarction (3%) and gastrointestinal haemorrhage (3%) (79).

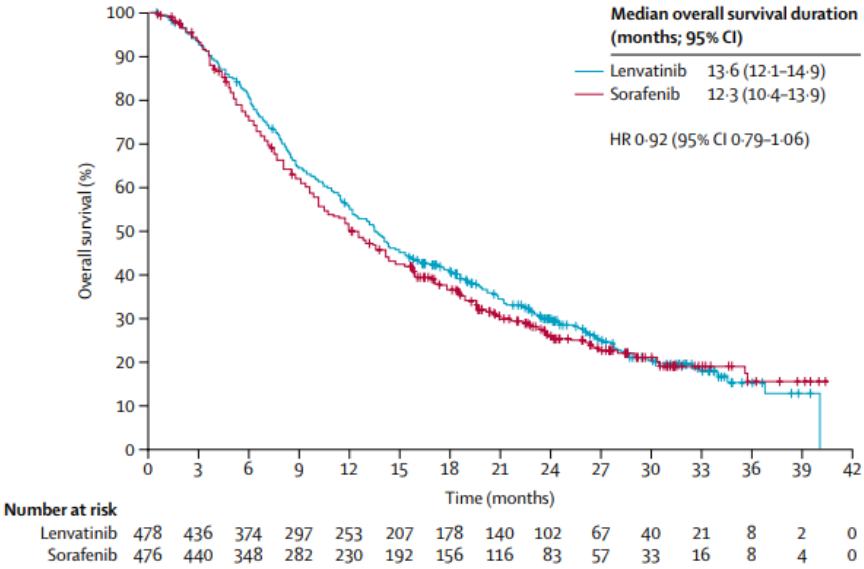
Again, these safety concerns are likely to have a detrimental impact on the patient's quality of life; however, despite HRQL data being collected in several RCTs investigating sorafenib in HCC (including the SHARP trial), very little has been made publicly available. In BRISK-FL, a large-scale RCT investigating the clinical efficacy and safety of brivanib versus sorafenib in patients with unresectable HCC, a decline in physical and role function was reported after 12 weeks of treatment in both groups (assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ-C30] questionnaire) (84). In clinical practice, the occurrence of Grade 3–4 AEs appears to reduce patient quality of life and threaten the continuation of treatment; this observation led to the design of a prospective real-world study investigating the impact of sorafenib on HRQL in clinical practice (81). From baseline to month 1 and to month 2, significant decrements were detected only for the Physical Well-Being subscale (month 1 and 2) and the Hepatobiliary Subscale (month 2) of the FACT-G disease-specific instrument, with improvements on measures of emotional well-being (81).

In an international survey of patients with HCC, including 256 patients across 13 countries, patients reported that side effects commonly associated with sorafenib and other kinase inhibitors, such as skin disorders, diarrhoea and fatigue, had the most impact on their HRQL. Two-thirds of patients experiencing any fatigue or skin disorders felt that they had a moderate-to-significant negative impact on their HRQL (n=103 and n=46, respectively). A fifth of respondents were prescribed sorafenib during their treatment (n=46). Sorafenib was the treatment most frequently perceived as having a negative impact on HRQL (for 81% of respondents, n=21). Similarly, patients taking sorafenib more frequently reported moderate-to-significant side effects affecting HRQL. The most common sorafenib-related side effect with a moderate-to-significant impact on HRQL was fatigue (66%, n=17), followed by skin disorders (50%, n=13) and diarrhoea (50%, n=13) (73).

5.2.2 Lenvatinib

Lenvatinib is a multi-kinase inhibitor, providing the same mechanism of action as sorafenib. Available in tablet form, lenvatinib is self-administered four-times daily and treatment is continued if clinical benefit is observed or until unacceptable toxicity. In the non-inferiority Phase III RCT, REFLECT, lenvatinib demonstrated non-inferiority regarding OS compared with sorafenib, as demonstrated in Figure 7.

Figure 7. Kaplan-Meier plot of OS in the REFLECT trial



Key: CI, confidence interval; HR, hazard ratio.
Source: Kudo et al. 2018 (85).

Although improvements were observed in response duration with a significantly extended time to progression reported (using the less common mRECIST assessment criteria), toxicity and associated quality of life detriments remain. In the REFLECT trial, treatment-related adverse events (TEAEs) led to drug interruption, dose reduction or drug withdrawal in 40%, 37% and 9% of patients treated with lenvatinib and 32%, 38% and 7% of patients treated with sorafenib, respectively (85). Grade ≥3 TEAEs occurred at similar rates in the lenvatinib and sorafenib arms at 3.2 and 3.3 episodes per patient-year, respectively. However, fatal events related to treatment occurred in 11 patients treated with lenvatinib compared to four patients treated with sorafenib; these included hepatic failures (three patients), cerebral haemorrhage (three patients), and respiratory failure (two patients). The most common TEAEs in the lenvatinib arm were hypertension (42%), diarrhoea (39%), decreased appetite (34%) and decreased weight (22%); the most common TEAEs in the sorafenib arm were palmar-plantar erythrodysaesthesia – a form of hand-foot skin reaction (52%), diarrhoea (46%), hypertension (30%) and decreased appetite (27%).

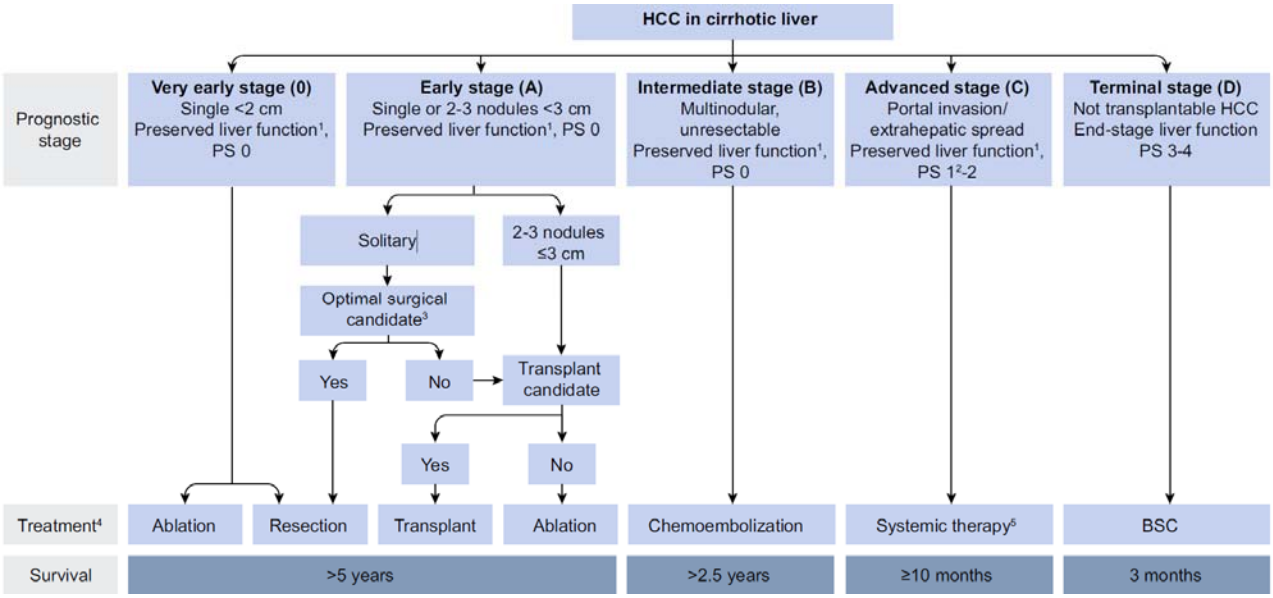
HRQL data were also collected in the REFLECT trial and showed a decline in patient quality of life during treatment with both multi-kinase inhibitors, although the complete data has not been presented to date (85). The authors report some differences in time to clinically meaningful deterioration across role functioning, pain and diarrhoea domains of the EORTC QLQ-C30 and nutrition and body image domains of the HCC specific EORTC QLQ-HCC18 questionnaire, with no overall differences for summary scores between treatment arms.

6 *Clinical pathway of care*

6.1 *Clinical Guidelines*

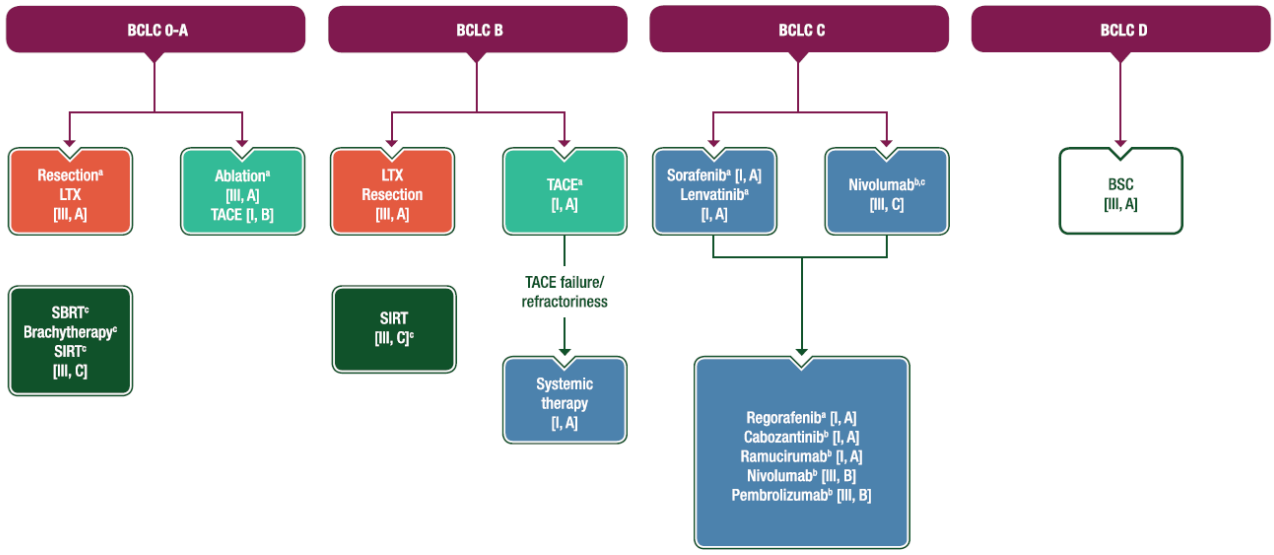
The latest editions of ESMO and EASL clinical practice guidelines recommend treatments based on BCLC stages, as shown below in Figure 8 and Figure 9.

Figure 8. Clinical pathway of care – EASL guidelines



Source: EASL 2018 (1)

Figure 9. Clinical pathway of care – ESMO guidelines



Key: BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; HCC, hepatocellular carcinoma; LTX, liver transplantation; SBRT, stereotactic body radiotherapy; SIRT, selective internal radiotherapy; TACE, transarterial chemoembolisation. Source: ESMO 2018 (9)

6.2 *Clinical practice in the UK*

Clinical decision-making in the UK is based on a combination of the BCLC staging system with other treatment eligibility criteria. While the BCLC classification has been repeatedly validated and recognised as the most relevant staging system for HCC (1, 9), the complexity of HCC is such that patients within a given BCLC stage will present with heterogeneous characteristics in terms of tumour burden, liver function and/or general health status. The heterogeneity of BCLC stages has also been acknowledged and treatment stage migration is a recognised concept: where some patients in each disease stage do not fulfil all the criteria for a specific treatment option, these patients should be offered the next most suitable treatment within the same stage or the next prognostic stage (1, 9).

Clinical decision-making in the UK includes some degree of deviation from the BCLC guidelines:

- Conventional TACE or DEB-TACE would be considered as options in patients with segmental portal vein involvement or thrombosis, or with an ECOG performance status of 1, although these patients are formally considered as having advanced stage HCC (BCLC C) for whom systemic therapy is the recommended treatment strategy according to the algorithm;
- Sorafenib or any other systemic therapies would not be considered in advanced stage patients with Child-Pugh B liver disease, due to poor clinical outcomes in this population and in accordance with NICE recommendations (39, 86, 87).

TACE and sorafenib have been the mainstay of therapy for unresectable HCC over the last decade (79, 88). Patients for whom TACE is not appropriate currently do not have access to an alternative locoregional therapy, despite intermediate or advanced stage HCC being confined to the liver. Those patients currently receive systemic therapy and therefore experience the adverse events associated with sorafenib and lenvatinib and their impact on HRQL. Furthermore, the BCLC staging system does not include the possibility for HCC to be down-staged from initially unresectable to being potentially amenable to curative therapy.

HCC is a complex, multifactorial disease due to the interactions between liver function and cancer progression. Numerous alternatives have been proposed to divide BCLC stages B and/or C into substages (89-96), usually defined based on tumour burden, liver function and/or general health status criteria (97). The addition of new treatment options for unresectable HCC will further challenge treatment selection based on the traditional BCLC staging system alone. There is wide consensus that any staging or clinical decision-making system should incorporate tumour burden, liver function and general health status (1, 9). Clinicians have reported that these factors are also the most relevant to clinical practice in the UK (5, 39). Finally, the most recent EASL guidelines have recommended that "the subgroup of patients benefitting from [SIRT] needs to be defined (evidence moderate)." (1).

In line with the above, this submission will therefore focus on populations identified by UK clinicians using measures of (A) tumour burden and (B) liver function which are considered relevant for SIRT:

(A) Tumour burden refers to the number of cancer cells, the size of a tumour, or the amount of cancer in the body. In this submission, tumour burden is defined as the percentage of cancerous liver tissue in the total liver volume. Patients considered good candidates for SIRT in the UK have a tumour burden ≤25% (8, 39).

The purpose of SIRT is to deliver radiation therapy to the liver tumours, minimising radiation exposure to non-malignant liver tissue. However, widespread disease throughout the liver may prevent adequate targeting (98). EASL guidelines have recommended considering a threshold of tumour burden for patient selection with TACE (1). Patients with significant tumour burden, particularly those with typical features of HCC, are more likely to

have a greater lung shunt fraction (14, 98, 99), which limits the possibility of using SIRT (14, 98). In consultation with UK clinicians, a threshold of ≤25% tumour burden was identified. This threshold is used in the largest randomised trial of SIRT in HCC (the SARAH trial (6)) and is considered clinically relevant considering HCC patient selection practice in Western countries (39).

(B) Liver function refers to the underlying performance of the liver and provides an indication of the capacity of the liver to tolerate treatments for cancer or further degradation of liver function (hepatic functional reserve). In this submission, liver function is defined using the Albumin-Bilirubin (ALBI) grade. Patients considered good candidates for SIRT in the UK have an ALBI grade of 1 (8, 39).

Liver function has traditionally been measured with the Child-Pugh classification; however, this has limited predictive power particularly within the Child-Pugh A class which may still contain heterogeneity in terms of functional reserve, prognosis and the ability to tolerate interventions (1). It is considered that the Child-Pugh classification does not adequately capture the hepatic functional reserve (35). Baseline albumin and bilirubin levels have long been identified as predictors of survival and toxicity outcomes of SIRT using SIR-Spheres (14, 26, 100-102). Albumin and bilirubin levels have been combined in the ALBI grade as a prognostic measure in HCC (103-105). Patients are classified, using the ALBI grade, into three different prognostic groups, ranging from a grade of 1 (fully preserved liver function) to 3 (impaired liver function). The ALBI grade has been further demonstrated as a valid instrument to predict outcomes of patients with HCC receiving locoregional therapy, including TACE (106) and SIRT (107). The ALBI grade is recognised in clinical guidelines as an instrument to stratify patients across BCLC stages and within Child-Pugh grade A liver function, in which it provides additional prognostic power (1, 9). Use of the ALBI grade is emerging in the UK and is expected by clinicians to become the mainstay of clinical practice in addition to the Child-Pugh score (8).

6.3 *Proposed positions in the clinical care pathway*

This submission therefore focuses on the clinically relevant patient populations for SIR-Spheres.

(1) [Population 1 – TACE-eligible]. People with unresectable early (BCLC stage A), intermediate stage (BCLC stage B) or advanced HCC (BCLC stage C), for whom transarterial chemoembolisation therapies (cTACE, DEB-TACE) are appropriate.

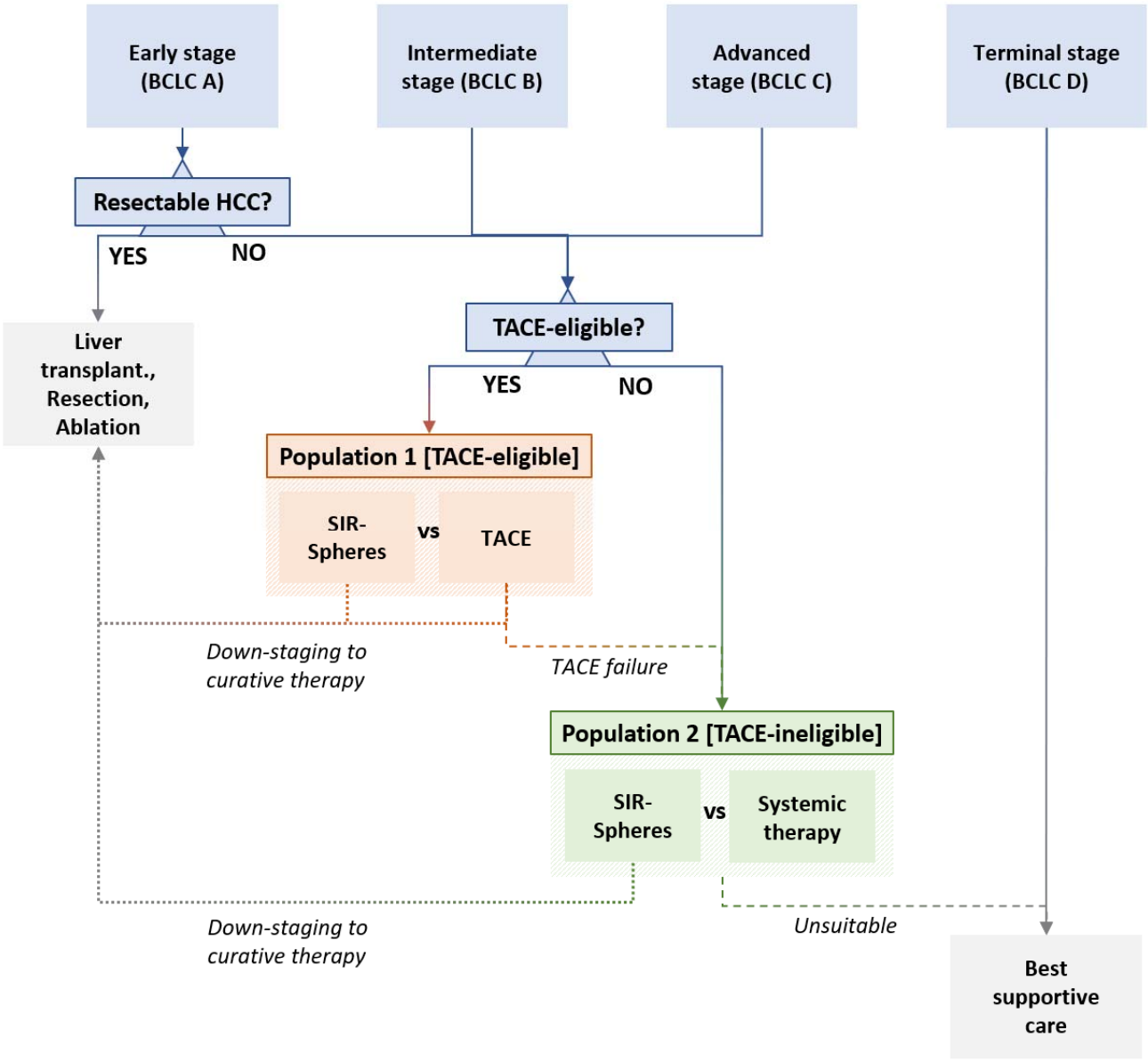
(2) [Population 2 – TACE-ineligible]. People with unresectable intermediate stage (BCLC stage B) or advanced HCC (BCLC stage C), for whom any transarterial embolisation are inappropriate, with or without portal vein thrombosis/involvement, without extrahepatic disease, with a tumour burden ≤25% and a preserved liver function (ALBI grade 1).

This submission focuses initially on patients for whom any transarterial embolisation therapies are inappropriate **(Population 2 – TACE-ineligible)**, because Phase 3 randomised trials of SIR-Spheres in HCC have been conducted in this population. Available evidence has allowed focus on the subgroup of patients with a tumour burden ≤25% and a preserved liver function (ALBI grade 1) who are most suitable for SIRT using SIR-Spheres and considered as clinically relevant in the UK.

This submission then includes all patients for whom transarterial chemoembolisation therapies (cTACE, DEB-TACE) are appropriate **(Population 1 – TACE-eligible)**, without focusing on a specific subgroup due to the lack of available evidence in this indication.

The proposed positions for SIR-Spheres in the clinical pathway of care are summarised in Figure 10.

Figure 10. Proposed positions for SIR-Spheres in the clinical pathway of care



7 *Clinical effectiveness and cost-effectiveness of SIR-Spheres in Population 2 – TACE-ineligible patients*

7.1 *Clinical effectiveness in Population 2 – TACE-ineligible patients*

7.1.1 Evidence base

The clinical efficacy of SIR-Spheres in this population **(Population 2 - [TACE-ineligible])** has been compared with sorafenib and lenvatinib via a mixed treatment comparison based on a systematic review of the literature. Following a feasibility study (Appendix D) SIR-Spheres have not been compared with TheraSphere or QuiremSpheres in the network meta-analysis or the economic model because no clinical trials of these interventions were identified in this population. Methods and outcomes of the literature review are described in detail in Appendix B.

The systematic literature review identified 4 randomised controlled trials (RCTs) of relevant interventions in patients with unresectable HCC for whom TACE was not appropriate:

- The SARAH Phase III RCT of SIR-Spheres versus sorafenib in 459 patients in France (6);
- The SIRveNIB Phase III RCT of SIR-Spheres versus sorafenib in 360 patients in Asia (7);
- The REFLECT RCT of sorafenib versus lenvatinib in 954 patients (85);
- The SHARP RCT of sorafenib versus placebo in 602 patients (79).

Studies comparing SIR-Spheres to a relevant comparator are described in Table 6. All studies are described in Appendix B section 2. The SARAH and SIRveNIB trials are the only Phase III RCTs comparing any form of SIRT to sorafenib with a head-to-head design.

Table 6. Evidence base on SIR-Spheres in Population 2 – TACE-ineligible patients

Study	SARAH (6)	SIRveNIB (7)
Study design	Phase III RCT	Phase III RCT
Population	Adults from France with locally-advanced unresectable HCC with or without portal vein invasion, or recurrent HCC after surgical or locoregional treatment or failure after up to 2 TACE procedures	Adults from the Asia-Pacific region with locally-advanced, BCLC stage B or C HCC with or without portal vein involvement who were ineligible for resection, with no prior sorafenib, EGFR inhibitors or radiotherapy and no more than 2 prior TACE
Intervention(s)	SIR-Spheres, separate delivery per lobe, BSA model for activity calculation	SIR-Spheres single delivery, partition model for activity calculation
Comparator(s)	Sorafenib 400 mg twice daily	Sorafenib 400 mg twice daily
Is trial used in the economic model?	Yes	No
Rationale for use/non-use in the model	Largest trial of SIRT in HCC, conducted in a French patient population most comparable to the UK population of interest.	Trial was conducted in the Asia-Pacific region with a population not representative of the UK population of interest, in terms of HCC aetiology.
Reported outcomes specified in the decision problem	Overall survival Progression-free survival Complete response Partial response Stable disease Disease progression Adverse events (all, grade 1-2, grade 3, grade 4, grade 5)	Overall survival Progression-free survival Time to progression Complete response Partial response Stable disease Disease progression Objective response rate Adverse events (grade 1-2, grade 3+)
All other reported outcomes	Disease control rate	

This submission has been developed for the subgroup of patients with a tumour burden ≤25% and an ALBI grade 1 as the base case population. Clinical parameters for the economic model were derived from subgroup analyses of the SARAH trial in this population wherever possible. Where required in the economic model and not available for the base case subgroup, parameters were derived from the overall intention-to-treat (ITT) population of the SARAH trial.

The SIRveNIB trial was conducted in the Asia-Pacific region, therefore patients enrolled in the trial had a high prevalence of hepatitis B and C as the underlying aetiology of HCC. Baseline characteristics of patients in the SIRveNIB trial were considered by clinical experts as not representative of the UK population (5) therefore, this study was excluded from the base-case analysis for this submission. This is in line with previous NICE technology appraisals (TAs) conducted in HCC (108, 109) in which studies conducted in Asian patients were considered as not being representative of the UK population due to differences in baseline characteristics of patients. In the NICE technology appraisal TA189, the Asia-Pacific trial of sorafenib was treated as supportive evidence only (109). The ERG stated, that since the "prognosis is distinctly different for Asian patients (hepatitis B regions) the ERG only sought European studies" (109). In the lenvatinib technology appraisal (108), the pivotal trial included patients from both Asia-Pacific and Western region. The ERG noted that there are important differences between these regions: "the Western subgroup had greater body mass, had more heart disease, less underlying cirrhosis, less hepatitis B and more pre-existing hepatitis C or alcohol related conditions". However, the overall ITT analysis of the lenvatinib pivotal trial was ultimately accepted.

The SARAH trial is included in the base case analysis as this trial was conducted in France, with HCC aetiology and other baseline characteristics considered comparable to the UK population (5).

7.1.2 Study design

The SARAH trial (*SorAfenib versus Radioembolization in Advanced Hepatocellular carcinoma*, NCT01482442) was a Phase III, multicentre, open-label RCT conducted in France (6). The objectives of SARAH were to compare the efficacy and safety of SIRT using Y-90 resin microspheres to that of sorafenib in patients with locally advanced and inoperable HCC. The SARAH trial was an investigator-initiated trial, independently sponsored by *Assistance Publique-Hôpitaux de Paris (AP-HP)*, with unconditional grant funding from Sirtex Medical.

The SARAH trial was initiated in 2009 and obtained ethics and regulatory approval in 2011 reflecting clinical practice at the time of the trial. Clinical practice has evolved in the UK and the rest of the world since this trial was conducted, both in terms of patient selection and administration of SIRT.

The SARAH trial was conducted in France, in a population of patients with HCC aetiology and underlying liver disease that reflects that of the French target population and is generally comparable to the UK population. However, the selection criteria in SARAH allowed inclusion of patients with abnormal liver function (serum bilirubin ≤2,9 mg/dL or 50 µmol/L) and complete occlusion of the main portal vein, who have a very poor survival prognosis. These patients would not receive SIRT in current clinical practice in the UK.

Furthermore, the administration schedule for SIRT in this trial differs from current clinical practice in the UK and the rest of the world (5, 26, 39, 67, 98). For example, the SARAH trial protocol mandated the sequential administration of Spheres to each respective liver lobe, for patients with bi-lobar HCC, and allowed for repeated treatments in previously treated lobes. In current clinical practice, most patients with HCC would receive a single administration of SIR-Spheres (5).

Despite the above limitations, the SARAH trial is used in the base case of this submission as this is the first and largest head-to-head trial of SIRT versus systemic therapy. Additional data sources have been used as model parameters where relevant to more closely reflect current clinical practice in the UK.

7.1.3 Baseline characteristics

The SARAH study was conducted in 467 patients who were randomised to receive SIR-Spheres, with activity calculated according to the BSA model, or oral sorafenib 400 mg twice daily. Patients were adults with locally advanced HCC (BCLC stage C), or new HCC not eligible for surgical resection, liver transplantation, or thermal ablation after a previously cured hepatocellular carcinoma (cured by surgery or thermoablative therapy), or HCC with two unsuccessful rounds of transarterial chemoembolisation. All patients had ECOG performance status ≤1 and were in Child-Pugh grade A or B7. Patients with extrahepatic metastases except lung tumours <1 cm and lymph nodes <2 cm were excluded (6).

Clinicians considered that patient selection in the overall ITT or per protocol populations of the SARAH trial (described in Appendix B) did not reflect UK clinical practice, as the trial included patients with a poor survival prognosis who would only be considered for systemic therapy or best supportive care, including:

- 34.0% (156/459) of patients with a tumour burden >25% of the liver volume;
- 19.0% (87/459) of patients with main portal vein thrombosis, including 7.8% (36/459) of patients with complete occlusion of the main portal vein, a recognised adverse prognostic factor (110);
- 16.1% (74/459) of patients with Child-Pugh B liver function, recognised as poor candidates for systemic therapy (1, 9, 86, 111);
- An unreported fraction of patients with serum bilirubin >2 mg/dL or 34 µmol/L, commonly used as a threshold for impaired liver function, such as in the Child-Pugh classification (see page 7) and as a patient eligibility criterion for SIR-Spheres (14, 25).

Clinicians therefore recommended further consideration of a subgroup of patients, among the ITT population of the SARAH trial, with both a tumour burden ≤25% and an ALBI grade of 1. Methods for clinical experts involvement are summarised in Appendix J. Clinicians believed these patients were most likely to benefit from SIR-Spheres among patients in **Population 2 – [TACE-ineligible],** due to these measures having been previously used in the SARAH trial (6, 15). Clinicians also supported that patients with a low tumour burden could have better targeting of their tumours using SIRT (14, 98, 99) and that patients with well-preserved liver function would experience a reduced toxicity of SIRT as a liver-directed treatment (14, 26, 100-107). These patients were considered the most appropriate candidates for SIR-Spheres considering clinical practice and treatment allocation in the UK (8). This subgroup was therefore investigated further and ultimately selected as the base case population for this submission. They are therefore also the base case population for the economic model presented in Section 7.2.

In the ITT population of the SARAH trial, 37 (16%) patients in the SIRT arm and 48 (22%) patients in the sorafenib arm had a tumour burden ≤25% and an ALBI grade of 1 and are included in the base case subgroup. Baseline characteristics of patients in the base case subgroup are reported in Table 7 (6).

Baseline characteristics are well-balanced between the randomisation arms, with no statistically significant or clinically relevant differences observed in favour of SIRT. Two negative prognostic criteria were more frequently observed among patients in the SIRT arm:

- 38% of patients in the SIRT arm vs 21% in the sorafenib arm had an ECOG performance status of 1, a known predictor of poor survival after treatment with both SIR-Spheres and sorafenib (26, 86, 112);
- 25% of patients in the SIRT arm vs. 12% in the sorafenib arm had bi-lobar liver involvement, a known predictor of poor survival after treatment with SIR-Spheres (26).

Baseline characteristics in the base case subgroup are therefore not expected to favour SIR-Spheres and could result in conservative estimates of OS and PFS compared with sorafenib. Other characteristics are balanced and

reflect a selection of patients with better prognosis than those in the overall trial population, with only 4% of patients having Child-Pugh B liver function and 10% having main portal vein thrombosis.

It should be noted that disease staging according to the BCLC staging system is very similar when comparing the subgroup of patients with a tumour burden ≤25% and an ALBI grade of 1 to the overall ITT trial population: 56% of patients in the subgroup versus 68% in the overall ITT population were considered to have advanced HCC (BCLC stage C). This confirms that there is significant heterogeneity among patients with advanced HCC and that the use of the ALBI grade and tumour burden as additional criteria can improve patient stratification and appropriate treatment selection among patients with advanced HCC.

Table 7. Baseline characteristics of patients in the base case subgroup - SARAH trial

Baseline characteristics	Sorafenib (n=48)	SIRT (n=37)
Age, years		
• **≥65**	48%	43%
• **<65**	52%	57%
ECOG performance status		
• **0**	79%	62%
• **1**	21%	38%
• **2**	0%	0%
BCLC stage		
• **A**	6%	3%
• **B**	35%	43%
• **C**	58%	54%
Number of tumour nodules (multifocal vs. single nodule)		
• **Multiple**	67%	57%
• **Single**	33%	43%
Number of tumour nodules		
• **<4**	92%	92%
• **≥4**	8%	8%
Macroscopic vascular invasion		
• **No**	48%	46%
• **Yes**	52%	54%
Child-Pugh grade		
• **A**	98%	95%
• **B**	2%	5%
• **missing**	0%	0%
Previous TACE		
• **No**	56%	49%
• **Yes**	44%	51%
Occlusion of main portal vein		
• **Absent**	90%	89%
• **Present**	10%	11%
Liver involvement		
• **Bi-lobar**	15%	24%
• **Uni-lobar**	85%	76%

Baseline characteristics of patients in the overall SARAH trial population and details of the additional studies identified in the systematic literature review are summarised in Appendix B.

7.1.4 Efficacy outcomes

7.1.4.1 Treatment assignment and patient eligibility

The SARAH trial found that 22% (53/237) of patients randomised to SIR-Spheres did not receive this treatment, of whom 49% (26/53) were treated with sorafenib instead. The mean delay between randomisation and receiving treatment was 29 days with SIR-Spheres compared with 7 days with sorafenib, due to the need for prior work-up before receiving SIR-Spheres that was not required for the sorafenib group.

Of those who failed to receive SIR-Spheres, 11 were excluded prior to work-up due to worsening disease, early death or medical decision. Another 42 underwent work-up but were then excluded, due to disease progression or unsuitable tumour vascularisation. Of these, 26 received sorafenib instead and 16 did not receive any treatment.

However, some of the patients who failed to receive SIR-Spheres may have been poor candidates for this therapy. As clinical experience with the technology increases over time, it is becoming clearer which patients are likely to benefit. As reported earlier, a substantial proportion of patients recruited to the SARAH study would not be considered suitable for treatment by current clinical judgement. This subgroup is over-represented in the group that failed to receive SIR-Spheres and had a worse prognosis (18).

Evaluation of the study flowchart confirms that some of the patients enrolled in the SARAH trial were poor candidates for SIRT, as the proportion of patients who receive SIR-Spheres after their randomisation is dependent on the patient population being considered.

Of the 37 patients in the base case subgroup with a tumour burden ≤25% and an ALBI grade 1 who were randomised to SIR-Spheres, 92% received this treatment. This confirms that patients within the subgroup are suitable candidates for SIRT: the 8% drop-out rate from work-up to SIRT treatment observed in the base case subgroup is consistent with those reported in the literature (99) and by clinical experts consulted in the Resource use survey for this appraisal. Drop-out rates of 3-11% were observed in the studies in real-world clinical practice, likely owing to better pre-work-up patient selection than in the overall population of the SARAH trial. These findings support the view that the overall ITT and per protocol populations of the SARAH trial are not reflective of clinical practice in the UK and that the base case population is appropriate to determine the clinical and cost-effectiveness of SIR-Spheres versus sorafenib.

7.1.4.2 Overall and progression-free survival

Methods

The primary objective of SARAH was to determine whether treatment with SIR-Spheres can prolong overall survival compared with sorafenib.

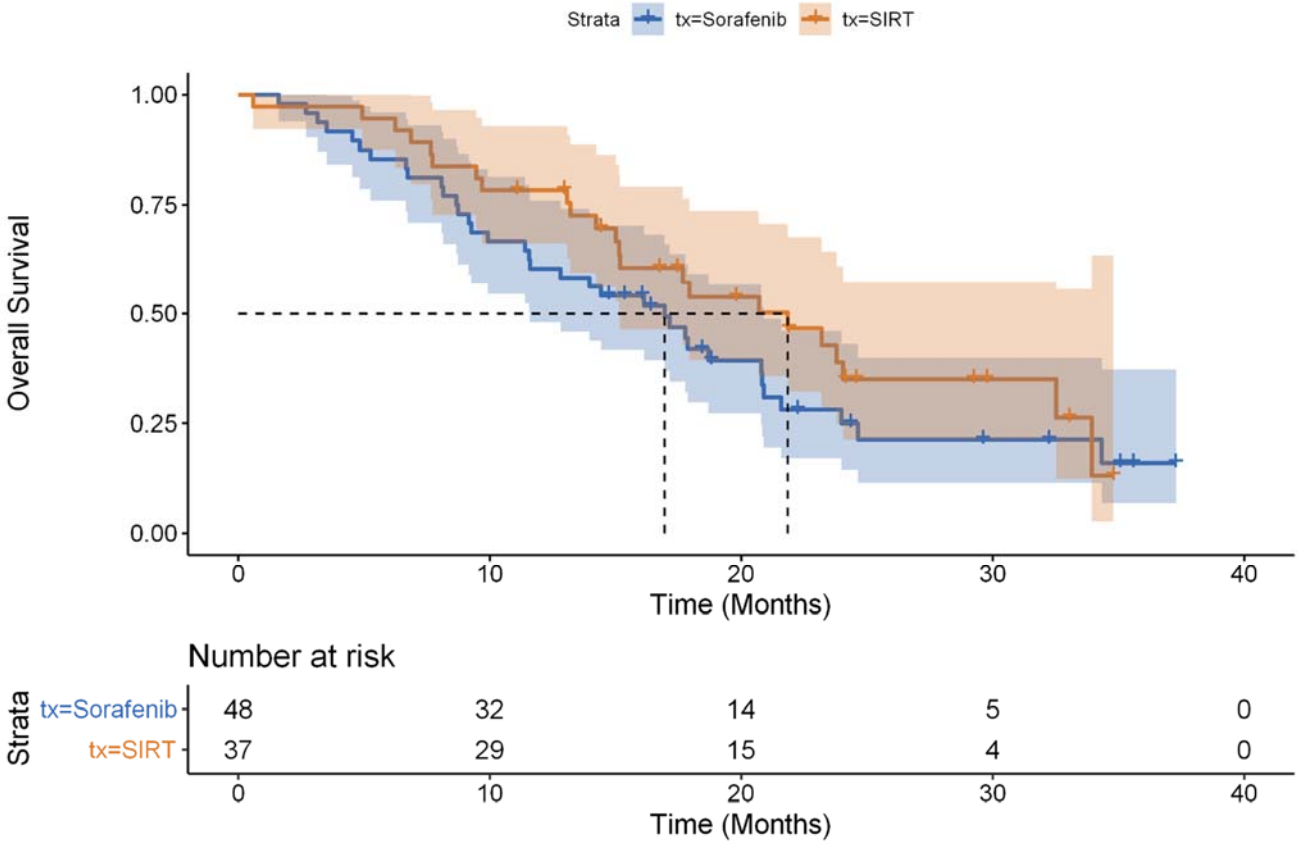
It was calculated that 200 patients had to be randomly assigned to each group to detect a 4-month difference (10.7 months in the sorafenib group vs 15 months in the SIRT group) in median overall survival (80% power, 5% type I error, 24-month accrual time, 12-month follow-up). Accounting for patients enrolled but not eligible for randomisation (i.e., not fulfilling eligibility criteria after the work-up, refusing treatment, or having worsening disease), the sample size was increased to 466 patients, in accordance with a protocol amendment (July 31, 2014).

Results

The SARAH trial did not meet its primary endpoint for the whole population studied: in the ITT population, median OS was 8.0 months (95% CI 6.7 to 9.9) in the SIR-Spheres group versus 9.9 months (95% CI 8.7 to 11.4) in the sorafenib group (HR 1.15; 95% CI 0.94 to 1.41; p=0.18). In the per protocol population of the trial, median OS was 9.9 months (95% CI 8.0 to 12.7) in the SIR-Spheres group, compared with 9.9 months (95% CI 9.0 to 11.6) in the sorafenib group (HR 0.99; 95% CI 0.79 to 1.24). PFS in the ITT population was 4.1 months (95% CI: 3.8 to 4.6) in the SIRT group and 3.7 months (95% CI: 3.3 to 5.4) in the sorafenib group (HR 1.03; 95% CI: 0.85 to 1.25; p=0.76).

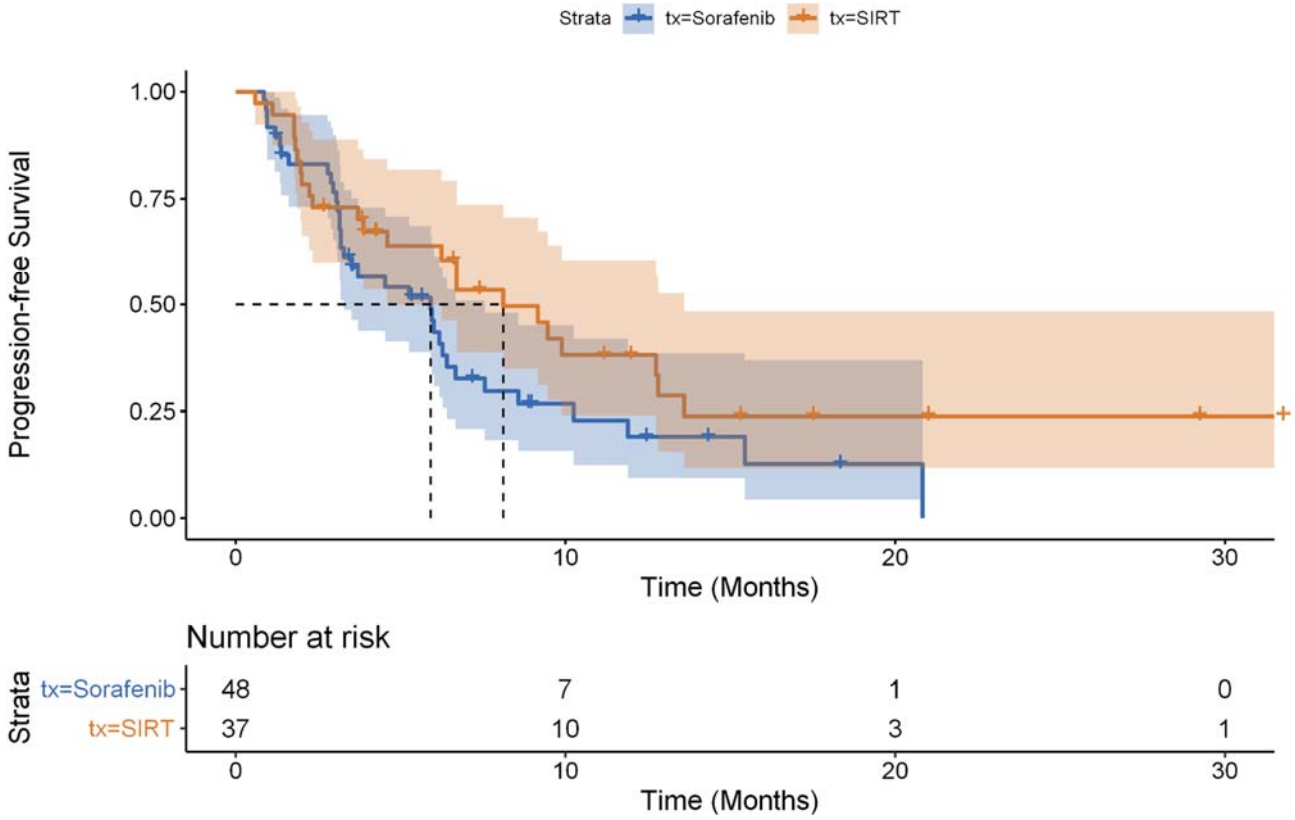
For the subgroup of 85 patients with a tumour burden ≤25% and an ALBI grade of 1, SIR-Spheres were associated with a benefit in terms of overall survival compared to sorafenib. In this subgroup the HR for OS comparing SIRT versus sorafenib was 0.73 (95% CI: 0.44 to 1.21, p=0.22). Median OS was 21.9 months (95% CI: 15.2 to 32.5) for SIRT versus 17.0 months (95% CI: 11.6 to 20.8) for sorafenib. Survival analyses for OS are presented in Figure 11. Although the reduction in the HR for OS is not statistically significant, this is likely to result from the small size of the subgroup. Treatment effect modification was investigated in the overall ITT population of the SARAH trial through a Cox proportional hazards survival regression. In the regression, the interaction effect between treatment and the combination of a tumour burden ≤25% and an ALBI grade of 1 was 0.609 (95% CI: 0.344 to 1.079, p=0.089) indicating that SIRT was relatively more effective in this subgroup.

