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

Assessment Report

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

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Declared competing interests of the authors

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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.

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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

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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

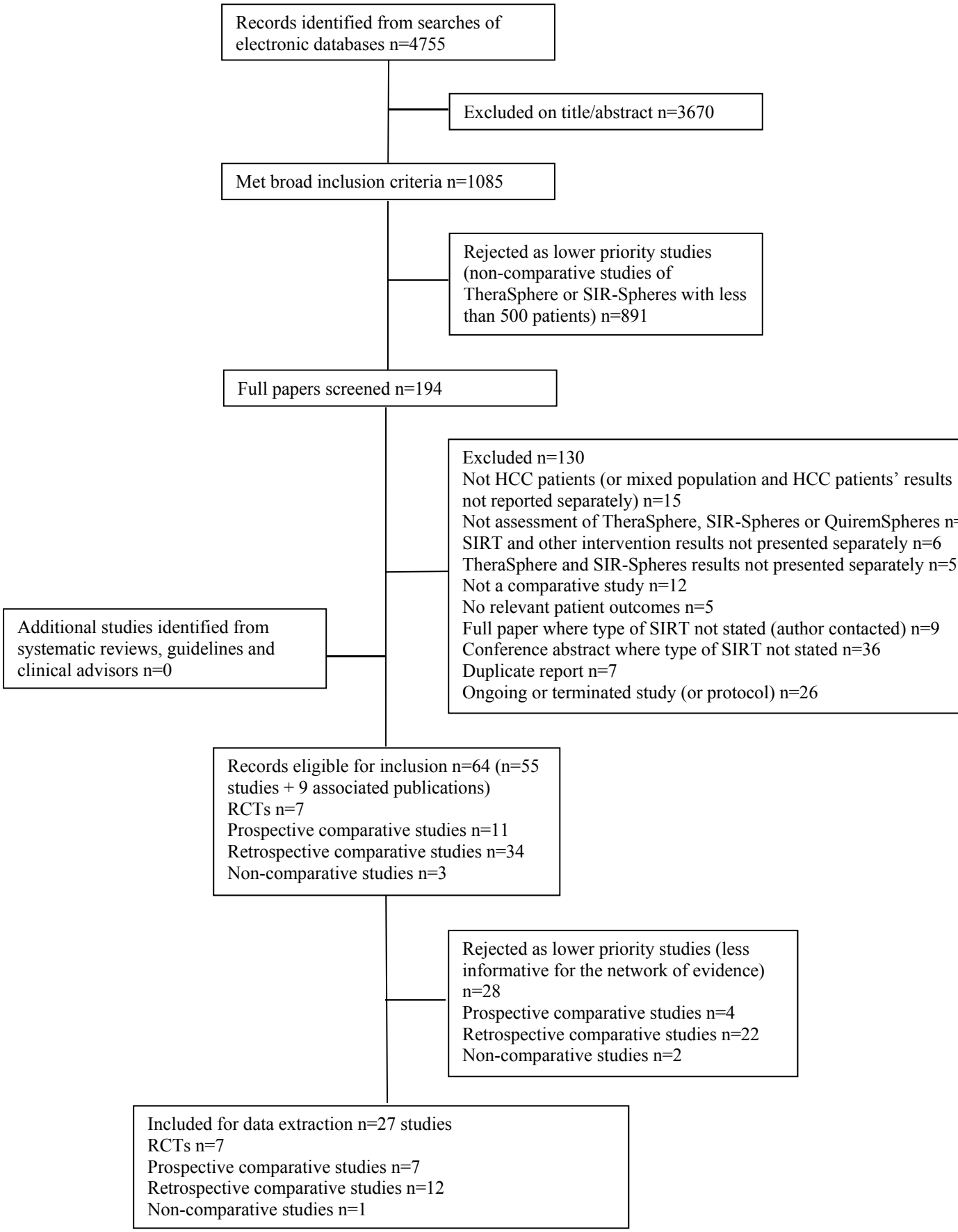


Table 3: Studies included in the systematic review of clinical effectiveness or considered for the network meta-analysis (n=27)

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

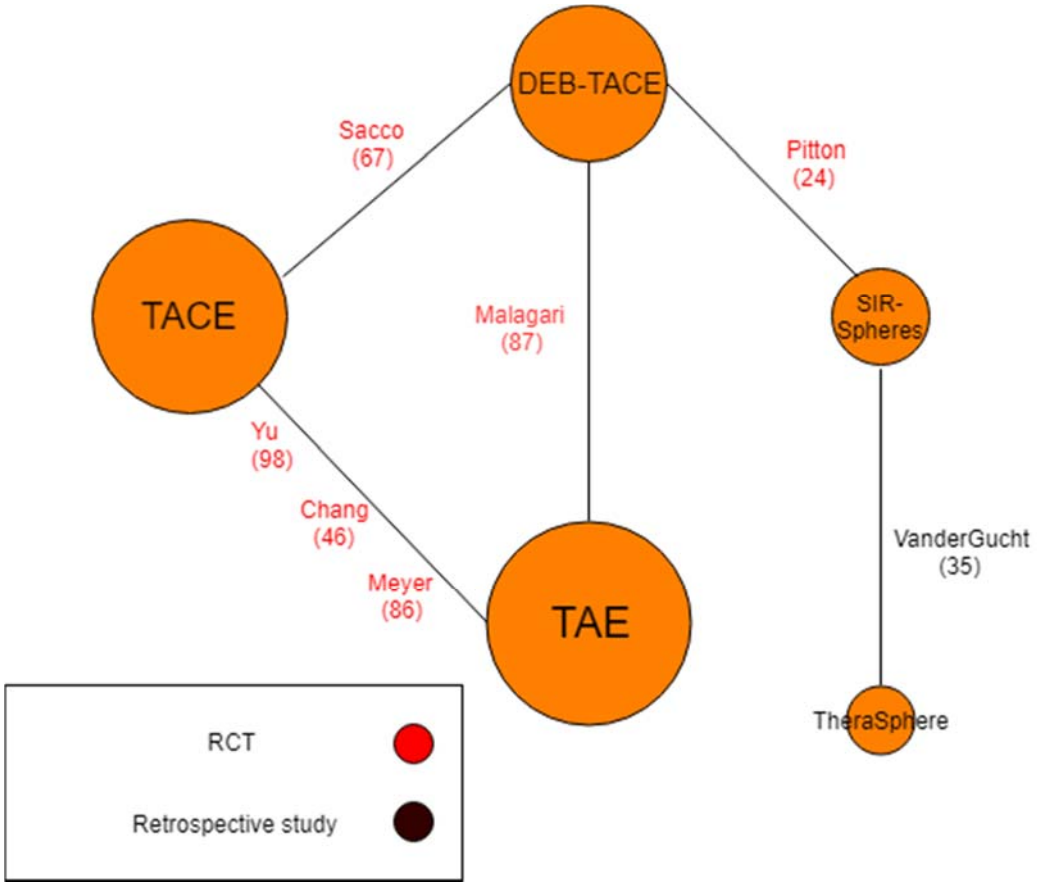


Table 8: Network 2: Adults with unresectable HCC who are eligible for conventional transarterial therapies

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.

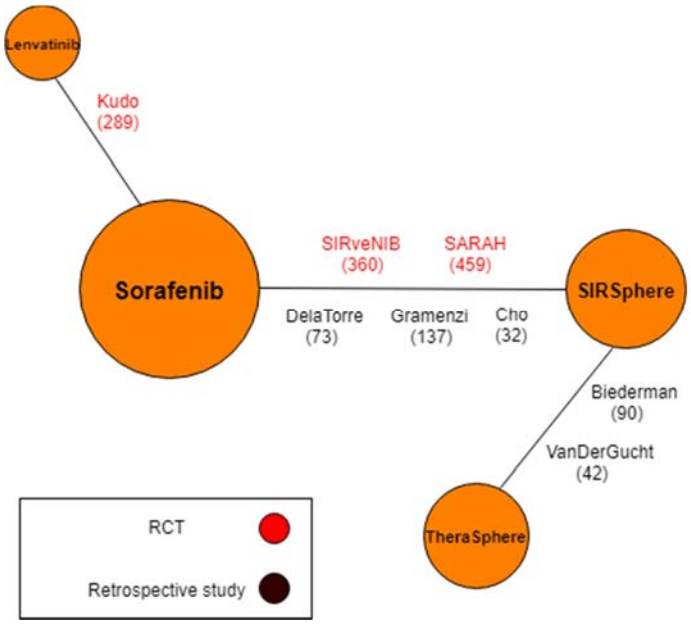
First author/study name	N	Intervention	Comparator	Study Design	Reason for inclusion/exclusion
Biederman, 2015[20]	97	SIR-Spheres	TheraSphere	Retrospective comparative	Patients with unresectable, advanced stage HCC with PVT, poor candidates for TACE.
D'Abadie, 2018[21]	45	SIR-Spheres	TheraSphere	Retrospective 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

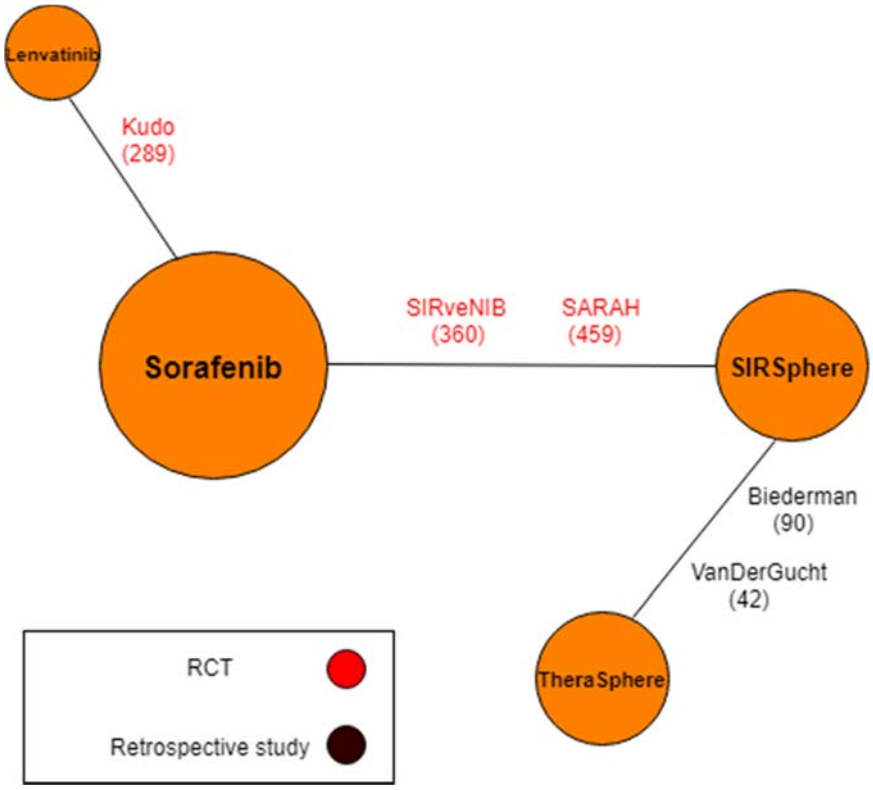


Figure 5: Flow diagram of the study selection process for the network meta-analysis of adults ineligible for conventional transarterial therapies