Figure 11. Kaplan-Meier plot of OS for SIRT vs sorafenib in the base case subgroup - SARAH trial



A similar benefit of SIR-Spheres was observed in terms of PFS in the base case subgroup of patients with a tumour burden ≤25% and an ALBI grade of 1. In this subgroup the HR for PFS comparing SIRT versus sorafenib was 0.65 (95% CI: 0.41 to 1.02, p=0.06). Survival analyses for PFS are presented in Figure 12.

Figure 12. Kaplan-Meier plot of PFS for SIRT vs sorafenib in the base case subgroup - SARAH trial



Interpretation of the results

Comparing outcomes of the SARAH trial for the subgroup of patients with a tumour burden ≤25% and an ALBI grade of 1 with the overall ITT and per protocol population, it is apparent that these criteria are treatment effect modifiers. This is most likely to be explained by the different mode of action of SIR-Spheres compared to sorafenib, and their relationship with (a) anatomical features of HCC within the liver and (b) functional liver reserve.

(a) The mode of action of SIR-Spheres is dependent on physiological disease characteristics of HCC within the liver, which may not be the case for sorafenib:

- As a loco-regional radiation therapy, the effectiveness of SIR-Spheres results from the ability to deliver a tumoricidal radiation dose to tumours, whilst avoiding exposure of the non-malignant liver cells to a toxic radiation dose, which could impair liver function and result in decompensation of the underlying liver disease (100).
- Clinicians have confirmed that several anatomical and physiological factors may impact on the capacity for SIRT to provide a tumoricidal dose to the tumours, such as their number, their maximum size, their dissemination throughout the two lobes of the liver or their degree of hypervascularisation. (8). Prior observational studies have reported correlations between these individual factors and survival outcomes following SIRT (26, 101, 102).
- Clinicians have recommended the measure of liver burden as a fraction of the volume of the liver as the most appropriate approach to capture and quantify this variability. Patients with a too extensive tumour burden are less likely to derive a benefit from SIR-Spheres (39).
- The relationship between tumour burden and the relative effectiveness of SIR-Spheres is further established by a subsequent subgroup analysis, showing that patients with a predicted tumour-absorbed dose of radiation ≥100 Gy had improved survival compared to those with a predicted dose

<100 Gy (see Section 7.1.6.). Post-hoc analyses of the SARAH trial have established a correlation between tumour burden and the predicted dose: a regression analysis indicated that a high tumour burden (≥25%) is associated with a reduction of [redacted] in the mean predicted dose, compared with a tumour burden <25%. Patients with a tumour burden <25% had a mean tumour-absorbed dose of [redacted].

- These disease characteristics can be overall prognostic factors for HCC. However, these were not found to be predictors of the benefit of sorafenib versus placebo: the number of tumours or their maximum size were not found to be treatment effect modifiers in Phase III trials of sorafenib versus placebo (112).

(b) The effectiveness and safety of SIR-Spheres are dependent on sub-clinical variations in the functional reserve of the liver which may not be relevant for sorafenib.

- There is a well-documented relationship between the functional reserve of the liver and the toxicity of SIRT to the non-tumoural liver parenchyma. The work-up for SIR-Spheres includes the assessment of liver function including serum bilirubin, and patients with poor liver functional reserve, such as those with a total bilirubin > 2mg/dL (or 34 µmol/L) should not be considered candidates for SIRT (14).
- Sorafenib has also been shown to be less effective in patients with impaired liver function (Child-Pugh B) (86, 111). However, due to the radical differences in mode of action between SIR-Spheres and sorafenib, different thresholds of liver function may be applicable to SIR-Spheres and sorafenib which may result in treatment effect modification within the Child-Pugh A class (39).
- The ALBI grade, used to select patients for inclusion in the base case subgroup, has been demonstrated as a valid instrument to stratify patients in prognostic subgroups, for treatment allocation to loco-regional therapy and within the Child-Pugh A class (14, 26, 100-102).
- While the ALBI grade can be used as an overall prognostic factor for HCC, this grade is not considered a predictor of the benefit of sorafenib versus placebo: the ALBI grade, serum bilirubin or serum albumin (the components of this grade) were not found to be treatment effect modifiers in Phase III trials of sorafenib versus placebo (112).
- No treatment effect modification was apparent in the overall ITT population of the SARAH trial using the Child-Pugh classification (6): this is most likely to be because this categorisation approach is not sufficiently sensitive to capture a finer relationship between liver function and the effectiveness of SIR-Spheres, as a liver-directed therapy.

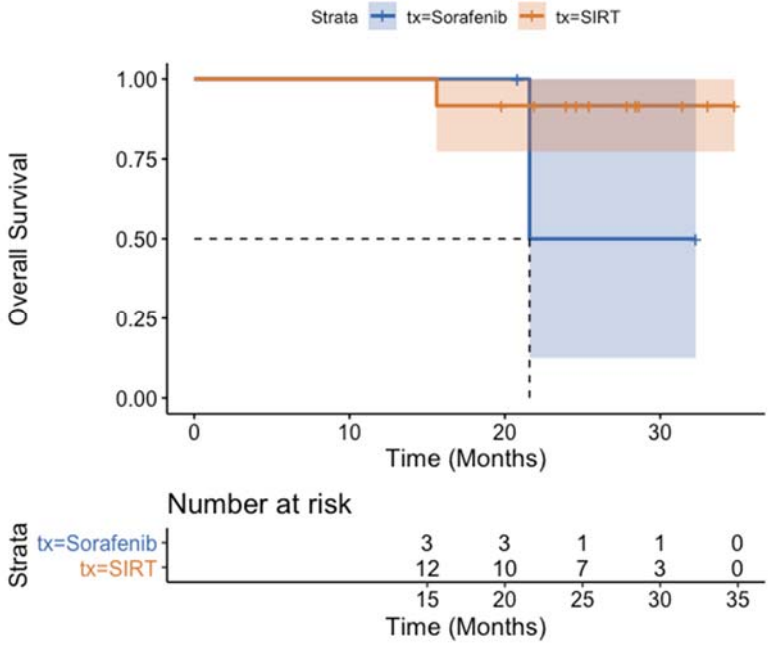
(c) Treatment effect modification is observed in the subgroup of patients both with a tumour burden ≤25% and a well-preserved liver function (ALBI grade 1) because of the complex nature of HCC. This combination of criteria is clinically meaningful because treatment decisions in HCC are relying on a balance between obtaining a sufficient anti-tumoural activity and preserving the liver from additional long-term damage, with both HCC and underlying liver disease being associated with independent risks of mortality.

The above analyses support the view that patient selection for SIR-Spheres according to the tumour burden ≤25% and ALBI grade 1 criteria are relevant to the decision problem and for UK clinical practice.

7.1.4.3 Tumour response and down-staging to radical therapy

It is recognised that a small proportion of patients who receive SIRT for HCC that is unresectable at presentation may be down-staged, i.e. may have a significant tumour response following therapy such that they will become eligible for potentially curative treatments, with long-term survival (9, 14). This was possible for 5.1% of patients who received SIR-Spheres overall in the SARAH study (6), all of whom were alive after a median follow-up of 27.9 months (18). In the sorafenib group, 1.4% of patients received potentially curative treatments. The overall survival curve for these patients is presented in Figure 13.

Figure 13. Kaplan-Meier plot of OS for ITT patients down-staged to curative therapy - SARAH trial



More patients received subsequent curative therapy after SIRT in the base-case subgroup, and this was also more frequent after SIRT than sorafenib in this subgroup (14% vs 2%).

It should be noted that all but one patient down-staged to curative therapy after SIRT or sorafenib were censored. Patients received their subsequent curative therapy after a median 15.84 months after randomisation (SD 8.98 months) and were followed-up for a median 25.0 months (range: 16.0-32.3). While these patients are expected to have long-term survival following curative therapy, most of the benefits of the increased rate of down-staging to curative therapy following SIRT compared to sorafenib is likely not captured in the SARAH trial analysis. Because this analysis assumed non-informative censoring, it was likely to underestimate overall survival with SIRT as the censoring in these patients was likely to be informative.

Down-staging to subsequent curative therapy was possible because of the improved tumour response observed following SIRT compared to sorafenib. Tumour response (defined as the best overall tumour response observed at any time during patient follow-up) was recorded for 164 patients who received SIR-Spheres and 188 who received sorafenib. Complete response was significantly more common with SIR-Spheres (2.4%) than sorafenib (1.1%, p=0.0237). Partial response was achieved by 17.1% of patients after SIR-Spheres compared with 11.2% after sorafenib, giving a tumour response rate (CR or PR) of 19.5% with SIR-Spheres and 12.2% with sorafenib (p=0.06). The feasibility and safety of surgery following treatment with SIR-Spheres was demonstrated in the P4S study (113).

Treatments with curative intent are an important treatment option for HCC patients, as they offer significantly extended survival (114, 115). A recently reported retrospective, single centre study in France assessed data collected from all consecutive patients undergoing SIRT between October 2013 and June 2017 (114). Of the 57 patients, 33 had advanced disease (BCLC stage C). Down-staging was defined as tumours becoming eligible for surgical treatment after RECIST and mRECIST evaluation in follow-up imaging six months after SIRT. Twenty-four patients were considered down-staged, and 14 patients had either received surgery (transplantation or resection) or had radiofrequency ablation. Overall survival at 24 months was significantly higher for those down-staged (54% ± 20%) and even higher for those receiving surgery after down-staging (77% ± 12%) than those not down-staged (log rank p<0.001).

7.1.5 Adverse events

SIR-Spheres are better tolerated than sorafenib, with similar or lower rates of most adverse events other than gastrointestinal ulceration and radiation pneumonitis, which affected a small proportion of patients. This is likely to be due to the short-term, one-off administration of SIR-Spheres compared with the longer-term, systemic administration of sorafenib, leading to greater general toxicity such as fatigue, anorexia, diarrhoea, nausea and vomiting and alopecia as well as specific adverse events including hand-foot skin reactions (HFSR) with sorafenib. Adverse events (AEs) associated with sorafenib can be severe and long-lasting, often requiring medical management for several months. Overall, 29% of 299 patients allocated to sorafenib in the SHARP study withdrew due to adverse events (79).

Table 8. Summary of adverse events occurring in the safety population - SARAH trial

Any treatment-related AE	SIR-Spheres (n=226)	Sorafenib (n=216)	p-value
All grade AEs, n patients (%)	173 (76,5%)	203 (94,0%)	**<0,001**
All grade AEs, n events	1 297	2 837	**<0,001**
Grade 3+ AEs, n patients (%)	92 (40,7%)	136 (63,0%)	**<0,001**
Grade 3+ AEs, n events	230	411	**<0,001**

Patients in the safety population of the SARAH trial and randomised to SIR-Spheres experienced fewer treatment-related AEs (TEAEs) than those randomised to sorafenib, with statistically significant reductions observed for all grade and grade 3+ events in terms of patients with events and total numbers of events (Table 8). Grade 3-4 TEAEs are included in the economic model of SIR-Spheres versus sorafenib developed in Section 7.2 and can have important consequences in terms of costs to the healthcare system.

Individual AE types observed during the SARAH trial are reported in Table 9. There were important reductions in the incidence of almost all AE types, across all grades of severity, for SIR-Spheres compared to sorafenib, including some of the most frequent and impactful AEs on patients' HRQL:

- Grade 3+ diarrhoea occurred for 1% of patients in the SIRT arm vs. 14% in the sorafenib arm; the total number of diarrhoea AEs was reduced almost 9-fold in the SIRT arm vs. sorafenib;
- Grade 3+ fatigue occurred for 9% of patients in the SIRT arm vs. 19% in the sorafenib arm;
- HFSR occurred for 17% (Grade 1-2) and 6% (Grade 3+) of patients in the sorafenib arm; in contrast only 1 patient in the SIRT arm had Grade 3+ HFSR;
- Anorexia was observed in almost a third of patients receiving sorafenib (Grade 1-2), and severe anorexia (Grade 3+) in 5% of these patients; fewer patients in the SIRT arm experienced this AE (11% of patients with Grade 1-2, 3% with Grade 3+ anorexia).

SIR-Spheres and sorafenib were associated with a similar incidence of liver failure or other abnormal liver function tests: SIR-Spheres is safe and does not result in degradation of liver function, despite being a liver-directed therapy. This may further allow a preservation of the functional reserve of the liver for subsequent therapy, including down-staging to potentially curative resection or ablation, or non-curative systemic therapy. Importantly, no events of radiation hepatitis (or radioembolisation-induced liver disease [REILD]) and only one case of Grade 3+ radiation pneumonitis have been observed for SIRT patients in the SARAH trial. This is a major finding demonstrating the safety of SIR-Spheres for patients with HCC, as REILD has been identified as one of the most severe complications potentially associated with SIRT (14).

Table 9. Adverse events occurring in the safety population - SARAH trial

Patients with AE, (% patients with AE), [total number of events]	SIR-Spheres (n=226)		Sorafenib (n=206)	
	Grade 1-2	Grade 3+	Grade 1-2	Grade 3+
Infection	6 (3%) [6]	3 (1%) [3]	16 (7%) [29]	10 (5%) [18]
Fever	13 (6%) [15]	0 [0]	17 (8%) [24]	3 (1%) [4]
Fatigue	81 (36%) [108]	20 (9%) [20]	123 (57%) [223]	41 (19%) [45]
Weight loss	14 (6%) [16]	0 [0]	40 (19%) [57]	6 (3%) [6]
Alopecia	0 [0]	0 [0]	35 (16%) [36]	0 [0]
HFSR	0 [0]	1 (0%) [1]	37 (17%) [65]	12 (6%) [13]
Rash or desquamation	2 (1%) [3]	1 (0%) [1]	20 (9%) [21]	0 [0]
Pruritus	7 (3%) [7]	1 (0%) [1]	18 (8%) [19]	1 (<1%) [1]
Dry skin	2 (1%) [2]	0 [0]	40 (19%) [58]	3 (1%) [3]
Other dermatological events	4 (2%) [4]	0 [0]	48 (22%) [71]	6 (3%) [6]
Anorexia	24 (11%) [27]	7 (3%) [7]	66 (31%) [121]	10 (5%) [11]
Diarrhoea	26 (12%) [34]	3 (1%) [3]	137 (63%) [279]	30 (14%) [37]
Nausea/vomiting	25 (11%) [39]	1 (0%) [1]	47 (22%) [83]	5 (2%) [5]
Abdominal pain	43 (19%) [59]	6 (3%) [6]	57 (26%) [97]	14 (7%) [16]
GI ulceration	2 (1%) [2]	3 (1%) [5]	0 [0]	1 (<1%) [1]
GI bleeding	1 (<1%) [1]	9 (4%) [11]	6 (3%) [7]	8 (4%) [10]
Ascites	19 (8%) [24]	11 (5%) [15]	15 (7%) [20]	10 (5%) [11]
Liver failure	28 (12%) [47]	25 (11%) [28]	30 (14%) [66]	27 (13%) [34]
Radiation hepatitis	0 [0]	0 [0]	0 [0]	0 [0]
Radiation pneumonitis	0 [0]	1 (0%) [1]	0 [0]	0 [0]
Hypertension	6 (3%) [7]	0 (0%) [0]	28 (13%) [48]	5 (2%) [5]
Congestive cardiac failure	25 (11%) [29]	3 (1%) [3]	24 (11%) [32]	11 (5%) [13]
Haemorrhage (non-GI)	5 (2%) [5]	1 (0%) [1]	19 (9%) [27]	2 (1%) [2]
Pulmonary embolism	0 [0]	0 [0]	1 (<1%) [1]	0 [0]
Hyperbilirubinaemia	25 (11%) [48]	8 (4%) [8]	21 (10%) [36]	9 (4%) [12]
Other increased liver values	53 (23%) [232]	20 (9%) [23]	46 (21%) [189]	16 (7%) [28]
Haematological biological abnormalities	41 (18%) [162]	23 (10%) [33]	53 (25%) [240]	30 (15%) [58]
Renal dysfunction (increased creatinine)	23 (10%) [59]	4 (2%) [4]	32 (15%) [67]	12 (6%) [13]
Hyponatraemia	11 (5%) [18]	2 (1%) [5]	21 (10%) [35]	4 (2%) [6]

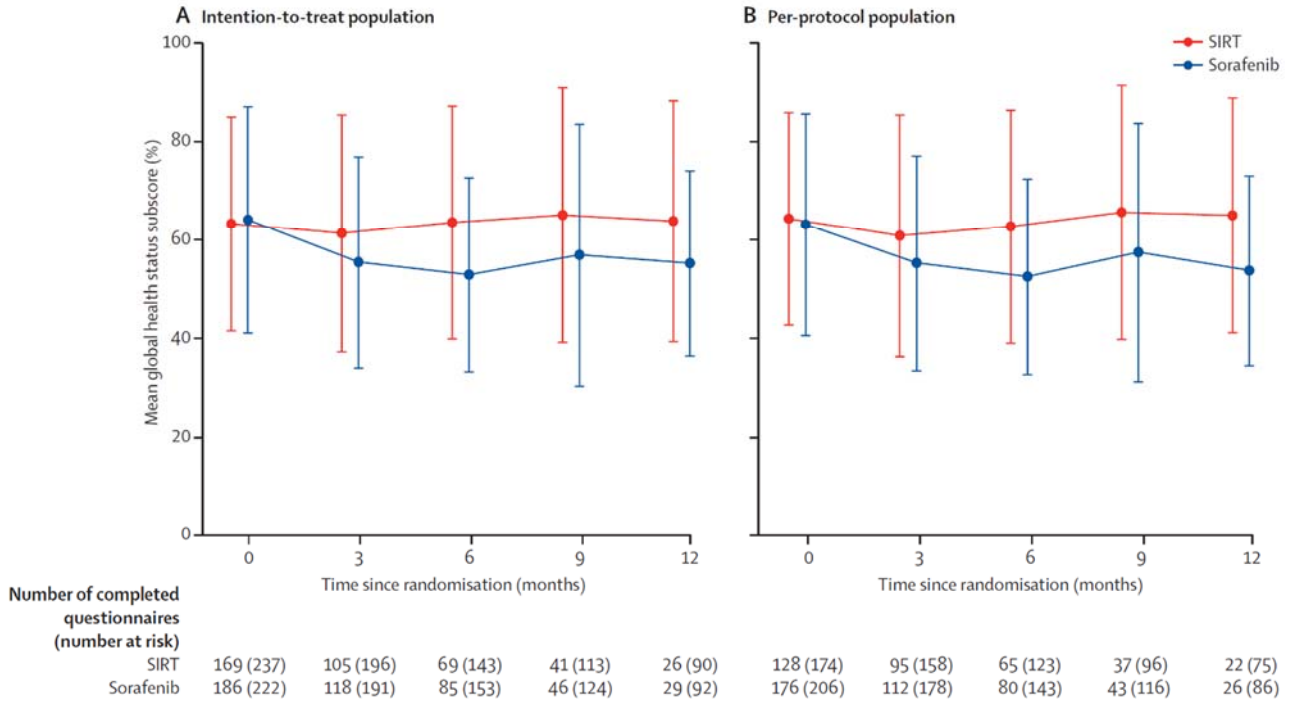
Key: GI: gastro-intestinal; HFSR: hand-foot skin reaction

The improved toxicity profile of SIR-Spheres compared to sorafenib is expected to be particularly relevant for patients' HRQL and activities of daily living. In an international survey of patients with HCC, conducted with 256 patients across 13 countries, side effects such as skin disorders, diarrhoea and fatigue were those identified by the patients as having the most significant impact on their quality of life (73). Major reductions in the incidence of these AE types have been observed for SIR-Spheres compared to sorafenib.

7.1.6 Health-related quality of life

In the SARAH trial, the difference in AE rates between SIR-Spheres and sorafenib is reflected in the global health status sub-score of the EORTC QLQ-C30, which was significantly better in the SIR-Spheres arm than the sorafenib arm (group effect p=0.0447, time effect p<0.0001) and the between-group difference tended to increase over time (group-time interaction p=0.0447) for both the intention-to-treat and the per-protocol populations, as shown below in Figure 14 (6).

Figure 14. Mean global health status scores (EORTC QLQ-C30) over time - SARAH trial



Source: Vilgrain 2017(6)

Thresholds of minimally important difference for the global health status score for HCC patients were not predefined in the SARAH study but generally 5 to 10-point changes are considered to represent a small difference, 10 to 20-point changes represent a moderate difference and changes of more than 20 points represent a large difference (116). Applying these thresholds, the change from baseline in the SIRT arm would represent a small improvement in HRQL and the differences in scores between the SIRT arm and the sorafenib arm would represent a moderate difference in HRQL from month 6 onwards.

7.1.7 Predicted dosimetry subgroup analysis

Patient selection and treatment planning can be further refined by calculating the predicted dose of radiation to the target tumour(s). This assessment, known as predicted dosimetry, is a method to predict the level of activity that is likely to be deposited in the tumour, and the resulting dose of radiation that will be administered to this tumour. A higher predicted tumour-absorbed dose indicates that most of the infusion of SIR-Spheres will get to the tumour and relatively small amounts will lodge in non-malignant tissues of the liver, lung, stomach or duodenum (14), maximising the effectiveness and reducing the toxicity of SIRT.

Predicted dosimetry can be determined as part of the work-up based on ^{99m}Tc-MAA SPECT/CT imaging with appropriate dosimetry software. In the SARAH study, the median tumour-absorbed dose was 112.2 Gy (IQR: 67.8–220.0); this was available for 121 of the 184 patients who ultimately received treatment with SIR-Spheres. A target of 120 Gy was previously recommended for treatment planning using SIR-Spheres (98). SARAH trial investigators used a threshold of 100 Gy to define a sufficient tumour absorbed-dose threshold for the subgroup analysis from this study (15). Patients with a tumour-absorbed dose of ≥100 Gy (n=67) had significantly longer overall and progression-free survival rates than patients with <100 Gy, and so will benefit most from SIR-Spheres (15).

A post-hoc analysis on patient-level data was performed to explore the comparative effectiveness of SIR-Spheres and sorafenib in a subgroup of patients with a tumour-absorbed dose of ≥100 Gy. Cox proportional

hazards regressions were conducted in the ITT population of the SARAH trial. Since predicted tumour-absorbed dose was only available for SIR-Spheres, comparisons between SIR-Spheres at a given dose and sorafenib were not randomised. Inverse probability of treatment weighting (IPTW) using propensity scores was used to account for potential confounding by differences in prognostic factors between the treatment arms. The sorafenib sample was reweighted to match the SIR-Spheres patients. For patients with a predicted dose ≥100 Gy, the HR for OS from the unweighted sample was [redacted]. After reweighting, the HR was [redacted]. Predicted mean OS was [redacted] months for SIR-Spheres vs [redacted] months for sorafenib.

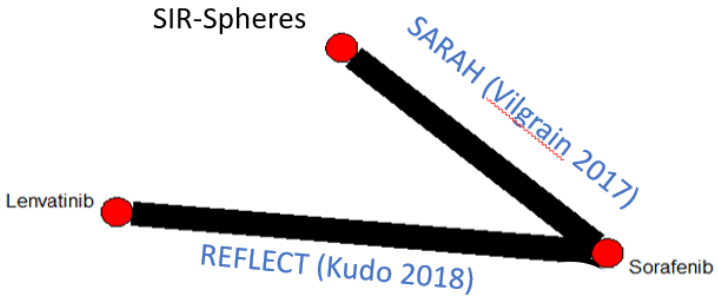
Figure 15. Kaplan-Meier plot of OS for SIRT ≥ 100Gy vs sorafenib in the SARAH trial (unadjusted)

Based on the above outcomes, UK clinicians have recommended the consideration of predicted dosimetry for patients referred for SIRT using SIR-Spheres, and that a predicted tumour-absorbed dose <100 Gy would be a factor to consider in the multidisciplinary team decision for treatment using SIR-Spheres versus systemic therapy (39). However, tumour-absorbed dose calculation using ^{99m}Tc-MAA SPECT/CT may not be part of the current standard of care for patients with unresectable HCC receiving SIRT in the UK and the development of personalised dosimetry may also result in new dose calculation methods being approved for SIR-Spheres.

7.1.8 Network meta-analysis

The NMA was informed by a systematic review of the literature, outlined in Appendix B. As mentioned in Section 7.1, four randomised controlled trials (RCTs) were identified and considered in the NMA feasibility assessment. The PICOS criteria outlined in Appendix D were applied in the feasibility assessment. In the base case analysis, studies including solely Asian patients have also been excluded, as HCC and the underlying liver disease typically have a different aetiology in Asian populations. Figure 16 shows the network of evidence for the main outcomes of interest: OS and PFS.

Figure 16. Network of studies for OS and PFS in Population 2 – TACE-ineligible patients



The REFLECT trial is included in this network (85), however, this trial did not report results for the subgroup of patients with a tumour burden <25% and an ALBI grade of 1, so comparative effectiveness of the three treatments could not be directly estimated for this subgroup. Comparative patient characteristics tables are provided in Appendix D. There were differences in the overall ITT populations of REFLECT and SARAH due to differences in terms of inclusion and exclusion criteria: REFLECT excluded patients with main portal vein thrombosis (PVT) and included patients with extrahepatic spread (EHS); SARAH included patients with main PVT but excluded patients with EHS. Due to these differences and the lack of data for key subgroups from the REFLECT trial, lenvatinib was included in the model as a scenario analysis and not the base case analysis.

Treatment effects were estimated in the ITT populations of the trials and in a subgroup excluding those with EHS, main PVT or any macroscopic vascular invasion (MVI). This allowed the NMA to be performed in a relatively homogeneous subgroup of patients, as OS results (but not PFS) were reported for this subgroup in both trials.

The proportional hazards assumption was tested for both SARAH and REFLECT in Appendix E. For this network, both fixed and random effects models were evaluated (117). The analysis was conducted using the JAGs software with Bayesian Markov chain Monte Carlo techniques. As the evidence network is limited, with only one study informing each comparison, random treatment effects models incorporated external evidence (118) on prior distributions for the treatment effect variance. The deviance information criteria (DIC) statistics for the fixed and random effects models are compared to determine goodness of fit. A full description of the models, prior and posterior distributions and functions used are provided in Appendix D.

Results of the NMA for HRs of OS are reported in Table 10. Other results including probability of ranking plots are included in Appendix D.

Table 10. OS hazard ratios from the NMA in Population 2 – TACE-ineligible patients

	Complete ITT population OS, mean (95% CrI)		**No MVI/EHS/main PVT OS, mean (95% CrI)**	
	Fixed Effects	**Random Effects**	**Fixed Effects**	**Random Effects**
Sorafenib (ref.)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
SIR-Spheres	1.15 (0.94, 1.40)	1.15 (0.49, 2.69)	1.05 (0.75, 1.46)	1.05 (0.43, 2.53)
Lenvatinib	0.92 (0.79, 1.06)	0.92 (0.39, 2.14)	1.05 (0.79, 1.39)	1.05 (0.44, 2.51)
DIC	-7	-7	-2	-2

CrI: credible intervals; DIC: deviance information criteria; Macrovascular invasion; EHS: Extrahepatic spread; PVT: Portal vein thrombosis

There were no statistically significant differences between any of the treatments in either the overall ITT population or the subgroup without EHS, main PVT or MVI (Table 10).

It should be noted that the results of the NMA were not directly used in the cost-effectiveness model. For the base case analysis, estimates of treatment effect were derived from the SARAH trial (6). For the comparison

with lenvatinib in scenario analyses, hazard ratios from the REFLECT trial (85) were applied to the survival curves for the sorafenib arm of the SARAH trial. This approach was taken as the REFLECT trial was the only other relevant trial evidence and the focus of the cost-effectiveness analysis was the comparison between SIR-Spheres and sorafenib. The NMA was conducted to provide further information on comparative effectiveness.

7.2 *Cost-effectiveness in Population 2 – TACE-ineligible patients*

7.2.1 Model design

Due to the lack of published economic analyses evaluating SIRT, a de novo economic model was developed to assess the cost-effectiveness of SIR-Spheres in HCC. The model was developed based on:

- The SARAH trial, which the first and largest trial of SIR-Spheres in HCC and is conducted in a European setting: published data (6) and post-hoc analyses (see Section 7.1and Appendices B and C),
- A systematic and targeted literature reviews (see Appendix B for the systematic and Appendix H for the targeted literature review),
- Registry data including Christie NHS Foundation Trust data, the Post SIR-Spheres Surgery Study (P4S) (see Appendix L), and the CIRSE Registry for SIR-Spheres Therapy (CIRT),
- Extensive consultation with clinical and health technology assessment experts through two surveys and three Advisory board meetings (see Appendix J).

7.2.1.1 Patient population

As described in Sections 1 and 6.3, the patient population that is the focus of the cost-effectiveness analysis includes patients matching the following criteria:

- Patients with unresectable intermediate (BCLC stage B) or advanced (BCLC stage C) HCC,
- for whom any transarterial embolisation therapies (TAE, cTACE, DEB-TACE) are inappropriate,
- with or without portal vein thrombosis / involvement,
- without extrahepatic disease,
- with a tumour burden ≤25%,
- and with a preserved liver function (ALBI grade 1).

This population is referred to as the “base case subgroup” for the economic model. While the Final Scope defines a broader population in line with the marketing authorisation of SIR-Spheres (11), this narrower population has been defined in conjunction with clinical experts (5, 8, 39) and is supported by the literature (see Sections 6.2 and 7.1.4.2):

- to reflect clinical practice and the clinical guidelines (1),
- to identify patients most likely to benefit from SIRT,
- to allow a high probability of subsequent treatments with curative intent (13.5% of patients had transplant, resection or ablation on the SIR-Spheres arm vs. 2.1% on the sorafenib arm), and
- to minimise unnecessary work-up by selecting patients most likely to receive SIR-Spheres (91.9% received SIR-Spheres after work-up in this population vs. 77.6% in the ITT population, which is in line with current clinical practice of 93% based on a survey of nine clinicians and two specialist nurses).

For further information on patient population, please see Section 1. At the same time, to allow for the assessment of the primary population patients were randomised for and that is reported from the SARAH trial (6), two additional scenarios analyses have been included using:

- the ITT population of the SARAH trial, as that was the primary population of the SARAH trial, and
- the per protocol (PP) population of the SARAH trial, to exclude the high number of patients who have not received SIR-Spheres despite being randomised to the SIRT arm.

7.2.1.2 Interventions and comparators

The main comparators include SIR-Spheres and sorafenib, which have comparative evidence. Additionally, lenvatinib is included in scenario analyses, however this comparison required multiple assumptions. QuiremSpheres and TheraSphere are not included due to the lack of evidence in this patient population. Regorafenib is recommended by NICE after sorafenib (119), thus, is included only as subsequent treatment. Best supportive care (BSC) in this population eligible for systemic treatments is not a relevant comparator, as it is only used if patients refuse, or are not suitable for all treatments. For more information, please see Section 5.

7.2.1.3 Model structure

7.2.1.3.1 General model structure

The economic model was developed using a partitioned survival approach with three main health states: progression-free, progressed or dead. This technique is commonly used in modelling oncology, and is appropriate in capturing progressive, chronic conditions which are described with clinical outcomes requiring an ongoing, time-dependent risk, such as progression and death (120, 121). This approach is also in line with prior NICE technology appraisals (TAs) in HCC (Table 11) (87, 108, 109, 119).

Table 11. Prior NICE TAs in unresectable HCC

	Population	Comparators	Guidance	Model structure
Sorafenib TA189 (109)	Adults with advanced HCC, unsuitable for local or loco-regional curative therapy or progressed after these	Sorafenib BSC	Not recommended	Partitioned survival analyses Monthly cycles
Sorafenib TA474 (87)	Adults with advanced HCC, unsuitable for local or loco-regional curative therapy or progressed after these	Sorafenib BSC	Recommended for advanced HCC with Child-Pugh grade A liver impairment	Partitioned survival analyses Monthly cycles
Regorafenib TA514 (119)	Adults with advanced, unresectable HCC who had prior sorafenib	Regorafenib BSC	Not recommended	Partitioned survival analyses 28-day cycle
Lenvatinib TA551 (108)	Adults with untreated advanced or unresectable HCC and Child-Pugh grade A liver function	Lenvatinib Sorafenib	Recommended for untreated, advanced, unresectable HCC with Child-Pugh grade A, ECOG PS 0-1	Partitioned survival analyses 28-day cycle

7.2.1.3.2 SIRT treatment eligibility after the work-up

As discussed in Section 7.1.4.1, a proportion of patients deemed eligible for SIRT will not receive it due to technical reasons such as lung shunting or worsening disease or deterioration of hepatic function. The proportion of patients not receiving SIR-Spheres has implications both on cost and health outcomes. Consequences on efficacy and AEs are implicitly included in the results from the post-hoc analysis of the SARAH trial, while the cost of additional work-ups that do not lead to SIRT procedures have been added explicitly.

In the overall population of the SARAH trial, 11 patients (5%) from those randomised in the SIRT arm did not receive a work-up and a further 42 (19%) did not receive SIR-Spheres after the work-up. This suggests that the overall trial population did not reflect appropriate patient selection and that patients enrolled in the SARAH trial may not have been good candidates for SIRT. In clinical practice in the UK, clinicians have reported that the

drop-off rate after workup is substantially lower (7%) (Resource use and short survey pooled results 2019). In the base case subgroup of patients with tumour burden ≤25% and ALBI grade 1, the proportion of patients not receiving SIR-Spheres after their work-up was to 2.9%.

7.2.1.3.3 Down-staging to curative therapy

In addition to progression and death used in previous HCC partitioned survival analysis models, SIR-Spheres also allows for down-staging to treatments with curative intent. Subsequent treatments with curative intent were defined as liver transplant, liver resection / surgery and ablation in line with clinical guidelines (1), and as seen in the P4S study (113). This has been observed not just among TACE-eligible, but also TACE-ineligible patients with SIR-Spheres, while it is rare for sorafenib (6). This is supported by the significantly higher proportion of patients achieving complete or partial tumour response in the SARAH trial (6).

Treatments with curative intent are an important treatment option for HCC patients, as they offer significantly extended survival (115). Outcomes for these patients are vastly improved compared to those receiving palliative treatments alone, which supports a separate modelling of OS outcomes for these patients in the model. In the SARAH trial for the base case subgroup population, 13.5% of patients received subsequent treatments with curative intent in the SIR-Spheres arm vs. 2.1% in the sorafenib arm (18). In other populations, the rate of proportion of patients with subsequent treatments with curative intent after SIR-Spheres ranged from [redacted] to 29% (Table 12).

Table 12. Proportion of patients receiving subsequent treatments with curative intent

Source	After SIR-Spheres	After sorafenib
SARAH trial: patients with tumour burden ≤25% and ALBI grade 1	13.5%	2.1%
SARAH trial: ITT population	5.1%	1.4%
SARAH trial: PP population	6.9%	1.5%
CIRT Registry (122)	[redacted]	-
Physician survey (See Appendix O)	5.6%	0.1%
Regnault 2019 (114)	24%	-
Inarrairaegui et al. 2012 (123)	29%	-

The survival benefit of treatments with curative intent is however not captured in the SARAH trial outcomes, as only 1 patient in each arm died after treatments with curative intent, with the rest of the patients being alive and censored at the end of the follow-up period. Patients received treatments with curative intent on average 16 months after randomisation in the SARAH trial. Survival analyses in the SARAH trial assume uninformative censoring, which is not considered a valid hypothesis as all but one of the down-staged patients were censored.

Therefore, treatments with curative intent have an important effect on health outcomes, which is not captured in the OS curve of the SARAH trial. An explicit modelling of the OS consequences of treatments with curative intent allows the inclusion of the corresponding costs and health outcomes into the analysis, as well as the flexibility of testing different scenarios regarding the proportion of patients receiving these treatments. Therefore, survival, HRQL and costs for patients receiving treatments with curative intent were modelled separately leading to a mixed model structure (Figure 17). Meanwhile, a conservative approach was used by assuming a single PFS curve for patients in the model, whether or not they received subsequent curative therapy, as there was less censoring of progression data.

In each cycle of the model, patients are assigned to one of four mutually exclusive health states according to the proportion of patients who are ’progression-free ‘, ‘received curative therapy’, ’progressed ‘, or ’dead‘ (Figure 17). Patients start in the ‘progression-free’ health state and on SIR-Spheres or sorafenib or in the indirect comparison also lenvatinib. Within each cycle of the model, patients can either:

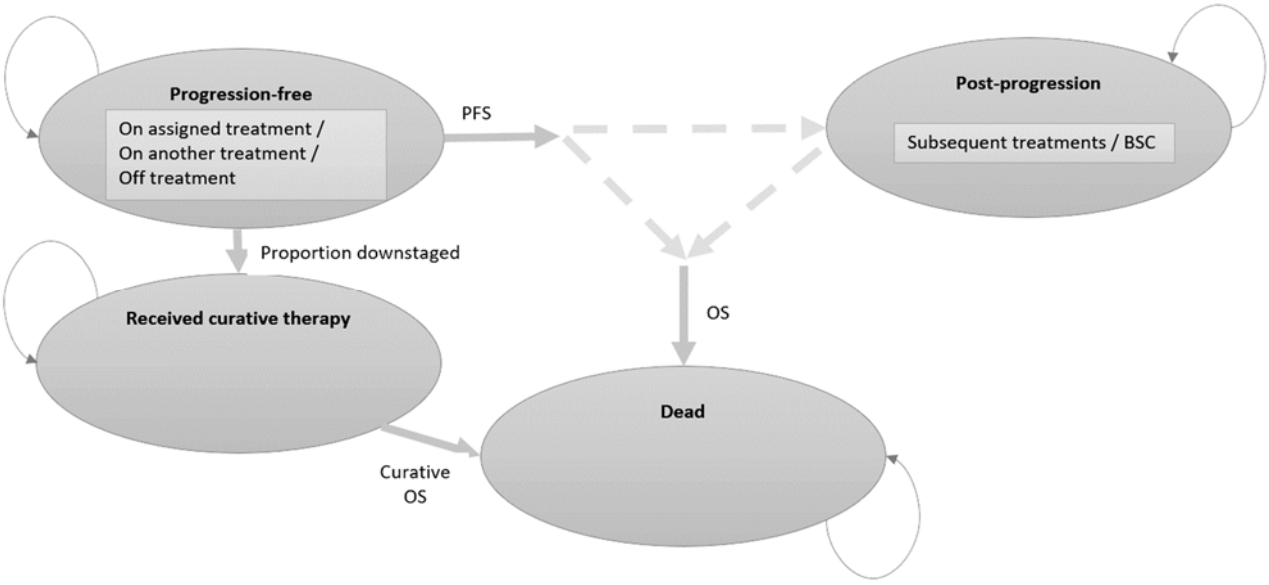
- Stay in that health state;
- Receive treatments with curative intent ('received curative therapy')
- Progress ('progressed') or
- Die ('dead')

Additionally, at 16 months, patients can receive subsequent treatments with curative intent in which case they switch to a separate OS curve.

Cycle length was one month, similarly to the previous TAs in HCC (Table 11). This accommodates the clinical assessment schedule of 3-6 months (1) and the monthly patient visits in the SARAH trial (6). A half-cycle correction was applied to all outcomes with the exception of drug and procedure costs, because these are accrued at the beginning of each cycle.

Each health state, in each treatment arm, is associated with a corresponding resource use and utility. All patients on treatment are exposed to the risk of adverse events (AEs). The consequences of AEs are calculated as costs for patients on treatment, while the utilities from the SARAH trial already include disutilities due to AEs.

Figure 17. Cost-effectiveness model structure in Population 2 – TACE-ineligible patients



To assess the cost-effectiveness of SIR-Spheres using a more traditional model structure, a structural scenario analysis was conducted with the partitioned survival analyses assuming no additional benefit from down-staging to curative treatments, while including all subsequent treatment costs. This underestimates the benefits with SIR-Spheres, since all but one patient were censored after receiving subsequent treatments with curative intent and thus any additional survival benefit for these patients was not included in the SARAH OS curve.

Other key characteristics of the model structure are summarised and compared to previous NICE TAs in

Table 13. The economic model is designed in accordance with the requirements of NICE (124) and the ISPOR-SMDM guidelines (125) and was developed in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA).

Table 13. Features of the economic analysis in the current and previous NICE TAs in unresectable HCC

Model design	Previous appraisals			Current appraisal	
	Sorafenib TA189 and TA474	**Regorafenib TA514**	**Lenvatinib TA551**	**Chosen values**	**Justification**
Time horizon	Lifetime	Lifetime	Lifetime	Lifetime	SIR-Spheres affects the differences in health outcomes and costs between the technologies being compared over the patients' lifetime (Guide to the methods of technology appraisal 2013: Section 5.15-5.17). In line with previous TAs
Treatment waning effect?	Included implicitly in the independent survival curves	Included implicitly in the independent survival curves	Included implicitly in the independent survival curves	Included implicitly in the independent survival curves	The Kaplan-Meier curves are close to complete, so the independent survival curves take waning effect into account. In line with previous TAs
Source of utilities	Pivotal SHARP RCT, FACT-G mapped to TTO utilities	EQ-5D values from pivotal RESOURCE RCT	EQ-5D values from pivotal REFLECT RCT	EORTC-QLQ-C30 results mapped to EQ-5D values from pivotal SARAH RCT	In line with the NICE Reference case (Guide to the methods of technology appraisal 2013: Section 5.3). In line with previous TAs
Source of costs	Resource use: RCT for treatment discontinuation Otherwise expert opinion. Unit costs: As recommended by Guide to the methods of technology appraisal 2013.	Resource use: RCT for treatment discontinuation Otherwise expert opinion. Unit costs: As recommended by Guide to the methods of technology appraisal 2013.	Resource use: RCT for treatment discontinuation Otherwise expert opinion. Unit costs: As recommended by Guide to the methods of technology appraisal 2013.	Resource use: RCT for treatment discontinuation Registries and expert opinion. Unit costs: As recommended by Guide to the methods of technology appraisal 2013.	Where available, resource use was taken from current clinical practice relevant for the UK. Otherwise expert opinion was used in line with previous TAs. Unit costs were in line with the NICE Reference case (Guide to the methods of technology appraisal 2013: Section 5.5). In line with previous TAs

7.2.2 Clinical parameters and variables

Clinical data (i.e., OS, PFS curves, treatment continuation curve for sorafenib, proportion of patients with curative treatments and AE risks) were derived from the SARAH trial, to inform the model's efficacy and safety parameters for SIR-Spheres and sorafenib. Hazard ratios (HRs) informing OS and PFS inputs for the scenario analyses including lenvatinib as a comparator were obtained through an indirect treatment comparison (Appendices D and E). A summary of clinical variables used in the economic model is presented in Table 14. Methods used to incorporate each parameter in the economic model are described in the following sections.

Table 14. Summary of clinical parameters applied in the economic model

Variable	Treatment	Data source
Overall survival (OS)	SIR-Spheres Sorafenib	SARAH trial post-hoc analyses For curative treatments: data from a targeted literature search, due to lack of data from the SARAH trial (See Appendix H)
	Lenvatinib	Indirect treatment comparison based on the SARAH and REFLECT (85) trials (See Appendices D and E)
Progression-free survival (PFS)	SIR-Spheres Sorafenib	SARAH trial post-hoc analyses
	Lenvatinib	Indirect treatment comparison based on the SARAH and REFLECT (85) trials (See Appendices D and E)
Time to treatment discontinuation (TTD)	Sorafenib	SARAH trial post-hoc analyses
	Lenvatinib	REFLECT trial (85)
Adverse events (AEs)	SIR-Spheres Sorafenib	SARAH trial post-hoc analyses
	Lenvatinib	REFLECT trial (85)

The efficacy inputs of OS and PFS matched the primary and secondary outcomes of the SARAH trial. However, because the model evaluates the impact of treatment on costs and health benefits over a lifetime horizon, and OS and PFS curves were not complete, they needed to be extrapolated beyond the end of the SARAH trial follow-up using parametric models, according to the recommendations by the Decision Support Unit (DSU) for NICE, published June 2011 and updated March 2013 (124), as well as recommendations from published literature (126). Parametric models assume that survival times for patients follow a given theoretical distribution (127).

Extrapolations were performed by fitting parametric models to the observed time-to-event data from the SARAH trial, using R. Commonly used parametric survival models (Weibull, log-normal, log-logistic, exponential, generalised gamma and Gompertz distributions) were fitted to the observed data. In all analyses, months were used as the time unit corresponding to the model cycle length.

The steps followed to conduct parametric survival analyses are described below:

First, an exploratory analysis was conducted where the fit of the distributions was tested using parametric plots, observed and predicted plots, long-term projections and goodness-of-fit statistics (i.e., Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC)) for each treatment arm (SIR-Spheres and sorafenib and a combined model for both groups with treatment as a predictor). The proportional hazard assumption was tested using log-cumulative hazards plots. Diagnostic plots and goodness-of-fit statistics were used to identify plausible fits; graphs of fit against the observed data provided an assessment of internal accuracy, and long-term projections served to assess the clinical plausibility of the fits (128). Based on these analyses, the best fitting distribution for the observed data was chosen.

Where the exploratory analysis showed that the optimal fit for each treatment arm was based on the same distribution and that the shapes of these fits were similar, modelling the two trial arms together including a treatment indicator as a predictor in the model was considered. Otherwise the treatment arms were chosen to be modelled separately.

7.2.2.1 Overall survival

Overall survival (OS) was defined as the time from the date of randomisation to death from any cause (or the date of the last follow-up if the patient is alive at the end of the trial).

Parametric survival analyses were conducted in each relevant population for OS data from the SARAH trial. For all populations, OS was calculated excluding patients down-staged to curative therapy, whose survival outcomes were modelled separately (see below). For the structural scenario analyses, down-staged patients were included in the overall population.

None of the diagnostic plots in Appendix R indicate that any one model fits better than another. The lines in the plots are not parallel in all cases, with some lines crossing, which may foster doubt about whether the proportional hazards assumption holds. The Schoenfeld residuals plot however, indicates that there is no significant deviation from proportional hazards. Therefore, it is inconclusive if the proportional hazards assumption stands. To be in line with the previous NICE HCC TAs (87, 108, 109) listed in

Table 13, the curves were fitted separately, and then joint fit was tested in scenario analysis.

AIC/BIC statistics are similar, except for the exponential distribution that has the highest AIC/BIC. In the visual inspection, the generalised gamma, Weibull and Gompertz curves crossed, which is not seen in the Kaplan-Meier curves until the last few patients. The lognormal and loglogistic distribution did not deviate in fit, nor did they cross. In the previous first line advanced HCC TAs, in line with this, lognormal (sorafenib TA) and loglogistic (for lenvatinib TA) models were found to be the most appropriate. In the ITT population, with the most data, lognormal distribution fitted the best both in terms of goodness of fit statistical criteria and visual inspection. Additionally, in the literature based on a systematic literature review of HCC survival, lognormal distribution is the most appropriate (127, 129). As a result, in the base case lognormal distribution was used. More details on the model fits are provided in Appendix F.

In the scenario analyses however, both loglogistic distribution (the other selected distribution) and the Weibull distribution (considered in both previous NICE first line HCC TAs) were tested.

For scenario analyses including lenvatinib as a comparator, the HR calculated from the NMA was used to multiply the sorafenib cycle hazards for OS. A HR of 0.92 (95% CI 0.79-1.06) was used for lenvatinib vs sorafenib (see Appendix E).

7.2.2.2 Overall survival for patients down-staged to curative therapy

The OS of patients down-staged to curative therapy was modelled separately since because one patient (in the sorafenib arm) died in the SARAH trial among those receiving these treatments. This highly informative censoring means, that the mortality consequences of receiving treatment with curative intent is not captured in the OS curves of the SARAH trial. External data are therefore required for the estimation of OS of these patients. For simplification, all patients receiving ablation, resection or transplantation were assumed to follow the same OS curve.

In the base case the HR comparing patients with intermediate or advanced HCC receiving and not receiving treatments with curative intent was from a prospective study in the US (115). HCC patients from eleven centres were enrolled between 2001-2007 and followed longitudinally. Potentially curative treatments were defined as

liver transplantation, surgical resection (wedge resection, segmental resection, lobectomy), or tumour ablation (alcohol injection ablation and radiofrequency ablation). Using Cox multivariate proportion hazards, the HR for OS with potentially curative treatments vs. non-curative treatment was 0.29 (95% CI: 0.18-0.47). For further information please see Appendix R.

Additionally, a targeted literature review was conducted to assess survival after treatment with curative intent for UK patients, including transplantation, resection and ablation. According to clinical expert opinion patients who have been successfully down-staged from an initially unresectable HCC to become eligible to receive treatments with curative intent have similar survival to those initially eligible for these treatments (8). As a result, the search focused on survival after all ablations and resections in HCC. While liver transplant patients have a good survival, only a small proportion of patients become eligible for transplantation (Table 22), so using survival estimates of transplanted patients for all treatments with curative intent would overestimate their survival. Conversely, the use of OS outcomes for patients receiving ablation or resection would underestimate survival, leading to a conservative approach. As a result, the review included articles looking at a combination of all these treatments, or ablation only or resection only. (For details of the targeted review, please see Appendix H.) Survival estimates from the model were compared to the results from the UK studies.

In the base case, the proportions of patients down-staged to curative therapy were estimated for SIR-Spheres and sorafenib based on the SARAH trial, for each population. A targeted literature review was conducted for alternative values in scenario analyses. Corresponding values are presented in Table 12.

7.2.2.3 Progression-free survival (PFS)

Progression-free survival (PFS) was defined according to RECIST 1.1 as the time from the closest date of radiologic examination before the first administration of the study treatment to disease progression (per investigator assessment) or death from any cause. As a progression event was observed for most patients down-staged to curative therapy, a single PFS curve was assumed for all patients in the model, whether or not they received subsequent curative therapy.

For PFS, jointly fitted log normal, independently fitted log normal and the jointly fitted log-logistic distributions had the lowest AIC/BIC. Similar to OS, none of the diagnostic plots indicate that any one model fits better than another and may suggest that the proportional hazards assumption does not hold. As a result, in the base case lognormal distribution was used. More details on the model fits are provided in Appendix F.

In the scenario analyses, similarly both loglogistic distribution and the Weibull distribution were tested. (For further information please see Appendix F.)

For scenario analyses including lenvatinib as a comparator, the HR calculated from the NMA was used to multiply the sorafenib cycle hazards for PFS. A HR of 0.65 (95% CI 0.58-0.73) was used for lenvatinib vs sorafenib. For further information please see Appendix E.

7.2.2.4 Time to treatment discontinuation

Time to treatment discontinuation (TTD) data were obtained from post-hoc analysis of the SARAH trial for sorafenib. Based on visual inspection of the time to discontinuation curves for sorafenib and AIC and BIC statistics, the best fitting model is the lognormal distribution. Data from the ITT population was used to populate this parameter in all populations. A median TTD of 2.8 months (95% CI: 1.0 to 5.8 months) was estimated, in accordance with published data (6). Please see Appendix F for further information.

For the indirect comparison with lenvatinib in the scenario analyses, the Kaplan-Meier curves from the lenvatinib NICE Technology Appraisal (108) were digitalised and the HR was estimated and used vs. sorafenib in

the SARAH trial. (For further information please see Appendix E.) Based on this analysis a HR of 0.75 (95% CI 0.65-0.85) was used for lenvatinib vs sorafenib. For further information please see Appendix E.

7.2.2.5 Adverse events

The numbers of patients with grade 3 and 4 AEs were taken from the safety populations of the clinical trial publications (Vilgrain 2017 for SARAH and Kudo 2018 for REFLECT)(6, 85). Incidence rates over the entire treatment period were used and costs applied as a lump sum at the start of treatment.

Only grade 3 or 4 AEs were included that occurred in more than 5% of the total population of the SARAH trial or the REFLECT trial publications as, in line with previous appraisals, they were assumed to have cost consequences (Table 15). Rarer or lower grade AEs were assumed not to have important cost consequences on a population level.

Table 15. Rate of AEs included in the economic model

	SIR-Spheres	Sorafenib	Lenvatinib	Reason of inclusion
Fatigue	9%	19%	4%	Grade 3/4 AE in ≥5% of SARAH Trial
Hand-foot skin reaction	0%	6%	3%	Grade 3/4 AE in ≥5% of SARAH Trial
Anorexia	3%	5%	5%	Grade 3/4 AE in ≥5% of SARAH Trial
Diarrhoea	1%	14%	4%	Grade 3/4 AE in ≥5% of SARAH Trial
Abdominal pain	3%	6%	2%	Grade 3/4 AE in ≥5% of SARAH Trial
Liver dysfunction	8%	13%	NR	Grade 3/4 AE in ≥5% of SARAH Trial
Cardiac failure, congestive	1%	5%	NR	Grade 3/4 AE in ≥5% of SARAH Trial
Other increased liver values	9%	7%	NR**	Grade 3/4 AE in ≥5% of SARAH Trial
Haematological biological abnormalities	10%	13%	NR**	Grade 3/4 AE in ≥5% of SARAH Trial
Hypertension	0%	2%	23%	Grade 3/4 AE in ≥5% of REFLECT Trial
Weight loss	0%	3%	8%	Grade 3/4 AE in ≥5% of REFLECT Trial
Blood bilirubin increase	4%	4%	7%	Grade 3/4 AE in ≥5% of REFLECT Trial
Proteinuria	1%*	4%*	6%	Grade 3/4 AE in ≥5% of REFLECT Trial
Gamma-glutamyltransferase increase	0%^	0%^	6%	Grade 3/4 AE in ≥5% of REFLECT Trial
Platelets decrease	0%#	0%#	6%	Grade 3/4 AE in ≥5% of REFLECT Trial
Aspartate aminotransferase increase	0%^	0%^	5%	Grade 3/4 AE in ≥5% of REFLECT Trial

*Was part of the AE increased creatinine level, so this was used as proxy, overestimating it slightly
^ Included in Other increased liver values
# Included in Haematological biological abnormalities
** Only Gamma-glutamyltransferase increase and Aspartate aminotransferase increase reported, and were included separately

7.2.2.6 Use of clinical expert opinion

Clinical experts' opinion was used to inform the clinical plausibility of the long-term extrapolation of the OS inputs, estimates for the administration of SIRT (proportion of patients dropping of after work-up, number and length of work-up and procedure) and disease management. For further details of the clinical expert interviews please see Appendix J.

7.2.3 Measurement and valuation of health effects

7.2.3.1 Base case methods and utility values

Utility values have been reported for HCC in the previous NICE TAs (87, 108, 109, 119) (Table 16). However, all the reported values are for targeted therapies (sorafenib, lenvatinib, regorafenib), not for SIRT or even loco-regional therapies. Since SIRT has a different AE profile than targeted therapies (see Section 7.1.5, page 46),

the utility values could also differ. Additionally, the population targeted by this cost-effectiveness analyses is a selected population based on SIRT clinical practice and evidence, which differs from the populations described in the SHARP, RESOURCE and REFLECT trials, therefore values from these trials are not applicable and utilities values specific to SIRT and in the appropriate population are required for the economic model.

Table 16. Utility values from previous NICE HCC TAs in unresectable HCC

	Source	Values	Comments
Sorafenib TA189 and TA474 (87, 109)	SHARP RCT, FACT-G mapped to TTO utilities based on published algorithm	• Pre-progression: 0.69 • Post-progression: 0.71 • Disutility for AE: -0.0087	Concerns regarding mapping: based on patient, not general population preference Concern with values: high post-progression value Sensitivity analyses with RCC values had small effect
Regorafenib TA514 (119)	EQ-5D values from RESOURCE RCT	• Pre-progression: 0.811 • Post-progression: 0.763 • Disutility for AE: 0.014	EQ-5D completed on the 1st day of each treatment cycle, when a patient had not had treatment for a week, so AEs not fully captured Concern with values: high values, small difference pre- and post-progression
Lenvatinib TA551 (108)	EQ-5D values from REFLECT RCT	• Baseline: 0.829 • Progression free: 0.745 • Progressed: 0.678 • AE assumed to be included	Concern with values: high post-progression value; scenario analysis with 0.5 has small effect

In the base case model, both utilities and efficacy inputs have been derived from the SARAH trial. While the SIRveNIB trial has reported EQ-5D values (7), the trial was conducted in Asia, where both the patient population and the treatment pattern differ from that in the UK. Previous NICE TAs for technologies in the treatment of HCC had concluded that "prognosis is distinctly different for Asian patients"(109) and that there were statistically significant and clinically relevant differences in baseline characteristics between Western and Asian populations, the former being "heavier, [having] more heart disease, less underlying cirrhosis, less hepatitis B and more pre-existing hepatitis C or alcohol related conditions" (108), all of which can affect baseline and post-treatment utilities.

The SARAH trial was conducted in France (6), and therefore, was more relevant for the UK population, however it reported HRQL with EORTC-QLQ C30.

The EORTC QLQ-C30 results were mapped to EQ-5D scores using the algorithm by Longworth et al. (2014)(130). The probabilities were multiplied by the UK general population weights. These weights were estimated as required by NICE using a choice-based method, time-trade off from the UK general population. The mapped UK EQ-5D utility values, similarly to the EORTC QLQ-C30 results, were relatively stable over time for both treatment arms both pre- and post-progression (for further details, please see Appendix G). This suggested that single health state utilities, defined by both progression status and treatment arm, are appropriate. Mean health state utility values were estimated using multi-variable analysis.

While utilities for patients in the SIR-Spheres arm were only slightly higher than for patients on sorafenib, EORTC QLQ-C30 showed a statistically significant improvement in global health status sub-score in the SIR-Spheres group compared to the sorafenib group (group effect $p=0.0048$; time effect $p<0.0001$) with the between-group difference tending to increase with time (group-time interaction $p=0.0447$). This supported the inclusion of treatment-specific utilities in the model. (For further details, please see Appendix G.)

Patients down-staged to curative therapy may have a different utility than those only receiving palliative treatments. However, limited data were available on these patients in the SARAH trial due to the low patient

numbers. For these patients, the same utility was used as for pre-progression in the SIR-Spheres arm to avoid incorporating the disutilities due to AEs of sorafenib.

All base case utility values are presented in Table 17.

Table 17. Summary of the base case utility values in the economic model

Comparator	Utility value: mean (Standard error)	Reference	Justification
Pre-progression SIR-Spheres	0.762 (0.078)	Post-hoc analyses of the SARAH trial for the low tumour burden + ALBI grade 1 subgroup, see Appendix G for further information	From the same source as the efficacy and safety data. From an RCT for the relevant comparators. EQ-5D values with weights estimated with a choice-based method, time-trade off from the UK general population.
Pre-progression sorafenib	0.746 (0.076)		
Post-progression SIR-Spheres	0.738 (0.075)		
Post-progression sorafenib	0.722 (0.074)		
After subsequent treatment with curative intent	0.762 (0.078)	Assumed same as the pre-progression utilities with SIR-Spheres	It includes an extended pre-progression state without the toxicities associated with sorafenib

7.2.3.2 Discussion and scenario analyses

The progression status results in only a small decrease in the utilities, which might not represent patient experience of the whole post-progression period. The utilities from the SARAH trial were however stable over time after progression, although data are limited towards the end of life (See Table 47 in Appendix G). There is limited evidence regarding changes in utilities towards end of life, however data from other cancer indications suggests (131, 132), that patients do not experience a major drop in HRQL at radiological progression, but only towards the end of life usually defined as the last 1-3 months of life. Since patients on both treatment arms go through this end of life period, there are no incremental differences, and thus is has no influence on cost-effectiveness results. Consequentially, this end of life utility has not been included.

For the scenario analyses including this comparator, utility values for lenvatinib were assumed to be the same as for sorafenib due to their similar mechanism of action and AE profile. The effect of AEs was incorporated in the health state utilities, as treatment specific utilities were used from the SARAH trial.

The pre-progression utility values are in line with those used in the lenvatinib NICE appraisal (108), with the sorafenib utilities being almost the same as the lenvatinib values based on EQ-5D values from the pivotal trial (Table 18). The post-progression utilities are higher; however, this is a selected population with lower tumour burden and better liver function. When not selecting patients with a better baseline prognosis and using the SARAH ITT analysis, the post-progression utility values are close to values used in the lenvatinib appraisal and sorafenib appraisals (87, 108, 109). Both lenvatinib and sorafenib appraisal values were included in scenario analyses.

Table 18. Alternative utility values pre-and post-progression

Data source	Pre-progression		Post-progression	
	SIRT	Sorafenib	SIRT	Sorafenib
SARAH (Base case subgroup)	0.762	0.746	0.738	0.722
SARAH (ITT)	0.710	0.703	0.666	0.659
NICE TA551 lenvatinib TA	0.745	0.745	0.678	0.678
NICE TA189 sorafenib **NICE TA474 sorafenib**	0.69	0.69	0.71	0.71

References: (6, 87, 108, 109), Sirtex data on file (18)

Alternative utility values were also explored in the literature for patients receiving subsequent treatments with curative intent. As no utility values were reported for patients down-staged after SIRT, values for patients with compensated cirrhosis after treatments with curative intent were explored. Thein et al. (2017) has reported multiple values for this patient population from a literature review and estimated pooled mean utilities of 0.71-0.77 (133). Additionally, utilities of 0.82 and 0.88 were used in economic evaluations after hepatic resection and radiofrequency ablation (134, 135).

Table 19. Utility values for patients with compensated cirrhosis in the literature

	Preference-based measures	Country	Mean	Standard error	Lower limit	Upper limit
Chong et al, 2003	EQ-5D	Canada	0.74	0.05	0.642	0.838
Chong et al, 2003	HUI3	Canada	0.74	0.05	0.642	0.838
Chong et al, 2003	SG	Canada	0.8	0.05	0.702	0.898
Sherman et al, 2004	SG	US	0.83	0.04	0.7516	0.9084
Sherman et al, 2004	TTO	US	0.9	0.03	0.8412	0.9588
Siebert et al, 2001	EQ-5D	Germany	0.74	0.02	0.7008	0.7792
Younossi et al, 2001	HUI2	US	0.82	0.04	0.7416	0.8984
Hsu et al, 2012	HUI2	Canada	0.73	0.012	0.70648	0.75352
Hsu et al, 2012	SF-6D	Canada	0.66	0.008	0.64432	0.67568
Hsu et al, 2012	TTO	Canada	0.78	0.021	0.73884	0.82116
Pooled mean utility using fixed effects model			0.71			
Pooled mean utility using random effects model			0.771			

Source: Thein et al. 2017

7.2.4 Cost and healthcare resource use identification, measurement and valuation

Resource use was based on the published literature, data from the Christie NHS Foundation Trust and expert opinion (oncologists, hepatologists, interventional radiologists and specialist nurses) through Resource use surveys (Appendix O) in line with previous NICE HCC TAs.

Unit costs of resources were obtained from National Schedule of Reference Costs 2017-18 (136) and the Personal Social Services Research Unit (PSSRU) report (137, 138) and unit costs of drugs were obtained from British National Formulary (2019) (139) and where available, the NHS Drugs and Pharmaceutical Electronic Market Information Tool (eMIT 2019)(140). Costs, where applicable were inflated to 2018/2019 using the Health Services Index presented in the PSSRU reports (137, 138).

Detailed calculation methods for itemised costs are presented in the following sections.

7.2.4.1 Initial treatment costs for the intervention and comparators

7.2.4.1.1 Costs of SIRT

Resource use identification

Cost of SIRT comprised the device costs, cost of the work-up and the treatment procedures. Patients receiving SIRT will undergo a work-up and a treatment procedure, performed as separate hospital admissions in UK clinical practice. Most patients receiving SIRT will undergo a single work-up and treatment procedure each. However, some patients can undergo a repeat SIRT treatment, especially to treat recurring HCC (new lesions observed in the treated or contralateral liver lobe). Furthermore, a very limited proportion of patients can undergo a second work-up, if the first work-up was not considered sufficient to inform accurate individual treatment planning. Another proportion of patients undergo a work-up, however will be deemed ineligible for the procedure. Calculation methods for these parameters in the model are described below.

Resource use measurement - Number of treatment procedures

Data regarding the number of treatment procedures were taken from two surveys of eleven medical professionals across medical specialties, with experience of SIRT in the UK (see details in Appendix 0). While the number of treatment procedures is also available from the SARAH trial, this number could not be included in the base case analysis, for the following reasons:

- The SARAH trial protocol (141) mandated the sequential treatment of patients with bi-lobar HCC (disease affecting both lobes of the liver): using this approach, the contralateral liver lobe is treated during a separate hospital admission, 30-60 days after the first. However, SIR-Spheres can be administered to both lobes of the liver during a single treatment session, with multiple infusions of the same source vial being performed selectively and in different arteries during the same procedure. This is discussed in more detail in Section 2.2, page 23. Single administration of SIR-Spheres to patients with bi-lobar disease was observed in the ENRY study (26)(141/147 [95.9%] of whole-liver treatments were performed in a single session through one or more injections) and in the European CIRSE Registry for SIR-Spheres Therapy (122), in which [redacted] patients [redacted] with bi-lobar disease received a single treatment.
- The SARAH trial was undertaken when clinicians had less experience in using SIR-Spheres. Clinical practice has evolved since the trial, which enrolled patients between December 2011 and March 2015. The trial protocol allowed repeated treatments of patients, for any cause, which is uncommon in clinical practice. Patients may have been re-treated in the SARAH trial due to incomplete administration of the first dose: procedural improvements in clinical practice after the trial conduct may have improved the complete administration of SIR-Spheres and patient experience of treatment (142, 143).
- The SARAH trial may only be relevant for the French clinical practice in terms of number of treatments. Analysis of the European CIRSE Registry for SIR-Spheres Therapy (CIRT) reported [redacted] in terms of number of procedures in a real-life setting after the SARAH trial. (122)

The CIRSE Registry for SIR-Spheres Therapy (CIRT) is an investigator-initiated, observational study sponsored by the Cardiovascular and Interventional Radiology Society of Europe and conducted in 6 European countries (Belgium, France, Germany, Italy, Spain, Switzerland). In total, [redacted] patients were treated with SIR-Spheres and enrolled in the CIRT registry between January 2015 and December 2017, among whom [redacted] patients with HCC. Patients in the registry are currently being followed-up and no results of the registry were published to

date, however CIRSE provided a preliminary analysis of baseline characteristics of the patients to Sirtex, for the purpose of this submission.

In the CIRT registry, patients with HCC received a single administration of SIR-Spheres in [redacted] of cases, with [redacted] of patients receiving two treatments, and another [redacted] patients [redacted] receiving three or four treatments. This equates to a total of [redacted] treatments for [redacted] patients, i.e. [redacted] treatments per patient with HCC. No data on the number of work-ups was collected in the registry. While these figures were consistent in most European countries, France was an outlier in terms of number of treatments, with [redacted] of patients receiving two treatments (average [redacted] treatments per patient). As the SARAH trial was conducted only in France, it may be hypothesised that the SARAH trial-mandated administration conditions have had persistent effect on clinical practice in France.

Consulted clinical experts have indicated that the number of SIR-Spheres treatments per patient in UK clinical practice is lower than in the SARAH trial, and would reflect European practice overall. This is reflected in the results of the Resource use survey, used in the base case analysis (Table 21), estimating an average 1.20 treatments per patient. Alternative data is also included in scenario analyses and obtained from the SIRveNIB trial (Chow 2018)(7), the ENRY study (26) and the Christie NHS Foundation Trust (28). The SIRveNIB randomised trial did not mandate two sessions for bi-lobar HCC, however is based on the Asian population; the ENRY study reflects UK clinical practice but may partly reflect patients with less advanced disease who may have been eligible for TACE; the Christie NHS Foundation Trust data is the most relevant for UK clinical practice, however it is [redacted] (For more information see Appendix L).

While all data sources differ, they show very consistent results with the number of procedures for SIR-Spheres varying between 1.02-1.20, with the survey results leading to the most conservative value.

Considering the above, the number of treatments from the SARAH trial was deemed unrealistic and only included in scenario analyses for transparency purposes, although this is not expected to reflect current UK clinical practice in any way. Despite the SARAH trial being the primary source of efficacy data for SIR-Spheres in the model, this was further excluded as the base case source of data for this input because the differences in number of treatments are not expected to affect the relative effectiveness of SIR-Spheres and sorafenib. While patients in the SIRveNIB trial received 1.02 SIR-Spheres treatment on average, the relative effectiveness of SIR-Spheres vs. sorafenib was similar between the overall patient populations of both trials: hazards ratio (HR) for overall survival in each trial were HR 0.86 [95% CI: 0.7 to 1.1] in the SIRveNIB trial versus HR 0.99 [95% CI: 0.79 to 1.24] in the SARAH trial, in the per protocol (treated) populations.

Resource use measurement - Number of work-up procedures

Patients assessed for SIR-Spheres typically undergo a single work-up in most cases, however the economic model includes the possibility for a limited fraction of patients to receive a second work-up, as can be observed. No data was identified on this parameter in any of the available sources, hence clinical opinion in the Resource use survey was used to inform this. Clinicians reported that patients would undergo 1.05 work-ups on average.

As required in the NICE final scope for this appraisal, additional costs were also considered for patients undergoing a work-up, but ultimately not receiving SIRT. Despite the limitations mentioned above regarding the estimations of number of treatments, this parameter was derived from the SARAH trial as the proportion of patients considered not eligible after their work-up was observed to vary significantly depending on the considered population. In the base case subgroup of patients with a tumour burden ≤25% and an ALBI grade of 1, 2.9% of patients who underwent a work-up but received no SIR-Spheres treatment. This value and those

used for the ITT and PP populations for the sensitivity analyses are reported in Table 20. In the per protocol analysis, this proportion was 0%, as by definition all patients received treatment with SIR-Spheres.

Table 20. Patient eligibility to SIR-Spheres after the work-up

	Proportion ineligible	SD
Base case subgroup	2.9%	2.8%
Scenario analysis: ITT population	18.6%	2.6%
Scenario analysis: per protocol population	0.0%	-

Patients considered not eligible for SIR-Spheres after the work-up are assumed to receive sorafenib instead, as this is the case in clinical practice in the UK (39). Costs of the work-up and sorafenib treatment are applied.

Valuation of the work-up and treatment procedures costs

The cost of hospitalisations for both the treatment and work-up procedures was obtained from the NHS Reference costs (2017/2018)(136). For the estimation of costs of one inpatient day, the total relevant HRG elective inpatient costs was divided by the mean number of inpatient days for that HRG (See Appendix N). The relevant HRG was identified based on OPCS procedure codes applicable to SIR-Spheres and their grouping into the corresponding HRG. The cost of the SIR-Spheres device, used during the treatment procedure, is £8,000.

Total mean costs per patient are estimated at £13,239 for a full course of treatment with SIR-Spheres (including both the workup(s) and the actual treatment procedure(s)). This is summarised in Table 21 below.

In the base case subgroup, the average cost per patient in the SIR-Spheres arm was lower, at £12,896. This is because 2.9% of patients did not go on receive treatment with SIR-Spheres after their work-up. These patients received sorafenib, which was however treated as an additional subsequent treatment in the model.

In the scenario analyses a micro-costing approach, where the hospitalisation costs were estimated based on a specialist nurse interview was tested. Another scenario analysis included the use of the total HRG costs for both work-up and procedure without correcting for length of stay and assuming no work-up or procedure is done in outpatient setting, despite the finding of the survey (see Appendix S).

Table 21. Calculation of SIR-Spheres costs

Cost item	Value	Source
Outpatient costs for code YR57Z	£1,123.15	National Schedule of Reference Costs 2017/18
Inpatient cost / day for YR57Z	£1,757.45	
SIR-Spheres	£8,000.00	Sirtex
Number of work-ups per patient	1.05	Resource use survey
Length of stay for work-up, days	0.69	
Number of treatments per patient	1.20	
Length of stay for treatment, days	1.19	
Cost of a single work-up	*£1,175.56*	*Subtotal*
Cost of a single treatment	*£2,500.13*	*Subtotal*
Total cost	**£13,239.33**	**-**

7.2.4.1.2 Costs of systemic therapy

For sorafenib, the daily dose was based on the SARAH trial (648.5mg); to make sure no partial pills are included, this was estimated to be equivalent to 24% of patients receiving four pills (800mg) and 76% of patients three pills (600mg). In scenario analyses including this comparator, the average daily dose of 9.4mg for lenvatinib retrieved from the NICE TA (108) was estimated to be equivalent to 65% receiving 8mg and the remaining patients 12 mg.

Time to treatment discontinuation (TTD) was based on the SARAH trial for sorafenib (Section 7.2.2.4, page 58) and for lenvatinib the HR compared to sorafenib was estimated from the NICE TA (108) (Appendix M). Unit costs were taken from the BNF (139) (Appendix N).

In scenario analyses, 10%, 20%, 30% and 40% discount rates were explored for the price of sorafenib to account for the patient access scheme (PAS) for this drug.

7.2.4.2 Subsequent treatment costs

7.2.4.2.1 Subsequent treatments with curative intent (after down-staging)

The distribution of the three treatment options identified as potentially curative treatments in HCC (liver transplantation, tumour resection and ablation) were estimated from the SARAH trial. This distribution was used only to calculate the cost of these treatments and not the survival consequences. The distribution of each type of treatment was taken from the ITT population of the SARAH trial due to the larger patient numbers. Distributions of treatments with curative intent observed in the SARAH trial are summarised in Table 22.

Table 22. Proportions of each treatment among subsequent treatments with curative intent

	After SIRT	After sorafenib
% of liver resection among treatments with curative intent	33.3%	0.0%
% of liver transplantation among treatments with curative intent	16.7%	33.3%
% of ablation among treatments with curative intent	58.3%	66.7%

Source: SARAH trial(6)

Unit costs for liver transplantation and tumour ablation were obtained from the NHS Reference Costs database (2019)(136) for transplant and ablation. For resection, the value from a previous NICE TA in colorectal cancer was inflated (144) and the costs of additional diagnostic procedures were added as being relevant for HCC based on clinical expert opinion. These included measures of fibrosis and portal pressure, IgG dye test and liver biopsy (see Appendix M for more details).

7.2.4.2.2 Subsequent treatments without curative intent

The subsequent treatments without curative intent observed in the SARAH trial were not representative of UK clinical practice as capecitabine and doxorubicin are not used in HCC in the UK according to expert opinion from the survey interviews. Therefore, results from the surveys were used to inform subsequent treatments (Table 23).

Results of the surveys included a substantially higher subsequent sorafenib use after SIR-Spheres than that observed in the SARAH trial (40% in the resource used survey vs. 21.9% in the SARAH trial). This results in conservative estimates of the relevant costs and effectiveness of SIR-Spheres, since only the costs, but not the potential effectiveness of the additional subsequent sorafenib use were included. Drug costs were taken from eMIT (140) and BNF (139) and are described in Appendix N.

Table 23. Subsequent treatment use, excluding treatments with curative intent

Treatments	After SIR-Spheres		After sorafenib	
	% of patients receiving	Length of treatment (months)	% of patients receiving	Length of treatment (months)
Sorafenib	42.08%	3.7	-	-
Lenvatinib	-	-	1.00%	8.2
Regorafenib	1.50%	3.6	18.94%	3.6
Gemcitabine+oxaliplatin	-	-	-	-
BSC	32.17%	Not applicable	55.63%	Not applicable

Source: Resource use survey (18)

7.2.4.3 Health-state unit costs and resource use

Identification and measurement of resource use

While the SARAH trial protocol included some resource use data collection to support a trial-based economic evaluation, there were multiple issues preventing the inclusion of this data in the present model for the UK:

- These data are published and Sirtex only has access to summary data, with some uncertainty on data collection methods;
- Data were observed only for a limited number of procedures in the SIRT arm (3 work-ups and 5 treatments in total for all ITT patients);
- Data collected only records some hospital episodes and no outpatient visits or treatments;
- Data collected is only relevant to French clinical practice (some differences having been identified between France and other European countries, see Section 7.2.4.1.1, page 63) and to limited clinical experience with SIRT.

Health state costs were also reported in previous NICE HCC TAs (87, 108, 109). However similarly to the utility values in previous TAs, there are multiple issues with these costs (Table 24):

- They were elicited for sorafenib. SIRT however is performed as one-off procedure(s) for most patients, which has different resource use implications.
- The resource use was elicited for a different patient population, that is for all patients eligible for systemic therapy. Patients considered in the model may need to be also eligible for loco-regional therapies and, in the base case subgroup, will have a good liver function as defined by ALBI grade 1 and low tumour burden (≤25%). This potentially also has resource use implications.
- Additionally, the majority of resource use in the sorafenib and lenvatinib TAs are based on values from 2007, when there was no experience with targeted therapies in HCC and no experience of SIRT.

Table 24. Resource use reported in previous NICE HCC TAs in unresectable HCC

	Source	Methods	Comments from NICE
Sorafenib TA189 and TA474 (87, 109)	RCT for treatment discontinuation. Expert opinion originally from 2007.	7.7% of patients continued sorafenib after progression, however, was later excluded. Disease management based on resource use survey, which was updated with 3 KOLs. Only direct medical costs.	Concerns regarding low number of KOLs Pooled results from old and new surveys.
Regorafenib TA514 (119)	RCT for treatment discontinuation. Expert opinion for second-line treatment.	Disease management based on resource use survey: pooled sorafenib surveys. Only direct medical costs.	Patients continued post-progression in RCT, while according to KOLs in clinical practice treatment mostly stops at progression, however, cannot be excluded as influences efficacy. Calculation of wastage is arbitrary. Required update for hospitalisations. Pooled surveys appropriate.
Lenvatinib TA551 (108)	RCT for treatment discontinuation. Expert opinion from sorafenib submission with updated/ inflated unit costs.	Disease management based on resource use survey. Only direct medical costs End of life costs were included. Post-progression therapies: sorafenib and regorafenib only. Only direct medical costs.	Wastage was not included. All post-progression treatments should be included.

Due to the above limitations, resource use for the health state costs were based on a new resource use survey that included SIRT (Appendix O).

Resource use valuation

Unit costs were obtained from:

- NHS Reference costs 2017/2018 (136) for inpatient stays, diagnostic procedures, treatments with curative intent and palliative care team.
- PSSRU (2018) for personal and social services, medical staff contacts assuming half an hour visits (follow-up visits last about 15-20 minutes based on expert opinion (8)).

Health state costs are presented in Table 25. For patients receiving subsequent treatment without curative intent, follow-up costs of the initial treatment in the pre-progression state were used for the duration of the treatment (based on expert opinion). For patients down-staged to curative therapy, the cost of follow-up after SIRT pre-progression was assumed. Although this is more intensive than the follow-up recommended by the EASL guideline (1) for patients receiving curative therapy, only follow-up costs were included for these patients (i.e. assuming no third line of treatment after transplantation, resection or ablation). As a result, a conservative approach on follow-up costs was deemed more appropriate. For further information on resource use and unit costs please see Appendices N and O.

Table 25. Health state costs in Population 2 – TACE-ineligible patients

	Pre-progression post SIRT (per month)	**Pre-progression on sorafenib / lenvatinib (per month)**	**At progression (one off)**	**Progressive disease (per month)**
Medical staff contact	£102.84	£126.49	£118.50	£222.96
Diagnostic procedures	£130.26	£134.58	£89.28	£6.15
Inpatient care	£6.80	£20.29	-	£78.50
Personal and Social Services	£5.83	£5.83	-	£191.76
Total	**£245.74**	**£287.19**	**£207.79**	**£499.37**

Health state costs were lower than those reported in the lenvatinib TA (108), especially in the Progressive disease health state (see Appendix Q). The lenvatinib TA estimated costs using a weighted average of the original 2007 sorafenib survey results and an update survey with three clinicians. The difference is mainly due to the substantial deviation from the current resource use compared with use observed in 2007 (detailed resource use is not available from the three additional clinicians), especially in:

- proportion of patients hospitalised post-progression (29% vs. 48% of patients in the current and 2007 surveys respectively);
- number of hospitalisation post-progression (1.4 vs. 4.8 hospitalisations annually);
- % of patients receiving funded rather than informal personal and social services.

Clinical opinion suggests these differences are due to changes in clinical practice since 2007 (8). At that point in time, clinicians were less familiar with sorafenib than now, and, more specifically, less experienced in understanding how to treat people progressing on sorafenib. In addition, most of the post-progression palliative care has now shifted to informal care. The lenvatinib TA (108) also used the NHS Reference costs (136) to determine the cost of outpatient consultations. However, this approach estimates the total cost of a consultation, while the current estimation costed each aspect of the consultation separately (e.g. nurse contact alongside the specialist). Unit costs from the PSSRU (137)were therefore used for medical staff contacts.

7.2.4.4 Adverse events costs

Adverse event (AE) costs were calculated based on the reported incidence of relevant Grade 3-4 treatment related AEs (TEAEs) that affected ≥5% of the population in the SARAH or REFLECT trials (6, 26) (Section 7.2.2.5, page 59). Costs for each adverse event were taken from the previous NICE HCC TAs and were inflated to a 2018 cost year, where applicable, with the exception of congestive cardiac failure, where the average of the relevant HRGs are used weighted by the number of activities (Table 26).