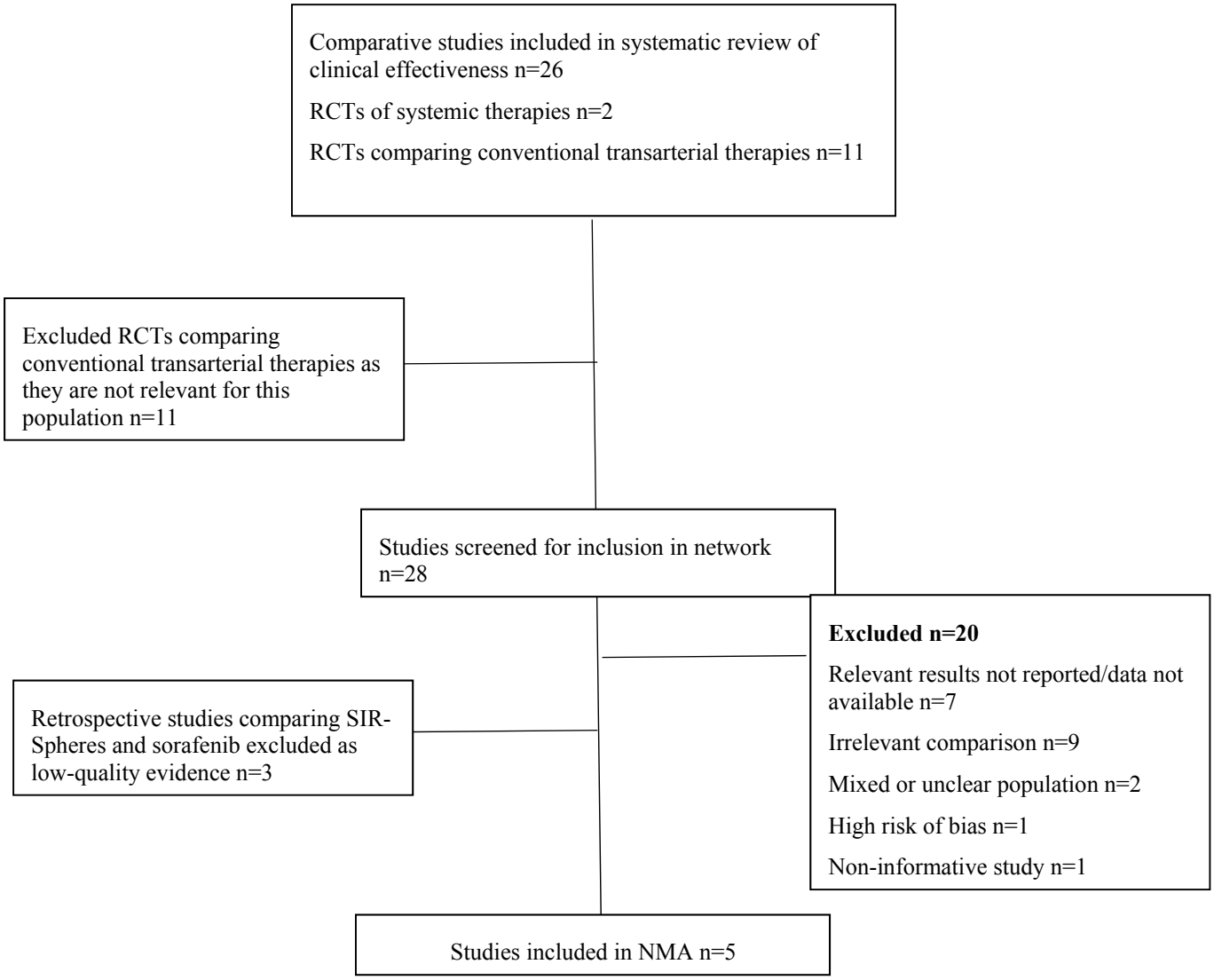


Table 9: Network 3: Adults with unresectable HCC who are ineligible for conventional transarterial therapies

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

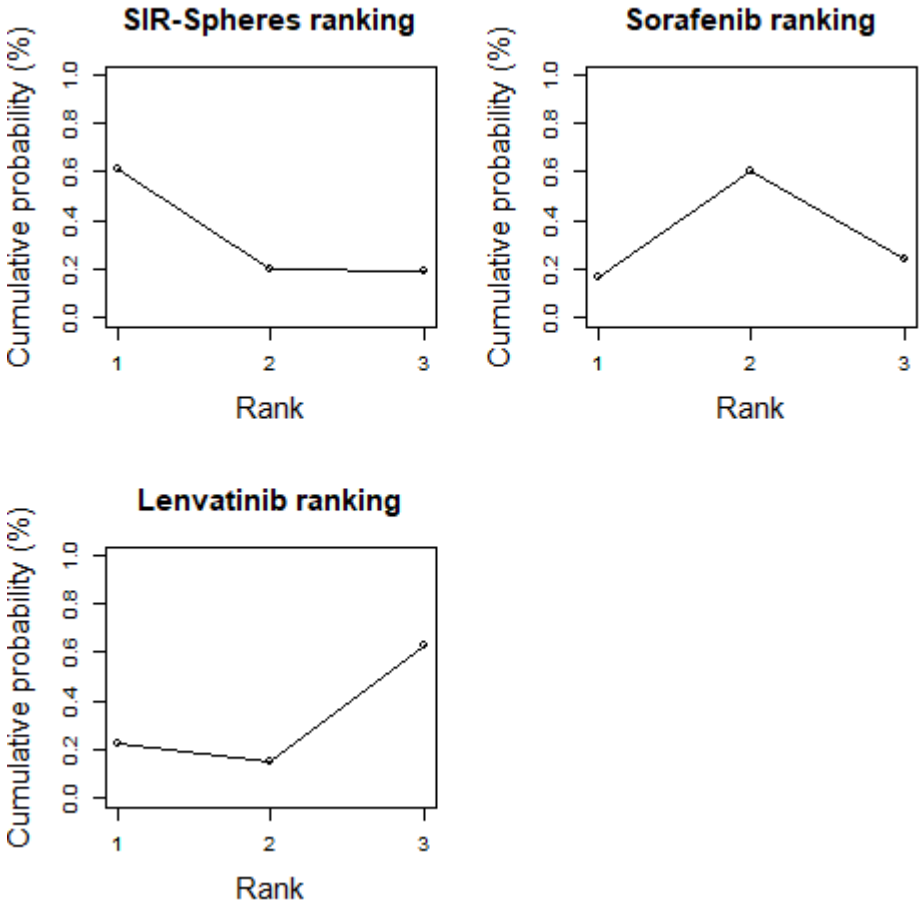
CrI: credible interval, SD: standard deviation, DIC: deviance information criterion, pD: number of parameters

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.

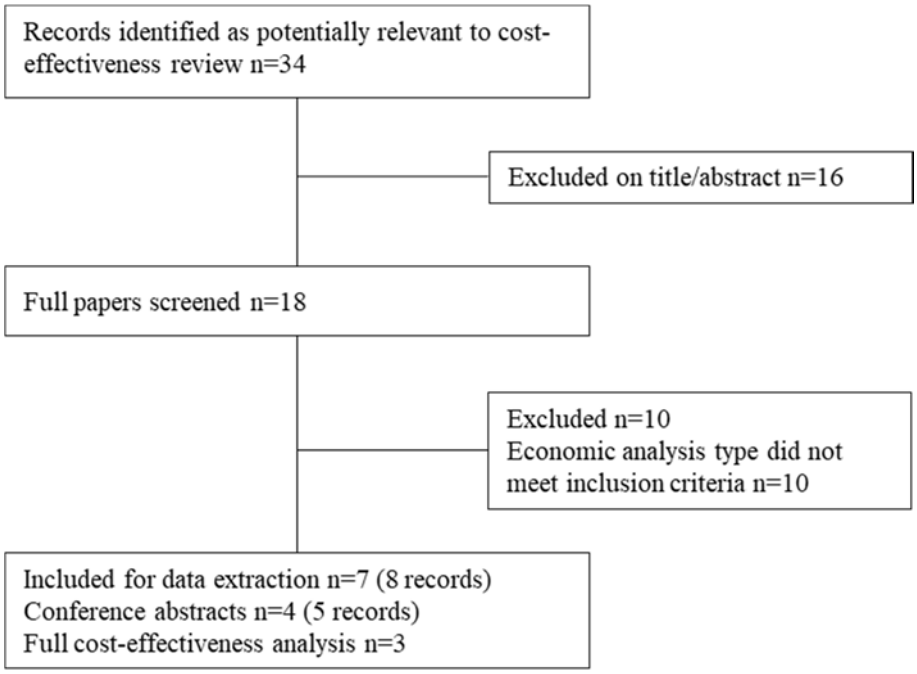
Study selection was conducted in two stages: (i) titles and abstracts identified by the search strategy were examined and screened as part of the clinical effectiveness review for any study potentially relevant to the cost-effectiveness review, (ii) full texts were then obtained and screened for inclusion. 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)

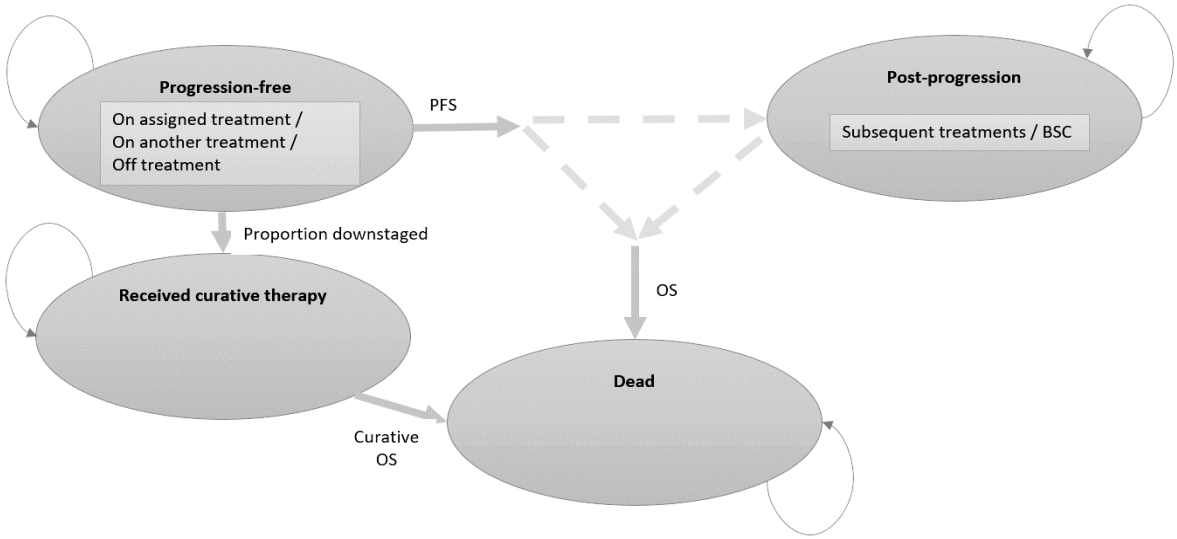
Model Component	Description
Population	The patient population that is the focus of the cost-effectiveness analysis includes patients matching the following criteria: • Patients with unresectable intermediate (BCLC stage B) or advanced (BCLC stage C) HCC, • for whom any transarterial embolisation therapies (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.