Table 26. Adverse event costs in Population 2 – TACE-ineligible patients

	Inflated cost	Reported costs	Costing year	Source
Abdominal pain	£42.19	£40.15	2014 / 15	NICE TA474 sorafenib TA
Alopecia	£18.59	£17.69	2014 / 15	NICE TA474 sorafenib TA
Anaemia	£1,319.84	£1,283.67	2015 / 16	NICE TA514 regorafenib TA
Anorexia	£657.86	£639.83	2016 / 17	NICE TA535 lenvatinib and sorafenib*
Ascites	£1,713.98	£1,667.00	2015 / 16	NICE TA514 regorafenib TA
Aspartate aminotransferase increased	£634.50	£617.11	2016 / 17	NICE TA551 lenvatinib TA
Asthenia	£677.68	£659.11	2016 / 17	NICE TA551 lenvatinib TA
Blood bilirubin increased	£916.47	£891.35	2016 / 17	NICE TA551 lenvatinib TA
Cardiac failure, congestive	£1,979.71	£1,979.71	2017 / 18	National Schedule of Reference Costs 2017/18: Weighted average HRG codes EB03A, EB03E
Diarrhoea	£605.13	£588.54	2016 / 17	NICE TA551 lenvatinib TA
Fatigue	£677.68	£659.11	2016 / 17	NICE TA551 lenvatinib TA
Gamma-glutamyl transferase increased	£634.50	£617.11	2016 / 17	NICE TA551 lenvatinib TA
Haematological biological abnormalities	£1,319.84	£1,283.67	2015 / 16	NICE TA514 regorafenib TA^
Haemorrhage	£0.00	£0.00	2014 / 15	NICE TA474 sorafenib TA
Hand foot skin reaction	£897.98	£873.37	2015 / 16	NICE TA514 regorafenib TA
Hypertension	£888.12	£863.78	2016 / 17	NICE TA551 lenvatinib TA
Hypophosphataemia	£1,297.52	£1,261.96	2015 / 16	NICE TA514 regorafenib TA
Liver dysfunction	£1,713.98	£1,667.00	2015 / 16	NICE TA514 regorafenib TA[$]
Nausea/vomiting	£82.18	£78.20	2014 / 15	NICE TA474 sorafenib TA
Other increase liver function	£634.50	N/A	N/A	NICE TA551 lenvatinib TA [#]
Palmar-plantar erthrodysaesthesia syndrome	£443.80	£431.64	2016 / 17	NICE TA551 lenvatinib TA
Platelet count decreased	£634.50	£617.11	2016 / 17	NICE TA551 lenvatinib TA
Proteinuria	£812.04	£789.78	2016 / 17	NICE TA551 lenvatinib TA
Rash/desquamation	£71.09	£67.65	2014 / 15	NICE TA474 sorafenib TA
Weight decreased	£665.35	£647.11	2016 / 17	NICE TA551 lenvatinib TA

* assuming same cost as for decreased appetite; ^ assumed same costs as for anaemia based on expert opinion; [$] assumed the same costs as ascites based on expert opinion; [#] assumed same as the average of aspartate aminotransferase increased and gamma-glutamyl transferase increased based on expert opinion

7.2.5 Summary of base-case analysis inputs and assumptions

All base case inputs are described in Appendix Q. The following assumptions have been made in the model:

- The efficacy data from the SARAH trial for the population with low tumour burden (≤25%) and good liver function (ALBI grade 1) is applicable to England and Wales and to the local treatment practices;

- The PFS and the OS observed in the two treatment arms, and TTD observed in the sorafenib arm over the trial duration, can be extrapolated to the desired time horizons, using independently fitted lognormal distributions;
- Resource use for disease management, based on UK resource use survey results, is assumed to be representative of the current treatment patterns;
- Follow-up after treatments with curative intent is assumed to be the same follow-up pre-progression after SIRT. Since curative treatments require less intensive follow-up, this is a conservative assumption.
- Follow-up after treatments without curative intent is assumed to be the same follow-up pre-progression with the initial treatment based on expert opinion (8);
- Only treatment-related grade 3 and/or 4 AEs that affected ≥5% of the population in the SARAH or REFLECT trials have important cost consequences at the population level;
- Post-progression utility values can be represented by a single health state value and quality of life decrements at the end of life are similar in both treatment arms.

7.2.6 Sensitivity analysis

Various sensitivity analyses were conducted to explore the main areas of uncertainty within the model, including parameter uncertainty and structural uncertainty. Parameter uncertainty was assessed in the univariate (one-way) sensitivity analysis and probabilistic sensitivity analysis (PSA). Structural uncertainty was explored using the alternative simple partitioned survival analysis without down-staging and in a series of scenario analyses, including assumptions around the structural form of OS and PFS, the sources used to inform parameters and assumptions regarding the underlying calculations.

7.2.6.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to account for variability in outcomes due to parameter uncertainty. The probabilistic analyses were run for 1,000 replications where parameter estimates were repeatedly sampled from probability distributions to determine an empirical distribution for costs and QALYs. PFS, OS, TTD, HRs, probabilities, costs and utilities were varied simultaneously and independently of each other. Time horizon and discount rates were excluded from the PSA, since they are not subject to parameter uncertainty. Drug costs were also excluded for the same reason.

Parametric distributions were varied using the means and variance-covariance matrices of the parameters in Cholesky decomposition (120). This helped to account for the correlation between parameters.

A gamma distribution was applied to the costs as these distributions cannot be negative (120). The risk of AEs was modelled using a beta distribution. For utilities a beta distribution was used due to the bounds of the distribution (i.e., 0 to 1), using the standard error as the source of variation to calculate alpha and beta parameters of the distribution (120, 121). For more details please see Appendix S.

7.2.6.2 Univariate sensitivity analyses

Univariate deterministic sensitivity analysis was performed where each parameter was varied according to its 95% CI or standard error, while holding all other parameters constant. Where the published study or source for parameter values did not report standard errors or CIs, 20% variation of the mean was assumed. All parameters with uncertainty were included in the sensitivity analyses. Time-horizon and discount rates were not varied as these where not subject to parameter uncertainty, however, the impact of alternative discount rates and time horizon were examined in scenario analyses, as described below. Unit costs and resource use for non-drug resources were not independently varied, but as health state costs. For a detailed list of parameters varied and range of variation tested in the one-way univariate sensitivity analysis see Appendix S.

7.2.6.3 Scenario analyses

Scenario analyses were conducted to test the robustness of the model considering the structural and methodological uncertainties. These included assumptions around:

- Time horizon;
- Discount rate;
- Population;
- Model structure;
- Extrapolation;
- Utilities;
- Costs; and
- Inclusion of assumed patient access schemes for sorafenib.

7.2.7 Results of base case and sensitivity analyses

7.2.7.1 Base case results

The base case analysis focuses on the cost-effectiveness of SIR-Spheres compared to sorafenib, in the base case subgroup of patients with a tumour burden ≤25% and an ALBI grade of 1, with efficacy inputs from the SARAH trial. The focus of all analyses is the discounted results; however, undiscounted results are also presented for completeness in Appendix R.

In the base case, SIR-Spheres increase overall survival (OS) compared to sorafenib with discounted survival outcomes of 2.637 versus 1.890 life-years gained [LYG] for SIR-Spheres and sorafenib respectively. The improved LYG outcome for SIR-Spheres is partly due to the increased proportion of patients being down-staged to curative therapy. The benefit of SIR-Spheres on LYG is observed in the pre-progression state and is partially offset by the reduced post-progression survival, due to patients receiving subsequent curative treatments being excluded from this value (Table 27). SIR-Spheres also result in a quality-adjusted life-years (QALYs) gain, mainly driven by the survival benefit: SIR-Spheres are associated with 1.982 QALYs versus 1.381 QALYs for sorafenib.

Table 27. Base case – Health outcomes (discounted)

	SIR-Spheres	Sorafenib
Progression-free life-years (undiscounted)	0.878	0.527
Years spent post-progression (undiscounted)	1.158	1.352
Years spent after treatments with curative intent (undiscounted)	0.871	0.128
Survival (undiscounted)	2.907	2.007
Survival (discounted)	**2.637**	**1.890**
QALYs gained (undiscounted)	2.185	1.467
QALYs gained (discounted)	**1.982**	**1.381**

Due to the one-off nature of SIRT and the different toxicity profiles, procedure/drug related, and AE costs are lower with SIR-Spheres, however due to the better PFS, disease management costs are slightly higher pre-progression (Table 28).

Subsequent treatment costs are higher for SIR-Spheres due to the large proportion of patients receiving subsequent sorafenib, and because these also include costs of sorafenib for patients deemed not eligible for SIR-Spheres after their work-up. Disease management costs are however lower in the post-progression phase, because fewer patients in the SIR-Spheres arm are treated only with subsequent non-curative treatments than

in the sorafenib arm. This is compensated by higher costs of SIR-Spheres in terms of subsequent curative treatments and disease management costs for patients receiving those treatments with curative intent.

Table 28. Base case – Costs (discounted)

	SIR-Spheres	Sorafenib
Pre-progression costs		
Procedure/drug-related	£12,993	£17,018
Adverse events	£492	£947
Diagnostics, visits, hospitalisations	£2,540	£1,800
Post-progression costs		
Subsequent treatments	£4,259	£3,730
Diagnostics, visits, hospitalisations	£5,734	£6,978
Subsequent treatments with curative intent costs		
Treatments with curative intent	£1,028	£143
Diagnostics, visits, hospitalisations	£2,098	£311
Total costs	**£29,143**	**£30,927**

The base case analysis results in SIR-Spheres achieving slightly lower costs and higher QALYs, that is, being a dominant alternative in this population. Treatment with SIR-Spheres is associated with an incremental net benefit (INB) of £13,801 using the £20,000/QALY threshold (Table 29).

Table 29. Base case – Incremental results (discounted)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incr. costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY)	INB (£) with £20,000 threshold
Sorafenib	£30,927	1.890	1.381	-	-	-	-	-
SIR-Spheres	£29,143	2.637	1.982	-£1,784	0.748	0.601	**Dominant**	**£13,801**

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; incr.: incremental

7.2.7.2 Probabilistic sensitivity analysis

Probabilistic results are presented as:

- probabilistic means and standard deviations (SD);
- on scatterplots showing the result of each iteration;
- as cost-effectiveness acceptability curves (CEACs) showing the probability of each treatment being cost-effective over a range of thresholds.

The probabilistic results show similar costs and better health outcomes for SIR-Spheres (Table 30, Figure 18), resulting in a 95% probability of SIR-Spheres being cost-effective at a £20,000/QALY threshold (λ) and a 92% probability at a £50,000/QALY threshold (Figure 19). Stabilisation of the PSA was observed after approximately 150 iterations as presented in Figure 20.

Table 30. Probabilistic sensitivity analysis

	SIR-Spheres	Sorafenib
Survival - mean	2.671	1.931
Survival - SD	0.526	0.328
QALYs gained - mean	2.009	1.408
QALYs gained - SD	0.414	0.261
Total costs - mean	£24,456	£26,435
Total costs - SD	£3,065	£2,133

Figure 18. Probabilistic sensitivity analysis – Total costs and QALYs

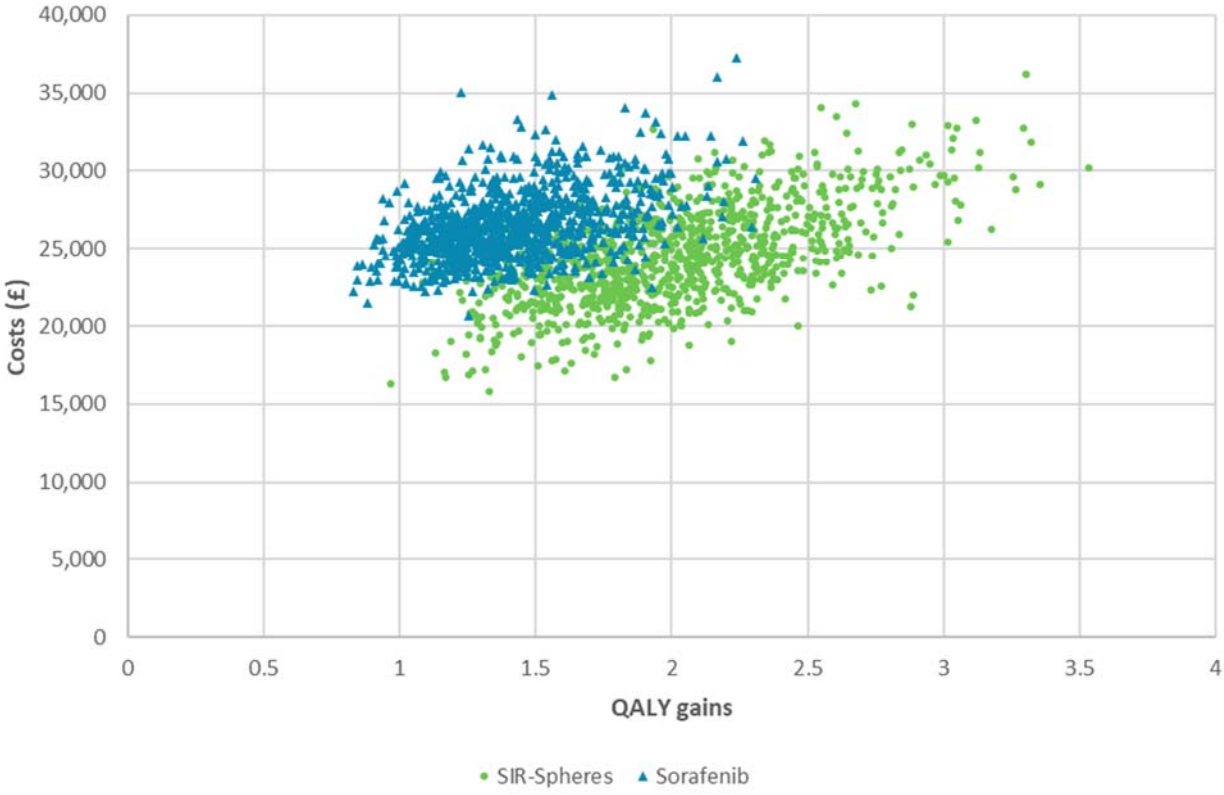


Figure 19. Probabilistic sensitivity analysis – Cost-effectiveness acceptability curve

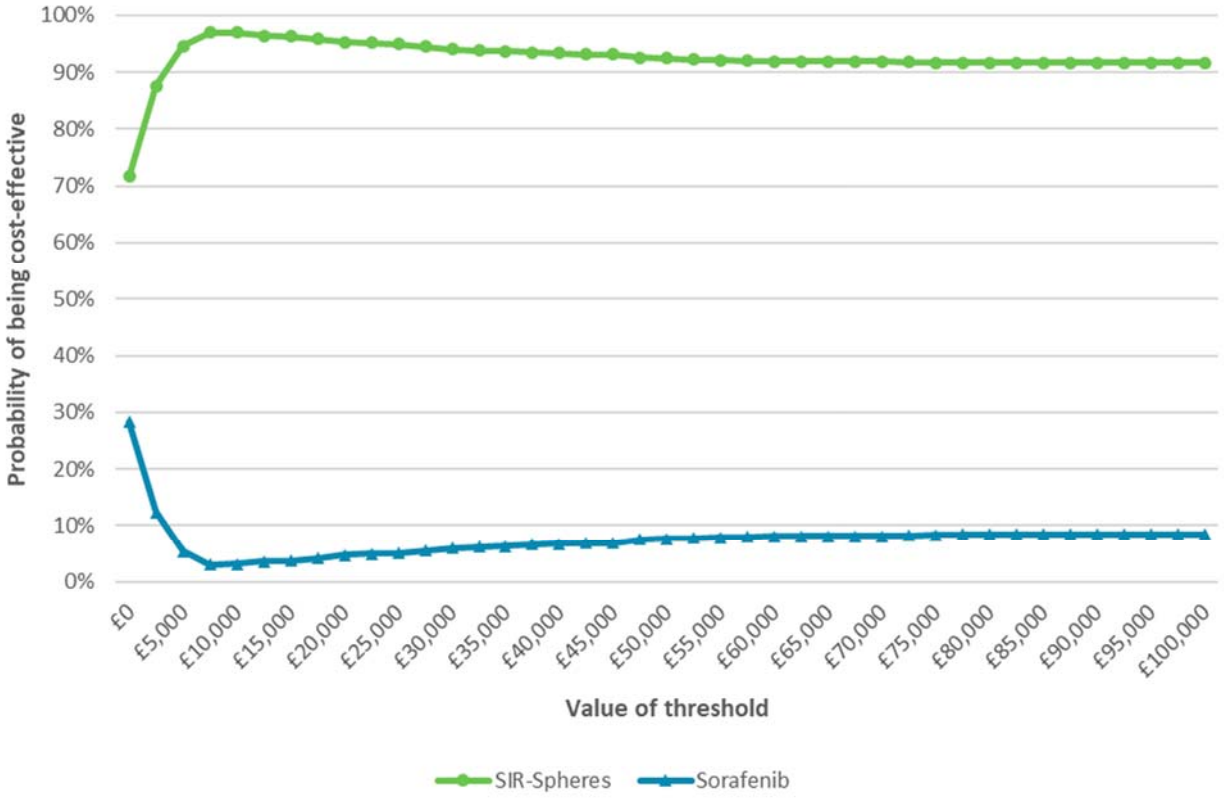
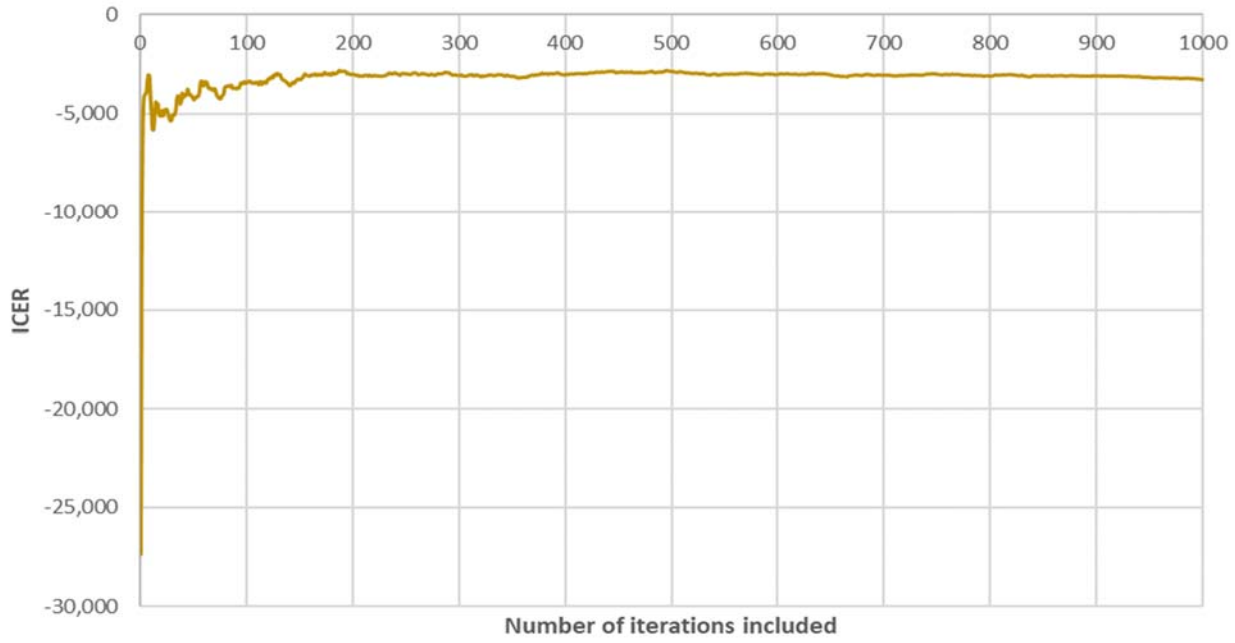


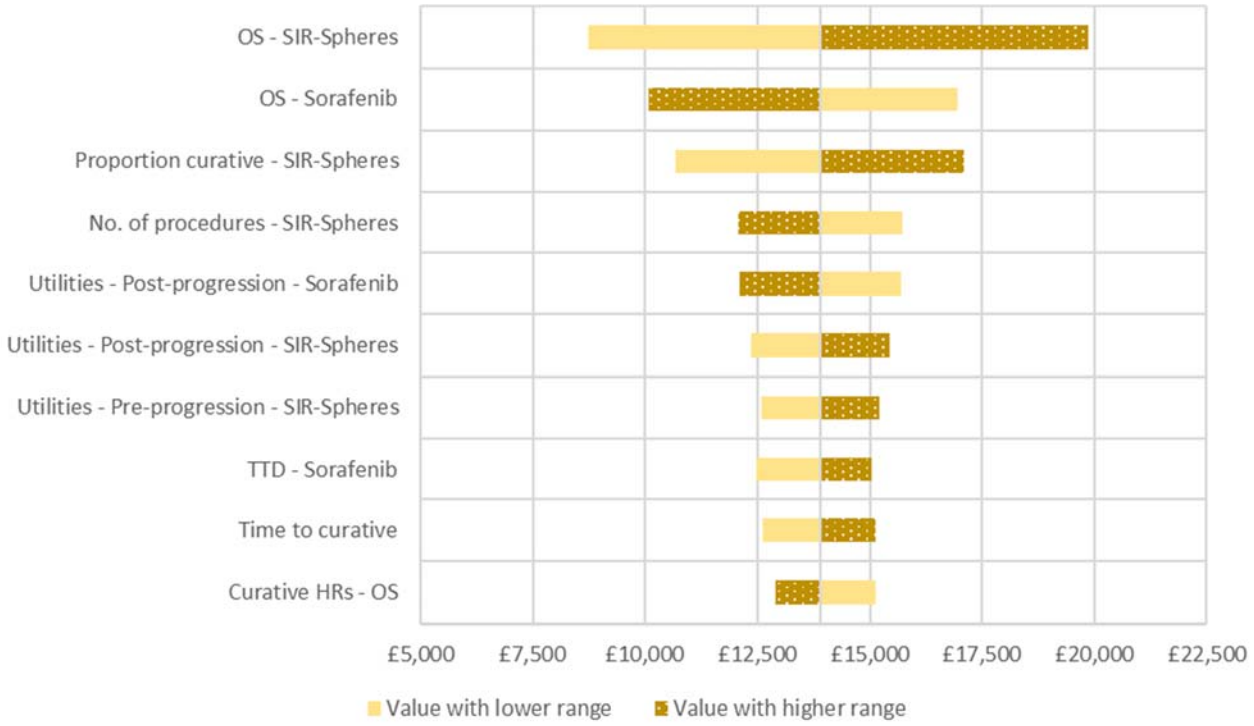
Figure 20. Probabilistic sensitivity analysis – Stability



7.2.7.3 Deterministic sensitivity analysis

Univariate sensitivity analyses were conducted by varying a single parameter with parameter uncertainty at a time to test its impact on the model results. As the results with the extreme values used in the one-way sensitivity analyses span more than one quadrant of the cost-effectiveness plane, incremental net benefit (INB) with the threshold of £20,000/QALY was used instead of ICERs. The parameters with the most impact on the INBs are displayed in Figure 21. The bars show the variation from base-case value using the high and low value for each parameter.

Figure 21. Deterministic sensitivity analysis – Tornado diagram



Results were most sensitive to OS with SIR-Spheres and sorafenib, and to the proportion of patients receiving treatment with curative intent after SIR-Spheres. Further details on the results are presented in Appendix S.

7.2.7.4 Scenario analyses

SIR-Spheres remained dominant with most of the changes tested in scenario analyses. Results are also reported in terms of INB with a £20,000/QALY threshold (λ). Changing the assumptions around time horizon and discount rates left SIR-Spheres dominant.

Two scenario analyses are presented considered broader patient populations than those relevant to UK clinical practice in the ITT and per protocol populations of the SARAH trial. In both populations, treatment using SIR-Spheres was still associated with lower costs than sorafenib. However, sorafenib was associated with a very small incremental benefit in terms of QALYs. For these scenario analyses, ICERs were therefore calculated for sorafenib versus SIR-Spheres (rather than SIR-Spheres vs. sorafenib):

- In the ITT population, sorafenib was associated with an additional £6,142 in costs over SIR-Spheres, and a benefit of 0.105 QALYs. This resulted in an ICER of £58,763 for sorafenib vs. to SIR-Spheres, therefore sorafenib was not considered cost-effective against SIR-Spheres. It can be observed that in this broader population of patients, including a proportion of patients who would not be considered good candidates for SIRT in UK clinical practice, SIR-Spheres remained a cost-effective alternative to sorafenib. This scenario is nevertheless associated with important uncertainty around the relative effectiveness of the compared strategies.
- In the per protocol population, sorafenib was associated with an additional £6,142 in costs over SIR-Spheres, however the benefit in effectiveness over SIR-Spheres was only 0.006 QALYs. This resulted in a high ICER of sorafenib vs. SIR-Spheres, at £680,276 per QALY, however this estimation was highly uncertain due to small benefit in effectiveness.

SIR-Spheres remained dominant with multiple options regarding the extrapolation of OS/PFS. Not allowing for downstaging, despite the evidence, and using a simple partitioned survival model approach leads to slightly higher costs for SIR-Spheres, but still important advantages in QALYs, leading to a very low ICER of £4,352 for SIR-Spheres vs. sorafenib (Table 31).

Results were not sensitive to changes in any of the utilities (Table 32**Error! Reference source not found.**). Similarly, SIR-Spheres stayed dominant when changing the assumptions behind the calculation of SIR-Spheres work-up/procedure costs, except for using the SARAH trial data or the Christie's NHS Foundation Trust data, which resulted in ICERs of £828/QALY and [redacted] respectively for SIR-Spheres vs. sorafenib (Table 33).

Assuming 10-40% discount rates for sorafenib reduced the costs for sorafenib and for rates of 20-40%, sorafenib was less costly though still less effective than SIR-Spheres. This resulted in ICERs up to £5,443/QALY for SIR-Spheres vs. sorafenib, well below the £20,000-£30,000 per QALY threshold. SIR-Spheres was also dominant against lenvatinib (Table 35).

Table 31. Scenario analyses around structural assumptions

Scenario	Technologies	Total costs (£)	Total QALYs	ICER SIR-Spheres vs. sorafenib (£/QALY)	INB assuming λ=£20,000/QALY
Base case	**SIR-Spheres**	**£29,143**	**1.982**	**Dominant (-£2,969)**	**£13,801**
	Sorafenib	**£30,927**	**1.381**		
Time horizon (5 years)	SIR-Spheres	£27,056	1.577	Dominant (-£8,527)	£9,542
	Sorafenib	£29,908	1.243		
Discount cost and benefits: 0%	SIR-Spheres	£30,314	2.185	Dominant (-£1,965)	£15,781
	Sorafenib	£31,726	1.467		
Discount cost and benefits: 5%	SIR-Spheres	£28,721	1.910	Dominant (-£3,400)	£13,115
	Sorafenib	£30,626	1.349		
Population: ITT	SIR-Spheres	£22,124	0.881	Sorafenib vs. SIR-Spheres: £58,763	£4,052
	Sorafenib	£28,266	0.986		
Population: PP	SIR-Spheres	£23,676	0.947	Sorafenib vs. SIR-Spheres: £680,276	£4,237
	Sorafenib	£28,041	0.954		
Not allowing downstaging	SIR-Spheres	£31,146	1.850	£4,322	£13,193
	Sorafenib	£27,509	1.009		
Downstaging rates based on the Resource use survey (5.6% vs. 0.07% for SIR-Spheres and sorafenib)	SIR-Spheres	£28,091	1.706	Dominant (-£4,775)	£9,801
	Sorafenib	£29,980	1.310		
Parametric curves with treatment covariate	SIR-Spheres	£29,235	1.966	Dominant (-£3,423)	£13,475
	Sorafenib	£31,205	1.390		
PFS: separately fitted loglogistic	SIR-Spheres	£28,989	1.983	Dominant (-£3,606)	£14,190
	Sorafenib	£31,156	1.382		
PFS: separately fitted Weibull	SIR-Spheres	£29,250	1.981	Dominant (-£1,008)	£12,608
	Sorafenib	£29,855	1.380		
OS: separately fitted loglogistic	SIR-Spheres	£28,638	1.907	Dominant (-£5,243)	£12,380
	Sorafenib	£31,209	1.416		
OS: separately fitted Weibull	SIR-Spheres	£26,155	1.485	Dominant (-£11,653)	£9,117
	Sorafenib	£29,512	1.197		

Table 32. Scenario analyses around utilities

Scenario	Technologies	Total costs (£)	Total QALYs	ICER SIR-Spheres vs. sorafenib (£/QALY)	INB assuming λ=£20,000/QALY
Base case	**SIR-Spheres**	**£29,143**	**1.982**	**Dominant (-£2,969)**	**£13,801**
	Sorafenib	**£30,927**	**1.381**		
Utilities: ITT	SIR-Spheres	£29,143	1.824	Dominant (-£3,241)	£12,792
	Sorafenib	£30,927	1.273		
Utilities : NICE TA551 lenvatinib TA	SIR-Spheres	£29,143	1.892	Dominant (-£3,135)	£13,162
	Sorafenib	£30,927	1.323		
Utilities : NICE TA189 sorafenib, NICE TA474 sorafenib	SIR-Spheres	£29,143	1.840	Dominant (-£3,492)	£12,000
	Sorafenib	£30,927	1.329		
Utilities for treatments with curative intent: literature: 0.82 (Stein 2002)	SIR-Spheres	£29,143	2.023	Dominant (-£2,805)	£14,504
	Sorafenib	£30,927	1.387		
Utilities for treatments with curative intent: literature: 0.88 (Molinari 2009)	SIR-Spheres	£29,143	2.066	Dominant (-£2,653)	£15,231
	Sorafenib	£30,927	1.393		
Utilities for treatments with curative intent: literature: 0.71 (Thein 2017 with fixed effect model)	SIR-Spheres	£29,143	1.945	Dominant (-£3,133)	£13,171
	Sorafenib	£30,927	1.375		
Utilities for treatments with curative intent: literature: 0.77 (Thein 2017 with random effects model)	SIR-Spheres	£29,143	1.987	Dominant (-£2,945)	£13,898
	Sorafenib	£30,927	1.382		

Table 33. Scenario analyses around costs

Scenario	Technologies	Total costs (£)	Total QALYs	ICER SIR-Spheres vs. sorafenib (£/QALY)	INB assuming λ=£20,000/QALY
Base case	**SIR-Spheres**	**£29,143**	**1.982**	**Dominant (-£2,969)**	**£13,801**
	Sorafenib	**£30,927**	**1.381**		
Costs: health state costs from NICE lenvatinib TA	SIR-Spheres	£58,202	1.982	Dominant (-£1,737)	£13,061
	Sorafenib	£59,246	1.381		
Costs: SIR-Spheres NHS Ref Costs - Christie NHS Foundation Trust data for procedures and work-ups	SIR-Spheres	[redacted]	1.982	[redacted]	[redacted]
	Sorafenib	£30,927	1.381		
Costs: SIR-Spheres NHS Ref Costs - SARAH for # procedures	SIR-Spheres	£31,424	1.982	£828	£11,520
	Sorafenib	£30,927	1.381		
Costs: SIR-Spheres NHS Ref Costs - SIRveNIB for # procedures	SIR-Spheres	£27,502	1.982	Dominant (-£5,701)	£15,443
	Sorafenib	£30,927	1.381		
Costs: SIR-Spheres NHS Ref Costs - ENRY for # procedures	SIR-Spheres	£28,014	1.982	Dominant (-£4,847)	£14,930
	Sorafenib	£30,927	1.381		
Costs: SIR-Spheres microcosting - Survey results	SIR-Spheres	£28,064	1.982	Dominant (-£4,764)	£14,880
	Sorafenib	£30,927	1.381		
Costs: SIR-Spheres microcosting - Christie NHS Foundation Trust data for procedures and work-ups	SIR-Spheres	[redacted]	1.982	Dominant [redacted]	[redacted]
	Sorafenib	£30,927	1.381		
Costs: SIR-Spheres microcosting - SARAH for # procedures	SIR-Spheres	£30,151	1.982	Dominant (-£1,292)	£12,794
	Sorafenib	£30,927	1.381		
Costs: SIR-Spheres microcosting - SIRveNIB for # procedures	SIR-Spheres	£26,563	1.982	Dominant (-£7,263)	£16,381
	Sorafenib	£30,927	1.381		
Costs: SIR-Spheres microcosting - ENRY for # procedures	SIR-Spheres	£27,032	1.982	Dominant (-£6,482)	£15,912
	Sorafenib	£30,927	1.381		
Costs: Using NHS Reference costs for work-up/procedure (assuming no outpatient work-up/procedure)	SIR-Spheres	£31,572	1.982	£1,073	£11,372
	Sorafenib	£30,927	1.381		

Table 34. Scenario analyses assuming patient access scheme for sorafenib

Scenario	Technologies	Total costs (£)	Total QALYs	ICER (£/QALY)	INB assuming λ=£20,000/QALY
Base case	**SIR-Spheres**	**£29,143**	**1.982**	**Dominant (-£2,969)**	**£13,801**
	Sorafenib	**£30,927**	**1.381**		
10% discount for sorafenib	SIR-Spheres	£28,705	1.982	Dominant (-£866)	£12,537
	Sorafenib	£29,225	1.381		
20% discount for sorafenib	SIR-Spheres	£28,267	1.982	£1,237	£11,274
	Sorafenib	£27,523	1.381		
30% discount for sorafenib	SIR-Spheres	£27,828	1.982	£3,340	£10,010
	Sorafenib	£25,821	1.381		
40% discount for sorafenib	SIR-Spheres	£27,390	1.982	£5,443	£8,747
	Sorafenib	£24,120	1.381		

Table 35. Scenario analysis with the inclusion of lenvatinib

	SIR-Spheres	Sorafenib	Lenvatinib
Survival discounted	2.591	1.862	2.015
QALYs gained - discounted	1.947	1.360	1.479
Total costs	£28,700	£30,544	£32,854
Incremental QALYs	-	-0.586	-0.468
Incremental costs	-	£1,845	£4,155
ICER (systemic therapy vs. SIR-Spheres)	-	-£3,146	-£8,886
INB assuming £20,000/QALY threshold (£)	-	-£13,565	-£13,515

7.2.8 Validation

To validate the predicted survival curves from the cost-effectiveness model, the medians from the predicted curves were compared with the published median OS/PFS outcomes reported in overall trial population (ITT analysis) by Vilgrain et al. (2017) (6). The predicted median OS matches the observed OS, while the PFS was slightly overpredicted in the model (Table 36). However, this overprediction was more pronounced in the sorafenib arm, leading to conservative estimates.

Table 36. Modelled vs observed PFS and OS outcomes – Overall ITT analysis

Predicted vs. observed median survival, months	PFS in ITT population SIR-Spheres	PFS in ITT population Sorafenib	OS in ITT population SIR-Spheres	OS in ITT population Sorafenib
Predicted (economic model)	4.42	4.28	7.95	9.87
Observed (SARAH trial, Vilgrain 2017)	4.1	3.7	8.0	9.9

Additional validation analyses were performed to compare predicted survival outcomes with those observed in post-hoc analyses of the SARAH trial, in the overall ITT trial population (Figure 22) and in the base case subgroup of patients with a tumour burden ≤25% and an ALBI grade 1 (Figure 23). Overall survival predicted by the model includes the OS of both patients down-staged to curative therapy and those not receiving subsequent curative therapy ("combined").

Figure 22. Modelled vs observed OS outcomes – Overall ITT analysis

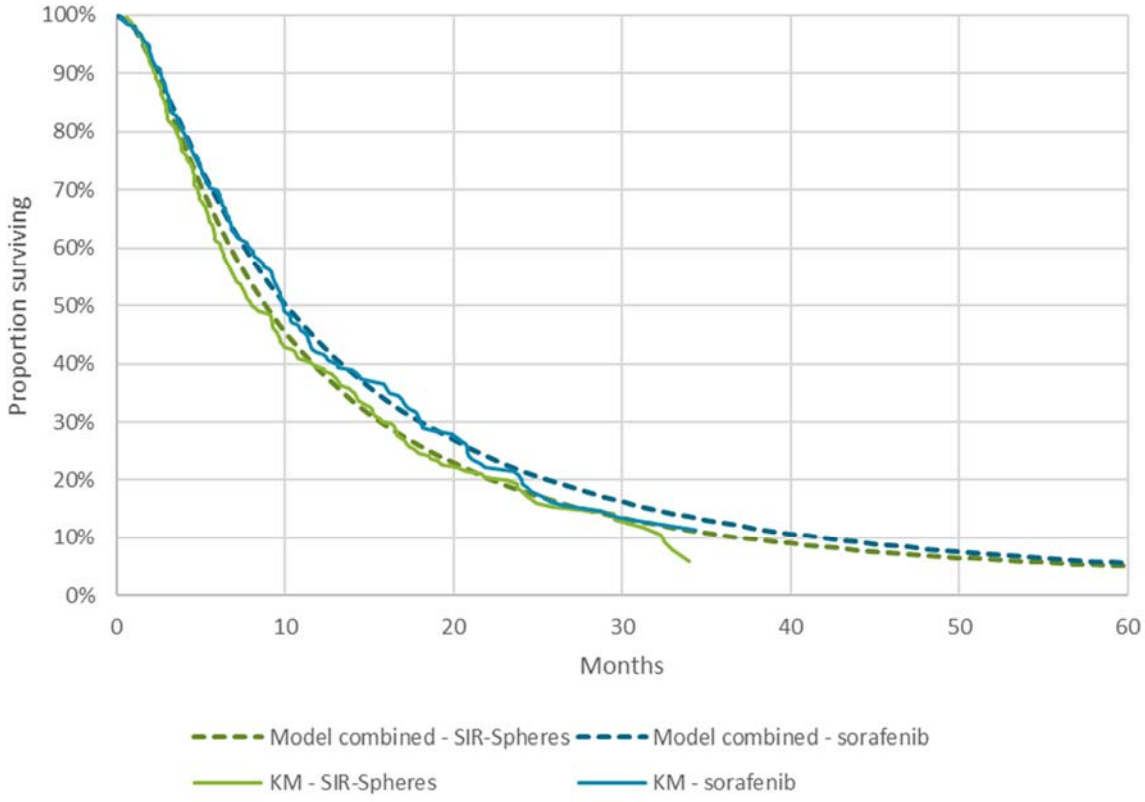
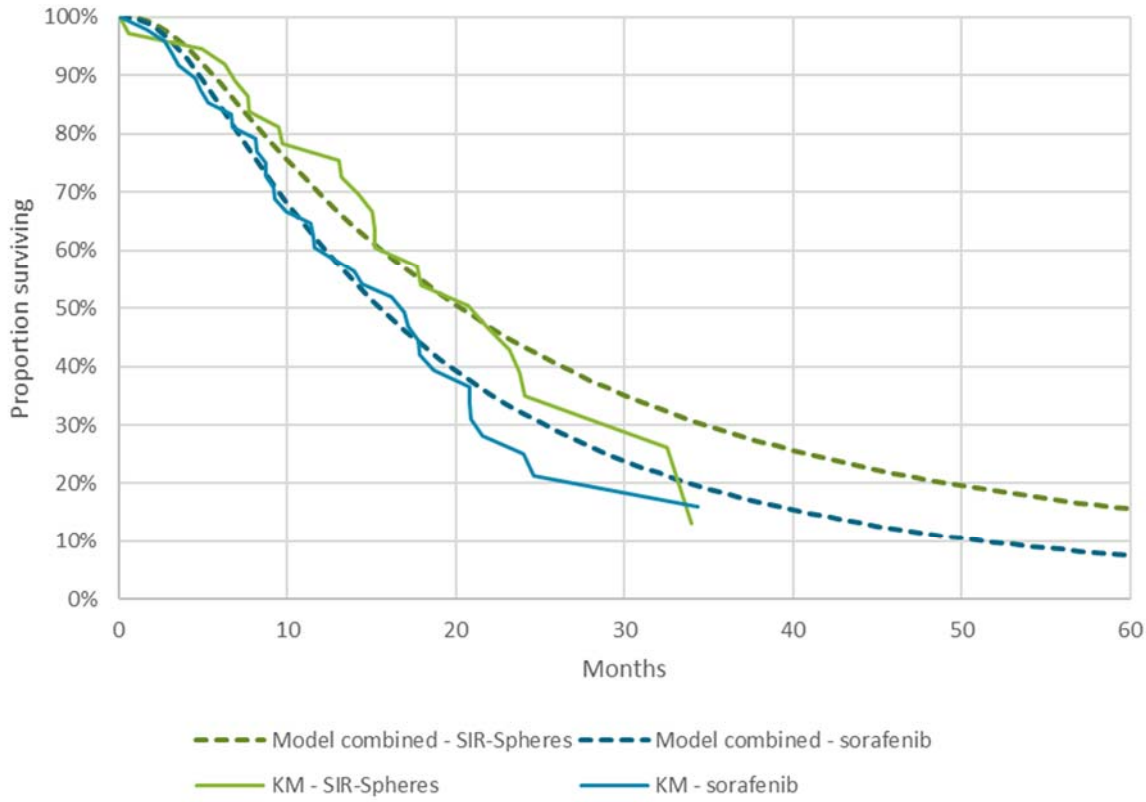


Figure 23. Modelled vs observed OS outcomes – Base case subgroup



Validation analyses in the figures above demonstrate that the economic model does not overestimate the survival of patients in the model. Patients received subsequent curative therapy after a median 15.8 months (SD 9.0 months) and were followed-up for a median 25.0 months. Of note, in the figures above, OS predicted by the model does not diverge before 25 months. This is coherent with informative censoring being observed in the SARAH trial, and the OS benefit of patients being down-staged to curative therapy not being captured in the trial analysis. This confirms the validity of the model structure incorporating a separate down-staging health state.

OS for treatments with curative intent was compared to survival after resection and ablation in the UK in the literature with the help of a targeted literature review. Results predicted by the model, except for one study, were in line with the observed survival from the literature. For further details, see Appendix H.

The cost-effectiveness analyses have undergone both conceptual and technical validation. Conceptual validation was provided by three advisory board meetings (5, 8, 39) including both health technology assessment experts and clinical experts (including oncologists, hepatologists, interventional radiologists and a surgeon). On these advisory board meetings, the model concept, the inputs and methods used, and the results were discussed. For more information please see Appendix J.

In addition to conceptual validation, a comprehensive and rigorous quality check was performed once programming was finished. A model validator not involved in the original programming (Alec Miners, Associate Professor in Health Economics, London School of Hygiene and Tropical Medicine) checked the calculation and reference formulas, and an additional team member checked the values of numbers supplied as model inputs.

7.3 *Interpretation and conclusions for Population 2 – TACE-ineligible patients*

7.3.1 Interpretation of clinical and economic evidence

In a selected subgroup of patients with unresectable HCC for whom any transarterial embolisation therapies are inappropriate, with a tumour burden ≤25% and a preserved liver function (ALBI grade 1), SIR-Spheres is associated with prolonged OS compared to sorafenib. These patients form a subgroup relevant to current clinical practice in the UK, who can be identified by clinicians using routine diagnostic measures, such as CT scan imaging and liver function tests. SIR-Spheres is considered an appropriate treatment option in these patients by UK clinicians as it allows an improved targeting of the liver tumours by the radioactive microspheres, maximising tumour response and minimising potential toxicities to the liver. In the SARAH trial, these outcomes have resulted in a prolonged overall survival and a greater proportion of patients being down-staged to subsequent curative therapy: while all patients in this population were considered initially unresectable, subsequent down-staging to transplantation, tumour resection or ablation can translate into long-term survival for patients compared to palliative treatment alone.

In the selected population of patients with a tumour burden ≤25% and a preserved liver function (ALBI grade 1), SIR-Spheres provide an alternative to sorafenib with lower costs and higher QALYs. Despite the uncertainties, results were robust in the sensitivity analyses with SIR-Spheres having a 95% probability of being cost-effective at a threshold of £20,000/QALY, and 92% probability of being cost-effective at a threshold of £50,000/QALY. Results were most sensitive to the patient population with a non-selective population resulting in lower costs and lower effectiveness for SIR-Spheres vs. sorafenib. Not allowing for one of the main advantages of SIR-Spheres, down-staging to treatments with curative intent, SIR-Spheres were still cost-effective with a very low ICER. Results were most sensitive to extreme changes in OS with sorafenib, proportion of patients receiving treatment with curative intent after SIR-Spheres, the number of procedures with SIR-Spheres.

In the overall population of patients enrolled in the trial, SIR-Spheres failed to demonstrate an OS benefit compared to sorafenib. However, treatment using SIR-Spheres was associated with a reduced toxicity compared to sorafenib, limiting the impact of treatment-related adverse events on the quality of life of patients. This translated into an improved HRQL for patients receiving SIR-Spheres compared to sorafenib, using a disease-specific instrument. In the cost-effectiveness model for this population, SIR-Spheres was associated with lower costs and a small decrement in QALYs but remained cost-effective compared to sorafenib despite increased uncertainty in terms of effectiveness.

In conclusion, SIR-Spheres are an effective, safe, cost-effective and cost-saving alternative for the treatment of HCC, in well-selected TACE-ineligible patients. Therapeutic options for these patients are currently restricted to systemic therapy, with a palliative intent. SIR-Spheres can provide an innovative loco-regional treatment option with the capacity for a proportion of patients to be down-staged to potentially curative therapy.

7.3.2 Innovation

Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

SIR-Spheres have been licensed for use in the UK since 2002. However, SIR-Spheres can be considered innovative due to their ability to alter the treatment paradigm for unresectable HCC:

- **SIR-Spheres offer a chance of potentially curative therapy to at least 5% of patients who would not otherwise have this opportunity.** In the SARAH trial, 5.1% of patients who received SIR-Spheres were down-staged after treatment and as such became eligible for potentially curative treatments, compared with 1.4% of the sorafenib group (6). In the subgroup of patients with a tumour burden ≤25% and a well-preserved liver function (ALBI grade 1), these proportions were 14% for SIR-Spheres vs 2% for sorafenib. A real-world observational in study found 25% of patients being down-staged and receiving subsequent, potentially curative therapy. Clinical experts have confirmed that they do not expect to see successful down-staging in patients with who receive systemic therapy (5). The use of SIR-Spheres in patients with unresectable HCC who are ineligible for TACE therefore offers a unique opportunity for some patients to receive potentially curative treatment that is not possible with other recommended treatments for this population, which are only palliative in intent.
- **SIR-Spheres are associated with a better quality of life for patients than sorafenib.** Quality of life is impaired with sorafenib due to the chronic administration of the therapy leading to long-lasting AEs. In the SARAH trial, the difference in AE rates between SIR-Spheres and sorafenib translated into a HRQL benefit measured by the global health status sub-score of the EORTC QLQ-C30 instrument, which was significantly better in the SIR-Spheres arm than the sorafenib arm (group effect p=0.0447, time effect p<0.0001) and the between-group difference tended to increase over time (group-time interaction p=0.0447) in the ITT population (6). The benefit of SIR-Spheres in terms of toxicity may not fully translate in terms of utilities because patients with HCC also have an underlying liver disease, which is affecting their HRQL. However, the reductions in the incidence of adverse events associated with sorafenib such as diarrhoea, fatigue and hand-foot skin reaction are relevant for patients, because these events adversely affect their quality of life (Gill 2018).
- **Selection of the target population for SIR-Spheres based on tumour burden and ALBI grade allows for this intervention to be offered to patients most likely to benefit.** The SARAH trial found that 22% (53/237) of patients randomised to SIR-Spheres did not receive this treatment, 42 of which had received a work-up (6). Some patients enrolled in the SARAH trial would not be considered good candidates for SIRT in current clinical practice in the UK. In this submission, a subgroup of patients was

identified in which this drop-out was much lower (8%) and in which SIR-Spheres resulted in a longer OS than sorafenib. The selection of patients with a tumour burden ≤25% and an ALBI grade of 1 can thus improve patients' outcomes while improving the cost-effective use of NHS resources.

Do you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?

The economic model structure proposed in section 7.2 for Population 2 – TACE-ineligible patients includes an estimation of the health-related benefits associated with the above innovations. However, SARAH trial analyses (6) are likely to underestimate the OS of patients who have been down-staged and have received subsequent potentially curative therapy. This is because these analyses have assumed uninformative censoring although most (13/15) of the down-staged patients were alive and censored at the end of the trial.

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

The data that underpins these benefits is presented in Table 37.

Table 37. Innovation and health-related benefits

Health-related benefit	Data available	Reference in submission (section and page number)
SIR-Spheres offer a chance of potentially curative therapy to at least 5% of patients who would not otherwise have this opportunity	Down-staging rates and censoring of patients in the SARAH trial, in the ITT and base case subgroup populations	Section 7.1.4.3, page 44
	Down-staging rates in other studies and in UK practice (Resource use survey)	Table 12, page 53
	Overall survival for patients down-staged to curative therapy	Section 7.2.2.2, page 57
SIR-Spheres are associated with a better quality of life for patients than sorafenib	AE incidence in the SARAH trial	Section 7.1.5, page 46
	Impact of AEs associated with sorafenib on patients' quality of life	Section 5.2.1, page 32
	Association of HCC with liver disease	Section 4.1, page 25
	EORTC QLQ-C30 data in the SARAH trial	Section 7.1.6, page 47
Selection of the target population for SIR-Spheres based on tumour burden and ALBI grade allows for this intervention to be offered to patients most likely to benefit	SIRT treatment eligibility	Section 7.1.4.1, page 41
	Relevance for patient selection in UK clinical practice	Section 6.2, page 34
	Outcomes of the economic model	Section 7.2.7, page 71

7.3.3 End-of-life criteria

Based on available clinical evidence, SIR-Spheres are expected to meet end-of-life criteria in **Population 2 – TACE-ineligible patients** (**Error! Reference source not found.**).

Table 38. End-of-life criteria in Population 1 – TACE-eligible patients

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median overall survival the SARAH and SIRveNIB trials was less than 10 months, in the overall ITT populations, for patients receiving sorafenib.	Section 7.1.4.2, page 41
	EASL clinical guidelines report that the life expectancy of patients receiving systemic therapy is ≥10 months.	Section 6.1, Figure 8, page 33
	The mean survival of patients receiving sorafenib in the base case subgroup of patients with a tumour burden ≤25% and an ALBI grade of 1 in the SARAH trial was 23 months.	Section 7.1.4.2, page 41 and Figure 11, page 42 Section 7.2.7.1, page 71 and Table 27, page 71
There is enough evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	In the base case subgroup of patients with a tumour burden ≤25% and ALBI grade 1, SIR-Spheres is associated with a mean 8.75 additional months of survival compared to sorafenib.	Section 7.1.4.2, page 41 and Figure 11, page 42 Section 7.2.7.1, page 71 and Table 27, page 71

8 *Clinical effectiveness and comparative cost of SIR-Spheres in Population 1 – TACE-eligible patients*

This section describes first the clinical efficacy and then the comparative costs of SIR-Spheres in **Population 1 – TACE-eligible:** this includes patients with unresectable HCC who are eligible for transarterial chemoembolisation (TACE, including both conventional TACE [cTACE] or TACE using drug-eluting beads [DEB-TACE]). These are based on a network meta-analysis (NMA) and a systematic review of the literature. Methods and outcomes of the literature review are described in detail in Appendix B.

8.1 *Clinical effectiveness in Population 1 – TACE-eligible patients*

8.1.1 Evidence base

Evidence was found in this population on two of the three interventions: SIR-Spheres and TheraSphere. The interventions were compared to cTACE and DEB-TACE. No evidence was found on either bland transarterial embolization (TAE) or QuiremSpheres therefore both were excluded.

This group is largely comprised of patients with early or intermediate HCC (BCLC stage A or B). The studies identified in this population were all very small and participants were not assessed for tumour burden or ALBI grade, so a target population including patients most likely to benefit of SIRT or TACE could not be determined. A feasibility assessment further concluded that a mixed treatment comparison would not be informative due to very low participant numbers and that a matched adjusted comparison (MAIC) was not feasible due to lack of comparable data. A cost-minimisation analysis (CMA) was therefore developed to compare SIR-Spheres and TheraSphere versus one another and versus cTACE and DEB-TACE respectively.

Studies comparing SIR-Spheres to a relevant comparator are described in Table 39. All studies are described in Appendix B. The SIRTACE (76) and Pitton 2015 (78) RCTs compared SIR-Spheres to cTACE and DEB-TACE respectively.

Table 39: Evidence base on SIR-Spheres in patients with HCC in Population 1 – TACE-eligible patients

Study	**SIRTACE (Kolligs et al., 2015)(76)**	**Pitton et al., 2015 (78)**
Study design	Phase II RCT	Phase IV RCT
Population	Adults from Germany and Spain with unresectable HCC without vascular invasion or extrahepatic spread	Adults in Germany with intermediate, BCLC stage B HCC
Intervention(s)	SIR-Spheres single delivery	SIR-Spheres separate delivery per lobe
Comparator(s)	cTACE with epirubicin 50 mg/m2 + embolising agent 150-300µm or 300-500 µm every 6 weeks	DEB-TACE with 150 mg doxorubicin per session via 100-300µm beads, 1 lobe per session, every 6 weeks
Is trial used in the economic model?	No	No
Rationale for use/non-use in the model	Uncertainty around clinical efficacy estimates prevented development of a cost-effectiveness model. A cost minimisation analysis was developed.	
Reported outcomes specified in the decision problem	Overall survival Progression-free survival Complete response Partial response Stable disease Disease progression Objective response rate Adverse events (grade 1-2, grade 3-4)	Overall survival Progression-free survival Time to progression
All other reported outcomes	Disease control rate	

8.1.2 Methods and baseline characteristics

The systematic literature review identified 5 RCTs in TACE-eligible patients that reported usable data on a relevant outcome:

- A phase IV RCT that compared SIR-Spheres with DEB-TACE in 25 patients (78);
- The Phase II SIRTACE RCT of SIR-Spheres versus cTACE (76);
- The phase II PREMIERE study of TheraSphere versus cTACE in 45 patients (145);
- An RCT of TACE versus DEB-TACE in 67 patients (146);
- The PRECISION-IT RCT that compared cTACE with DEB-TACE in 177 patients (64).

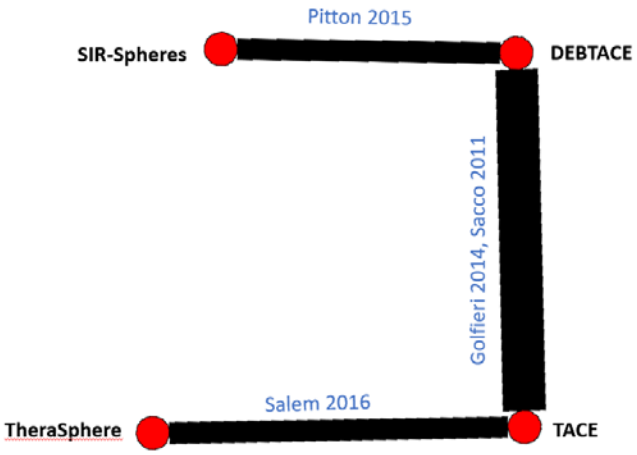
Methods of the identified studies and baseline characteristics of patients are described in Appendix B.

8.1.3 Overall and progression-free survival

The SIRTACE trial (76) found no difference in overall and progression-free survival between SIR-Spheres and cTACE. Pitton et al (2015)(78) found similar OS, PFS and time to progression (TTP) with SIR-Spheres and DEB-TACE. The PREMIERE study found that there was a significantly longer TTP with TheraSphere than TACE but no significant difference in OS rates (145). The PRECISION-IT (64) and Sacco et al. (2011)(146) studies found no significant differences between TACE and DEB-TACE for OS. No studies comparing SIR-Spheres and TheraSphere have been identified.

Figure 24 shows studies that were included in the OS network. The SIRTACE trial (76) did not report median OS as an outcome or present Kaplan-Meier survival analyses, so this trial could not be included further in the NMA. Only one study (78) reported PFS outcomes and so a network for this endpoint was not possible. The network of evidence is connected, but reliant upon studies with very small (N<45) sample sizes (78, 145).

Figure 24. Network of studies for OS in Population 1 – TACE-eligible patients



None of the studies reported HRs for OS and estimates of relative effect were calculated by fitting a Cox proportional hazards model to reconstructed individual patient data (IPD). Details of this methodology are provided in Appendix D.

The similarity of the trials in the network was assessed as part of the feasibility assessment, and comparative tables are provided in Appendix D. Both fixed and random effects models were used in the analysis, based upon recommendations in the NICE DSU guidance (117). The analysis was conducted using Bayesian Markov chain Monte Carlo techniques in the JAGs software. A full description of the models, prior and posterior distributions, and the likelihood and link functions used are provided in Appendix D.

Estimates of HRs for OS are presented in Appendix E. Confidence intervals around the HRs are wide and reflect a high degree of uncertainty around the comparative effectiveness of the different treatments. This is likely due to the network being underpinned by studies with very small sample sizes. The network meta-analysis was run with fixed treatment effects and random treatment effects with an informative prior (there were too few studies to estimate the random effects variance from the available data). The DIC was similar for both analyses (Fixed effect 13, Random effect 14). The residual deviance was similar to the number of data points for both models indicating a good fit to the data. Hazard ratios and probability of ranking plot were also generated and included in Appendix E which also reflects this uncertainty in the results. Due to the important uncertainty around comparisons of effectiveness between SIRT and TACE, it was decided not to conduct a cost-effectiveness analysis in this population. Instead, results of a cost-minimisation analysis are presented in Section 8.2.

8.1.4 Tumour response and down-staging to curative therapy

The SIRTACE trial (76) found a benefit of SIR-Spheres over cTACE in terms of tumour response. Partial response rates (PR) for target lesions were 13.3% for cTACE vs 30.8% for SIR-Spheres, based on RECIST 1.0 criteria. Disease control rates (complete response [CR] + PR + stable disease [SD]) were 76.9% for TACE vs 73.3% for SIR-Spheres. Two patients in each group (14% in total) were down-staged to either liver transplantation or radiofrequency ablation. Pitton et al (2015) (78) did not report response data but 3 patients within the study were down-staged to transplantation or tumour ablation (12%).

The PREMIERE study (145) enrolled a highly-selected population with all patients having early-stage (BCLC stage A) HCC and 25/45 being enrolled on a liver transplantation waiting list prior to treatment and 35/45 being within the Milan criteria for eligibility to transplantation. In total 44% (20/45) of patients in the PREMIERE study received a liver transplant.

The PRECISION-IT (64) found no persistent differences in tumour response rates between cTACE and DEB-TACE. Ten patients in the study received a subsequent liver transplantation, 2 patients a tumour ablation and 1 a surgical resection; in total 8% (14/177) of patients were down-staged to a potentially curative therapy Sacco et al. (2011) (146) found a CR in 70.6% of patients with cTACE vs 51.5% with DEB-TACE, at 1-month follow-up, but did not report any down-staging cases.

Clinicians in the UK advised that patients with large solitary tumours (≥ 5-7 cm), bi-lobar HCC or HCC with segmental or branch portal vein thrombosis would be considered as ideal candidates for SIRT versus TACE, due to the increased tumour response observed with SIRT, with the potential for down-staging to potentially curative therapy (5). However, the available evidence base was not sufficient to conduct subgroup analyses of tumour response according to these characteristics.

8.1.5 Adverse events

TACE is frequently associated with toxicities that can affect patients' quality of life, including a frequent post-embolisation syndrome (62). Adverse events requiring prolonged admission lasting 5 to 7 days have been reported in one of 26 (4%) of patients who received cTACE and readmission due to complications occurred in one of 17 (6%) patients who received DEB-TACE in one UK centre in 2006 to 2012 (147). Analysis of the National Inpatient Sample of 19,058 adults who received TACE for HCC between 2002 to 2012 in the USA found procedure-related complications occurred in 24.2% and post-procedure complications in 17.6% of patients (148).

Despite the toxicities frequently associated with TACE, the number of adverse events were not statistically significantly different in the SIR-Spheres and cTACE groups of the SIRTACE study (76), or in the SIR-Spheres and DEB-TACE groups of the Pitton et al. 2015 study (78). In the former study, 12/13 (92%) patients who received

SIR-Spheres had at least one adverse event, considered treatment-related in 3 patients (23%), compared with 10/15 (67%) patients in the cTACE group, considered treatment-related in 5 patients (33%). More patients had gastrointestinal events after SIR-Spheres (6 patients) than after cTACE (1 patient, p=0.029), but all other adverse events were not significantly different. The PREMIERE study found an increased incidence of diarrhoea (21 vs 0%, p=0.031) and of hypoalbuminemia (58% vs 4%, p<0.001) in patients receiving cTACE compared to SIRT (145). These studies could have been pinned down by their low sample size and potentially inconsistent adverse event reporting.

Clinical experts in the UK advise that TACE is generally not used in patients with impaired liver function because these patients are most at risk of having high pain scores, cardiotoxicity and severe fatigue after the procedure. Secondly, TACE may further worsen liver function by damaging the non-malignant liver parenchyma (5). This hepatotoxicity also means that TACE should not be repeated when substantial necrosis has not been achieved after two rounds of treatment or when patients develop untreatable progression, involving either extensive liver involvement and extrahepatic spread, or more minor intrahepatic spread associated with impaired liver function and worse performance status (1). Unlike SIRT with SIR-Spheres, which has minimal embolic effect, cTACE and DEB-TACE should also not be used in patients with macroscopic portal vein thrombosis (1, 5). In these clinical situations, in the absence of extrahepatic disease, SIRT could provide an additional locoregional treatment option.

8.1.6 Health-related quality of life, impact on patients and healthcare resource utilisation

Overall HRQL scores at 12 weeks on the FACT-Hep questionnaire were not significantly different between SIR-Spheres and cTACE in the SIRTACE study (76). However, other studies have shown that global EORTC QLQ-C30 HRQL scores deteriorate immediately after TACE, with a 12% decrease reported in one German study (72).

An important difference between SIR-Spheres and TACE is in the number of sessions required and the impact of greater toxicity from TACE on length of stay for each session. Studies of cTACE identified in the systematic literature review found that patients received a mean of 3.4 sessions (76) of cTACE and a mean 3.8 sessions of DEB-TACE (78). In the SIRTACE study, patients received one administration of SIRT, compared with a mean 3.3 administrations of cTACE (76).

Each of the TACE administrations is associated with a lengthy hospital stay (3 to 6 days on average) (64, 74-78). TACE treatment sessions can be painful with high rates of post-embolisation syndrome and reduced quality of life after each session (40, 62, 70, 71).

In contrast, SIR-Spheres was given as one session in 33% (78) and 100% (76) of patients. The ENRY registry found that 91.4% of patients required just one session of SIR-Spheres when these were given first-line, and 91% to 100% of patients had only one SIR-Spheres session as second-line therapy. This was despite 53% of patients in the ENRY register having bi-lobar disease (24). In the CIRT real-word registry conducted in Europe, [redacted] of patients with HCC received a single administration of SIR-Spheres, with a mean [redacted] administrations per patient.

In current practice in the UK, SIR-Spheres are usually given in one session that follows a prior work-up session. Patients with tumour in both lobes can be treated in the same session and the good tolerability means that patients can usually be treated as day-cases. In contrast, TACE cannot be administered to both lobes of the liver on the same occasion due to the risk of hepatotoxicity, which also means that few patients are treated as day-cases.

TheraSphere is also administered segmentally or to one lobe of the liver per administration, leading to a greater mean number of administrations per patient:

- Comparing each of the largest, published observational studies on SIRT-Spheres and TheraSphere in HCC, the mean numbers of procedures per patient were 1.08 treatments for SIR-Spheres (26) versus 1.58 treatments for TheraSphere (145).
- These numbers were consistent with the only available UK data reporting on this parameter, provided by the Christie's Hospital NHS Foundation Trust: patients with HCC treated with SIR-Spheres received [redacted] administrations on average, versus [redacted] administrations of TheraSphere (28).

The observed differences in numbers of treatments per patient were modelled in the cost-minimisation analysis presented in Section 8.2.

Although it may not yet be usual practice, SIR-Spheres also allows a possibility for services to be redesigned to allow work-up and administration of SIR-Spheres on the same day (17), substantially reducing delay to treatment and hospital costs by preventing multiple visits and overnight admissions.

8.2 *Cost-minimisation analysis in Population 1 – TACE-eligible patients*

Due to the lack of comparative clinical evidence available for this population, and results of the NMA being highly uncertain with large confidence intervals, a cost-effectiveness analysis would not be meaningful. Therefore, a simple cost minimisation analysis (CMA) was conducted using multiple sources of data comparing SIR-Spheres, TheraSphere and TACE (both cTACE and DEB-TACE). No data were available for QuiremSpheres, similarly to the previous population. The CMA include initial treatment costs, additional hospitalisations as well as AE management costs.

Costs for TACE were mainly based on single centre retrospective database study from in the UK for cTACE/DEB-TACE (147). Data were collected for 101 procedures and 43 patients in 2006-2012. As resource use might have changed since, NHS Reference costs (2017/2018) (136) were also used to estimate the cost of hospital stay. The Resource use survey results were also included in a scenario analysis to estimate the number of procedures and the proportion of patients using DEB-TACE vs cTACE.

Calculation of SIRT costs were the same as for Population 1 – TACE-ineligible patients, since the differences in population were not assumed to affect unit costs (see Section 7.2.4.1.1). The SARAH and SIRveNIB trials were excluded as data sources as they are not relevant for this patient population. Costs associated with TheraSphere were based on the survey data except for the number of treatments, which was based on the literature (27, 145).

Additionally, since according to expert opinion SIRT work-up and procedure can be potentially done as an outpatient procedure, a scenario analyses was undertaken to test the effect of using only outpatient costs. The numbers of subsequent hospitalisations were collected in the Resource use survey with unit costs from the NHS Reference Costs (2017/2018) (136).

AE rates were from the literature (145) and were assumed similar for TheraSphere and SIR-Spheres (Table 40). Unit costs were obtained from previous NICE appraisals. Please see Appendix T for further details.

Table 40. Adverse event costs in Population 1 – TACE-eligible patients

AE	TACE (n=19)	TheraSphere (n=24)	Unit costs	Source for unit cost
Abdominal pain	0%	4%	£42.19	NICE TA474 sorafenib TA
Elevated aspartate aminotransferase	11%	0%	£634.50	NICE TA551 lenvatinib TA
Hypoalbuminemia	0%	4%	£634.50	Assumed average of elevated aspartate aminotransferase and blood bilirubin
Increased blood bilirubin	5%	8%	£916.47	NICE TA551 lenvatinib TA
Leukopenia	0%	4%	£215.00	NICE TA509 pertuzumab
Neutropenia	11%	0%	£2,097.50	NHS Reference Costs 2017/18 (WJ11Z)
Total costs	**£346.34**	**£108.99**		

Depending on the source of data, TACE costs were between £9,257-£14,167 (Table 41). SIR-Spheres costs (£11,185-[redacted]) overlapped with TACE costs, and using similar assumptions, were lower than costs for TheraSphere (£12,026-[redacted]) (Table 42).

Table 41. TACE costs in Population 1 – TACE-eligible patients

TACE costing options	Procedure costs	Hospitalisation	AEs	Total
TACE cost from literature	£8,792.59	£118.17	£346.34	**£9,257**
TACE resource use from literature with NHS Reference Costs	£11,454.91	£118.17	£346.34	**£11,919**
TACE resource use from survey, literature with NHS Reference Costs	£13,702.37	£118.17	£346.34	**£14,167**

Table 42. SIR-Spheres and TheraSphere costs in Population 1 – TACE-eligible patients

SIRT costing options	SIR-Spheres costs	TheraSphere costs	Hospitali-sation	AEs	Total SIR-Spheres	Total TheraSphere
With NHS Reference Costs						
Survey results	£13,239	£13,239	£70	£109	£13,419	£13,419
Survey results with outpatient procedures	£12,082	£12,082	£70	£109	£12,261	£12,261
The Christie NHS Foundation Trust results	[redacted]	[redacted]	£70	£109	[redacted]	[redacted]
Sangro 2011, Salem 2016 for # procedures, rest survey	£12,043	£14,294	£70	£109	£12,222	£14,474
Sangro 2011, Salem 2018 for # procedures, rest survey	£12,043	£17,090	£70	£109	£12,222	£17,269
With microcosting						
Survey results	£12,099	£12,099	£70	£109	£12,279	£12,279
Survey results with outpatient procedures	£11,847	£11,847	£70	£109	£12,026	£12,026
The Christie NHS Foundation Trust results	[redacted]	[redacted]	£70	£109	[redacted]	[redacted]
Sangro 2011, Salem 2016 for # procedures, rest survey	£11,005	£13,064	£70	£109	£11,185	£13,244
Sangro 2011, Salem 2018 for # procedures, rest survey	£11,005	£15,621	£70	£109	£11,185	£15,800

8.3 *Interpretation and conclusions for Population 1 – TACE-eligible patients*

8.3.1 Interpretation of clinical and economic evidence

The evidence for efficacy and safety of relevant interventions in **Population 1 – TACE-eligible patients** is limited and heterogeneous, resulting in uncertainty around the comparative effectiveness of SIR-Spheres, TheraSphere, cTACE and DEB-TACE in this population.

Available studies have shown that SIR-Spheres has similar OS, PFS and TTP compared to cTACE in the SIRTACE study, and to DEB-TACE in the Pitton et al., 2015 study. A small Phase II randomised trial showed that TheraSphere is associated with longer TTP compared to cTACE, but this did not result in longer OS. No studies were available comparing SIR-Spheres and TheraSphere. The network of evidence in the NMA was limited by the small sample size of studies identified in the systematic literature review.

Due to the important uncertainty surrounding comparative effectiveness estimates, a cost-minimisation analysis was conducted to compare the interventions and comparators. Costs of SIRT and TACE were in a comparable range, with costs of TheraSphere being higher than those of SIR-Spheres based on similar assumptions, due to an increased number of procedures per patient.

In UK clinical practice, clinicians have reported that SIR-Spheres would be beneficial for TACE-eligible patients presenting with characteristics usually associated with poor outcomes of TACE, including large solitary tumours (≥ 5-7 cm), bi-lobar HCC or HCC with segmental or branch portal vein thrombosis (5). Available evidence did not allow for a stratification of patients according to these criteria. However, the addition of SIR-Spheres to the existing treatment options in the NHS would address a poorly met medical need and provide an additional loco-regional treatment option for patients with HCC, especially those who are considered poor candidates to TACE.

8.3.2 Innovation

Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

SIR-Spheres has been licensed for use in the UK since 2002. However, SIR-Spheres can be considered innovative due to its ability to alter the treatment paradigm for unresectable HCC.

SIR-Spheres offer a step-change in the management of patients with unresectable HCC who are eligible for TACE.

Studies of TACE identified in our review found that patients received a mean of 3.4 sessions (76) and a mean 3.8 sessions of DEB-TACE (78). In contrast, SIR-Spheres was given as one session in 33% (78), 63% (6), 97% (7) and 100% (76) of patients. The ENRY registry found that 91.4% of patients required just one session of SIR-Spheres when this was given first-line, and 91% to 100% of patients had only one SIR-Spheres session as second-line therapy (26).

In current practice in the UK, SIR-Spheres is usually given in one session that follows a prior work-up session. Patients with tumour in both lobes can be treated in the same session and the good tolerability means that patients can usually be treated as day-cases. In contrast, TACE cannot be administered to both lobes of the liver on the same occasion due to the higher level of adverse events, which also mean that few patients are treated as day-cases. TheraSphere is also administered segmentally or to one lobe of the liver per

administration, leading to a greater mean number of administrations per patient [redacted] compared with [redacted] administrations with SIR-Spheres (28).

Although it may not yet be common practice, SIR-Spheres allows a possibility for services to be redesigned to allow work-up and administration of SIR-Spheres on the same day, substantially reducing delay to treatment and hospital costs by preventing multiple visits and overnight admissions.

SIR-Spheres is associated with a better quality of life than TACE.

Quality of life is substantially impaired in patients after each session of TACE (40, 70-72). The average number of TACE interventions per patient is estimated at 3–4, with each session requiring a hospital stay of 3–6 days (64, 74-78). In contrast, single administration of SIR-Spheres to patients with bi-lobar disease was observed in the ENRY study (26)(141/147 [95.9%] of whole-liver treatments were performed in a single session through one or more injections) and in the European CIRSE Registry for SIR-Spheres Therapy (122), in which [redacted] patients [redacted] with bi-lobar disease received a single treatment.

8.3.3 End of life criteria

Based on available clinical evidence, SIR-Spheres are not expected to meet end-of-life criteria in **Population 1 – TACE-eligible patients** (Table 43)**.**

Table 43. End-of-life criteria in Population 1 – TACE-eligible patients

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	EASL clinical guidelines report that the life expectancy of patients receiving TACE is ≥25 months.	Section 6.1, Figure 8, page 33
	The median OS for patients treated with DEB-TACE in the Pitton et al. 2015 study was 26 months.	Section 8.1.3, page 86
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	No differences have been established in the available evidence in terms of OS for SIRT compared to TACE.	Section 8.1.3, page 86

9 References

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. Journal of Hepatology. 2018;69:182-236.

2. Durand F, Valla D. Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD. J Hepatol. 2005;42 Suppl(1):S100-7.

3. Yin J, Bo WT, Sun J, Xiang X, Lang JY, Zhong JH, et al. New Evidence and Perspectives on the Management of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus. J Clin Transl Hepatol. 2017;5(2):169-76.

4. NICE. Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma. Final scope. 2019.

5. Advisory Board 1. 11 January 2019.

6. Vilgrain VP, H; Assenat, E;. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. The Lancet Oncology. 2017;18:1624-36.

7. Chow PG, M; Tan, SB; Win Khin, M; Khasbazar, A; Ong, J; et al. SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma. Journal of Clinical Oncology. 2018;36(19):1913-21.

8. Advisory Board 3. 26 April 2019.

9. Vogel A, Cervantes A, Chau I, Daniele B, Llovet J, Meyer T, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018;29(Supplement_4):iv238-iv55.

10. Miller JB, LS; Kalva, SP;. Selective internal radiation therapy—tackling the tumor, sparing the organ. US Oncological Review. 2008;4(1):68-71.

11. Sirtex. SIR-Spheres Y-90 resin microspheres package insert (HCC) 2018 [Available from: http://www.radmed.com.tr/usr_img/sir_spheres/pdf/package_insert_sirtex.pdf.

12. Kennedy A, Brown DB, Feilchenfeldt J, Marshall J, Wasan H, Fakih M, et al. Safety of selective internal radiation therapy (SIRT) with yttrium-90 microspheres combined with systemic anticancer agents: expert consensus. J Gastrointest Oncol. 2017;8(6):1079-99.

13. Bilbao JI dMA, de Luis E, et al. . Biocompatibility, Inflammatory Response, and Recannalization Characteristics of Nonradioactive Resin Microspheres: Histological Findings. Cardiovasc Intervent Radiol. 2009;32(4):727-36.

14. Sangro BM-U, D; Bester, L;. Prevention and treatment of complications of selective internal radiation therapy: Expert guidance and systematic review. Hepatology. 2017;66(3):969-82.

15. Hermann AD, A; Maxime, R; Manuel, S; Helena, P; Gilles, C; Laurent, C; Rachida, L; Vilgrain, V. Role of 99mTc-Macroaggregated Albumin SPECT/CT based dosimetry in predicting survival and tumor response of patients with locally advanced and inoperable hepatocellular carcinoma (HCC) treated by selective intra-arterial radiation therapy (SIRT) with yttrium-90 resin microspheres, a cohort from SARAH study. EASL2018.

16. Sirtex. SIR-Spheres Y-90 resin microspheres package insert (unresectable metastatic liver tumors from primary colorectal cancer) 2019 [Available from: https://www.sirtex.com/media/155126/ssl-us-13.pdf; .

17. Li MD, Chu KF, DePietro A, Wu V, Wehrenberg-Klee E, Zurkiya O, et al. Same-Day Yttrium-90 Radioembolization: Feasibility with Resin Microspheres. J Vasc Interv Radiol. 2019;30(3):314-9.

18. Sirtex. Data on file. 2019.

19. BTG. TheraSphere™ yttrium-90 glass microspheres instructions for use 2015 [Available from: https://btgplc.com/BTG/media/TheraSphere-Documents/PDF/TheraSphere-Package-Insert_USA_Rev-14.pdf.

20. Terumo Europe. QuiremSpheres FAQs 2018 [Available from: https://www.terumo-europe.com/Relevant%20Product%20Info/QuiremSpheres%20FAQs.pdf. .

21. Kennedy AN, S; Salem, R;. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. Int J Radiat Oncol Biol Phys. 2007;68(1):13-23.

22. Pasciak AS, Bourgeois AC, Bradley YC. A Microdosimetric Analysis of Absorbed Dose to Tumor as a Function of Number of Microspheres per Unit Volume in 90Y Radioembolization. J Nucl Med. 2016;57(7):1020-6.

23. Walrand S, Hesse M, Jamar F, Lhommel R. A hepatic dose-toxicity model opening the way toward individualized radioembolization planning. J Nucl Med. 2014;55(8):1317-22.

24. Sangro BM, CL; Ettorre, GM; Cianni, R; Golfieri, R; Gasparini, D; et al. Radioembolisation in patients with hepatocellular carcinoma that have previously received liver-directed therapies. European Journal of Nuclear Medicine and Molecular Imaging. 2018.

25. Lau WY, Teoh YL, Win KM, Lee RC, de Villa VH, Kim YH, et al. Current role of selective internal radiation with yttrium-90 in liver tumors. Future Oncol. 2016;12(9):1193-204.

26. Sangro B, Carpanese L, Cianni R, Golfieri R, Gasparini D, Ezziddin S, et al. Survival after yttrium-90 resin microsphere radioembolization of hepatocellular carcinoma across Barcelona clinic liver cancer stages: a European evaluation. Hepatology. 2011;54(3):868-78.

27. Salem R, Gabr A, Riaz A, Mora R, Ali R, Abecassis M, et al. Institutional decision to adopt Y90 as primary treatment for hepatocellular carcinoma informed by a 1,000-patient 15-year experience. Hepatology. 2018;68(4):1429-40.

28. Christie HHS Foundation Trust. Data on File. 2019.

29. Cancer Research UK. Cancer Research UK. Liver cancer statistics 2019 [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/liver-cancer/incidence#heading-Three; .

30. Cancer Today. [Internet]. 2019. Available from: https://gco.iarc.fr/today/online-analysis-table?v=2018&mode=cancer&mode_population=continents&population=900&populations=826&key=asr&sex=0&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&nb_items=5&group_cancer=1&include_nmsc=1&include_nmsc_other=1#collapse-group-0-4.

31. Zakim D, Boyer TD. Hepatology: a textbook of liver disease (4th edition)2002.

32. Sendensky A, Dufour J-F. Liver Physiology 2011 [updated 2011. Available from: http://www.springer.com/cda/content/document/cda_downloaddocument/9781607618652-c1.pdf?SGWID=0-0-45-1016248-p174023797.

33. Abdel-Misih SB, M. Liver Anatomy. Surg Clin North Am. 2010;90(4):643-53.

34. Bowen RA, L; Rouge, M. Pathophysiology of the digestive system: Colorado State University; 2006.

35. Villanueva A. Hepatocellular Carcinoma. The New England Journal of Medicine. 2019;380:1450-62.

36. Sun VS, L;. Symptom Management in Hepatocellular Carcinoma. Clin J Oncol Nurs. 2008;12(5):759-66.

37. Crissien AF, C;. Current Management of Hepatocellular Carcinoma. Gastroenterol Hepatol (N Y) 2014;10(3):153-61.

38. Kumar MP, D;. Role of Supportive Care for Terminal Stage Hepatocellular Carcinoma. J Clin Exp Hepatol. 2014;4(3):s130-s9.

39. Advisory Board 2. 14 March 2019.

40. Fan SE, C; Ho, MC;. Health-related quality of life in patients with hepatocellular carcinoma: a systematic review. Clin Gastroenterol Hepatol. 2010;8(7):559-64.

41. Zabora JB, K; Curbow, B;. The prevalence of psychological distress by cancer site. Psychooncology 2001;10(1):19-28.

42. Qiao CZ, XF; Ling, CQ;. Health-related quality of life evaluated by tumor node metastasis staging system in patients with hepatocellular carcinoma. World J Gastroenterol. 2012;18(21):2689-94.

43. Shih WH, PJ; Chen, ML; Lin, MH;. Experiences of family of patient with newly diagnosed advanced terminal stage hepatocellular cancer. Asian Pac J Cancer Prev 2013;14(8):4655-60.

44. Scalone L, Fagiuoli S, Ciampichini R, Gardini I, Bruno R, Pasulo L, et al. The societal burden of chronic liver diseases: results from the COME study. BMJ Open Gastroenterol. 2015;2(1):e000025.

45. Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC

update and future prospects. Semin Liver Dis. 2010;30(1):61-74.

46. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet. 2003;362(9399):1907-17.

47. National Comprehensive Cancer Network. Hepatobiliary cancers. 2018.

48. GlobalData. Hepatocellular Carcinoma – Opportunity Analysis and Forecasts to 2024. 2015.

49. European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012;56(4):908-43.

50. Curley SI, F; Ellis, LM;. Radiofrequency Ablation of Hepatocellular Cancer in 110 Patients With Cirrhosis. Ann Surg. 2000;232(3):381-91.

51. Lencioni RC, D; Crocetti, L;. Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. Radiology. 2005;234(3):961-7.

52. Fuks DD, S; Paradis, V;. Benefit of initial resection of hepatocellular carcinoma followed by transplantation in case of recurrence: an intention-to-treat analysis. Hepatology. 2012;55(1):132-40.

53. Lee DL, JM; Lee, JY; . Radiofrequency Ablation of Hepatocellular Carcinoma as First-Line Treatment: Long-term Results and Prognostic Factors in 162 Patients with Cirrhosis. Radiology. 2014;270(3):900-9.

54. Reuter NW, CE; Scoggins, CR;. Radiofrequency ablation vs. resection for hepatic colorectal metastasis: therapeutically equivalent? . J Gastrointest Surg. 2009;13(3):486-91.

55. Tabrizian PJ, G; Shrager, B;. Recurrence of hepatocellular cancer after resection: patterns, treatments, and prognosis. Ann Surg. 2015;261(5):947-55.

56. Hori TN, K; Hasuike, S;. Risk factors for the local recurrence of hepatocellular carcinoma after a single session of percutaneous radiofrequency ablation. J Gastroenterol. 2003;38(10):977-81.

57. Poon RF, ST; Ng, IOL; Wong, J;. Significance of Resection Margin in Hepatectomy for Hepatocellular Carcinoma: A Critical Reappraisal. Ann Surg. 2000;231(4):544-51.

58. Inoue KT, T; Higaki, T;. Clinical significance of early hepatocellular carcinoma. Liver Transpl. 2004;10(2):s16-s9.

59. Xu QK, S; Ye, X; Meng, X;. Comparison of hepatic resection and radiofrequency ablation for small hepatocellular carcinoma: a meta-analysis of 16,103 patients. Sci Rep. 2014;4:7252.

60. Lencioni RP, P; Crocetti, L;. Chemoembolization of Hepatocellular Carcinoma. Semin intervent Radiol. 2013;30(1):003-11.

61. Shin S. The Current Practice of Transarterial Chemoembolization for the Treatment of Hepatocellular Carcinoma. Korean J Radiol. 2009;10(5):425.

62. Oliveri RS, Wetterslev J, Gluud C. Transarterial (chemo)embolisation for unresectable hepatocellular carcinoma. Cochrane Database Syst Rev. 2011(3):Cd004787.