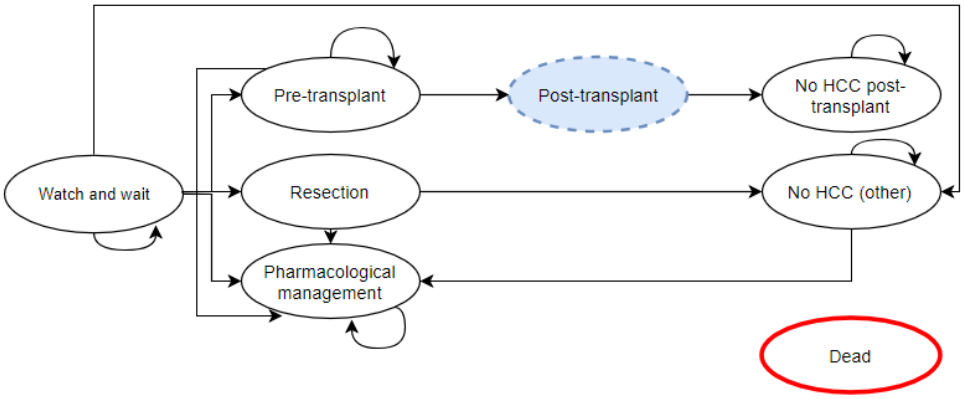
Table 23: BTG model scope (CTT-eligible population)

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

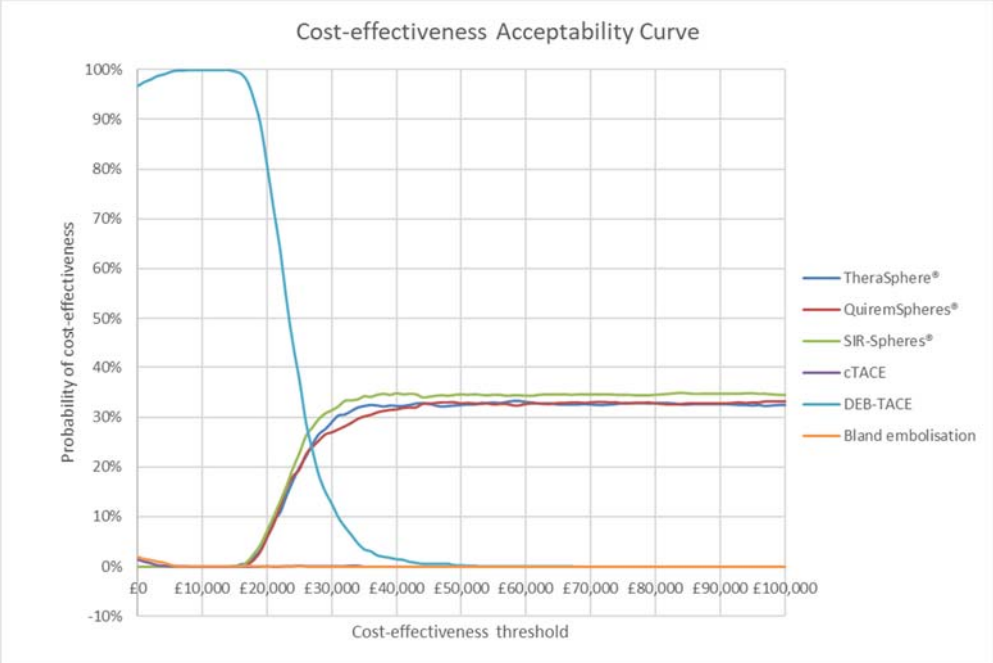
TACE	£43,488	1.393	£4,053	0.000	Dominated
TheraSphere	£57,338	2.119	£17,903	0.726	£24,647
QuiremSpheres	£57,361	2.119	£17,925	0.726	£24,647
SIR-Spheres	£57,361	2.119	£17,925	0.726	£24,647

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)

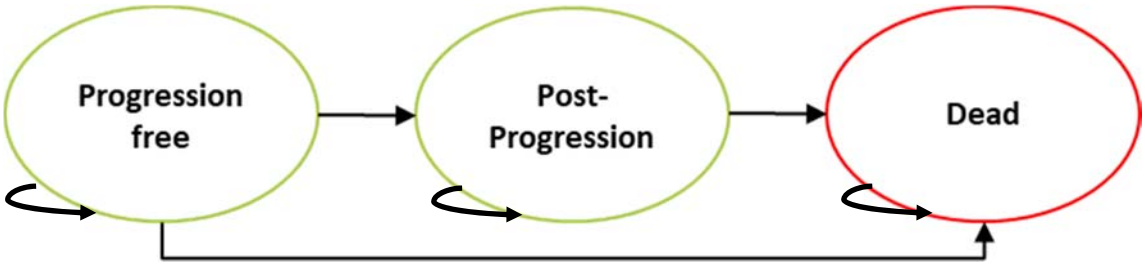
Model Component	Description
Population	The patient population that is the focus of the cost-effectiveness analysis includes patients matching the following criteria: • People with latter stage disease who are ineligible to receive CTT.
Intervention	Selective internal radiation therapies (SIRT): • TheraSphere • 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.

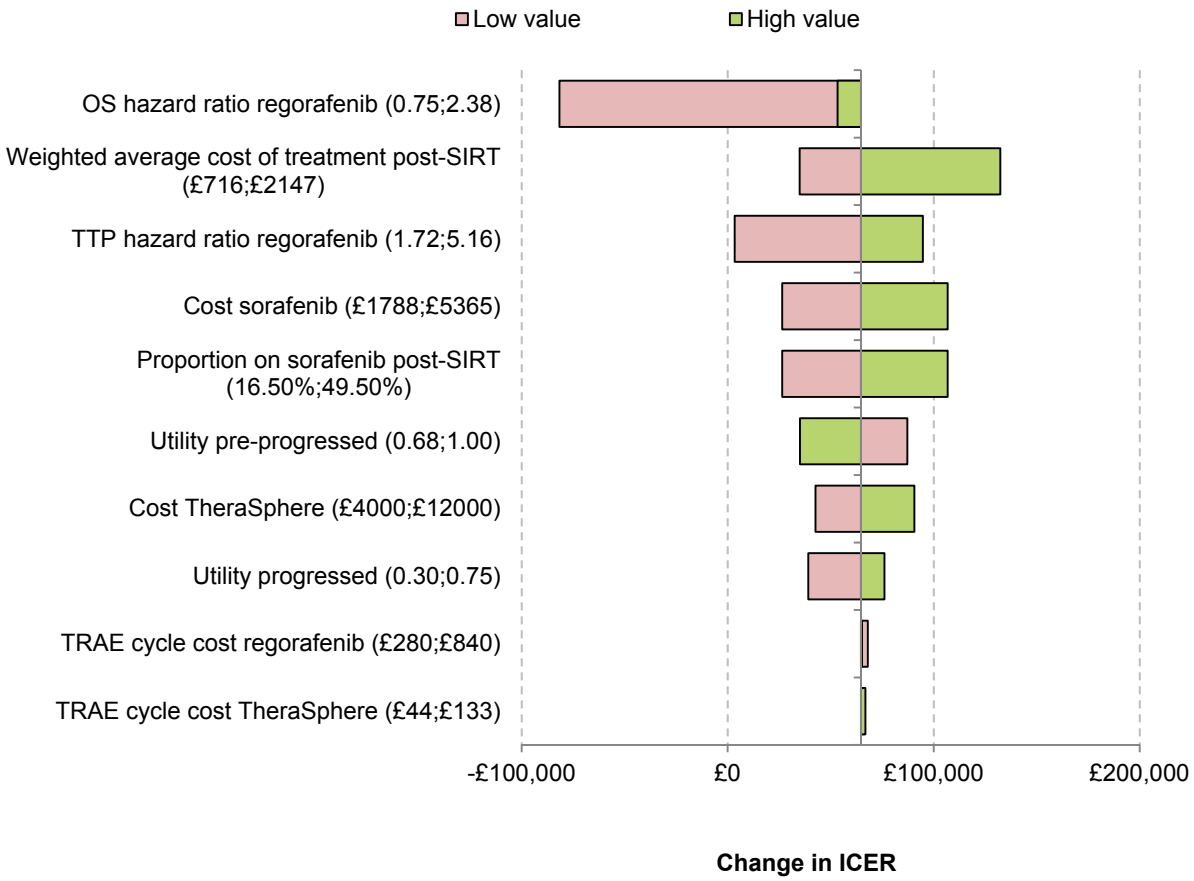
The estimated ICER for TheraSphere compared with regorafenib was £69,070 per QALY and estimated that TheraSphere generates an additional 0.185 QALYs at an additional cost of £12,778. The deterministic version of the model produces similar results with an ICER relative to regorafenib of £66,624 per QALY.

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

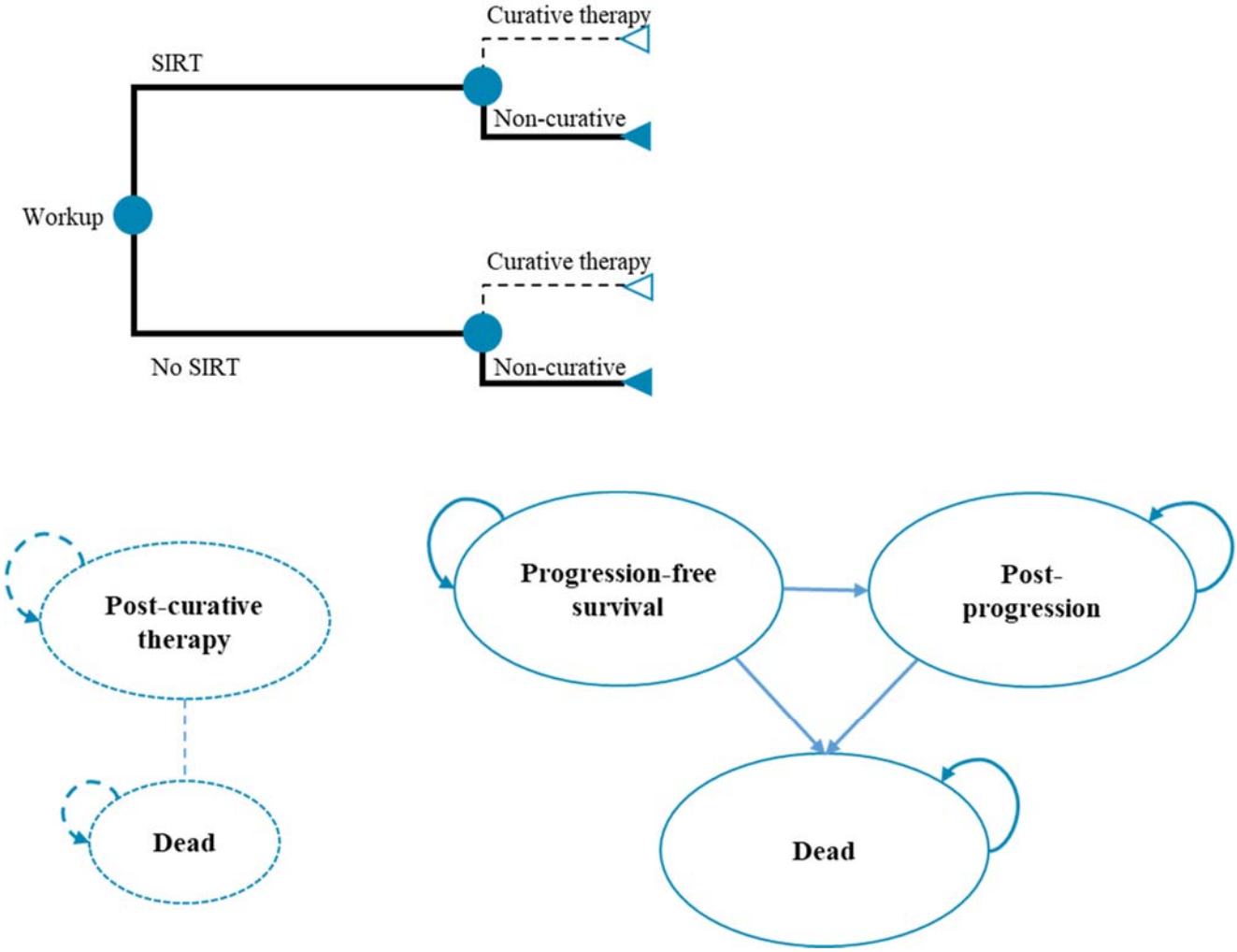
The structure of the AG model is presented in Figure 14. The AG model consists of a three-state partitioned survival model and decision tree for those intended to receive SIRT. Also presented is the structure of the downstaging scenario (see dashed lines), for whom the outcomes of patients successfully 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

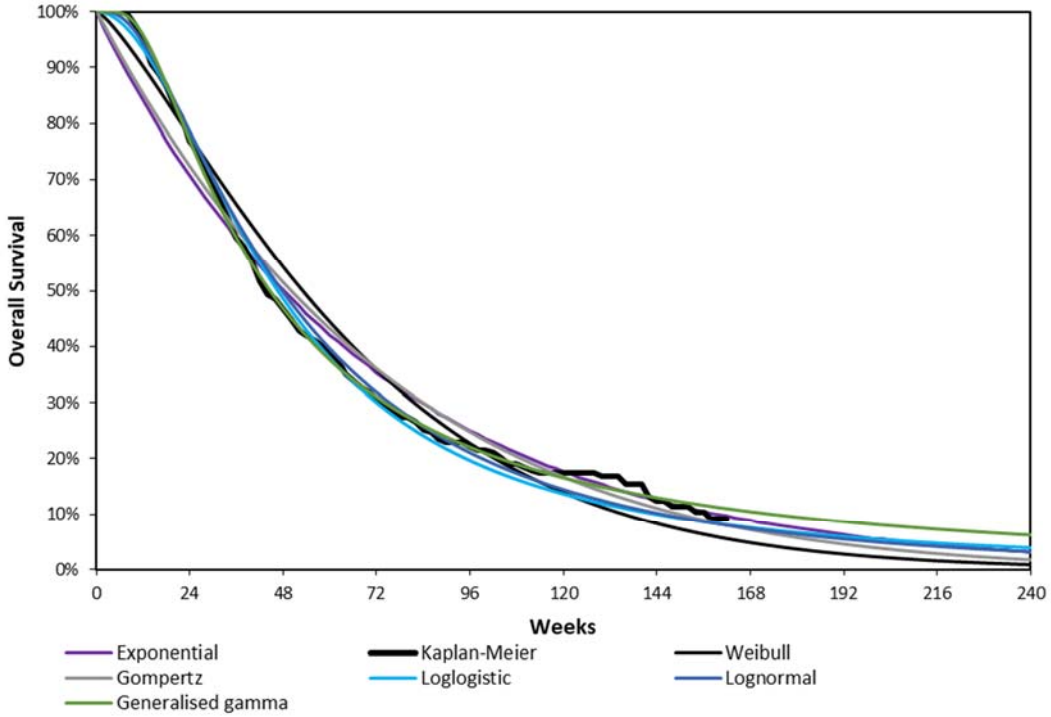
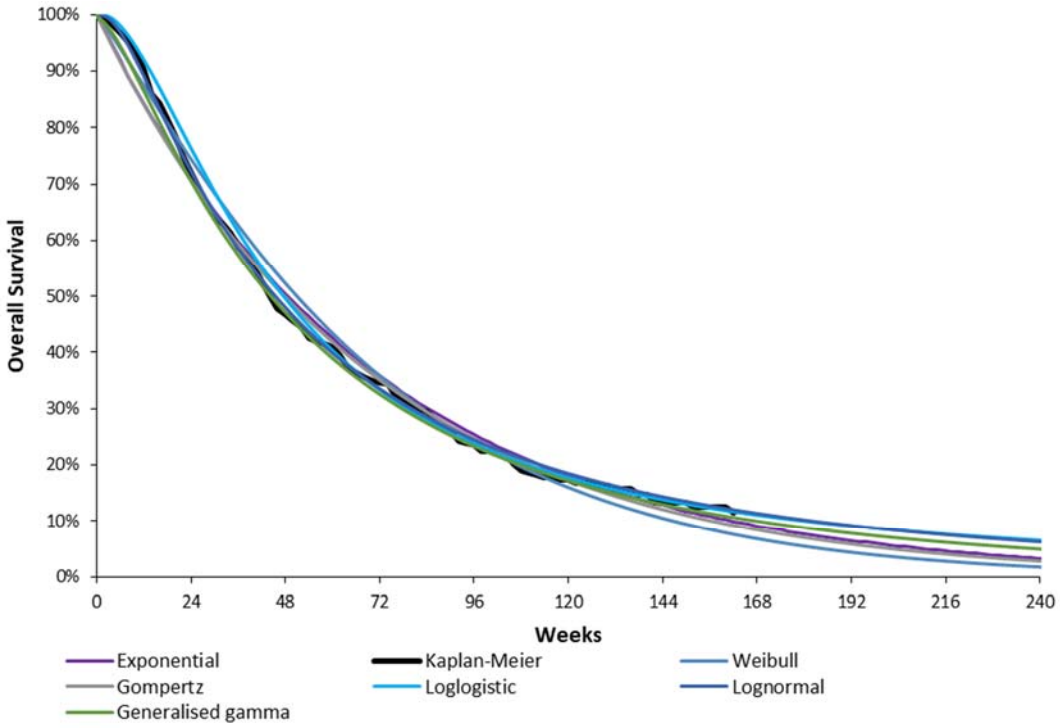


Figure 16: Extrapolation of OS Sorafenib



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

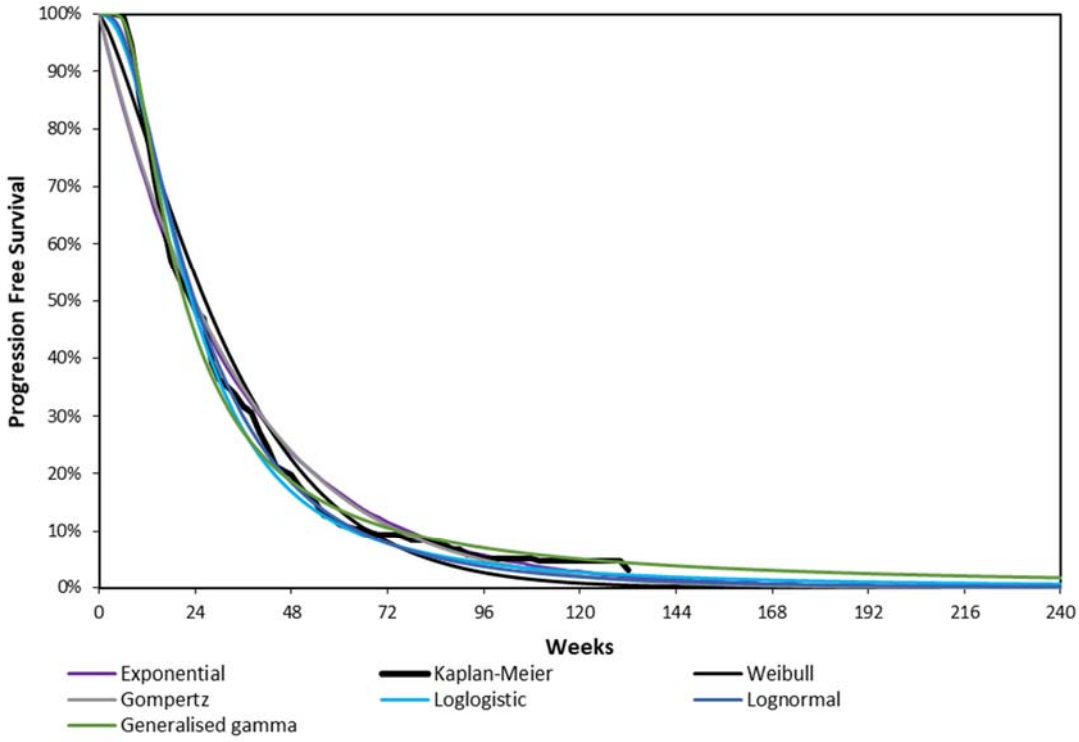
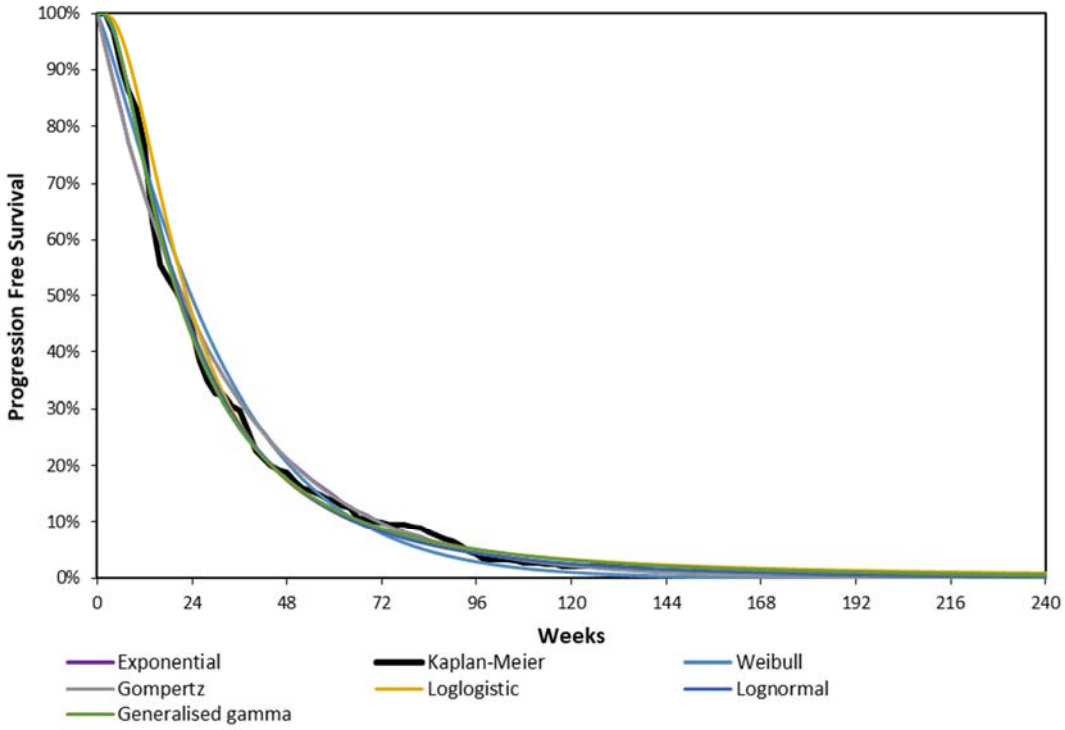