63. Lammer JM, K; Vogl, T; Pilleul, F; Denys, A; Watkinson, A;. Prospective Randomized Study of Doxorubicin-Eluting-Bead Embolization in the Treatment of Hepatocellular Carcinoma: Results of the PRECISION V Study. Cardiovasc Intervent Radiol. 2010;33(1):41-52.

64. Golfieri RG, E; Renzulli, M;. Randomised controlled trial of doxorubicin-eluting beads vs conventional chemoembolisation for hepatocellular carcinoma. Br J Cancer. 2014;111(2):255-64.

65. Xing MK, N; Prajapati, HJ; Close, O; Ludwig, JM; Kim, HS;. Survival in unresectable AJCC stage I and II HCC and the effect of DEB-TACE: SEER versus tertiary cancer center cohort study. Journal of Comparative Effectiveness Research. 2016;5(2):141-54.

66. Bruix J SM, Llovet JM. Chemoembolization for hepatocellular carcinoma. Gastroenterology. 2004;127(5):s179-88.

67. Sangro BI, M;. Radioembolization for Hepatocellular Carcinoma: Evidence-Based Answers to Frequently Asked Questions. J Nucl Med Radiat Ther [Internet] 2011.

68. Sangro BI, M; Bilbao, JI;. Radioembolization for hepatocellular carcinoma. Journal of hepatology. 2012;56(2):464-73.

69. Raoul JS, B; Forner, A; Mazzaferro, V; Piscaglia, F; Bolondi, L;. Evolving strategies for the management of intermediate-stage hepatocellular

carcinoma: Available evidence and expert opinion on the use of transarterial chemoembolization. Cancer Treatment Reviews 2011;37(3):212-20.

70. Ahmed S dSN, Qiao W. Quality of Life in Hepatocellular Carcinoma Patients Treated with Transarterial Chemoembolization. HPB Surg. 2016.

71. Steel JE, DT; Cella, D;. Clinically meaningful changes in health-related quality of life in patients diagnosed with hepatobiliary carcinoma. Ann Oncol. 2006;17(2):304-12.

72. Hinrichs JB, Hasdemir DB, Nordlohne M, Schweitzer N, Wacker F, Vogel A, et al. Health-Related Quality of Life in Patients with Hepatocellular Carcinoma Treated with Initial Transarterial Chemoembolization. Cardiovasc Intervent Radiol. 2017;40(10):1559-66.

73. Gill JB, A; Clark, PJ; Langford, A; Latiff, J; Yang, P-M; . Insights into the hepatocellular carcinoma patient journey: results of the first global quality of life survey. Future Oncol [Internet] 2018.

74. Megias Vericat JGM, R; Lopez Briz, E;. Trans-arterial chemoembolization with doxorubicin-eluting particles versus conventional trans-arterial chemoembolization in unresectable hepatocellular carcinoma: A study of effectiveness, safety and costs. Radiologia. 2015;57(6):496-504.

75. Marelli LS, R; Triantos, C;. Transarterial Therapy for Hepatocellular Carcinoma: Which Technique Is More Effective? A Systematic Review of Cohort and Randomized Studies. Cardiovasc Intervent Radiol. 2006;30(1):6-25.

76. Kolligs FB, JI; Jakobs, T;. Pilot randomized trial of selective internal radiation therapy vs. chemoembolization in unresectable hepatocellular carcinoma. Liver Int 2015;35(6):1715-21.

77. Kooby DE, V; Srinivasan, S;. Comparison of yttrium-90 radioembolization and transcatheter arterial chemoembolization for the treatment of unresectable hepatocellular carcinoma. J Vasc Interv Radiol. 2010;21(2):224-30.

78. Pitton MK, R; Ruckes, C;. Randomized comparison of selective internal radiotherapy (SIRT) versus drug-eluting bead transarterial chemoembolization (DEB-TACE) for the treatment of hepatocellular carcinoma. Cardiovasc Intervent Radiol. 2015;38(2):352-60.

79. Llovet JM, Ricci, S., Mazzaferro, V., et al. . Sorafenib in advanced hepatocellular carcinoma. New England Journal of Medicine. 2008;369(4):378-90.

80. Frenette C. Targeted systemic therapies for hepatocellular carcinoma: Clinical perspectives, challenges and implications. WJG. 2012;18(6):498.

81. Brunocilla PB, F; Carucci, P;. Sorafenib in hepatocellular carcinoma: prospective study on adverse events, quality of life, and related feasibility under daily conditions. Medical Oncology. 2013;30(1):345.

82. Cabrera R. Multicenter, randomized pilot study of the effect of sorafenib dosing schedule on tolerability and drug delivery. American Association for the Study of Liver Diseases (AASLD) Washington2017.

83. Brose MF, CT; Keefe, SM; Stein, SM. Management of sorafenib-related adverse events: a clinician's perspective. Semin Oncol. 2014;41(Supplement 2):s16.

84. Johnson PQ, S; Park, JW; Poon, RTP; Raoul, JL; Philip, PA;. Brivanib Versus Sorafenib As First-Line Therapy in Patients With Unresectable, Advanced Hepatocellular Carcinoma: Results From the Randomized Phase III BRISK-FL Study. JCO. 2013;31(28):3517-24.

85. Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391(10126):1163-73.

86. King J, Palmer DH, Johnson P, Ross P, Hubner RA, Sumpter K, et al. Sorafenib for the Treatment of Advanced Hepatocellular Cancer - a UK Audit. Clin Oncol (R Coll Radiol). 2017;29(4):256-62.

87. NICE. TA474. Sorafenib for treating advanced hepatocellular carcinoma (Cancer Drugs Fund reconsideration of TA189) (Final Appraisal Determination). 2017.

88. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009;10(1):25-34.

89. Bolondi L, Burroughs A, Dufour J. Heterogeneity of patients with intermediate (BCLC B)

Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions. Semin Liver Dis 2012;32(4):348-59.

90. Kadalayil LB, R; Pallan, L; . A simple prognostic scoring system for patients receiving transarterial embolisation for hepatocellular cancer. Ann Oncol. 2013;24(10):2565-70.

91. Lee SK, BK; Song, K;. Subclassification of Barcelona Clinic Liver Cancer B and C hepatocellular carcinoma: A cohort study of the multicenter registry database. J Gastroenterol Hepatol. 2016;31(4):842-7.

92. Ogasawara SC, T; Ooka, Y; . A prognostic score for patients with intermediate-stage hepatocellular carcinoma treated with transarterial chemoembolization. PLoS ONE 2015;10(4):e0125244.

93. Kudo MA, T; Ueshima, K;. Subclassification of BCLC B Stage Hepatocellular Carcinoma and Treatment Strategies: Proposal of Modified Bolondi's Subclassification (Kinki Criteria). Dig Dis. 2015;33(6):751-8.

94. Weinmann AK, S; Sprinzl, M;. Survival analysis of proposed BCLC-B subgroups in hepatocellular carcinoma patients. Liver Int 2015;35(2):591-600.

95. Hucke FP, M; Graziadei, I; . How to STATE suitability and START transarterial chemoembolization in patients with intermediate stage hepatocellular carcinoma. J Hepatol 2014;61(6):1287-96.

96. Pinato DK, G; Ishizuka, M;. The Kings Score refines prognostic prediction in hepatocellular carcinoma: a novel application. Liver Int 2015;35(11):2458-65.

97. Golfieri RB, I; Spreafico, C; Trevisani, F; . Patients with Barcelona Clinic Liver Cancer Stages B and C Hepatocellular Carcinoma: Time for a Subclassification. Liver Cancer. 2019;8(2):78-91.

98. Lau WK, AS; Kim, YH; Lai, HK; Lee, R-C; Leung, TWT;. Patient selection and activity planning guide for selective internal radiotherapy with yttrium-90 resin microspheres. Int J Radiat Oncol Biol Phys. 2012;82(1):401-7.

99. Sancho LR-F, M; Bilbao, JI; Beorlegui Arteta, C; Iñarrairaegui, M; Moran, V;. Is a Technetium-99m Macroaggregated Albumin Scan Essential in the Workup for Selective Internal Radiation Therapy with Yttrium-90? An Analysis of 532 Patients. J Vasc Interv Radiol. 2017;28(11):1536-42.

100. Gil-Alzugaray BC, A; Inarrairaegui, M; Bilbao, J. I; Rodriguez-Fraile, M; Rodriguez, J; Benito, A; Dominguez, I; D'Avola, D; Herrero, J. I; Quiroga, J; Prieto, J; Sangro, B;. Prognostic factors and prevention of radioembolization-induced liver disease. Hepatology. 2013;57(3):1078-87.

101. Khor AY, Toh Y, Allen JC, Ng DC, Kao YH, Zhu G, et al. Survival and pattern of tumor progression with yttrium-90 microsphere radioembolization in predominantly hepatitis B Asian patients with hepatocellular carcinoma. Hepatol Int. 2014;8(3):395-404.

102. Mantry PS, Mehta A, Madani B, Mejia A, Shahin I. Selective internal radiation therapy using yttrium-90 resin microspheres in patients with unresectable hepatocellular carcinoma: a retrospective study. J Gastrointest Oncol. 2017;8(5):799-807.

103. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. J Clin Oncol. 2015;33(6):550-8.

104. Hiraoka AK, T; Michitaka, K;. Newly proposed ALBI grade and ALBI-T score as tools for assessment of hepatic function and prognosis in hepatocellular carcinoma patients. Liver Cancer. 2018.

105. Pinato DJ, Sharma R, Allara E, Yen C, Arizumi T, Kubota K, et al. The ALBI grade provides objective hepatic reserve estimation across each BCLC stage of hepatocellular carcinoma. J Hepatol. 2017;66(2):338-46.

106. Waked I, Berhane S, Toyoda H, Chan SL, Stern N, Palmer D, et al. Transarterial chemo-embolisation of hepatocellular carcinoma: impact of liver function and vascular invasion. Br J Cancer. 2017;116(4):448-54.

107. Hickey R, Mouli S, Kulik L, Desai K, Thornburg B, Ganger D, et al. Independent Analysis of Albumin-Bilirubin Grade in a 765-Patient Cohort Treated with Transarterial Locoregional Therapy for Hepatocellular Carcinoma. J Vasc Interv Radiol. 2016;27(6):795-802.

108. NICE. TA551. Single Technology Appraisal - Lenvatinib for advanced, unresectable, untreated hepatocellular carcinoma (Committee papers). 2018.

109. NICE. TA189. Single Technology Appraisal (STA) - Sorafenib (Nexavar) for the treatment of hepatocellular carcinoma (HCC) 2009.

110. Shi J, Lai EC, Li N, Guo WX, Xue J, Lau WY, et al. Surgical treatment of hepatocellular carcinoma with portal vein tumor thrombus. Annals of surgical oncology. 2010;17(8):2073-80.

111. Marrero JA, Kudo M, Venook AP, Ye SL, Bronowicki JP, Chen XP, et al. Observational registry of sorafenib use in clinical practice across Child-Pugh subgroups: The GIDEON study. J Hepatol. 2016;65(6):1140-7.

112. Bruix J, Cheng AL, Meinhardt G, Nakajima K, De Sanctis Y, Llovet J. Prognostic factors and predictors of sorafenib benefit in patients with hepatocellular carcinoma: Analysis of two phase III studies. J Hepatol. 2017;67(5):999-1008.

113. Pardo F, Sangro B, Lee RC, Manas D, Jeyarajah R, Donckier V, et al. The Post-SIR-Spheres Surgery Study (P4S): Retrospective Analysis of Safety Following Hepatic Resection or Transplantation in Patients Previously Treated with Selective Internal Radiation Therapy with Yttrium-90 Resin Microspheres. Annals of surgical oncology. 2017;24(9):2465-73.

114. Regnault HP, C; Amaddeo, G; Chalaye, J; Tacher, V; Luciani, A; Azoulay, D; Costentin, C; Herin, E; Kobeiter, H; Reizine, E; Roudot Francois, R; Calderaro, J;. P07-06 yttrium -90 trans arterial radioembolisation (tare) is an effective treatment for the downstaging of patients with hepatocellular carcinoma: a monocentric experience in a tertiary center. HCC Summit; Lisbon2019.

115. Kanwal FB, A; Chari, R.S; Marrero, J; Kahn, J; Afdhal, N; et al. Potentially curative treatment in patients with hepatocellular cancer—results from the liver cancer research network. Alimentary Pharmacology and Theraputics. 2012;36:257-65.

116. Osoba DR, G; Myles, J; Zee, B; Pater, J;. Interpreting the significance of changes in health-related quality-of-life scores. JCO. 1998;16(1):139-44.

117. Dias SW, N.J.; Sutton, A.J.; Ades, A.E. NICE DSU technical support document 2: A generalised linear modelling framework for pairwise and netweok meta-analysis of randomised controlled trials.: Decision Support Unit, ScHARR; 2011.

118. Turner RD, J; Clarke, MJ; Thompson, SG; Higgins, JPT;. Predicting the Extent of Heterogeneity in Meta-Analysis, Using Empirical Data from the Cochrane Database of Systematic Reviews. International Journal of Epidemiology 2012;41(3):818-27.

119. NICE. TA514. Single Technology Appraisal of Regorafenib for previously treated unresectable hepatocellular carcinoma (Committee papers). 2017.

120. Briggs AHC, K; Sculpher, M.J., editor Decision modelling for health economic evaluation. Oxford University Press; 2006; USA.

121. Stahl JE. Modelling methods for pharmacoeconomics and health technology assessment: an overview and guide. Pharmacoeconomics. 2008;26(2):131-48.

122. CIRSE Registry for SIR-Spheres Therapy. CIRSE Registry for SIR-Spheres Therapy (CIRT): preliminary data on patients with HCC. 2019.

123. Iñarrairaegui MP, F; Bilbao, JI; Rotellar, F; Benito, A; D'Avola, D; Herrero, JI; Rodriguez, M; Martí, P; Zozaya, G; Dominguez, I; Quiroga, J; Sangro, B. Response to radioembolization with yttrium-90 resin microspheres may allow surgical treatment with curative intent and prolonged survival in previously unresectable hepatocellular carcinoma. Eur J Surg Oncol. 2012;38(7):594-601.

124. NICE. Guide to the methods of technology appraisal. 2013.

125. Siebert U, Alagoz O, Bayoumi AM, Jahn B, Owens DK, Cohen DJ, et al. State-transition modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force--3. Value Health. 2012;15(6):812-20.

126. Kleinbaum DK, M;. Survival Analysis (2nd edition)2005.

127. Ishak KK, N; Benedict, A; Muszbek, N;. Overview of parametric survival analysis for health-economic applications. Pharmacoeconomics. 2013;31(8):663-75.

128. Latimer N. Survival analysis for economic evaluations alongside clinical trials—extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. Medical Decision Making. 2013;33(6):743-54.

129. Muszbek N, Kreif N, Valderrama A, Benedict A, Ishak J, Ross P. Modelling survival in hepatocellular carcinoma. Curr Med Res Opin. 2012;28(7):1141-53.

130. Longworth L, Yang Y, Young T, Mulhern B, Hernandez Alava M, Mukuria C, et al. Use of generic and condition-specific measures of health-related quality of life in NICE decision-making: a systematic review, statistical modelling and survey. Health Technol Assess. 2014;18(9):1-224.

131. Batty A, Pennington B, Lebmeier M, Rowen D, Lee D. A comparison of patient and general-population utility values for advanced melanoma in health economics modelling. ISPOR; Berlin2012.

132. NICE. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy. 2017.

133. Thein HH, Isaranuwatchai W, Qiao Y, Wong K, Sapisochin G, Chan KKW, et al. Cost-effectiveness analysis of potentially curative and combination treatments for hepatocellular carcinoma with person-level data in a Canadian setting. Cancer Med. 2017;6(9):2017-33.

134. Molinari M, Helton S. Hepatic resection versus radiofrequency ablation for hepatocellular carcinoma in cirrhotic individuals not candidates for liver transplantation: a Markov model decision analysis. Am J Surg. 2009;198(3):396-406.

135. Stein K, Rosenberg W, Wong J. Cost effectiveness of combination therapy for hepatitis C: a decision analytic model. Gut. 2002;50(2):253-8.

136. NHS. National Schedule of Reference Costs 2017-2018 2018 [Available from: https://improvement.nhs.uk/resources/reference-costs/.

137. Personal Social Services Research Unit. Unit Costs of Health and Social Care 2018 [Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2018.

138. Personal Social Services Research Unit. Unit Costs of Health and Social Care 2017 [Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2017/.

139. British National Formulary. 2019 [Available from: https://bnf.nice.org.uk/.

140. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT) 2019 [Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit.

141. Vilgrain V, Abdel-Rehim M, Sibert A, Ronot M, Lebtahi R, Castera L, et al. Radioembolisation with yttrium90 microspheres versus sorafenib for treatment of advanced hepatocellular carcinoma (SARAH): study protocol for a randomised controlled trial. Trials. 2014;15:474.

142. Ahmadzadehfar HM, C; Pieper, C.C; Bundschuh, R; Muckle, M; Gartner. F. Evaluation of the delivered activity of yttrium-90 resin microspheres using sterile water and 5 % glucose during administration. . EJNMMI Res 2015;5(1):54.

143. Paprottka KL, S; Fendler, WP; Ilhan, H; Rominger, A; Sommer, W;. Reduced Periprocedural Analgesia After Replacement of Water for Injection with Glucose 5% Solution as the Infusion Medium for 90Y-Resin Microspheres. . J Nucl Med. 2016;57(11):1679-84.

144. NICE. TA439. Cetuximab and panitumumab for previously untreated metastatic colorectal cancer. 2017.

145. Salem R, Gordon AC, Mouli S, Hickey R, Kallini J, Gabr A, et al. Y90 Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma. Gastroenterology. 2016;151(6):1155-63.e2.

146. Sacco R, Bargellini I, Bertini M, Bozzi E, Romano A, Petruzzi P, et al. Conventional versus doxorubicin-eluting bead transarterial chemoembolization for hepatocellular carcinoma. J Vasc Interv Radiol. 2011;22(11):1545-52.

147. Fateen W, Khan F, O'Neill RJ, James MW, Ryder SD, Aithal GP. Healthcare costs of transarterial chemoembolization in the treatment of hepatocellular carcinoma. J Hepatocell Carcinoma. 2017;4:123-30.

148. Mumtaz K, Patel N, Modi RM, Patel V, Hinton A, Hanje J, et al. Trends and outcomes of transarterial chemoembolization in hepatocellular carcinoma: a national survey. Hepatobiliary Pancreat Dis Int. 2017;16(6):624-30.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple technology appraisal

Selective Internal Radiation Therapy (SIRT) with Holmium-166 microspheres (QuiremSpheres®) for treating unresectable hepatocellular carcinoma and Holmium-166 Microspheres Work-up Procedure (QuiremScout™)

Document B
Company evidence submission

May 2019

File name	Version	Contains confidential information	Date
	1	Yes	28-05-2019

Contents

Tables and figures

List of Abbreviations

Acronym	Definition
Tc-99m-MAA	Technetium 99mTc macro aggregated albumin
AIMD	Active Implantable Medical Device
BCLC	Barcelona Clinic Liver Cancer
CR	Complete response
DEM-TACE	Transarterial chemoembolisation using drug-eluting microspheres
ESMO	European Society for Medical Oncology
HCC	Hepatocellular carcinoma
IPG	Interventional Procedure Guidance
MELD	Model for End-Stage Liver Disease (MELD)
MRI	Magnetic Resonance Imaging
MTA	Multiple Technology Appraisal
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
PD	Progressive disease
PR	Partial response
PLLA	Poly-L-lactic acid
REILD	Radioembolisation induced liver disease (REILD)
SD	Stable disease
SIRT	Selective internal radiation therapy

TAE	Transarterial embolisation
TACE	Transarterial chemo-embolisation
TARE	Transarterial radioembolisation

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

On the basis of an identical therapeutic mode of action (beta radiation) and similar amounts of beta radiation provided to the tumour cells, holmium-166 microspheres (QuiremSpheres®) can be regarded as a technical variant of yttrium-90 microspheres (SIR-Spheres®, TheraSphere®) within the framework of selective internal radiation therapy (SIRT).

This rationale has been confirmed by the Interventional Procedure Committee at NICE that considers QuiremSpheres® to be a minor modification (variation) of existing yttrium-90 SIRT products.

This multiple technology appraisal covers the appraisal of holmium-166 Selective internal radiation therapy (SIRT) (QuiremSpheres®) alongside yttrium-90 SIRT (TheraSphere® and SIR-Spheres®) in the treatment of adult patients with unresectable hepatocellular carcinoma. It should be noted that the Interventional Procedure Committee at NICE recently considered that *"QuiremSpheres® should not be evaluated separately and didn't fall within their remit. They considered that it is a minor modification (variation) of existing procedures, IPG460, IPG401, IPG459, which have already been considered by the Interventional Procedures".* Moreover, the recent review of the SIRT Interventional Procedure Guidance in intrahepatic cholangiocarcinoma published in October 2018 evaluated the procedure irrespective of the product used (SIR-Spheres®, TheraSphere™ and QuiremSpheres®).

On the basis of a similar therapeutic mode of action based on beta radiation and similar amounts of radiation dose provided to the tumour cells, the Zorginsituut in their assessment of holmium-166 SIRT for the Netherlands, considered QuiremSpheres® to be a technical variant of yttrium-90 SIRT and concluded that holmium-166 SIRT therefore satisfied the *'state of the art of science and practice'* and therefore belongs to the treatment to be insured under the Dutch Healthcare Insurance Act.[4]

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	• People with unresectable early (BCLC stage A), intermediate-stage (BCLC stage B) and advanced (BCLC stage C) hepatocellular carcinoma (HCC) (with or without portal vein thrombosis/involvement).	• People with unresectable early (BCLC stage A), intermediate-stage (BCLC stage B) and advanced (BCLC stage C) HCC (with or without portal vein thrombosis/involvement).	—
Intervention	Selective internal radiation therapies (SIRT): • QuiremSpheres® • TheraSphere® • SIR-Spheres®	Selective internal radiation therapies (SIRT) and patient selection work-up procedure: • QuiremSpheres® • QuiremScout®	• This submission will address the efficacy and safety of QuiremSpheres® in the treatment of HCC. • On the basis of the many similarities between the microspheres, Terumo regard holmium-166 microspheres as a technical variant of yttrium-90 microspheres. • The work up procedure and post treatment assessment are integral to the efficacy and safety of QuiremSpheres® and will, therefore, present the efficacy and safety of QuiremScout™ within this submission.
Comparator(s)	Unresectable HCC: • The interventions will be compared with each other • Transarterial embolisation (TAE)	• Other selective internal radiation therapies (SIRT)	• Terumo considers SIRT procedures TheraSphere® and SIR-Spheres® to be the only comparator, as the Interventional Procedure Committee at NICE recently stated

	• Conventional transarterial chemoembolisation using lipiodol (TACE). • Transarterial chemoembolisation using drug-eluting beads (DEB-TACE) (doxorubicin and cisplatin do not currently have a marketing authorisation in the UK for HCC). For people for whom any transarterial embolisation are inappropriate • Established clinical management without SIRT (including but not limited to target chemotherapy).		that the procedure described in this MTA (QuiremSpheres®) "is considered to be a minor modification (variation) of existing procedures, IPG460, IPG401, IPG459". Terumo regard holmium-166 microspheres as a technical variant of yttrium-90 microspheres.
Outcomes	The outcome measures to be considered include: • Overall survival • Progression-free survival • Time-to-progression • Response rates • Rates of liver transplant or surgical resection • Adverse effects of treatment • Health-related quality of life	The outcome measures presented in this submission include: • Response rates o CR o PR o SD o PD • Radioembolisation induced liver disease (REILD) • Model for End-Stage Liver Disease (MELD) • Adverse effects of treatment	• Differences from the final scope are to ensure that the outcomes reflect the endpoints specified in the study presented in this submission (Radosa *et al.*), and consist of the following: • The Radosa study collected response rate data, safety data and data on radioembolisation-induced liver disease (REILD) and model for End-Stage Liver Disease (MELD).

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. The economic modelling should include the costs associated with any work-up phase to identify patients that are not likely to benefit from SIRT. A sensitivity analysis should be provided without the cost of the work-up phase. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the comparator technologies will be taken into account.	Terumo has developed a budget impact model to analyse the (positive) financial impact of including QuiremSpheres® and QuiremScout™ in the NHS for England and Wales.	Terumo has considered a cost-effectiveness analysis however, given the limited data that currently exists, no formal cost-effectiveness analysis was performed. However, a budget impact model was developed to show the positive financial impact of QuiremSpheres® and QuiremScout™ to the NHS in England and Wales

B.1.2 Description of the technology being appraised

QuiremSpheres® microspheres have an identical therapeutic mode of action to existing yttrium-90 based SIRT products: the microspheres emit beta radiation that kills tumour cells from close range.

QuiremSpheres® is the only commercially available SIRT product based on holmium-166. Holmium has unique imaging properties, which means QuiremSpheres® microspheres can be visualised with single-photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI), even in low concentrations.

Selective Internal Radiation Therapy as a treatment for HCC

SIRT is a minimally invasive procedure, which delivers a high dose of beta-radiation directly to the tumour via microspheres that are administered through the arterial hepatic vasculature. Since blood from the hepatic artery flows preferentially towards tumour tissue, most microspheres get trapped in the capillary bed of the tumour(s). This eventually results in higher dosages of radiation delivered to the tumour tissue than compared to the normal healthy liver tissue. Following lodging of the microspheres, tumour cell death (necrosis) is subsequently induced by local emission.

SIRT relies on the pathophysiological distribution of microspheres in the micro-capillaries in and around tumours. By definition, the absorbed dose distribution will therefore not be homogenous. This is an important difference with external beam radiation therapy. The more heterogeneous the absorbed dose distribution is, the higher the tolerance of the normal liver. The number of microspheres administered therefore is one of the most important characteristics of the different types of microspheres used.

Currently, three types of microspheres are approved for clinical use, resin microspheres (SIR-spheres; SirTex Medical) and glass microspheres (TheraSphere; BTG International Ltd.), both of which are loaded with yttrium-90. The third type, QuiremSpheres® consist of holmium-166 loaded poly-L-lactic acid (PLLA) microspheres. Yttrium-90 and holmium-166 emit similar beta-radiation with a maximum energy of 2.28 MeV and 1.78 MeV, respectively. As the treatment effect is induced by beta-radiation, both yttrium-90 and holmium-166 would expect to exhibit the same therapeutic effect with regards to efficacy and safety.

QuiremSpheres® as a SIRT therapy

QuiremSpheres® consist of PLLA microspheres. These microspheres have an average diameter of 30 µm, which is comparable to resin and glass microspheres. Due to the small diameter, the microspheres preferentially reside in the microvasculature surroundings of the tumour, maximising necrosis of the tumour as well as minimising risks for the healthy liver. With a half-life of 26.8 hours, QuiremSpheres® provide 90% of the radiation within the first 4 days following the implantation procedure. Holmium is paramagnetic and emits low-energy primary gamma photons allowing for quantification of the post-treatment particle (bio)distribution and deposited dose by means of MRI and SPECT. See Table 2 for an overview of the main characteristics of each product.

Table 2. Main characteristics of QuiremSpheres® and Yttrium-90 microspheres (SIR-Spheres® and TheraSphere™).[1-3]

Technique	QuiremSpheres®	SIR-Spheres®	TheraSphere®
Radioactive isotope	Holmium-166	Yttrium-90	Yttrium-90
Microspehere material	Poly (L-lactic acid)	Resin	Glass
Therapeutic mode of action	Beta radiation	Beta radiation	Beta radiation
Mean diameter of the microsphere	30 µm	32 µm	25 µm
Specific gravity	1.4 (130%)	1.6 (150%)	3.2 (300%)
Half-life of the radioactive isotope	26.8 hours	64.4 hours	64.4 hours
Specific activity in Bq per microsphere	350	50	2500-250
Typical number of microspheres administered (x million)	20-30	20-40	1-20
90% of dose deposited	4 days	11 days	11 days
Gamma radiation	Yes	No	No

The density (specific gravity) of QuiremSpheres® is the lowest of all three products and the closest to that of blood (1.4 g/cm^3 versus 1.06 g/cm^3 for blood). PLLA microspheres mostly resemble the specific gravity of resin microspheres (1.6 g/cm^3), whereas the specific gravity of glass microspheres is a two-fold higher (3.2 g/cm^3). The diameter of the three different microspheres are comparable. The typical number of particles that are administered for QuiremSpheres® is approximately 20-30 million,

20-40 million for SIR-Spheres® and 1-20 million for TheraSphere™, depending on the specific activity and the prescribed activity. The half-life of holmium-166 in QuiremSpheres® is 26.8 hours. Besides, the clinical principle of administering radioactive microspheres into the hepatic artery is similar for all three treatment options (QuiremSpheres®, TheraSphere® and SIR-Spheres®); blood from the hepatic artery flows preferentially towards tumour tissue, and most microspheres get trapped into the capillary bed of the tumour tissue. This eventually results in higher dosages of radiation delivered to the tumour tissue than to the normal healthy liver tissue, leading to tumour necrosis.

In an assessment by the Dutch healthcare institute, the Dutch Health Care Council stated that they regard holmium-166 microspheres as a technical variant of yttrium-90 microspheres.[4] While the main characteristics of QuiremSpheres®, SIR-Spheres® and TheraSphere® are comparable, it was observed that QuiremSpheres® closer resemble resin microspheres. In fact, looking at specific activity and the number of administered microspheres (i.e. the most important characteristics), the characteristics of QuiremSpheres® are 'in between' those of SIR-Spheres® and TheraSphere®.

The added value of QuiremScout™

QuiremScout™ is the first SIRT workup product that utilises the same particle (poly-L-lactic acid microspheres loaded with holmium-166) as therapeutic microspheres. The difference between QuiremSpheres® and QuiremScout™ lies in the activity per particle, which is lower for QuiremScout™ microspheres. The exact same morphological properties increase the predictive power of work-up distribution for therapy distribution. The work-up procedure is critical in selecting patients who will benefit the most from the procedure and “de-select” patients who will not benefit from SIRT.

Published clinical data has demonstrated that QuiremScout™ is safe and efficacious. Not only is it a safe alternative for the currently used 99m-technetium macroaggregates (Tc-99m-MAA), it is also a more accurate predictor for lung shunt, extrahepatic deposition and intrahepatic distribution.

Holmium-166 SIRT is unique because holmium-166 microspheres can be visualized in low quantities and with high resolution with SPECT and MRI, respectively.

A small amount of holmium-166 microspheres with a low activity (also known as a “scout-dose”) can therefore be used in the SIRT work-up. QuiremScout™ is the first SIRT workup product that utilises the same particle (poly-L-lactic acid microspheres loaded with holmium-166) as the therapeutic microspheres. This is important because it allows for a more accurate prediction of where the therapeutic microspheres will be deposited due to the QuiremScout™ and QuiremSpheres® particles being identical. QuiremScout™ aims to improve SIRT patient selection by accurately predicting the microspheres positioning in the organ and assessing the ratio of particle uptake in the tumours versus normal liver tissue. This information helps clinicians to make an informed clinical decision whether SIRT will be safe and effective prior to performing the SIRT procedure.

Imaging of the microspheres is of great value for the optimal application of SIRT, since imaging during work-up phase or post-treatment can help enable better treatment planning and post-treatment distribution assessment of the particles and provides healthcare professionals with better informed decision making on patient inclusion and potential follow-up treatment possibilities.

Table 3. Technology being appraised

UK approved name and brand name	QuiremSpheres® QuiremScout™
Mechanism of action	Selective internal radiation therapy (SIRT), or trans-arterial radioembolisation (TARE) is a treatment option for patients with unresectable liver tumours. During a SIRT procedure, microspheres loaded with holmium-166 are administered into the hepatic artery. Since blood from the hepatic artery flows preferentially towards tumour tissue, most microspheres get trapped in the capillary bed of the tumour(s). This eventually results in higher dosages of radiation, delivered to the tumour tissue than to the normal healthy liver tissue. Following lodging of the microspheres, tumour cell death is subsequently induced by local emission and absorption of high-energy beta radiation.
Marketing authorisation/CE mark status	The therapeutic holmium-166 microspheres QuiremSpheres® received CE Mark on 1 April 2015, and is classified as an Active Implantable Medical Device (AIMD) per Directive 90/385/EEC. QuiremSpheres® is manufactured by Quirem Medical B.V. and distributed exclusively by Terumo. QuiremScout™ received CE-mark 29th of November 2018 and is classified as an Active Implantable Medical Device (AIMD) per Directive 90/385/EEC.QuiremScout™ is manufactured by Quirem Medical B.V. and distributed exclusively by Terumo
Indications and any restriction(s) as described in the instructions for use (IFU)	QuiremSpheres® is indicated for the treatment of unresectable liver tumours QuiremScout™ is intended for evaluation of lung-shunt, extrahepatic deposition and intrahepatic distribution of intra-arterially injected microspheres.
Method of administration	Before administration of QuiremSpheres® or QuiremScout™, a microcatheter is placed in the branch of the hepatic artery responsible for the main blood supply of liver tumour(s). Subsequently, the microspheres are injected through the microcatheter into the arterial bloodstream, which transports the microspheres to the tumour where they lodge in the microvasculature and irradiate the tissue. Patients that are eligible for SIRT as determined by a multidisciplinary tumour board, will undergo a work-up

	phase to confirm the safety and efficacy of the SIRT procedure by simulating the therapy using a surrogate marker which mimics the particle distribution for therapy. The work-up phase is necessary as inadvertent distribution of radiation to organs other than the liver may cause damage to healthy tissue and may result in serious complications. The surrogate marker may also be used as a tool to assess the distribution of microspheres inside the liver (i.e. intrahepatic distribution), to predict the efficacy of the treatment. It is therefore important to have a good match between the distribution of the surrogate marker and the therapy particles. In combination with Yttrium-90 SIRT therapy, typically Tc99m-MAA is used as surrogate marker. The Tc-99m-MAA particles have different morphology compared to the therapeutic particles. QuiremScout™ is a new product for the work-up procedure which has identical morphological properties to QuiremSpheres®, eliminating distribution differences induced by differences in shape and size of Tc99m-MAA particles compared to SIRT therapy particles.
Additional tests or investigations	No additional tests or investigations required.
List price and average cost of a course of treatment	According to NICE published documents, the average cost of a course of SIRT treatment is £21,550[5,6] List price for QuiremSpheres® (holmium-166 therapeutic microspheres) is £9,896 and list price of QuiremScout™ (holmium-166 diagnostic work-up microspheres) is [redacted]. The cost of Q-Suite (software for treatment planning and evaluation) is included in the cost of QuiremSpheres® and QuiremScout™.
Patient access scheme (if applicable)	N/A

B.1.3 Health condition and position of the technology in the treatment pathway

The prognosis for patients with HCC is poor. International guidelines recommend SIRT as one of the options for selected HCC patients. It aims to increase overall survival in patients with advanced HCC tumours that have failed previous treatments with TACE.

In early stage HCC patients SIRT also aims to allow for curative intent treatments such as bridging to transplantation by offering tumour control to allow a patient to stay on the transplant waiting list for a longer time.

It may also be used for downstaging patients' tumours to allow them to undergo a resection that they weren't previously eligible for.

Disease overview and epidemiology

Liver cancer is the sixth most common cancer worldwide with 841,080 new cases in 2018, and the fourth cause of all cancer-related death with 781,631 cases. Liver cancer accounts for 4.7% of all new cancers. An estimated 82,000 new cases of liver cancer were reported in Europe in 2018.[7] Hepatocellular carcinoma (HCC) is the most common form of liver cancer accounting for 55% of primary liver cancer diagnoses in men and 28% of diagnoses in women.[8] In England and Wales, 4,993 people are annually diagnosed with HCC. Along with the higher incidence in men, HCC incidence increases with age, with the average age at diagnosis being 66 years, and is also more common in black and Asian patients than white patients in the UK.[9] Incidence rates for HCC continue to grow and are projected to increase by 43% in men and 21% in women in the UK between 2014 and 2035[10] to approximately 15 cases per 100,000 people.[9]

Liver cancer is most often related to cirrhosis which accounts for 70 to 90% of all cases reported. Liver cirrhosis is most often caused by chronic inflammation of the liver, viral infection through hepatitis B or C, or alcohol abuse.[11,12] In the UK the main reasons for the development of HCC are obesity leading to non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), smoking, infections and alcohol consumption.[9]

Prognosis for patients with HCC is poor, the age standardised one and five year survival rates for HCC in the UK currently stand at 36.7% and 12.1% respectively.[13] With early diagnosis, surgical resection of the liver (partial hepatectomy) or transplantation may provide a cure for patients. However, over 50% of patients are diagnosed in advanced stages of the disease, often for these patients the cancer is unresectable and transplantation is no longer an option.[14]

Current UK clinical pathway versus anticipated place of QuiremSpheres® in clinical practice

There are currently no treatment guidelines for the UK with regard to HCC. The available guidelines published by ESMO and EASL have been described below, as well as the guidance that NICE provides through the NICE pathways.

ESMO guideline

The guideline published by the European Society for Medical Oncology (ESMO), for diagnosis, treatment and follow-up of hepatocellular carcinoma, describes the Barcelona Clinic Liver Cancer (BCLC) staging system as one of the instruments that combines tumour stage, liver function, cancer-related symptoms and performance score, which helps healthcare professionals in their decision-making with regard to specific treatment algorithms. Patients are classified into different stages; namely, early (stage 0-A), intermediate (stage B), advanced (stage C) or have a poor prognosis and low life expectancy (stage D). See Figure 1 for an overview of the different treatment options for liver cancer per BCLC stage. The ESMO guideline, recommended SIRT for patients with BCLC 0-A and stage B liver cancer.[15]

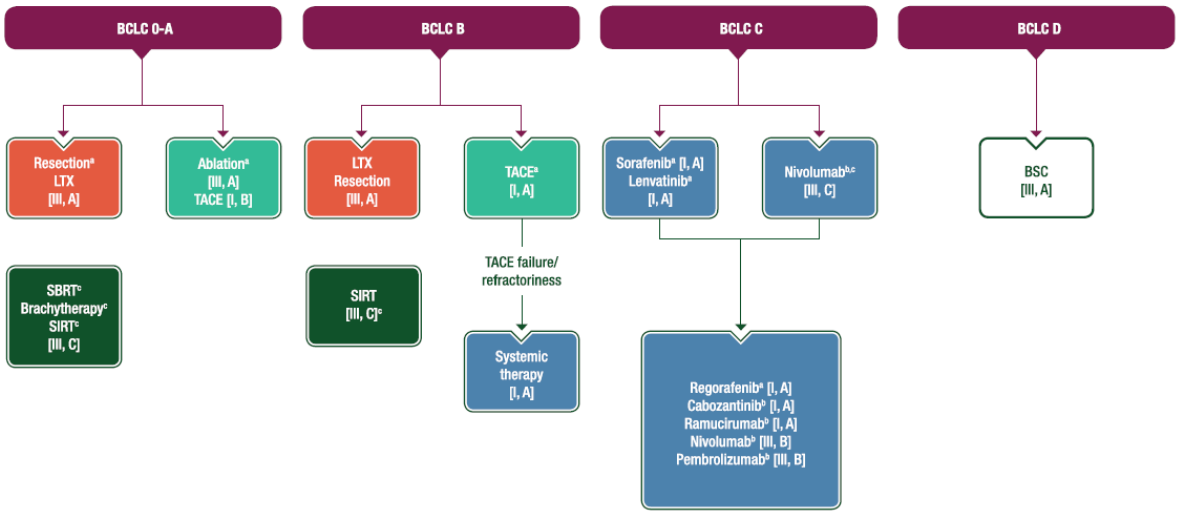


Figure 1. treatment options per BCLC stage[15]

EASL guideline

The guidelines published by the European Association for the Study of the Liver (EASL) indicate that the subgroup of patients benefitting from SIRT needs to be defined.[16] It states that two randomised controlled trials have been conducted to analyse efficacy and safety of SIRT versus sorafenib.[17,18] In both of these studies, the primary endpoint was not reached, no statistical significant differences were observed in terms of overall survival. However, the tumour response rate was significantly higher with SIRT. In the study published by Vilgrain *et al.* (SARAH trial) sorafenib was associated with twice as many treatment-related adverse events per patient compared to SIRT. This included grade ≥3 treatment-related adverse events.[18] In the trial published by Chow *et al.* (SIRveNIB), SIRT was associated with significantly higher progression-free survival and time to progression compared to sorafenib.[17] Hence, it was concluded that although there seems no additional benefit in terms of overall survival with SIRT, better tumour responses, and increased progression-free survival and time to progression are observed in patients, whereas fewer treatment-related adverse events were reported.[17,18] Subsequently as the additional survival benefit of SIRT compared to sorafenib in patients with advanced HCC has not been proven, use of SIRT in combination with systemic therapy or alone should only be carried out following a multidisciplinary board discussion.[16]

With respect to the evidence base comparing SIRT and TACE the EASL guidelines state that this consists of retrospective studies with small sample sizes. SIRT was associated with lower toxicity, led to significant increases in time to progression and increased tumour control, whilst patients maintained a higher quality of life. However, SIRT did not induce increased overall survival compared to TACE.[19-21]

NICE pathway for liver cancer

NICE provides guidance on the clinical pathway of patients that are diagnosed with liver cancer in the UK by its NICE pathways; after a diagnosis of liver cancer people are referred to secondary care, specific therapy is then selected based on several criteria; i.e. the location and stage of the liver cancer, and liver function. Treatment options aim to slow progression, improve quality of life and extend the patient's life. There also exist options to "down-stage" the primary liver cancer after which patients might be eligible for either surgical resection with curative intent or liver transplant.