Figure 18: Extrapolation of PFS Sorafenib



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 £5,178.32 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	£5,178.32	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.

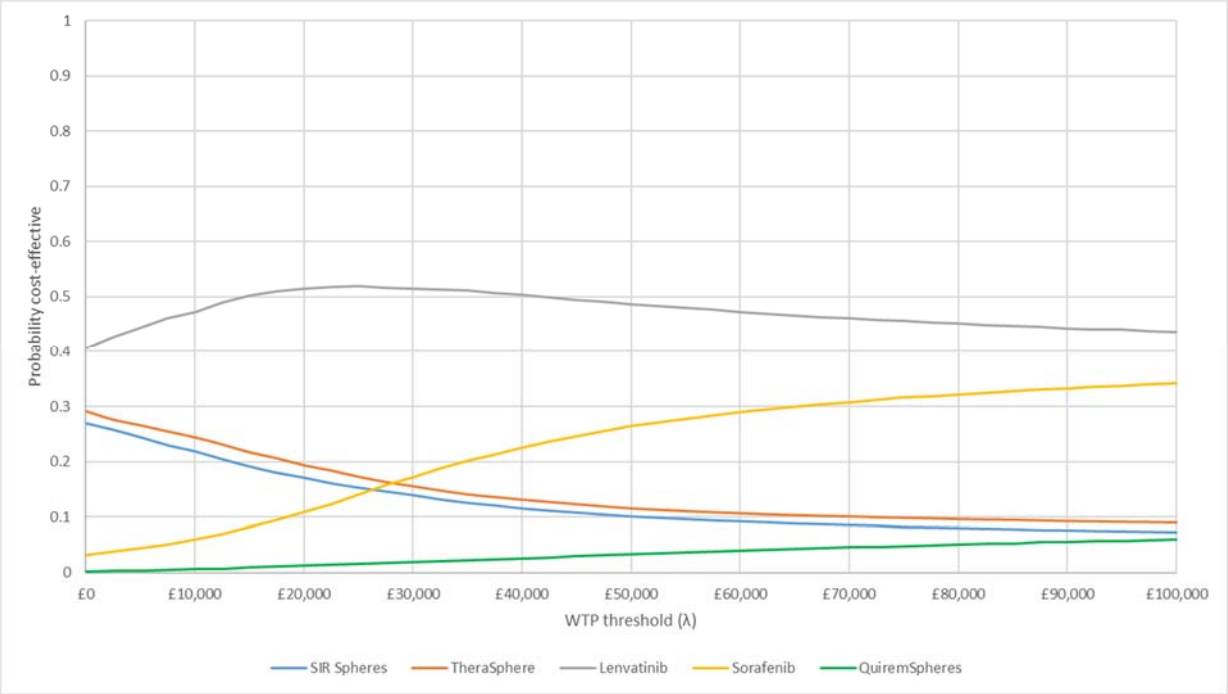
For results including the confidential PAS discounts for sorafenib, lenvatinib, regorafenib, and QuiremSpheres, the confidential appendix.

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.

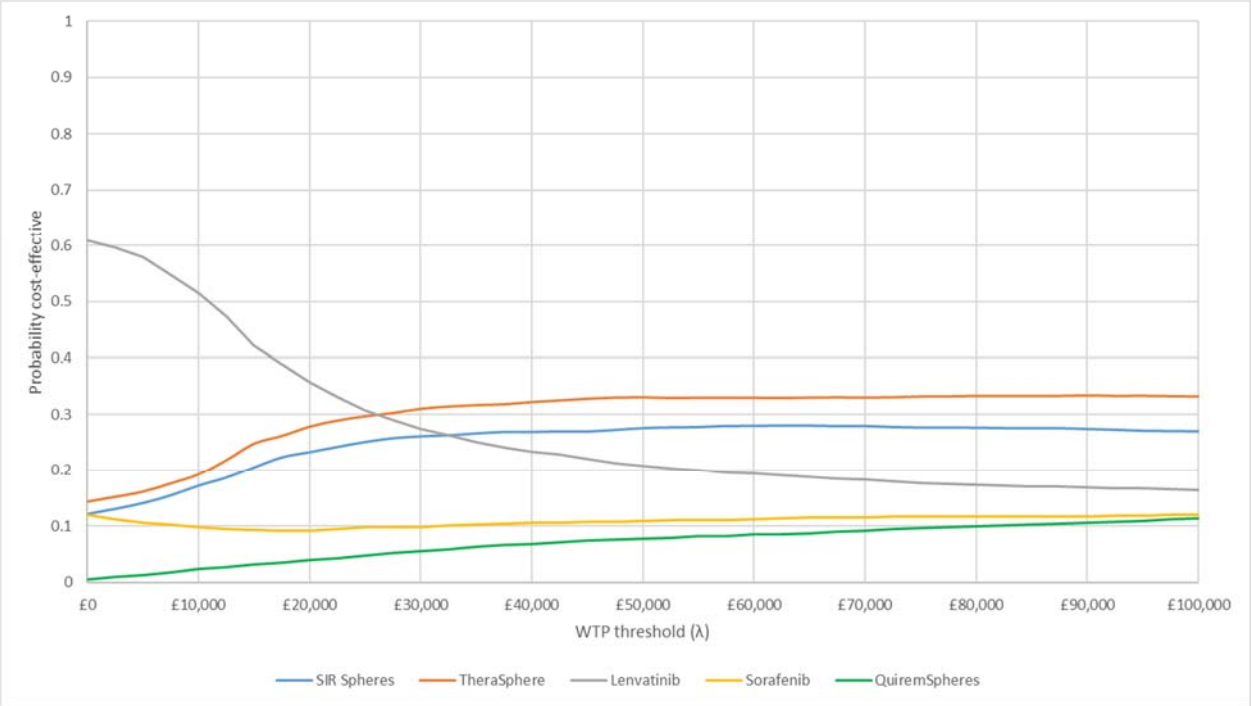
Results including the confidential PAS discounts for sorafenib, lenvatinib, regorafenib, and QuiremSpheres can be found in the confidential appendix.

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

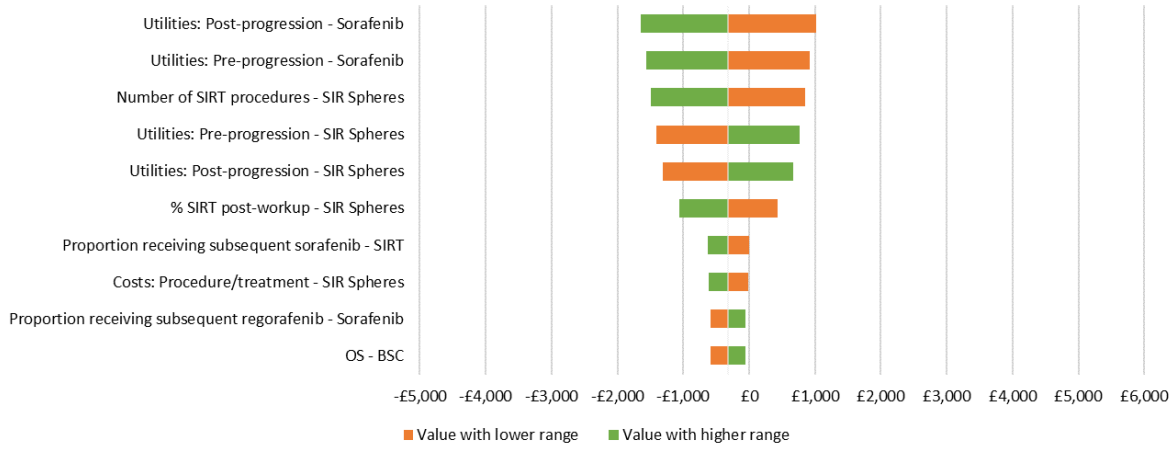
Intervention	Incremental NMB Rank (vs baseline)																	
	Base case	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10	S11	S12	S13	S14	S15	S16	S17
SIR-Spheres	4	4	2	4	4	4	2	3	4	3	2	4	4	3	4	4	4	3
TheraSphere	2	3	**1**	3	**1**	3	**1**	2	3	2	**1**	3	3	2	3	3	3	2
QuiremSpheres	5	5	5	5	5	5	5	5	5	5	3	5	5	5	5	5	5	5
Lenvatinib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

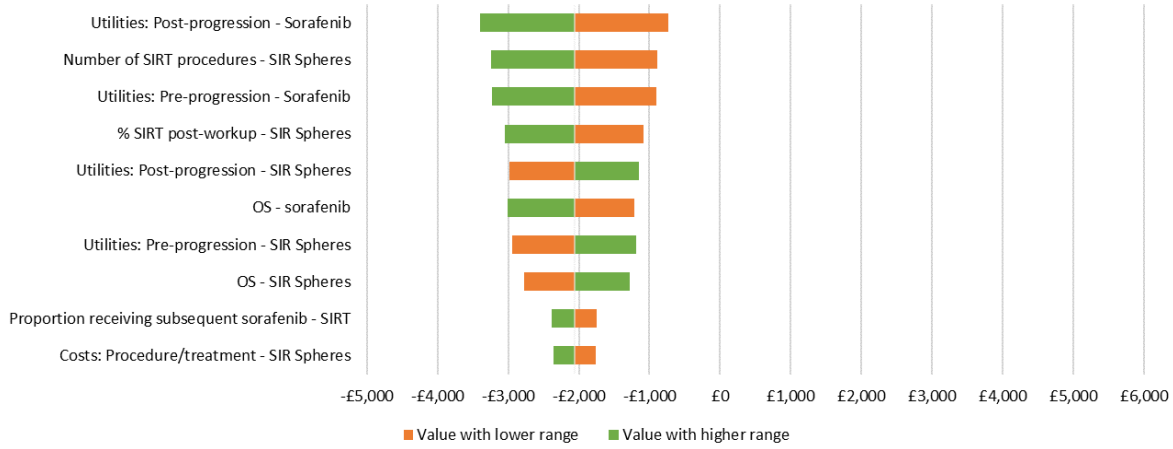
The AG base-case analysis (Figure 21) was robust to a range of parameters, with the most influential parameters providing a range of NMB between approximately -£1,600 and £1,000, with the base-case NMB as -£315. The most influential parameters were the health state utilities, the number of SIRT procedures 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)



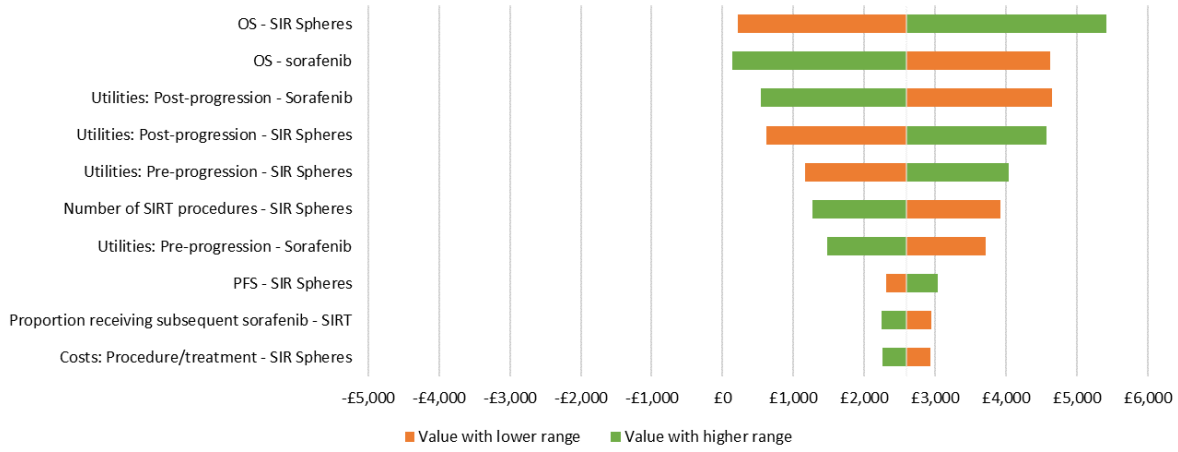
In Scenario 1, with efficacy data based on SARAH only, varying the parameters in the DSA had a larger impact on NMB than in the base-case analysis, although the variation remains small (Figure 22). Similarly to the base-case analysis, the results were most sensitive to health state utilities and SIRT 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)



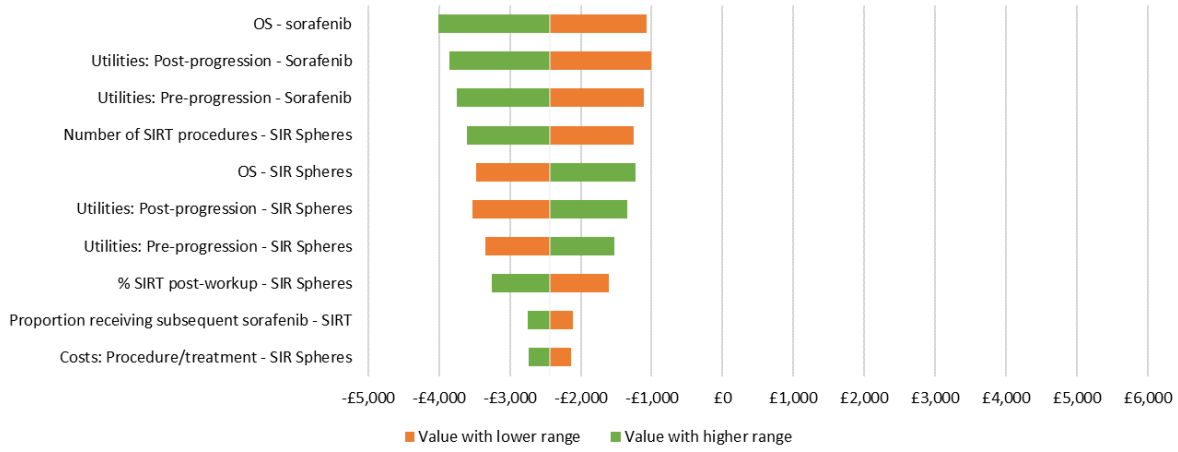
The most influential parameters in the low tumour burden/ALBI 1 subgroup was OS for both SIR-Spheres and sorafenib (Figure 23). SIR-Spheres remained cost-effective compared with sorafenib over the range of parameters; however, when the confidential PAS for sorafenib was applied, this was no longer the case.

Figure 23: Tornado diagram – SIR-Spheres versus sorafenib, low tumour burden/ALBI 1 subgroup (Scenario 2)



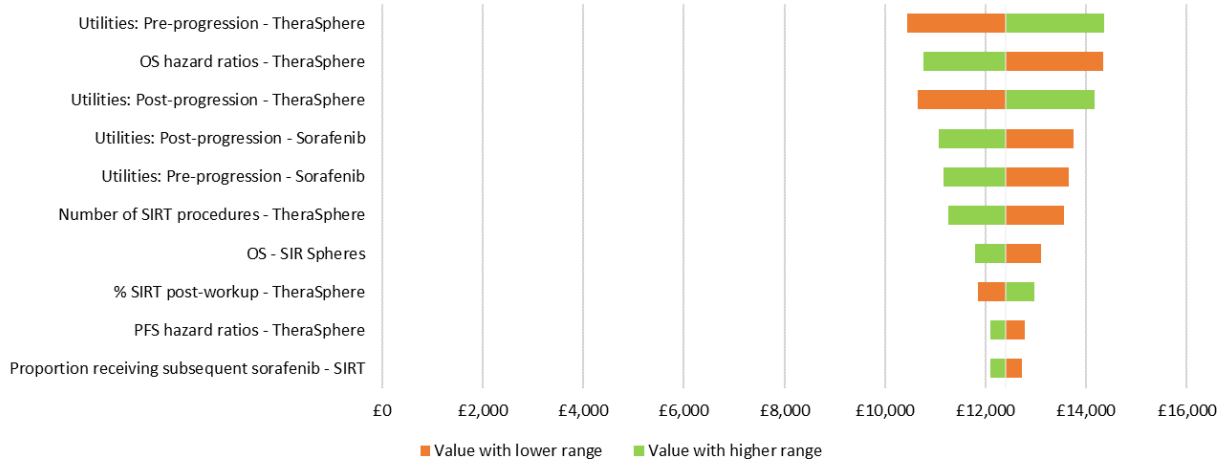
In the 'no MVI' subgroup, the most influential parameters were the health state utilities, and OS for sorafenib and SIR-Spheres (Figure 24). There were are no scenarios in which SIR-Spheres was estimated to be cost-effective compared with sorafenib.

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.

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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

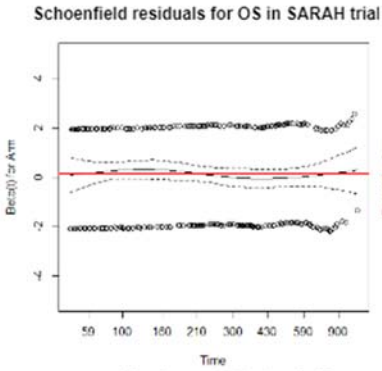
Trial	Risk of bias arising from the randomisation process	Risk of bias due to deviation from the intended interventions	Missing outcome data (primary outcomes)	Risk of bias in measurement of the outcomes	Risk of bias in selection of the reported result	Overall judgement of risk of bias
Yu (2014)[65]	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

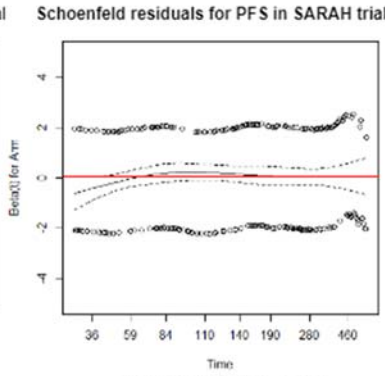
13.10 Study details and results for studies of comparators included in the network meta-analysis

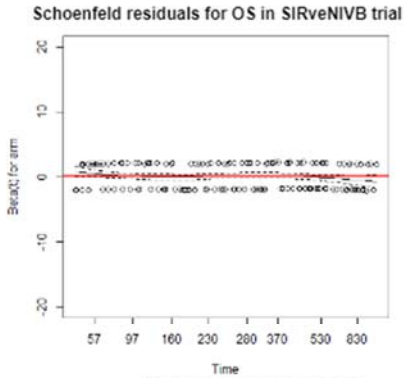
Study name and location	Study design and funding source	Population	Intervention	Comparator	Main results
Yu, 2014[65] China	Parallel group RCT Funding: Not reported	Patients with unresectable HCC with Child Pugh A or B and ECOG <2	TAE (n=45)	TACE (n=45)	**Overall survival:** TAE: median 24.3 months (95% 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

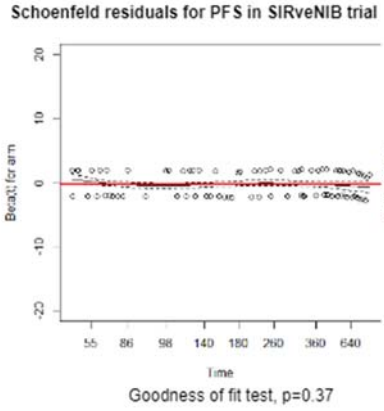
					Time to progression: TACE: mean 24.2 months DEB-TACE: mean 15.6 months
Meyer, 2013[64] UK	Phase II/III RCT Funding: NIHR, Experimental Cancer Medicine Centre Network	Patients with unresectable HCC with Child-Pugh class A or B and ECOG 0-2	TAE (n=42)	TACE (n=44)	**Overall survival:** Hazard ratio of 0.91, 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