Anticipated place of QuiremSpheres®

Where the tumour is unresectable options for treatment include chemotherapy (systemic or chemoembolisation), brachytherapy (SIRT), stereotactic body radiation therapy (SBRT), transarterial embolisation (TAE) and microwave or radiofrequency ablation. Chemotherapy is administered systemically (orally or by intravenous transfusion/injection) or by transarterial chemo-embolisation (TACE). SIRT has been investigated in patients with BCLC-A for bridging to transplantation or downstaging to resection, in patients with BCLC-B to compare with TACE, and in patients with BCLC-C to compare with sorafenib. As reported above the available data reports good safety profiles and local tumour control but fail to show overall survival benefit compared to sorafenib in BCLC-B and -C patients".[16]

However, patients with BCLC stage A, B and C HCC represent a heterogeneous population, characterised by varying tumour burden, liver function, and disease etiology.[22] For this reason, multiple factors influence the choice and appropriateness of treatment including contraindications, technical considerations and treatment related toxicities. There exists a high unmet need for treatment options in these patients and the availability of SIRT, TACE and other options allows for physicians to

select a treatment which delays tumour progression whilst maintaining health related quality of life and delaying the introduction of systemic therapy.[15]

Figure 2 provides an overview of the anticipated place of QuiremSpheres® in the clinical landscape of patients treated for liver cancer.

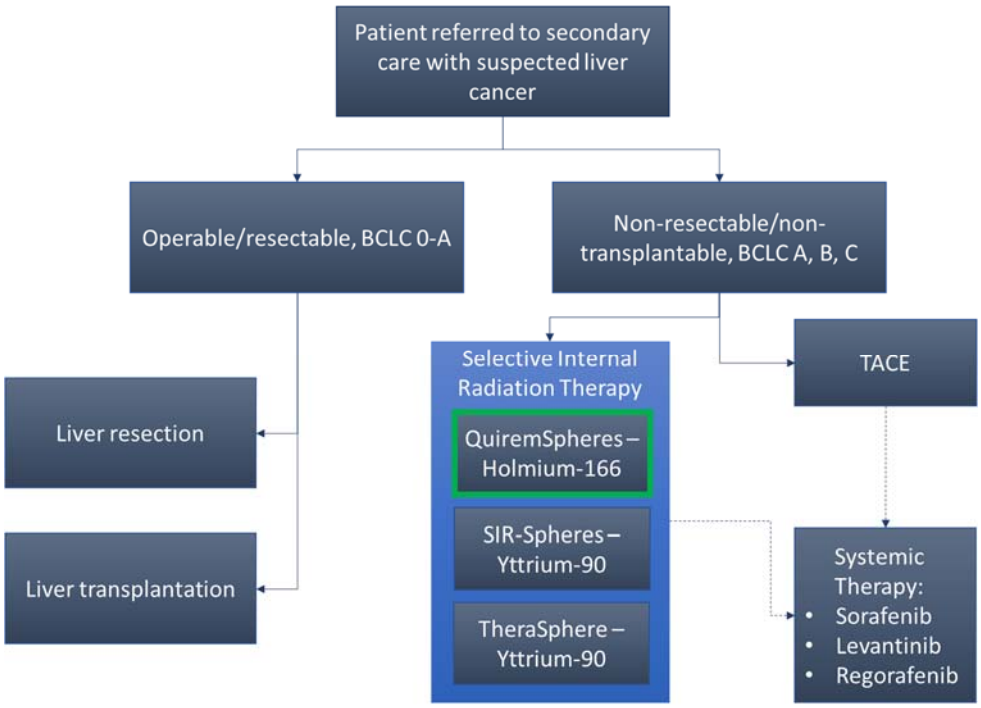


Figure 2. UK clinical pathway and anticipated place of QuiremSpheres®

B.1.4 Equality considerations

No equality issues are presented by Terumo concerning the treatment of HCC or use of QuiremSpheres® or SIRT in general.

B.2 Clinical effectiveness

Holmium-166 microspheres is considered a technical variant of yttrium-90 microspheres, wherein a similar effectiveness is to be expected based on a similar therapeutic mode of action (beta radiation).

Three published studies, Radosa et al, HEPAR I and HEPAR II, have confirmed the safety and efficacy of QuiremSpheres® in HCC and liver metastases, and five published studies have confirmed the safety and effectiveness of the QuiremScout™ work up procedure.

Multiple studies are ongoing to further expand the evidence base for clinical efficacy and safety of QuiremSpheres® in HCC.

B.2.1 Identification and selection of relevant studies

Following a discussion with the NICE team, and following the process guide for an MTA, no systematic literature review has been conducted There is currently limited evidence for QuiremSpheres® in this indication (HCC). Moreover, as we are aware of all the SIRT procedures using QuiremSpheres®, we are not expecting any clinical data to be published soon. One clinical study – HEPAR Primary – is ongoing in HCC but the study results will not be available before the completion of the NICE MTA. Radosa et al published evidence for QuiremSpheres® in HCC in CardioVascular and Interventional Radiology in 2018. The study showed that holmium-166 SIRT with QuiremSpheres® is a feasible and safe treatment option with no significant hepatotoxicity for the treatment of HCC.[23]

Other studies in which QuiremSpheres® have been assessed are:

- HEPAR I by Smits *et al.* 2012; Holmium-166 radioembolisation in patients with unresectable, chemorefractory liver metastases (HEPAR trial): a phase 1, dose-escalation study.[24]
- HEPAR II by Prince *et al.* 2015; Efficacy of radioembolisation with holmium-166 microspheres in salvage patients with liver metastases: a phase 2 study.[25]

Although the HEPAR I and II studies showed good outcomes and a similar safety and efficacy profile for holmium-166 SIRT as known from literature for yttrium-90 based

SIRT, these studies were not considered because the patient population under investigation only included patients with chemorefractory liver metastasis in which the liver tumour was not the primary tumour. However, relevant data to support the outcomes of the Radosa study has been added to sections 2.6 and 2.10. In addition, a summary of the study characteristics has been provided in Appendix D.

Therefore, the clinical effectiveness evidence relevant to QuiremSpheres® in patients with an unresectable HCC therefore consists of one retrospective study, further detailed in Section B.2.2 to Section B.2.7. Ongoing clinical studies (such as HEPAR Primary), as well as a synopsis of a retrospective analysis comparing the 3 SIRT technologies will also be described in sections B.2.9.

B.2.2 List of relevant clinical effectiveness evidence

The primary source of evidence for this multiple technology appraisal is the study published by Radosa *et al.* in 2018 [23] The study aimed to research the clinical feasibility and toxicity of holmium-166 SIRT procedure (QuiremSpheres®) as a new treatment option for patients with HCC. Additionally, researchers intended to analyse exact dosimetry via post-treatment calculations based on magnetic resonance images. See Table 4 for an overview of the study published by Radosa *et al.* in 2018.

Table 4. Clinical effectiveness evidence – Radosa et al.

Study	Radosa study: Holmium-166 SIRT in Hepatocellular Carcinoma: Feasibility and Safety of a New Treatment Option in Clinical Practice.[23]				
Study design	Patients were retrospectively identified after examination of a prospectively maintained service database based on whether patients received Holmium-166 SIRT between March 2017 and April 2018 in a single-centre setting.				
Population	Patients that underwent Holmium-166 SIRT with a diagnosis of HCC according to European Association of the Study of the Liver (EASL) criteria and were staged according to BCLC criteria.				
Intervention(s)	QuiremSpheres® (Holmium-166 SIRT)				
Comparator(s)	None				
	Yes			Yes	

Indicate if trial supports application for marketing authorisation	No	✓	Indicate if trial used in the economic model	No	✓
Rationale for use/non-use in the model	No cost-effectiveness model was developed for this submission.				
Reported outcomes specified in the decision problem	The outcome measures presented in the Radosa study and specified in the decision problem include: response rates of; compete response (CR), partial response (PR), stable disease (SD), progressive disease (PD). Additionally, safety of holmium therapy was measured.				
All other reported outcomes	There are no other outcomes reported in the Radosa study.				

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

Patients were retrospectively identified after examination of a prospectively maintained service database based on whether patients received Holmium-166 SIRT (QuiremSpheres®) between March 2017 and April 2018 in a single-centre setting. Baseline characteristics are described in Table 5. In total, 9 patients were enrolled that underwent Holmium-166 SIRT. These patients had a confirmed diagnosis of HCC according to European Association of the Study of the Liver (EASL) criteria and were staged according to BCLC criteria.[23]

Table 5. Baseline characteristics of patients with hepatocellular carcinoma in the study published by Radosa *et al.*[23]

Baseline characteristic	**Holmium-166 SIRT (n=9)**
Demographic	
Age, in years Median (range)	73 (64 — 78)

Sex, n (%)	
Male	8 (89%)
Female	1 (11%)
Cirrhosis, n (%)	
Present	7 (78%)
Absent	2 (22%)
Etiology of cirrhosis	
Alcohol abuse	5 (71%)
HCV	1 (17%)
Unknown	1 (17%)
Child–Pugh classification	
A	4 (57%)
B	3 (43%)
ECOG performance status, n (%)	
0	6 (67%)
1	2 (22%)
≥2	1 (11%)
BCLC classification, n (%)	
B	6 (67%)
C	3 (33%)
Prior liver treatments	
Resection	4 (45%)
Resection and TACE	2 (22%)
None	3 (33%)
Treatment approach	
Right lobe	5 (56%)
Left lobe	1 (11%)
Whole liver	3 (33%)

Table 6. Study characteristics – Radosa *et al.* [23]

Trial number (acronym)	Radosa study; no trial acronym provided
Trial design	Design: retrospective Masking: Open-label Duration: 6 months of follow-up
Inclusion criteria	Patients with a confirmed diagnosis of hepatocellular carcinoma according to European Association of the Study of the Liver (EASL) criteria and staging was assessed according to BCLC criteria.
Exclusion criteria	Contraindications for QuiremSpheres® were chosen accordingly to these applied for Yttrium-90 SIRT. Previous treatments like resection,

	thermal ablation or TACE, just like single lobe or whole liver disease were no exclusion criteria.[26]
Settings and locations where the data were collected	Single-centre study
Trial intervention (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])**	Subjects with holmium-166 SIRT (QuiremSpeheres®) were retrospectively enrolled to this study (n=9) <u>QuiremSpheres®:</u> To calculate the required Holmium-166 activity, a maximum whole liver dose of 60 Gy was aimed according to the published maximum tolerated radiation dose of the HEPAR trial and adjusted to the targeted liver mass, using the following formula as described by Smits *et al.*: A(MBq) = liver dose (Gy) x 63 MBq/J x LW (A = administered activity, liver dose = aimed whole liver absorbed dose, LW = liver weight) Mean dose on healthy liver tissue (whole liver inclusive the tumor) as well as mean dose on tumor tissue were calculated as MR-based dosimetry using the T1-weighted multi-gradient echo sequences (pre- and posttreatment) and Q-Suite™ (v1.2, QuiremSpheres®). Administered Holmium-166 activity (GBq): Median 3.7, range: 1.7–5.9 Calculated[a] whole liver dose (Gy): Median 41, range: 21–55 Calculated[a] tumor dose (Gy): Median 112, range: 61–172 [a]MR-based absorbed dose
Primary outcomes (including scoring methods and timings of assessments) ***(state pre-specified or posthoc)***	No primary outcomes were specified for this study, however, prespecified outcomes in the Radosa study included: Treatment response according to mRECIST criteria (efficacy endpoint) after 6 months of follow-up: • Complete response • Partial response • Progressive disease • Stable disease Safety endpoints included: • Presence of radioembolisation-induced liver disease (REILD) after 60 days, defined by jaundice, ascites and a bilirubin increase of over 50 µmol/l • Model for End-Stage Liver Disease (MELD) score 1-day pre-radioembolisation, 1 day and 60 days post-radioembolisation (The procedure was performed by a board-certified radiologist with more than 10 years' experience in performing radioembolisation (SIRT) and a board-certified nuclear medicine physician and images were evaluated by board-certified radiologists.)

	• Adverse events (grade 3-4) defined by CTCAE 1 day after radioembolization (Defined by CTCAE version 5)
Pre-planned subgroups and pre-planned subgroup stratification	No pre-planned subgroups were reported in the paper by Radosa *et al.*

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The study by Radosa is a small case-series and therefore subject to bias. However, it represents a real-world application of QuiremSpheres® in patients with HCC. The summary of the statistical analysis of the Radosa study is summarised in Appendix D in Table 12 and presents a summary of the statistical analysis carried out.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Quality assessment was performed in line with guidance for undertaking reviews in health care issued by the Centre for Reviews and Dissemination (University of York).[27] The quality assessment of the Radosa study is summarised in Appendix D in Table 13 in which the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies has been used to assess the quality of the Radosa study. This tool has been provided by the National Heart, Lung, and Blood Institute (NIH). As expected, the study is a small case-series and therefore subject to bias, however, it represents a real-world application of QuiremSpheres® in patients with HCC and in the absence of other published studies provides an indication of their safety and efficacy.

B.2.6 Clinical effectiveness results of the relevant trials

QuiremSpheres® microspheres have an identical therapeutic mode of action to existing yttrium-90 based SIRT products: the microspheres emit beta radiation that kills tumour cells from close range. The study by Radosa et al. suggests that QuiremSpheres® is clinically effective in patients with HCC.

HEPAR II is a useful reference point in liver metastases to illustrate the evidence available for QuiremSpheres®, see section B.2.8.

The study by Radosa *et al.*, measured different response rates (i.e. complete response, partial response, stable disease and progressive disease) after 2 months and 6 months. See Table 7 for an overview of the observed responses.

Table 7. Treatment responses – Radosa *et al.*[23]

Follow-up	1 day before SIRT (n=9)	1 day after SIRT (n=9)	60 days after SIRT (n=9)	6 months after SIRT
Treatment response				
Complete response	NE	NE	0	1 (11%)
Partial response	NE	NE	5 (56%)	4 (45%)
Stable disease	NE	NE	3 (33%)	3 (33%)
Progressive disease	NE	NE	1 (11%)	1 (11%)

NE, not evaluated, according to mRECIST

Of the 9 patients, 5 patients (56%) experienced a CR or PR, 3 patients (33%) maintained a stable disease and 1 patient experienced progressive disease. In comparison, studies of Yttrium-90 SIRT, report tumour response rates ranging from 25 to 50%, lower than the observed 56% tumour response rate in the Radosa trial.[23,28]

B.2.7 Adverse reactions

The study by Radosa et al. suggests that QuiremSpheres® has an acceptable safety profile among SIRT products in patients with HCC.

HEPAR I and HEPAR II are useful reference points in liver metastases to illustrate the evidence available for QuiremSpheres®, see section B.2.8.

Overall, the safety results from the Radosa study suggest that QuiremSpheres® has an acceptable safety profile in patients with unresectable HCC.

Sixteen (16) reportable adverse events occurred in 9 patients (see Table 8). There were no reported Grade 3-4 CTCAEs. Radioembolisation-induced liver disease (REILD) as measured by jaundice, ascites and a bilirubin increase of over 50 µmol/l did not occur after 60 days of follow-up.[23]

Table 8. REILD, MELD-score and CTCAEs; all or grade 3-4 – Radosa *et al.*[23]

Follow-up	1 day before SIRT	1-day after SIRT	60 days after SIRT
Presence of REILD[a]	**NE**	**NE**	**0**
MELD-score (median, range)	**8 (7–13)**	**8 (6–11)**	**8 (6–14)**
Numbers of CTCAE: all (grade 3–4 events)			
Nausea	NE	3 (0)	NE
Abdominal pain	NE	2 (0)	NE
Fatigue	NE	3 (0)	NE
Vomiting	NE	3 (0)	NE
Fever	NE	**1** (0)	NE
Ascites	NE	2 (0)	NE
Liver abscesses	NE	**0**	NE
Bilirubin	NE	1 (0)	NE

NE, not evaluated; [a]Jaundice, ascites and a bilirubin increase of over 50 µmol/l; REILD, radioembolisation-induced liver disease; MELD, model for End-Stage Liver Disease; CTCAE, Common Terminology Criteria for Adverse Events

Importantly, the median MELD-Score did not significantly change between the pre- and post-therapeutic and 60 day scores after SIRT. Thereby, the hepatotoxicity of Holmium-166 SIRT showed no significant effect on the severity of chronic liver disease during the course of the study.

B.2.8 Benchmark of the clinical effectiveness & safety of SIRT

HEPAR I and HEPAR II studied the safety and effectiveness of QuiremSpheres in liver metastases. Their results can be used to benchmark the safety and clinical effectiveness of QuiremSpheres®.[24,25]

The HEPAR I study is a non-randomised, open label, safety study in which patients with unresectable, chemorefractory liver metastases were treated with Holmium-166 SIRT in 4 cohorts of 3 to 6 patients, according to a standard dose escalation protocol with whole-liver absorbed doses of 20 Gy,40 Gy, 60 Gy or 80 Gy. This study provided

safety data for QuiremSpheres®.[24] A summary of the study characteristics has been provided in Appendix D, Table 10.

The HEPAR II trial is a non-randomised, single-arm, interventional, single-centre phase II study in which patients with liver metastases refractory to systemic therapy and ineligible for surgical resection were treated with the maximum tolerated radiation dose of 60 Gy of holmium-166 SIRT as observed in HEPAR I. This study reported clinical effectiveness in terms of treatment response and overall survival, as well as safety.[25] A summary of the study characteristics has been provided in Appendix D, Table 11.

In the sections below, we describe the clinical effectiveness and clinical safety of QuiremSpheres® in patients with liver metastases from HEPAR I and HEPAR II.

Clinical effectiveness of QuiremSpheres® in patients with liver metastases

The response rates described in the paper by Radosa were consistent with those observed in the HEPAR II study in patients with colorectal liver metastases. Table 9 shows the treatment response 3 months after Holmium-166 SIRT in the HEPAR II study.

Table 9. Response 3 months after Holmium-166 SIRT[25]

Treatment response	Liver specific
Complete response	-
Partial response	5 (14%)
Stable disease	13 (35%)
Progressive disease *	19 (51%)
Total	37 (100%)

Overall survival was not reported in the Radosa study, so to complement and support the evidence that is provided in the study by Radosa, we highlight overall survival data from the HEPAR II study. The median overall survival for patients with colorectal liver metastases was 13.4 months (95% CI 8.2-15.7).

Clinical safety of QuiremSpheres® in patients with liver metastases

The most common AE's reported in both trials (HEPAR I and HEPAR II) were gastrointestinal complaints associated with post-radioembolisation syndrome, nausea, abdominal pain and vomiting in addition to fatigue, though the rate of Grade 3 and 4 events was lower in Radosa.[23-25] These adverse events are also consistent with those observed in studies of yttrium-90 SIRT.[29]

B.2.9 Ongoing studies

Multiple studies have been initiated or are ongoing, to expand the evidence base for QuiremSpheres®. The following trials have been initiated and focus on treatment for HCC:

• HORA EST HCC: HOlmium Radioembolisation as Adjuvant Treatment to Radiofrequency Ablation for Early STage Hepatocellular Carcinoma	NCT03437382
• HEPAR Primary: Holmium-166-radioembolisation in Patients With Unresectable Hepatocellular Carcinoma (HCC); a Multi-center, Interventional, Non-randomized, Non-comparative, Open Label, Early Phase II Study.	NCT03379844
• Hope^{166}: Observational, Multicenter Study to Further Confirm The Efficacy and Safety of QuiremSpheres® (Holmium-166 Microspheres) Selective Internal Radiation Therapy (SIRT) in Unresectable Liver Cancer Patients.	NCT03563274
• A comparative retrospective analysis of HCC patients treated with QuiremSpheres® versus historical control with TheraSpheres® and SIR-Spheres®.	N/A

The HORA EST study is single arm dose escalation study that aims to enrol 20 patients with early stage HCC. The purpose of the study is to identify the treatment area dose for QuiremSpheres® to grant optimal delivery of a radiation absorbed dose of ≥ 120Gy to the target area in ≥90% of patients. In addition, the study aims to measure toxicity, local tumour recurrence, time to progression, progression-free survival, and quality of life.

The HEPAR Primary study will enrol approximately 30 patients with unresectable HCC. These patients will be treated with QuiremSpheres® following a diagnostic work-up with QuiremScout™. The primary goal of this study is to determine the safety and toxicity of QuiremSpheres®. Secondary outcomes aim to assess tumour response, changes in tumour marker alpha fetoprotein, quality of life, biodistribution or dosimetry based on quantitative assessment of MRI scans and any changes in hepatic function as measured by hepatobiliary scintigraphy.

The Hope[166] study will collect real-world data from more than 100 patients with primary or secondary liver tumours including HCC. The aim of this study is to further assess treatment efficacy and safety of QuiremSpheres® in terms of treatment response and frequency and severity of adverse events in patients with unresectable liver tumours. Secondary outcome measures aim to estimate the time to progression, progression-free survival, overall survival rate, and proportion of patients downstaged and eligible for surgery, transplantation or local ablation therapy.

In this retrospective analysis, patients treated with QuiremSpheres®, SIR-Spheres® and TheraSphere® in HCC between 2017-2019 will be matched for their disease state and general characteristics and outcomes will be compared. It is intended that this study will report in summer 2019.

B.2.10 Innovation

The unique features of QuiremScout™ and QuiremSpheres® (with the support of the Q-Suite software) represent a substantial innovation which can drive improved patient selection, and enable a more personalised procedure.

QuiremScout™ is the first SIRT workup product that utilises the same particle (poly-L-lactic acid microspheres loaded with holmium-166) as the therapeutic microspheres. This is important because it allows for a more accurate prediction of where the therapeutic microspheres will be deposited due to the QuiremScout™ and QuiremSpheres® particles being identical. QuiremScout™ aims to improve SIRT patient selection by accurately predicting the microspheres positioning in the organ and assessing the ratio of particle uptake in the tumours versus normal liver tissue. This information helps clinicians to make an informed clinical decision whether SIRT will be safe and effective prior to performing the SIRT procedure.

Patient selection - current process

Following a tumour board's decision that a patient is eligible to undergo SIRT, a work-up phase is needed to confirm the safety (and efficacy) of the procedure by simulating the therapy using surrogate particles (Technetium 99mTc macro aggregated albumin (Tc-99m-MAA)). This step is needed because inadvertent distribution of activity to organs other than the liver may cause damage to healthy tissue and may result in serious complications. The surrogate particles may also be used as a tool to assess the distribution of microspheres inside the liver (i.e. intrahepatic distribution), to predict the efficacy of the treatment. In current clinical practice, Tc-99m-MAA is used as the surrogate marker for yttrium-90 SIRT workup. Published data has demonstrated that the predictive value of Tc-99m-MAA may be inherently limited. Not only does it overestimate the activity in the lungs, it is also a poor predictor of the intrahepatic distribution. The poor predictive value, may be largely explained by the fact that Tc-99m-MAA particles have a completely different shape, size, stability, and density compared to the therapy microspheres (Figure 3).

The work-up phase is followed by a calculation of activity (that is to be injected) using generic models based on a one-size-fit-all approach.

Over the last decade, the field of SIRT has taken a strong interest in developing a better understanding of the relation between dose and outcome, also known as dose-effect relationships. Based on a recently published studies, it is widely recognised that a better understanding of the SIRT procedure and dosimetry will positively impact treatment outcome.[18,30]

In the post-hoc dosimetry analysis of the SARAH Study, the role of Tc-99m-MAA SPECT/CT based dosimetry (tumour-absorbed-dose) in predicting overall survival and tumour response of patients with locally advanced and inoperable HCC treated by SIRT with yttrium-90 resin microspheres was assessed[15]. For this analysis, the tumour dose was a predicted dose based on Tc-99m-MAA distribution. It showed that in the patient population for which the tumour absorbed dose was more than 100 Gy, median overall survival was significantly prolonged compared to patients with a tumour absorbed dose below 100 Gy (14.1 months vs. 6.1 months). Among patients who received more than 100 Gy (n=67), those with a good visual agreement between Tc-99m-MAA and therapy distribution (n=24) had the longest median OS (24.9 months).

This means only 36% (24/67) had both optimal targeting and more than 100Gy tumour absorbed dose. This data shows that there is a subgroup that benefitted from SIRT with a high OS, i.e. those with a high tumour absorbed dose. It is therefore key to identify those patients that will have a good tumour absorbed dose after therapy. Furthermore, it shows that a scout dose of Tc-99m-MAA has limited agreement of the Tc-99m-MAA distribution and the actual treatment distribution – and therefore the confidence in the predicted tumour absorbed dose using this technique is suboptimal.

This retrospective analysis underlines (1) the importance of accurate patient selection to optimise treatment outcome and (2) the poor predictive value of Tc-99m-MAA to perform such patient selection.

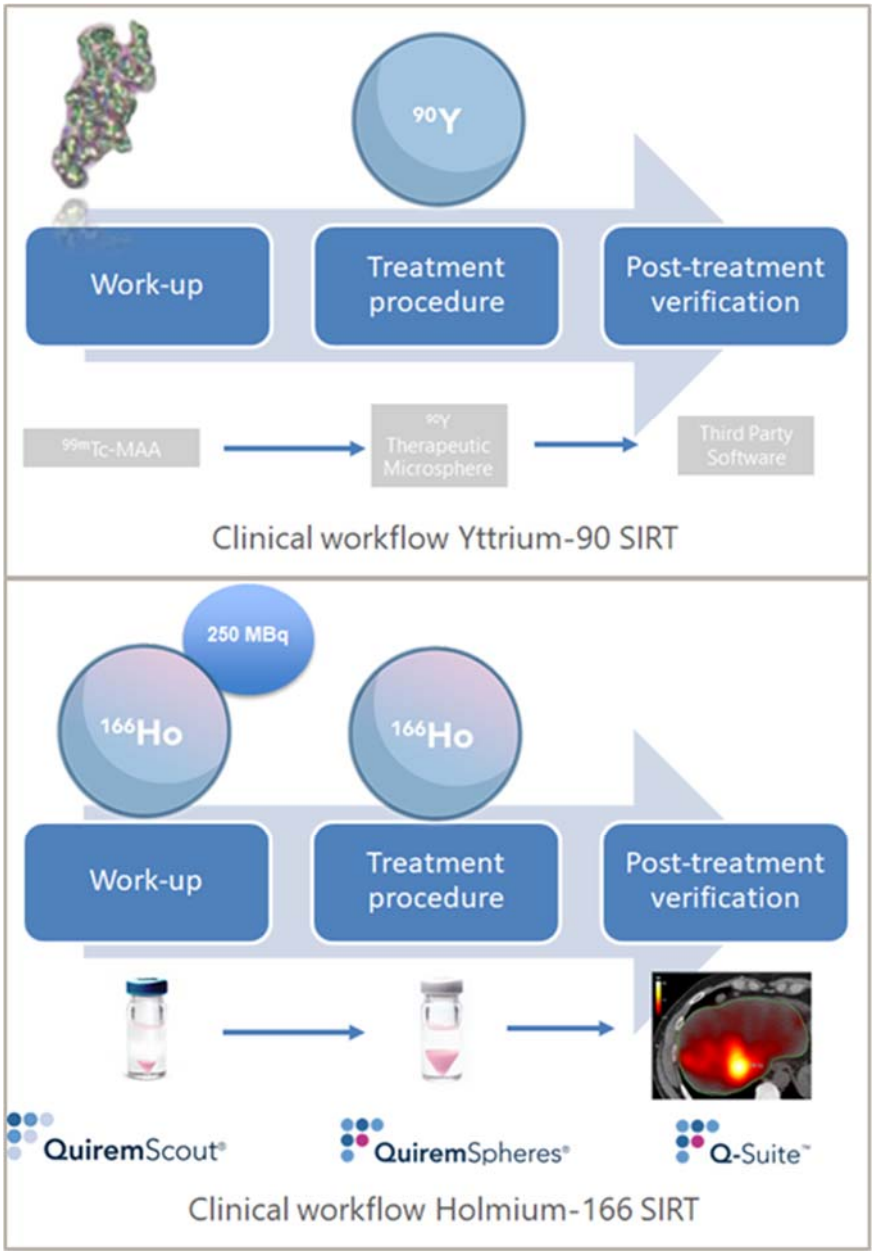


Figure 3. Comparison of clinical workflow yttrium-90- and holmium-166 SIRT

As described in Figure 3, the clinical workflow of holmium-166 is similar to that of yttrium-90, but with fundamental improvements in the patient selection workup phase. With holmium-166 microspheres, it is now possible to use the exact same particle for simulation and treatment.

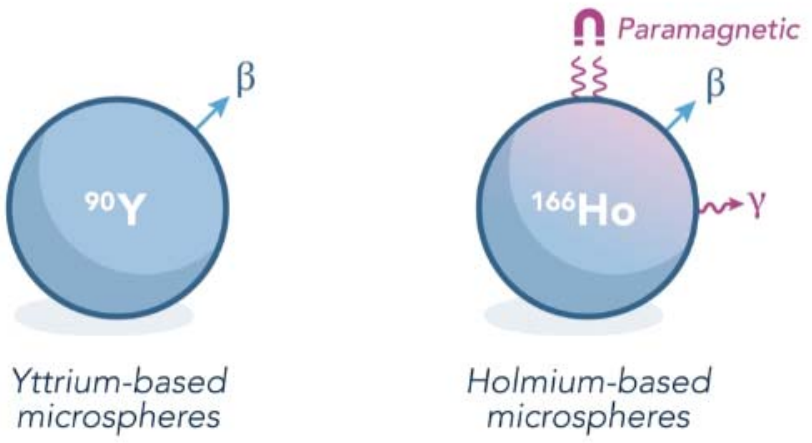


Figure 4. Properties of Yttrium-90 and Holmium-166

Unlike yttrium-90, holmium-166 emits gamma photons and is paramagnetic as illustrated in Figure 4. The low energy gamma radiation passes through and out of the body and can be imaged with SPECT or SPECT/CT. This unique property makes it possible to determine the distribution of QuiremSpheres® inside the patient with high sensitivity and good resolution. In addition, the metal holmium can be visualised with MR imaging. Imaging of the microspheres enables better treatment planning and post-treatment distribution assessment and allows for treatment quantitative evaluation directly after the SIRT procedure allowing precise decision making on follow-up treatment. The imaging characteristics of holmium-166 allow low quantities of these microspheres to be used as a scout dose (QuiremScout™).

QuiremScout™ aims to improve SIRT patient selection by accurately assessing the ratio of particle uptake in the tumours versus normal liver tissue. Moreover, the unique imaging characteristics of holmium-166 allow quantitative verification after QuiremSpheres® treatment, to ensure the patient has been treated as planned. This verification step can be easily executed using Q-Suite imaging software – specifically developed to support evaluation of holmium-166 SIRT based on MR or SPECT images of the in vivo QuiremSpheres® distribution. The ability to perform quantitative post-treatment verification means that it is now possible to easily and accurately assess if sufficient dose was deposited to the lesions.

In short, the unique features of QuiremScout™ and QuiremSpheres® (with the support of the Q-Suite software) represent a substantial innovation which can drive improved patient selection, and enable a more personalised procedure, and is anticipated to positively impact both the efficacy and safety of SIRT with QuiremSpheres® in patients with HCC.

Clinical studies supporting the use of QuiremScout™

Clinical data has demonstrated that QuiremScout™ is a safe alternative of Tc-99m-MAA. Additionally, it has been shown that QuiremScout™ is a more accurate predictor than Tc-99m-MAA. Specifically, QuiremScout™ more accurately predicts activity distribution to the lung and within the liver and improves patient selection by accurately assessing the ratio of particle uptake in the tumours versus normal liver tissue. This information helps clinicians to make an informed clinical decision if SIRT will be safe and effective prior to performing the SIRT procedure.

The safety of ^{166}Ho scout-dose (QuiremScout™) has been retrospectively assessed in 82 patients in a study published by Braat *et al.*.[32] This study showed that ^{166}Ho scout-dose before initiating SIRT was a safe alternative to the surrogate marker.[32]

Another study by Elschot et al. showed that Tc-99m-MAA overestimates lung shunting, as a result potentially eligible patients for SIRT treatment were not treated.[33]

Recently, data was presented by Dassen et al at the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) 2018 conference, highlighting that Holmium-166 scout-dose seemed better in predicting intrahepatic distribution compared to Tc-99m-MAA. In this study, two blinded nuclear medicine physicians rated the agreement between SPECT images after Tc-99m-MAA, 166Ho-scout and 166Ho-therapeutic dose scans using a 5-point scale. In total, 24 procedures were assessed, of which 182 segments, 82 lesions in 23 patients. Results from the qualitative analysis showed that on a 5 point scale, holmium scout was superior to Tc-99m-MAA (3.5 versus 2.5, p-value <0.001), meaning physicians had a clear preference for the Ho-scout and Ho-therapy distribution in terms of better agreement between the images. Quantitatively the agreement was also assessed, comparing the (predicted) dose in regions of interest across several images (Ho-Scout SPECT, MAA SPECT and Ho-Therapy SPECT). In this analysis they found that Ho-Scout is better at predicting the therapy

dose than MAA (both surrogate particles have a relatively large range of variability in predicting the actual therapy dose in the regions of interest).[34]

B.2.11 Interpretation of clinical effectiveness and safety evidence

For the purposes of this submission we have presented the rationale that holmium-166 microspheres (QuiremSpheres) is a technical variant of yttrium-90 microspheres (TheraSphere® and SIR-Spheres®). All microspheres have the same mode of action: they emit beta radiation that kills tumor cells from close range. Therefore, similar effectiveness would be expected based on the clinical evidence available from Radosa *et al*, HEPAR I and HEPAR II.

Indeed, the Zorginstituut in their assessment of holmium-166 SIRT for the Netherlands, considered QuiremSpheres® to be a technical variant of yttrium-90 SIRT and concluded that holmium–166 radioembolisation therefore satisfied the 'state of the art of science and practice' and therefore belongs to the treatment to be insured under the Dutch Healthcare Insurance Act.[4]

We are conscious that the clinical data currently available for QuiremSpheres® in HCC is limited. The study by Radosa is the first study to publish data with regards to the safety, efficacy and toxicity of QuiremSpheres® in patients with HCC.[23] A tumour response rate of 56% after QuiremSpheres® was reported in the publication by Radosa *et al.*. [23] Tumour response rates after yttrium-90 SIRT range from 25 to 50%.[27]

The study by Radosa was too short to estimate overall survival and whilst not directly comparable, published studies in metastatic colorectal cancer can be useful reference points.[23] In the study published by Prince *et al*, a median overall survival of 13.4 months (95% CI 8.2-15.7) was observed after treatment with QuiremSpheres®.[25],[25]

Safety results from the Radosa study suggest that QuiremSpheres® has an acceptable safety profile in patients with unresectable liver tumours.[23] Adverse event rates were comparable to those observed in earlier studies of holmium-166 SIRT published by Smits *et al.* and Prince *et al.* in patients with colorectal cancer with metastases in the liver, HEPAR I, and HEPAR II, respectively.[24,25] In addition, the safety and efficacy of SIRT has been established by yttrium-90 SIRT in a number of clinical trials in HCC.

Overall, it can be concluded that QuiremSpheres® have a favourable safety profile in patients with unresectable liver tumours.

To strengthen the evidence base for QuiremSpheres®, several studies have been initiated in HCC (HORA EST HCC, HEPAR Primary, and HOPE[166]).

B.4 References

1. Burrill J, Hafeli U, Liu DM. Advances in Radioembolization - Embolics and Isotopes. *Journal of Nuclear Medicine & Radiation Therapy.* 2011;2(1):1-6.
2. Westcott MA, Coldwell DM, Liu DM, Zikria JF. The development, commercialization, and clinical context of yttrium-90 radiolabeled resin and glass microspheres. *Advances in radiation oncology.* 2016;1(4):351-364.
3. Prince JF, Smits ML, Krijger GC, et al. Radiation emission from patients treated with holmium-166 radioembolization. *Journal of vascular and interventional radiology : JVIR.* 2014;25(12):1956-1963.e1951.
4. Dutch National Health Care Institute; Zorginstituut Nederland: Standpunt holmium–166 radioembolisatie (QuiremSpheres®) bij inoperabele levertumoren. Available: https://www.zorginstituutnederland.nl/publicaties/standpunten/2018/04/05/standpunt-holmium%E2%80%93166-radioembolisatie-bij-inoperabele-levertumoren Accessed: May 2019.
5. SIR-Spheres for treating inoperable hepatocellular carcinoma Medtech innovation briefing. Available: https://www.nice.org.uk/advice/mib63 Accessed: May 2019.
6. TheraSphere for treating operable and inoperable hepatocellular carcinoma Medtech innovation briefing. Available: https://www.nice.org.uk/advice/mib62 Accessed: May 2019.
7. GLOBOCAN 2018, Cancer Incidence and Mortality Worldwide: IARC Cancer Base [Internet]. Lyon, France: International Agency for Research on Cancer; 20128. Available from: http://globocan.iarc.fr, accessed September 2018.
8. National Cancer Registration and Analysis Service. Trends in incidence of primary liver cancer subtypes. Available from: http://www.ncin.org.uk/publications/data_briefings/trends_in_incidence_of_primary_liver_cancer_subtypes. Accessed on: April 2019. .
9. Cancer Research UK. Liver cancer statistics. 2015. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/liver-cancer#heading-Zero. Accessed: April 2019.
10. Smittenaar CR, Petersen KA, Stewart K, Moitt N. Cancer incidence and mortality projections in the UK until 2035. *British journal of cancer.* 2016;115(9):1147-1155.
11. Parkin DM. 11. Cancers attributable to infection in the UK in 2010. *British journal of cancer.* 2011;105 Suppl 2:S49-56.
12. Das D, Chattopadhyay D, Aslam T, et al. NAFLD and the changing face of hepatocellular cancer (HCC). *Gut.* 2011;60(Suppl 1):A243.
13. Office for National Statistics. Cancer survival in England: Patients diagnosed between 2012 and 2016. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed. Accessed on: April 2019.
14. National Institute for Health and Care Excellence. Sorafenib for treating advanced hepatocellular carcinoma resource impact template. 2017. Available from: https://www.nice.org.uk/guidance/ta474/resources. Accessed: April 2019

15. Vogel A, Cervantes A, Chau I, et al. Hepatocellular carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology.* 2018;29(Supplement_4):iv238-iv255.
16. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol.* 2018;69(1):182-236.
17. Chow PKH, Gandhi M, Tan SB, et al. SIRveNIB: Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2018;36(19):1913-1921.
18. Vilgrain V, Pereira H, Assenat E, et al. Efficacy and safety of selective internal radiotherapy with yttrium-90 resin microspheres compared with sorafenib in locally advanced and inoperable hepatocellular carcinoma (SARAH): an open-label randomised controlled phase 3 trial. *The Lancet Oncology.* 2017;18(12):1624-1636.
19. Salem R, Lewandowski RJ, Kulik L, et al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology.* 2011;140(2):497-507.e492.
20. Salem R, Gilbertsen M, Butt Z, et al. Increased quality of life among hepatocellular carcinoma patients treated with radioembolization, compared with chemoembolization. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2013;11(10):1358-1365.e1351.
21. Salem R, Gordon AC, Mouli S, et al. Y90 Radioembolization Significantly Prolongs Time to Progression Compared With Chemoembolization in Patients With Hepatocellular Carcinoma. *Gastroenterology.* 2016;151(6):1155-1163.e1152.
22. Sacco R, Tapete G, Simonetti N, et al. Transarterial chemoembolization for the treatment of hepatocellular carcinoma: a review. *Journal of hepatocellular carcinoma.* 2017;4:105-110.
23. Radosa CG, Radosa JC, Grosche-Schlee S, et al. Holmium-166 Radioembolization in Hepatocellular Carcinoma: Feasibility and Safety of a New Treatment Option in Clinical Practice. *Cardiovascular and interventional radiology.* 2019;42(3):405-412.
24. Smits ML, Nijsen JF, van den Bosch MA, et al. Holmium-166 radioembolisation in patients with unresectable, chemorefractory liver metastases (HEPAR trial): a phase 1, dose-escalation study. *The Lancet Oncology.* 2012;13(10):1025-1034.
25. Prince JF, van den Bosch M, Nijsen JFW, et al. Efficacy of Radioembolization with (166)Ho-Microspheres in Salvage Patients with Liver Metastases: A Phase 2 Study. *Journal of nuclear medicine : official publication, Society of Nuclear Medicine.* 2018;59(4):582-588.
26. Salem R, Thurston KG. Radioembolization with 90Yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 1: Technical and methodologic considerations. *Journal of vascular and interventional radiology : JVIR.* 2006;17(8):1251-1278.
27. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. Centre for Reviews and Dissemination,

University of York. 2009. https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf.
28. Salem R, Lewandowski RJ, Mulcahy MF, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology.* 2010;138(1):52-64.
29. Kennedy AS, Ball D, Cohen SJ, et al. Multicenter evaluation of the safety and efficacy of radioembolization in patients with unresectable colorectal liver metastases selected as candidates for (90)Y resin microspheres. *Journal of gastrointestinal oncology.* 2015;6(2):134-142.
30. Bastiaannet R, Kappadath SC, Kunnen B, Braat AJAT, Lam MGEH, de Jong HWAM. The physics of radioembolization. *EJNMMI physics.* 2018;5(1):22-22.
31. Hermann AL, Dieudonné A, Maxime R, et al. Role of 99mTc-Macroaggregated Albumin SPECT/CT based dosimetry in predicting survival and tumor response of patients with locally advanced and inoperable hepatocellular carcinoma (HCC) treated by selective intra-arterial radiation therapy (SIRT) with yttrium-90 resin microspheres, a cohort from SARAH study. *Journal of Hepatology.* 2018;68:S13.
32. Braat A, Prince JF, van Rooij R, Bruijnen RCG, van den Bosch M, Lam M. Safety analysis of holmium-166 microsphere scout dose imaging during radioembolisation work-up: A cohort study. *European radiology.* 2018;28(3):920-928.
33. Elschot M, Nijsen JF, Lam MG, et al. Tc-99m-MAA overestimates the absorbed dose to the lungs in radioembolization: a quantitative evaluation in patients treated with 166Ho-microspheres. *European journal of nuclear medicine and molecular imaging.* 2014;41(10):1965-1975.
34. Lam MG. Presentation during Cardiovascular and Interventional Radiological Society of Europe (CIRSE) 2018. Title: The predictive value of the intrahepatic distribution of 99mTc-macroaggregated albumin and holmium-166 scout dose prior to holmium-166 radioembolization. Available from: https://cslide.ctimeetingtech.com/cirse2018/attendee/person/142031 Accessed: May 2019

B.5 Appendices

Appendix C: Instructions for Use (IFU)

C1.1 IFU QuiremSpeheres®

The instructions for use for QuiremSpheres® can be found in the attached object.