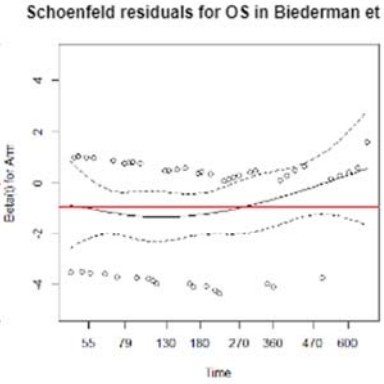
13.11 Schoenfield residual plots for the studies included in the network meta-analysis for adults with unresectable HCC who are ineligible for CTT

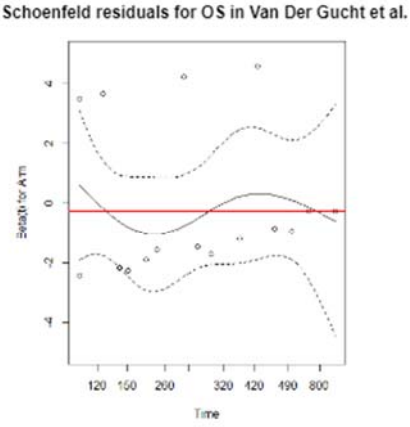


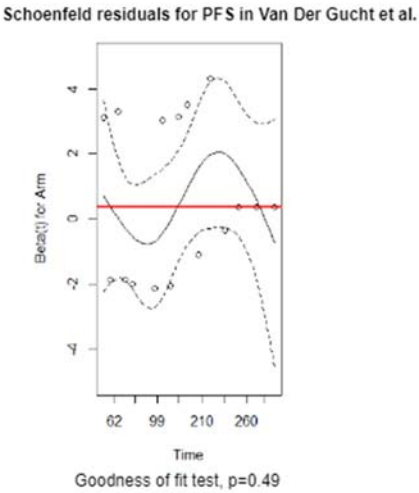












13.12 Hazard ratio estimates for each treatment comparison for all patients in the NMA ITT population

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

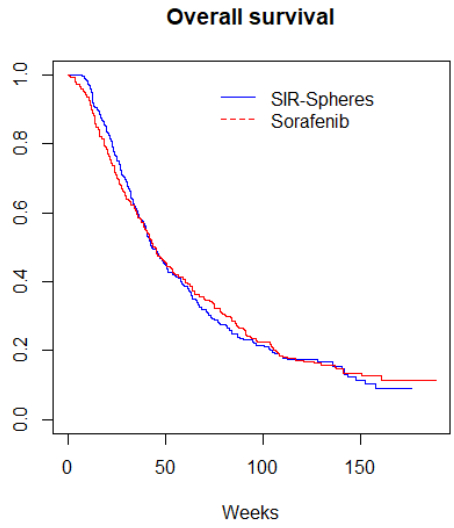


Figure 27: Kaplan-Meier plot of overall survival, for SIR-Spheres and sorafenib, from pooled SARAH and SIRveNIB dataset

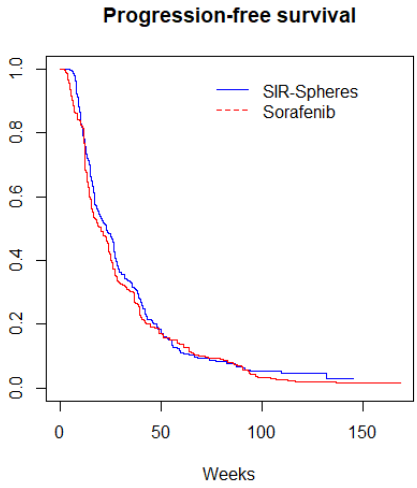


Table 71: Summary of observed survival estimates for SIR-Spheres and sorafenib, SARAH and SIRveNIB pooled dataset

	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

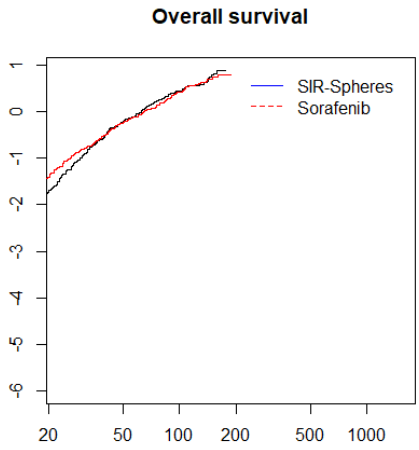


Figure 29: Log-cumulative hazard plot of progression-free survival, for SIR-Spheres and sorafenib, from pooled SARAH and SIRveNIB dataset

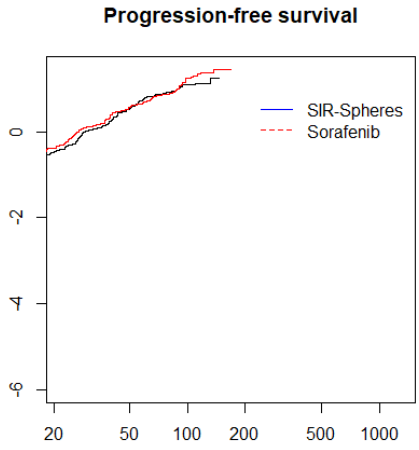


Table 72: AIC and BIC - Overall survival for SIR-Spheres and sorafenib, from pooled SARAH and SIRveNIB dataset (survival analysis conducted by AG)