IFU
QuiremSpheres®

C1.2 IFU QuiremScout™

The instructions for use for QuiremScout® can be found in the attached object.

IFU QuiremScout™

Appendix D: Identification, selection and synthesis of clinical evidence

D1.1 Identification and selection of relevant studies

Following a discussion with the NICE team, and following the process guide for an MTA, no systematic literature review has been conducted There is currently limited evidence for QuiremSpheres® in this indication (HCC). Moreover, as we are aware of all the SIRT procedures using QuiremSpheres®, we are not expecting any clinical data to be published.

To complement the argument that holmium-166 microspheres is a technical variant of yttrium-90 microspheres. We've included supportive clinical effectiveness evidence in the tables below. In total, 2 non-comparative studies were available in which the effectiveness of radioembolisation with holmium-166 microspheres in liver metastases was studied. In these studies, a total of 29 patients with colorectal liver metastases were enrolled. A maximum tolerated radiation dose of 60 Gy was used in 25 of these patients. Both studies were performed in the same Dutch centre. See Table 10 and Table 11 for an overview of the study characteristics.

Table 10. Supportive clinical effectiveness evidence – Smits *et al.*

Study	Smits study: Holmium-166 radioembolisation in patients with unresectable, chemorefractory liver metastases (HEPAR trial): a phase 1, dose-escalation study
Trial number (acronym)	NCT01031784
Trial design	Design: Prospective, non-randomised Masking: Open-label Duration: 12 weeks of follow-up
Study design	A non-randomised, open label, safety study. Patients were treated in 4 cohorts of 3-6 patients, according to a standard dose escalation protocol (20 Gy, 40 Gy, 60 Gy, and 80 Gy, respectively)
Population	Patients with unresectable, chemorefractory liver metastases, undergoing Holmium-166 SIRT.
Inclusion criteria	Eligibility criteria were: presence of liver-dominant, unresectable, chemorefractory liver metastases of any

	primary tumour; age 18 years or older; an estimated life expectancy of over 3 months; WHO performance status score 0–2; at least one measurable lesion of at least 10 mm on CT; and a negative pregnancy test for women.				
Exclusion criteria	Patients were excluded whenever they had: impaired haematological function (leucocytes <4·0×10⁹ cells per L and platelet count <150×10⁹/L), impaired renal function (serum creatinine >185 µmol/L), impaired cardiac function (relevant morphological changes on electrocardiography or New York Heart Association classifi cation of heart disease score ≥2), impaired hepatic function (alanine aminotransferase [ALT], aspartate aminotransferase [AST], or alkaline phosphatase over five times the upper limit of normal, or serum bilirubin over 1·5 times the upper limit of normal), patients who had received chemotherapy or abdominal surgery over the previous 4 weeks, those with incompletely healed surgical incisions, and those with contraindications for MRI.				
Settings and locations where the data were collected	Single-centre study				
Intervention(s)	QuiremSpheres® (Holmium-166 SIRT); 20 Gy, 40 Gy, 60 Gy, and 80 Gy				
Comparator(s)	None				
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])**	The amount of administered Holmium-166 SIRT radioactivity at the time of the procedure was calculated using the aimed whole-liver absorbed dose (20, 40, 60, or 80 Gy) and the liver weight. • Whole-liver absorbed dose: 20 Gy, n=6 • Whole-liver absorbed dose: 40 Gy, n=3 • Whole-liver absorbed dose: 60 Gy, n=3 • Whole-liver absorbed dose: 80 Gy, n=3				
Indicate if trial supports application for marketing authorisation	Yes		Indicate if trial used in the economic model	Yes	
	No	✓		No	✓
Reported outcomes specified in the decision problem	The primary objective was to establish the maximum tolerated radiation dose of Holmium-166 SIRT microspheres Secondary objectives were: • Tumour response • Quality of Life				

All other reported outcomes	• Biodistribution • Performance status • Comparison of 166Ho-PLLA-MS safety dose and the Tc-99m-MAA dose with regard to the ability to accurately predict microsphere distribution
Primary outcomes (including scoring methods and timings of assessments) *(state pre-specified or posthoc)*	Pre-specified primary outcome was the maximum tolerated radiation dose (MTRD). The study was stopped after assessing the 80 Gy cohort, whereas the MTRD was identified as 60 Gy.
Pre-planned subgroups and pre-planned subgroup stratification	No pre-planned subgroups were reported in the paper by Smits *et al.*

Table 11. Supportive clinical effectiveness evidence – Prince *et al.*

Study	Prince study: Efficacy of Radioembolization with ^{166}Ho-Microspheres in Salvage Patients with Liver Metastases: A Phase 2 Study
Trial number (acronym)	NCT01612325
Trial design	Design: Interventional, non-randomised Masking: Open-label Duration: Median follow-up of 13.3 months (with a range of 2.5–39.3 months). From May 2012 until March 2015
Study design	A single-arm, interventional, single-centre phase II study.
Population	Patients with liver metastases refractory to systemic therapy and ineligible for surgical resection
Inclusion criteria	Patients were eligible for this study if they had been diagnosed with metastatic liver lesions of any primary origin and limited disease outside the liver as determined on ^{18}F-FDG PET/CT. Second, patients were unable or unwilling to undergo (further) chemotherapy or surgery (salvage patients); had an estimated life expectancy of >3 months; had adequate liver, renal, and bone marrow function; and had a World Health Organization performance score of ≤2.
Exclusion criteria	Not reported
Intervention(s)	QuiremSpheres® (Holmium-166 SIRT)
Comparator(s)	None

<table>
<tr><td>Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered)

Intervention(s) (n=[x]) and comparator(s) (n=[x])</td><td colspan="5">The total amount of radioactivity through Holmium-166 SIRT at the time of the procedure was adjusted to the targeted liver mass measured on CT (aimed absorbed dose, 60 Gy or 3.8 GBq/kg of liver tissue, including the 166Ho scout dose) and was contained in a fixed number of microspheres. In total, 38 patients received treatment.</td></tr>
<tr><td rowspan="2">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td></td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td></td></tr>
<tr><td>No</td><td>✓</td><td>No</td><td>✓</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">The primary outcome was disease control rate on target lesions 3 months after therapy, assessed by using RECIST, version 1.1.

Secondary outcomes included:
Overall tumor response
Overall survival
Toxicity
Quality of Life,</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">Time to imaging progression
Quantification of the microspheres on SPECT and MRI.</td></tr>
<tr><td>Primary outcomes (including scoring methods and timings of assessments) (state pre-specified or posthoc)</td><td colspan="5">Pre-specified primary outcome was disease control rate based on the target lesion three months after therapy as measured y RECIST 1.1. Disease control rate is a composite endpoint of complete response, partial response an stable disease.</td></tr>
<tr><td>Pre-planned subgroups and pre-planned subgroup stratification</td><td colspan="5">No pre-planned subgroups were reported in the paper by Prince et al.</td></tr>
</table>

Table 12. Summary of statistical analysis – Radosa *et al.*[23]

Hypothesis objective	The authors did not define a primary objective. The study analysed the clinical effectiveness, and safety of Holmium-166 SIRT (QuiremSpheres®), as well as the required dosimetry by using MRI from a "real world" perspective.
Statistical analysis	Descriptive statistics were used to summarise efficacy data. Data were collected in an Excel database (Excel 2016; Microsoft Corporation, Redmond, WA, USA), and statistical analyses were performed with SPSS

	software version 23 (SPSS, Chicago, IL, USA). Data were reported as medians with ranges. No hypothesis testing was conducted for safety endpoints. MELD-scores were analysed with the Friedman test in which a P-value of <0.05 was considered statistically significant. Descriptive statistics were used to summarise safety data by timepoint. Summaries of AEs were restricted to CTCAE grade 3/4 events.
Sample size, power calculation	The study by Radosa *et al.* did not provide any power calculation and aimed to retrospectively enrol eligible patients from a single hospital. In total, 9 patients were included.
Data management, patient withdrawals	The study by Radosa *et al.* did not provide any formal methods with regard to data management. In total 9 patients were included, of which all 9 patients were followed up to 6 months.

To assess the risk of bias of the study published by Radosa, the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies has been used. This tool has been provided by the National Heart, Lung, and Blood Institute (NIH). See Table 13**Error! Reference source not found.** for a summary of the quality assessment.

Table 13. Summary of quality assessment – Radosa *et al.*[23]

Criterium	Assessment
1. Was the study question or objective clearly stated?	Yes, the objective of the study was to study feasibility, technical success and toxicity of Holmium-166 SIRT in patients suffering from HCC within the clinical routine.
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	Yes, however, it is not clear what contra-indications have been considered when selecting the patients from the prospectively maintained service database.
3. Were the participants in the study representative of those who would be eligible for the intervention in the general or clinical population of interest?	Yes, these patients were eligible and treated according to a real-world setting based on a confirmed diagnosis of HCC and have been staged according to the BCLC criteria.
4. Were all eligible participants that met the prespecified entry criteria enrolled?	Not clear, the study had a retrospective design, hence these entry criteria were used to identify relevant participants. However, it is not clear how many patients have not been enrolled in the study due to criteria that were unmet.
5. Was the sample size sufficiently large to provide confidence in the findings?	Unclear (the study included 9 patients from a single-centre)

6. Was the intervention clearly described and delivered consistently across the study population?	Yes, both the procedure and dosing strategy have been described. Patients' dosage was assessed during a work-up phase and adjusted based on multiple parameters among which liver weight.
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	Yes, efficacy key endpoints have been described (treatment response), together with the safety analyses (REILD, MELD and CTCAE grade 3-4) and were assessed across all study participants.
8. Were the people assessing the outcomes blinded to the participants' interventions?	Not clear, this has not been described in the paper.
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	Not clear, this study had a retrospective design. Loss to follow-up has not been described.
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	No, only descriptive statistics were used. In addition, ample size of the population is relatively small. Friedman test has been used to evaluate the MELD scores.
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?	No, only MELD score was assessed 1 day before the procedure, 1 day after the procedure and 60 days after the procedure. Adverse events were measured 1 day after SIRT, whereas treatment response was measured 60 days after the procedure.
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?	No, individual-level data was not provided in the paper.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (MTA)

Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276]

Thank you for agreeing to give us your views on the treatment(s) being evaluated by NICE in this appraisal and how it/they could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment(s).

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages. If you think your response will be significantly longer than this, please contact the NICE project team to discuss.

When answering the questions from section 3 onwards, please make sure to say which treatment (s) you are commenting on.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: British Liver Trust

Your position in the organisation: [redacted]

Brief description of the organisation:

The British Liver Trust is the leading UK patient charity for adults living with liver disease. It is funded entirely by voluntary donations apart from restricted funding from Public Health Wales to help implement the Welsh Liver Plan, and deliver patient services in Wales until 2020. We receive no other statutory funding.

Our services reach over a million people every year. The website receives over 100,000 visits from new unique users each month. We have a monthly newsletter which goes to around 30,000 people living with liver disease and liver cancer, an online support forum with over 15,000 involved users, an active social media following of over 13,500. We regularly raise awareness of liver issues in the media with over 600 pieces in national and regional media since January 2019. We support people with liver disease by providing evidence based information (both online and in print) and run a nurse-led Helpline where people are able to ask questions and receive advice. We use the qualitative and quantitative data from our services to provide feedback to clinicians and policy makers.

To support the information in this submission, we have put a call out through our various channels for people living with liver cancer and for those who have had access to SIRT to come forward and provide information. We also keep a confidential quote log of Helpline callers and also monitor our online social media communities (which include open and closed Facebook groups). As part of this process, we also conducted in depth interviews with people who have liver cancer, carers and people who have experienced SIRT as a treatment.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: We do not have any links or funding from the tobacco industry.

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

About 85% of people diagnosed with primary liver cancer will have Hepatocellular Carcinoma (HCC). Compared with other cancers, there is a very poor survival rate - on average only 12% of those diagnosed will live for five years. There are often no symptoms in the early stages

and patients are usually diagnosed very late. People diagnosed frequently also have advanced liver disease (as well as cancer) which means treatment is more complicated than for many other types of cancers. We have many calls to our Helpline where the diagnosis of cancer comes at the same time as the diagnosis of underlying liver disease. Symptoms at an advanced stage may include unexplained weight loss, jaundice, itchy skin, a very swollen abdomen (ascites), nausea and vomiting.

If HCC is detected early, potentially curative treatment options are available such as transplant or surgical removal but for advanced HCC there are no specific symptoms, and so less than 30% of patients are diagnosed in the early stages of the disease where potentially curative treatment is available.

Patients with advanced HCC have a very poor prognosis and there are very few treatment options. Patients are often relatively young and are completely shell shocked and devastated on hearing about the poor prognosis on diagnosis. Patients also report feeling extremely unwell, very tired and weak. Some quotes include:

"Emotionally it was tough. I felt like I couldn't cope and it all just caught up with me. I felt like every time I put my head up above water I got shot down."

"Immediately after diagnosis I was shell shocked. I took my house in order, made my will. But I made changes to things. Death was imminent in my mind. Having a transplant makes me realise how lucky I am but I wish there had been another option. Liver disease doesn't seem to get the attention of other cancers."

"We were just devastated. My husband was prescribed medication and underwent a radiofrequency ablation procedure. He was extremely tired and in pain. He was put on the waiting list, then he had to be taken off the list as the cancer had grown whilst waiting. He was 42 years old, had never drunk in his life and we were told he would die in about six weeks. The rug was completely taken from under my feet … my whole life crumbled and ten years on I am still in pain."

Relatives have described the condition as "brutal - the worst possible way to go".

Patients live with uncertainty, hopelessness and often stigma and isolation due to the image of liver disease. When patients are diagnosed with HCC, they often experience depression from the poor prognosis and a range of symptoms including severe pain that cannot be treated without worsening their liver condition. Other severe symptoms include ascites, fluid in the abdomen that can press on the stomach making it difficult to eat and even to breathe. Hepatic encephalopathy can make everyday functions including conversation, writing and staying awake difficult. Only a very few patients are offered curative treatment, and even then, many live with the uncertainty about whether they will receive a liver transplant before the tumour spreads, or whether they will die as a complication of surgery (liver resection has a relatively high mortality rate).

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

A diagnosis of HCC is devastating as the prognosis is very poor – only 12% of patients liver for 5 years. The main treatment outcomes that are important are extending life (longevity) and quality of life. Patients also spoke about reducing the length of hospital stays and limiting nasty and debilitating side effects. Because patients are often relatively young, extra time is of particular importance to people who may have young families and working lives to put in order before death.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these different treatments and which are preferred and why?

Treatment options for people with liver cancer are severely limited. If there is no option for surgery or liver transplant, the current only life extending treatment options for patients with advanced liver cancer are sorafenib (Nexevar) or lenvatinib (Lenvima). Patients report side effects and for some people these are severe.

Once sorafenib stops working, they can then use Regorafenib (Stirvaga). Once these options are exhausted the only option is palliative care.

HCC patients are disadvantaged purely because they have a disease which does not have an extensive number of treatments available. For example in many other cancers, there are several life-extending chemotherapy treatments available, and it may be appropriate to consider whether new medicines are effective. This is not the case in liver cancer.

4. What do patients or carers consider to be the advantages of the treatment(s) being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)

- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment(s) being appraised.

The Trust has had contact from patients who have had access to selective internal radiation therapy. The stories from some of these patients who have received treatment have been inspiring and offered real hope. Some patients have shared their story on our online forum and discussions have taken place with other sufferers and their carers. The feedback has been that for some people it has been successful and prolonged life. One person we interviewed for this process, for example, had lived for an additional 18 months and been able to see and spend precious time with their granddaughter.

The Trust has had contact from patients concerned that as Commissioning through Evaluation (CtE) programme has now closed; patients are not currently eligible to receive SIRT funded by the NHS. We have explained that the data is currently being looked at but patients are very concerned that this treatment may no longer been an option. We have had patients in tears asking us to explain why it is unavailable in England but patients can receive it in many parts of Europe or in the USA. We had patients ask us how to access SIRT privately and we had to stress that they needed to go back to speak to their consultants as it is only suitable for a limited number of patients. Patients were also very concerned about 'equality of access'. Some asked for centres which provided private access (we do not hold this information or give it out), some reported that they believed it was possible to get the treatment at other hospitals in the UK or through particular clinicians who were offering 'trials'. One patient asked how it was possible to access treatment in Europe. We have explained that all medicines have to be considered for patient safety and that NICE need to carefully consider the evidence for how clinically effective a treatment is for patients – however as these callers have limited life expectancy it has resulted in a number of very difficult calls.

Selective internal radiation therapies (SIRT) are for a very limited number of patients. However, for some they are life extending and life changing. We are unable to differentiate between the different SIRT treatments as the patients were not aware of the specific type of SIRT they had been given. We feel the best way to explain the advantages are to tell the stories of some of the patients we have spoken to:

One patient we spoke to had contracted hepatitis C in 2005. Doctors believe he had had it (undiagnosed) since his teenage years. He was a CEO and is now 58. He was extremely fit and well and highly articulate. He has no idea how he originally contracted hepatitis C (he has never taken drugs). It took 11 years for him to clear the virus and as a result went into went

into the normal 'liver' system –having 2-3 ultrasounds per year at his hospital. In April 2017, he went for a scan and lesions were found on his liver. This was then confirmed via a CT scan. He was very shocked by the diagnosis. The tumour was 6-7cm.

He had TACE as a first treatment. He woke up feeling terrible and in immense pain. However, he fully expected TACE to work and then have to have a liver transplant. He never thought he wouldn't be 'well' again but the TACE results showed that the tumour was more aggressive and signs of vascular invasion. This was a really low point and he was really scared. He knew his chances were not good and felt he was in "last chance saloon". He was then offered SIRT as part of a trial. He felt this was his last chance to live. Tests showed he was deemed suitable for SIRT – he was told that if SIRT did not deliver a significant improvement then he probably had 6-9 months left to live. He had SIRT in July 2017 and CT scans after 6-12 weeks showed that he was a responder to the treatment. He felt fatigued but recovered reasonably swiftly. He had some small amount of pain. He was extremely fit prior to getting cancer and he feels his general fitness made it reasonably easy to get over the fatigue. He was back running after 3 weeks. He felt the recovery from TACE procedure was far worse and needed more painkillers.

He's a very positive individual. Some direct quotes from the interview with this person:

"SIRT literally saved my life. End of story" "What price do you put on 2 years" "I got a run of time I wouldn't have got"

"My daughter had come back from working in Singapore to be present when SIRT took place as she wanted to be around him. My relationship with her has just been fantastic – every moment is precious."

"After SIRT I felt like I had been jiggled about with and a tiny bit of pain but nothing like the same as after TACE or the liver resection surgery 'partial hepatectomy'.

"I felt like ~I've got a breather here – if I keep surviving I might get an option for another treatment. SIRT is not curative but it is life prolonging – I feel it may allow me to move into other cancer pathways."

Since speaking he has received further surgery.

Please explain any advantages described by patients or carers for the treatment(s) being appraised compared with other NHS treatments in England.

The patients who had experienced this treatment that contacted us reported relatively few side effects or that the dise effects had been well tolerated. One person said that the side effects for them when they had taken sorafenib had been "horrendous, literally nonstop diarrhoea which meant I couldn't leave the house" whereas by comparison SIRT had been relatively free of side effects "I felt tired and had a bit of tummy ache." Patients also reported that they felt it had given them a 'breathing space' so doctors could assess how aggressive the tumor was and allowed time for other treatments to be considered. Two patients reported

that for them it had been effective in downsizing their tumours – it enabled one patient that we spoke to to go on to the transplant list.

If you know of any differences in opinion between patients or carers about the benefits of the treatment(s) being appraised, please tell us about them.

The British Liver Trust does not provide specific medical advice (as we do not have access to patient medical records or history) but aims to empower patients to go back to clinicians with information so they can discuss their case. Our request for people to come forward (to support this submission) resulted in over 40 people contacting us. It was clear that patients are very unsure about different treatment options, what types of treatment may be appropriate and at what stage of their liver cancer journey these would be appropriate.

5. What do patients and/or carers consider to be the disadvantages of the treatment(s) being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Some people were aware that this treatment option is only relevant for a limited number of patients and some were aware that the level of cirrhosis was a factor in them not being eligible or that the cancer had “spread throughout the liver”. All of the patients that we spoke to were desperate and would give anything a chance if doctors felt that it could extend life.

Please list any concerns patients or carers have about current NHS treatments in England.

Lack of options and side effects are the most commonly reported concerns.

Please list any concerns patients or carers have about the treatment(s)

being appraised.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment(s) being appraised, please tell us about them.

6. Patient population

Are there any groups of patients who might benefit more from the treatment(s) than others? If so, please describe them and explain why.

We see this as a clinical decision to be made in a MDT setting. Our understanding is that good outcomes are predicted for patients with unresectable disease and a life expectancy of more than three months, Child Pugh of < 7 points who do not have signs of advanced liver disease or liver failure. It may offer particular benefit for patients where the lesions are difficult to reach and offer an option as a bridging treatment. It is an alternative to TACE and may offer a particular benefit for those who have failed TACE.

Are there any groups of patients who might benefit less from the treatment(s) than others? If so, please describe them and explain why.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment(s)?

☐ Yes x☐ No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment(s) as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in the assessment of the treatment(s) in clinical trials?

If already available in the NHS, are there any side effects associated with treatment(s) being appraised that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes ☐ No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

SIRT is an innovative treatment that will probably (if approved) only ve available in a limited number of centres. Patients understand this – however the referral pathways need to be clear for equality of access.

Are there groups of patients who would have difficulties using the treatment(s) being appraised or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

9. Other issues

Do you consider the treatment(s) being appraised to be innovative?

x Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition. (If this applies to more than one treatment that is being appraised, please give reasons for each one.)

An innovative targeted treatment that involves delivering millions of tiny radioactive 'beads' directly to the tumours.

Are there any other issues that you would like the Appraisal Committee to consider?

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- A diagnosis of liver cancer is devastating and the prognosis is very poor (average 5 year survival of 12 years)
- There are very few treatment options currently available
- For some of the patients we spoke to, receiving SIRT had prolonged their life and provided them with a real chance of survical
- Patients feel it is very 'unfair' that people in other parts of Europe and the USA have access to this treatment
- SIRT is only suitable for a relatively small number of patients

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NICE National Institute for Health and Care Excellence

Professional organisation submission

British Society of Interventional Radiology

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**British Society of Interventional Radiology (BSIR)**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? X a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**National charitable organisation representing UK Interventional Radiologists**
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or	SIRT for HCC can be used in different patient populations across the Barcelona Cancer Liver Cancer (BCLC) staging system. It can be used in early and intermediate stage HCC as an alternative to TACE with a view to prolong survival or downstage to curative therapies such as resection or transplantation.

disability.)	SIRT can be used in the advanced BCLC stages as an alternative to sorafenib with similar outcomes but better side effect profile to palliate those without metastatic disease and offer prolonged survival comparable to sorafenib.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	An objective treatment response is represented by a reduction in tumour size of the index lesion and/or hypervascularity as per mRECIST criteria.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	There is a clear unmet need in patients who are not good TACE candidates (lesion size ≥7cm) who have unilobar disease within the intermediate stage of BCLC. Our members have had excellent outcomes in this patient cohort and have successfully downstaged patients who are not appropriate for TACE within BCLC B to curative resection. (Mafeld et al. Liver resection after SIRT with Yttrium-90: safety and outcomes, J Gastrointest Cancer, 2019). Other patient groups may benefit including patients bridging to transplantation and in the advanced stage +/-with portal vein thrombosis. In the advanced stage, the improved side effect profile compared to systemic therapies is felt a valuable benefit of SIRT.
What is the expected place of the technology in current practice?	

9. How is the condition currently treated in the NHS?	Early stage bridging therapies are treated with ablation and TACE. Intermediate HCC is treated with TACE. Advanced stage HCC is treated with systemic therapies such as Sorafenib.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	BCLC
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The BCLC is an evidenced based guideline used to inform HCC treatments. It is widely used throughout the world. Other guidelines exist but in the UK the BCLC is widely used.
• What impact would the technology have on the current pathway of care?	SIRT would be a valuable addition in the treatment of HCC. It can be used as a bridge to transplant (BCLC A), as a treatment in BCLC B, particularly in cases not ideally suited to TACE (due to index lesion size ≥7 cm) and in cases of failed TACE in unilobar disease, and in the advanced setting in patients with portal vein thrombosis, where TACE is contraindicated, and/or as an alternative to systemic therapies with an improved side effect profile.
10. Will the technology be used (or is it already used) in	The technology has already been used and continues to be used in NHS clinical practice in appropriate

the same way as current care in NHS clinical practice?	cases in some institutions, although practice is limited due to lack of funding.
• How does healthcare resource use differ between the technology and current care?	Current care is TACE and sorafenib. SIRT would be delivered by the existing liver directed therapy MDT using this technology in place of TACE and/or systemic therapy.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	SIRT should be limited to selected tertiary centres with experience in SIRT and appropriate facilities as per the metastatic colorectal (mCRC) SIRT commissioning policy.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The clinical experience and facilities to provide SIRT in tertiary centres across the UK are already established. There are ten centres in England that are commissioned to provide SIRT for mCRC in England.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	We expect SIRT to provide clear benefits, particularly in unilobar, large volume disease seen in BCLC B intermediate stage that is too large for TACE (≥7 cm). In this group we expect patients to have prolonged survival compared to TACE and systemic therapy (systemic therapy is often given to this group due to treatment stage migration). A much higher proportion of this group is expected to be downstaged to curative resection than with alternative treatments.

• Do you expect the technology to increase length of life more than current care?	Yes in the group noted above in 11.
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. SIRT is better tolerated than cTACE and sorafenib. (Salem et al. Institutional decision to adopt Y90 as primary treatment for HCC informed by a 1,000-patient 15-year experience, Hepatology 2017).
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The group noted in point 11. This particularly applies to those without evidence of chronic liver disease who have a great potential to be downstaged to curative resection. SIRT has been shown to facilitate resection in the unilobar disease group as it treats the tumour in the diseased lobe whilst promoting growth in the untreated lobe (future liver remnant FLR), and embeds a biological test of time, thus facilitating the option of curative resection.
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical	SIRT is a two stage procedure. The first stage (work up) is performed to assess suitability and the second stage (treatment) is when the Y90 microspheres are delivered. It can be carried out as two day case procedures (or one overnight stay post SIRT) separated by ten days to two weeks. It has been shown to be better tolerated than TACE and sorafenib.

implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	It is important that the economic modelling incorporates SIRT as a potentially curative treatment in the intermediate stage. Patients who are downstaged to resection or transplant will have the greatest impact on the QALY calculation.

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The technology is much more likely to provide a curative outcome in a subgroup of patients than current available therapies and it is better tolerated than TACE and sorafenib. This technology is capable of delivering substantial health-related benefits for BCLC B and some BCLC C (PVT) patients who are without a potentially curative option.
• Is the technology a 'step-change' in the management of the condition?	In the patients with large volume unilobar disease (particularly those without cirrhosis and with good liver function) who are inherently poor TACE candidates, SIRT has great potential to induce excellent clinical responses, prolong life, bridge or downstage to transplant or resection.
• Does the use of the technology address any particular unmet need of the patient population?	In the subgroup noted above. PATIENT SELECTION Radiation lobectomy applies to Child-Pugh A patients who would otherwise be resected but: a) have inadequate future liver remnant (FLR); and/or b) embedded test-of-time is desired for tumour biology; and/or

	c) need the treated tumour to be retracted away from hepatic vein and/or IVC d) demonstrating tumour response prior to surgery is preferable. 2. Patients should be considered potentially operable candidates without comorbidities that would preclude surgery.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The most common side effect is fatigue. The side effect profile is better than alternative treatments such as cTACE and sorafenib. REILD (Radio Embolisation Induced Liver Disease) is significantly reduced by patient selection, appropriate treatment (avoiding whole liver treatments) and personalised dosimetry.
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	No. The patient cohort noted above are not represented in the clinical trials that focus on direct comparison with sorafenib in the advanced stage or as a direct comparator to TACE in BCLC A/B.
• If not, how could the results be extrapolated to the UK setting?	Key findings from SARAH and SIRvenIB: • no significant improvement in overall survival (primary endpoint not met) • significantly better-tolerated treatment • significantly reduced frequency and severity of side effects

	• significantly better quality of life • significantly improved PFS and TTP in the SIRveNIB study (overall and in the liver; treated population) These studies are in advanced stage disease and showed benefit over sorafenib in the palliative setting. Awaiting publication of STOP HCC.
• What, in your view, are the most important outcomes, and were they measured in the trials?	The most important outcomes are objective response and time to progression, as this is a local regional therapy. The greatest gains in overall survival are achievable when SIRT is used as a bridge to transplant, downstage to transplant/resection, and in PVT patients who have a poor prognosis and limited treatment options.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Objective response rate and time to progression will translate to overall survival benefit in correctly selected patients with personalised dosimetry as demonstrated in the DOSISPHERE study and post SARAH analysis when tumours received >100 Gy.
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No. The treatment is better tolerated than existing therapies.
19. Are you aware of any	Dosimetry for SIRT is increasingly recognised as vital for optimal responses. Early data from the

relevant evidence that might not be found by a systematic review of the trial evidence?	DOSISPHERE clinical RCT demonstrates excellent objective response rates in HCC when tumour dose >205 Gy. Patient selection in this study was also important, treating patients with an index lesion ≥7 cm. Overall survival data is expected to be presented at ASCO GI.
20. Are you aware of any new evidence for the comparator treatment(s) (if applicable) since the publication of NICE technology appraisal guidance?	No.
21. How do data on real-world experience compare with the trial data?	Patient selection, technology, personalised dosimetry and procedural technique have advanced significantly since the design of the RCTs mentioned above. In selected patients, SIRT is able to deliver great benefit and this is represented in real-world clinical experience, which is widely reported. This has been difficult to demonstrate in trial settings due to the challenges in delivering RCTs with a complex medical device. As outlined above, the UK experience, which is limited in the absence of funding, is that SIRT can be used successfully as a curative intent strategy and it is better tolerated in patients in the palliative setting.
Equality	

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No.
22b. Consider whether these issues are different from issues with current care and why.	Not applicable.
Key messages	

23. In up to 5 bullet points, please summarise the key messages of your submission.

1. SIRT offers great potential to extend life as a bridge to transplant and to facilitate curative resection in the unilobar large volume disease group that are not good TACE candidates (tumour size ≥7 cm, particularly in patients with good liver function).
2. SIRT treats the tumour and facilitates growth of the contralateral untreated liver that facilitates resection (radiation lobectomy). This is not seen with other catheter directed therapies such as TACE and is not seen with systemic therapies.
3. SIRT is better tolerated that cTACE in the intermediate stage and sorafenib in the advanced stage.
4. SIRT is an effective local regional therapy for patients with portal vein thrombosis and can enable resection in this group.
5. SIRT is most commonly a single treatment (compared with the potential for multiple treatments with TACE and systemic therapy).

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276]

Thank you for agreeing to give us a statement on your view of the technologies and the way they should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technologies within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:
Teik Choon SEE

Name of your organisation
Cambridge University Hospitals NHS Foundation Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technologies (e.g. involved in clinical trials for the technologies)? Yes
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technologies? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? Consultant Interventional Radiologist and Clinical Director in Imaging
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: No

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

What is the expected place of the technologies in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technologies, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technologies?

In what setting should/could the technologies be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technologies are already available, is there variation in how they are being used in the NHS? Are they always used within their respective licensed indications? If not, under what circumstances does this occur? Are 'work-up' procedures used? If so, how do they influence subsequent treatment?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Current treatment of HCC

Currently HCC is managed by multidisciplinary team in the NHS including hepatologists, transplant and liver surgeons, oncologists, interventional and diagnostic radiologists, palliative care specialists, and specialist nurses. Treatment options include transplantation, resection, loco-regional therapies (such as ablative techniques, transarterial chemo-embolisation or embolization – TACE/TAE), sorafenib or immune mediated approaches, and best supportive care. Another option not commonly used but also being explored is stereotactic body radiotherapy.

Transplant and surgical resection is only available in transplant and major HPB centre. Loco-regional therapies are increasingly being used in centres that do not offer transplant or resection. These centres tend to have network link with specialist centres and overall the management algorithm tend to be similar. However, some variations may exist in terms of what factors or criteria used for resection and those suitable for loco-regional treatments. This may be attributable to experience, local expertise and support, and resource. There are also variations in terms of availability of technologies e.g. radiofrequency vs microwave, regime of chemoembolization or embolisation, imaging and follow up strategies.

As SIRT is currently not funded, treatment is only available under clinical trials, self or insurance funded category, or on compassionate ground by the industry. As a result, SIRT treatment is generally only be considered after unsuccessful loco-regional

therapies. If funding cannot be secured, patient will usually be considered for sorafenib. There is no direct 'alternative' treatment therapy available as SIRT is a completely different treatment therapy compared to those available. The advantages and disadvantages of other therapies are well recognised.

Patient subgroup

The prognosis of HCC patients are well described by the BCLC classification. For intermediate stage (B) HCC, treatment involves the use of TACE/TAE. This group of patients may be considered for SIRT. SIRT may also be considered in those patients that failed to respond to TACE/TAE, or those with BCLC with extensive bilobar disease. Patients with portal vein thrombosis not suitable for TACE/TAE may be a candidate for SIRT. There is a potential role of SIRT in downstaging. Ongoing research and evidence is required to fully establish its specific role.

Setting

The use of SIRT should be in a secondary or tertiary centre which comprises the full multidisciplinary team. The interventional radiology team that performs the procedure should have current provision for other loco-regional therapies including TACE/TAE. The department should also have a radiopharmacy unit with ARSAC licence holder. Specialist nurses are integral in patient care particularly for liaison in the community.

The technology

The technology is already available. The two commonly used yttrium-90 microspheres in the NHS are made from resin (Sir-spheres) or glass (Thera-spheres). Holmium-166 (Quirem-spheres) is a third product that are relatively new. It uses a different radioisotope and currently not being used in the NHS.

The use of SIRT in HCC tends to follow the criteria set up by the clinical trials and in general are being used in their licenced indications. Work up procedure is mandatory to assess, plan and prepare the patient for SIRT including dosimetry. If the work up identify that the disease is far too extensive, or with significant pulmonary shunt, or aberrant vasculature not amenable for correction, this will preclude safe treatment with SIRT.

Clinical Guidelines

https://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Hepatocellular-Carcinoma

https://www.esmo.org/Guidelines/Gastrointestinal-Cancers/Hepatocellular-Carcinoma/eUpdate-Treatment-Algorithms

https://www.journal-of-hepatology.eu/article/S0168-8278(18)30215-0/pdf

The British Society of Gastroenterology guideline on HCC was published in 2002.

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Multiple Technology Appraisal (MTA)

The advantages and disadvantages of the technologies

NICE is particularly interested in your views on how the technologies, when they become available, will compare with current alternatives used in the UK. Will the technologies be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technologies; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technologies, please comment on whether the use of the technologies under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The technology

The technology (SIR-speheres and Thera-spheres) is currently available in the UK. Those centres that provide the treatment are those that already are providing SIRT for colorectal liver metastasis patients. The technique is essentially the same, although the selection criteria are different due to different disease conditions.

Patient selection should be based the current available evidence and clinical guidelines as outlined above. Pre-procedure work up is mandatory and the unit should also have a radiopharmacy department and ARSAC licence holder.

SIRT in HCC trials:

SARAH (sorafenib vs. radioembolization in advanced hepatocellular carcinoma

SORAMIC (compare the efficacy and safety of combining liver-directed SIRT and sorafenib with using sorafenib alone)

SIRveNIB (Selective Internal Radiation Therapy Versus Sorafenib in Asia-Pacific Patients With Hepatocellular Carcinoma.)

Safety profile, Overall Survival and Progression Free Survival were documented.

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Overall survival did not significantly differ. The SORAMIC trial did observe a survival benefit in younger patients, those with a non-alcoholic aetiology of the cirrhosis, and those with no cirrhosis at all.

Quality of life and improved toxicity may inform treatment choice.

Side effects

Apart from post-embolisation syndrome which is also common in TACE/TAE, specific side effects from SIRT may include non-target radio-isotope delivery to other organs such as stomach, small bowel and gall bladder causing inflammation and ulceration. There is also potential pneumonitis due to shunting into the lungs. Radiation induced liver disease is also recognised.

Compared to sorafenib, SIRT is generally better tolerated as evidenced from the trials. Management of side effects is symptomatic although careful planning, dosimetry and delivery are key to prevention.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;

- Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technologies are unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within

3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on these technologies affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

As mentioned the technology is already available in the UK and in particular SIRT is now available in the NHS for colorectal liver mets treatment. The facilities, equipment, staff training and other resources are transferable for SIRT in HCC.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

NICE National Institute for Health and Care Excellence

Multiple Technology Appraisal (MTA)

Patient expert statement

Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma [ID1276]

Thank you for agreeing to give us your views on these technologies and their possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Mark Thornberry**

2. Are you (please tick all that apply):	**X** a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	British Liver Trust
4. Did your nominating organisation submit a submission?	**X** yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**X** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	**X** I have personal experience of the condition I was first diagnosed with Hepatocellular Carcinoma (HCC) at the end of April 2017. There was diffuse tumour in the right lobe of the liver associated with infiltration into the regional portal vein branch. I also have cirrhosis (first diagnosed in September 2005). **X** I have personal experience of the technologies being appraised Following diagnosis I underwent TACE (transarterial chemoembolization) as initial treatment for HCC with Doxorubicin beads. There was a suboptimal response with tumour growth and increased infiltration. I was subsequently advised that SIRT was a further treatment option. However, I would require a 'significant' treatment response to turn round a 6-9 months overall survival prognosis. I did receive an'excellent' treatment response, both radiologically and in terms of the AFP profile. ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:

Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	HCC is a condition that unless 'caught' early, does not provide curative outcomes for patients. Having had a number of loco-regional interventions/treatments with no long term survival in view, life effectively revolves around one's next scan. Patients have different coping strategies for these 'time blocks'. For me, it is trail running/hiking and a large focus on fundraising. This has become more difficult after a hepatectomy and three months post resection, imaging showed evidence for recurrent HCC with peritoneal disease. The challenge is to stay positive and keep out of what I call the 'Dark Rooms'. It is not easy and has got harder with a secondary cancer diagnosis. My 'carer' is my wife. She finds it incredibly difficult mentally to rationalise that my overall survival is limited/indeterminate…especially when compared to cancers such as breast cancer, where survival rates are on the whole far more superior than HCC.
Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	From my perspective, HCC is one of the poorer relations of the cancer family. Its relationship with cirrhosis adds treatment complexity…and the involvement of a surrogate bio-marker AFP, (where approximately 40% of patients do not correlate) is still far from satisfactory. Treatment is generally non-curative and there is a high incidence of recurrence. Therapeutic choices are extremely limited, especially for Stage 4 patients. For example, it took 11 years after the first, first line systemic drug (Sorafenib) to be joined by another (Lenvatinib)
10. Is there an unmet need for patients with this condition?	Without doubt. See above (9). Whilst there are more Clinical Trials addressing late stage HCC, to the layman's eye these possible treatments can take a a long time to come to market. Immunotherapy, which has been described as the next breakthrough treatment type, which in my experience attracts the most interest for patients, has proven successful in a monotherapy setting (e.g.as evidenced by some types of lung cancer) whereby this approach has proven non-superior for HCC. Combination therapies are being researched and trialled. As a side bar, with my HCC metastasising to the peritoneal cavity I commenced systemic combination therapy in May 2019. This is with Lenvatinib plus or either Pembrolizumab or Placebo.

Advantages of the technologies	
11. What do patients or carers think are the advantages of the technologies?	To my view, SIRT was a game changer. It undoubtedly extended my life. As a treatment type it has proven to be non-invasive, with limited and very tolerable side effects. I was fit enough to start running 2-3 weeks after hospital discharge. Six weeks later I ran nearly 150 miles along the Grand Union Canal from Birmingham to London. TACE on the other hand was very painful immediately post-procedure and in the weeks before SIRT.
Disadvantages of the technologies	
12. What do patients or carers think are the disadvantages of the technologies?	None
Patient population	
13. Are there any groups of patients who might benefit more or less from the technologies than others? If so, please describe them and explain why.	Not qualified to answer given the 'personal' nature of each patient's HCC.

Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technologies?	Not that I am aware of.
Other issues	
15. Are there any other issues that you would like the committee to consider?	My understanding is that SIRT has been used as a bridging treatment, particularly for surgery. SIRT has similarly been a 'time-buyer' for me. My over-riding thought, given a non-curative prognosis, is to kick the ball ahead'. The rate of change in new treatment possibilities is accelerating; I am physically and emotionally invested in the potential benefits that may accrue. Any treatment that can help provide more time is fundamental to making this happen.
Key messages	
16. In up to 5 bullet points, please summarise the key messages of your statement: • SIRT can be a highly tolerated treatment • Post procedure time to 'normality' is short • Provides the patient with a strong 'chance' for reasonable longevity – the 'kick the ball ahead' factor • HCC is an underfunded and underprovided (treatment wise) form of cancer • There is a growing and accelerating range of treatments coming to market	

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

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