	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

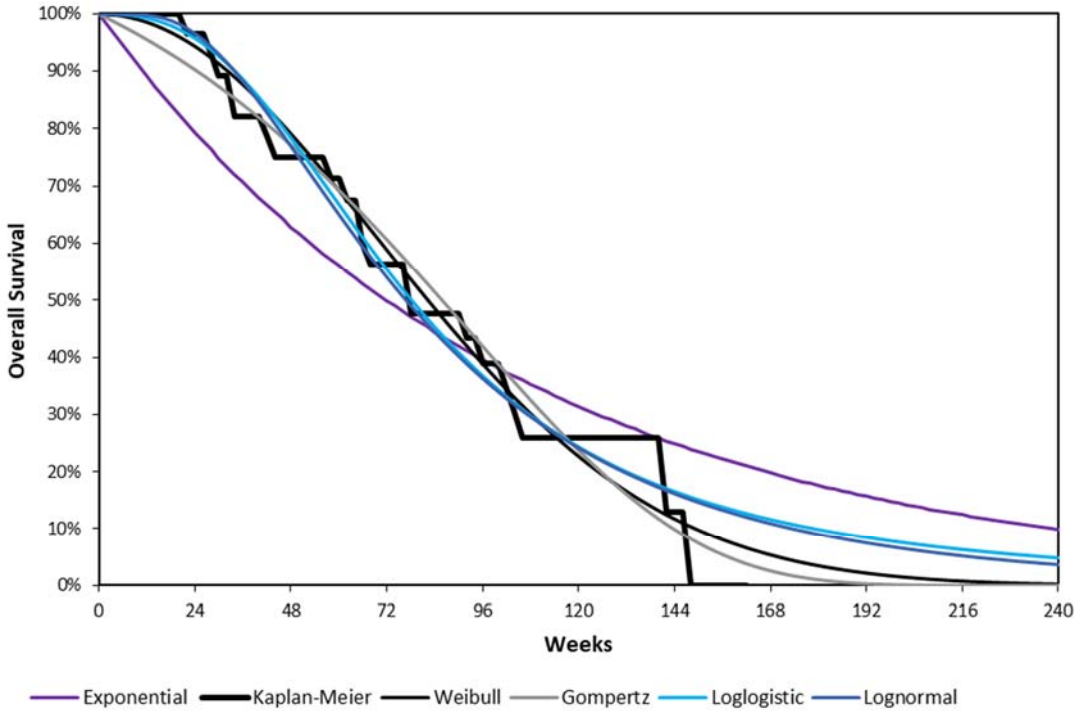


Figure 31: Extrapolation of OS No MVI subgroup: SIR-Spheres

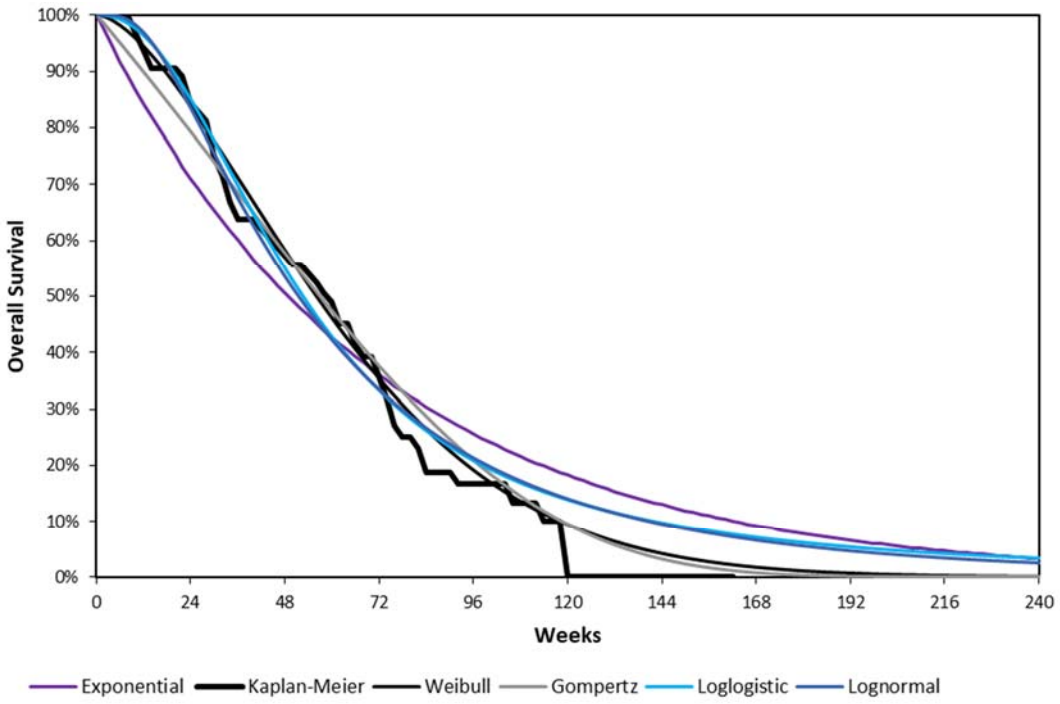


Figure 32: Extrapolation of OS Low tumour burden and ALBI 1 subgroup: Sorafenib

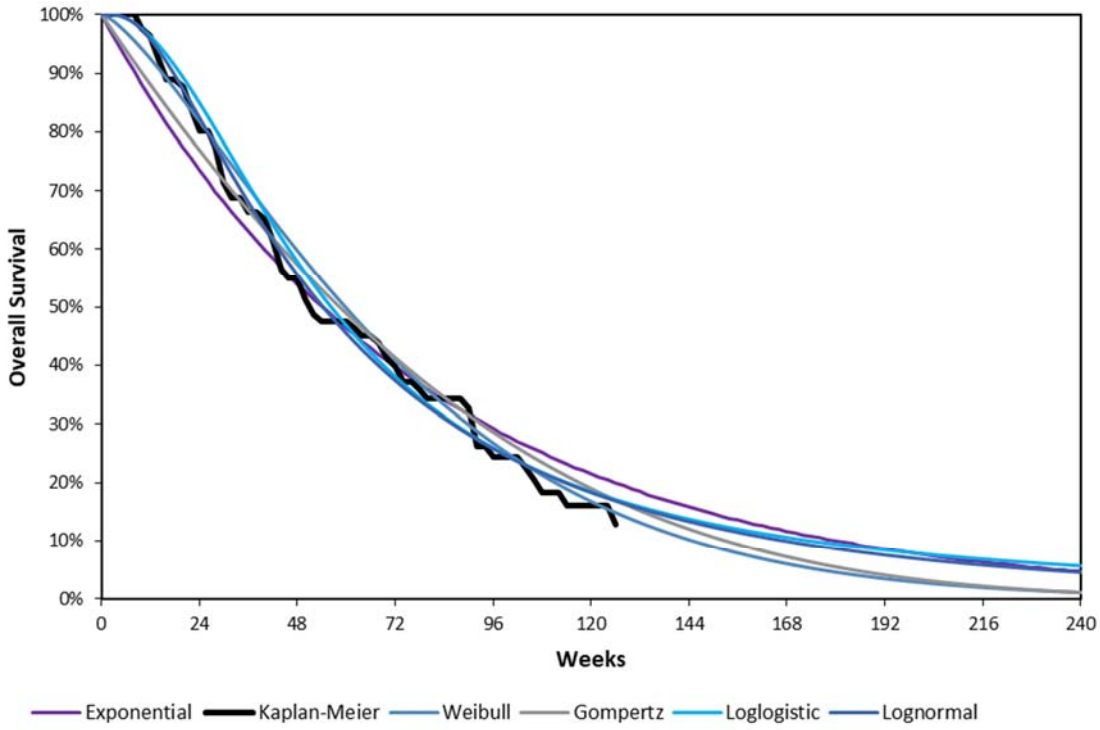


Figure 33: Extrapolation of OS No MVI subgroup: Sorafenib

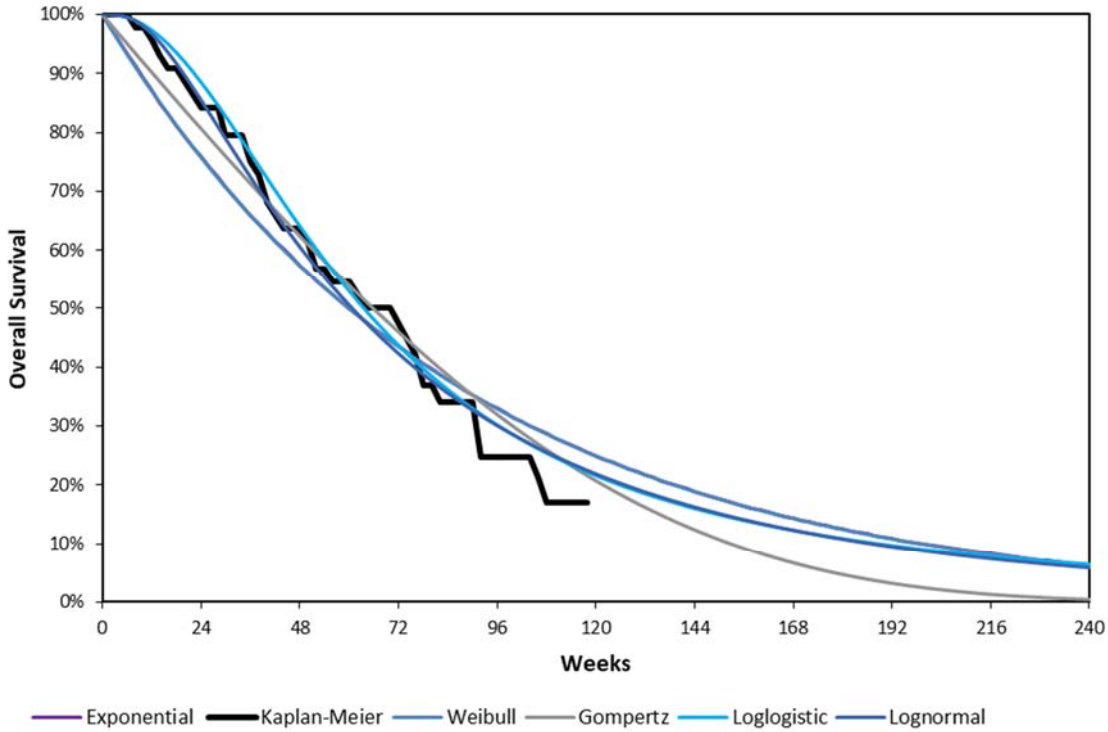


Figure 34: Extrapolation of PFS Low tumour burden and ALBI 1 subgroup: SIR-Spheres

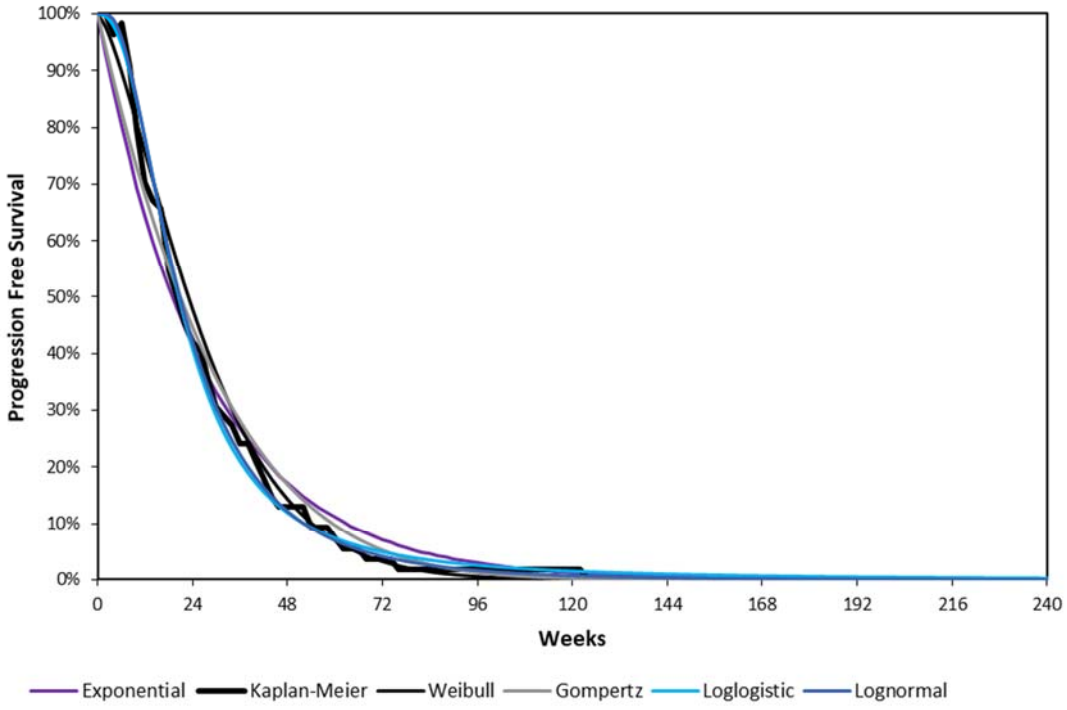


Figure 35: Extrapolation of PFS No MVI subgroup: SIR-Spheres

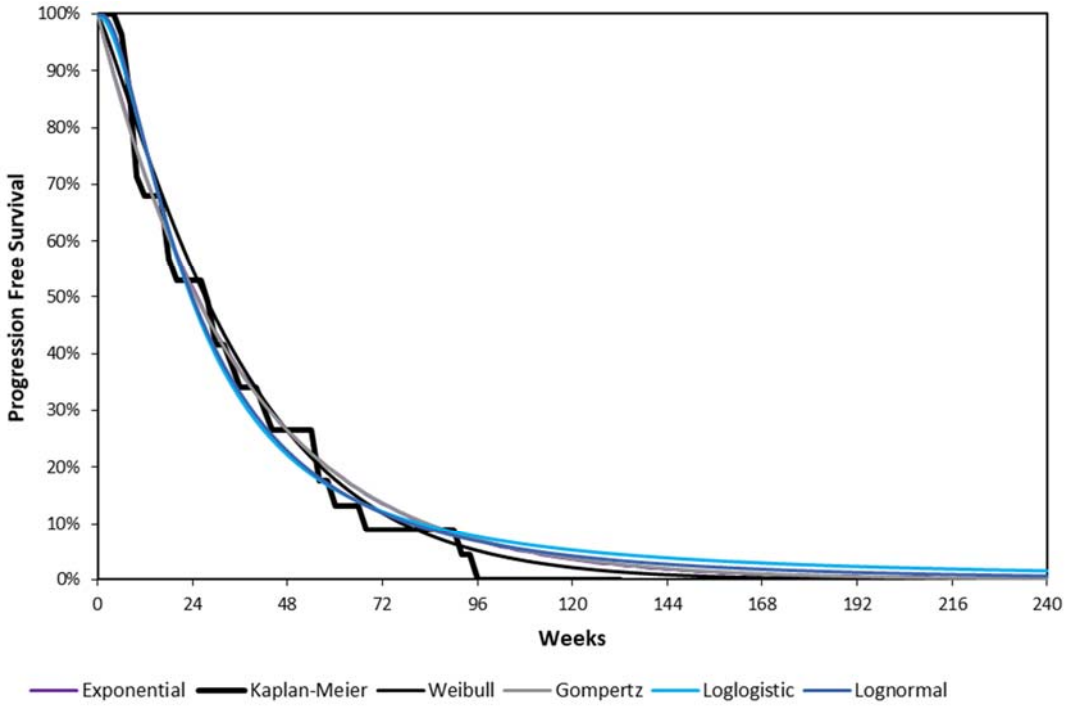


Figure 36: Extrapolation of PFS Low tumour burden and ALBI 1 subgroup: Sorafenib

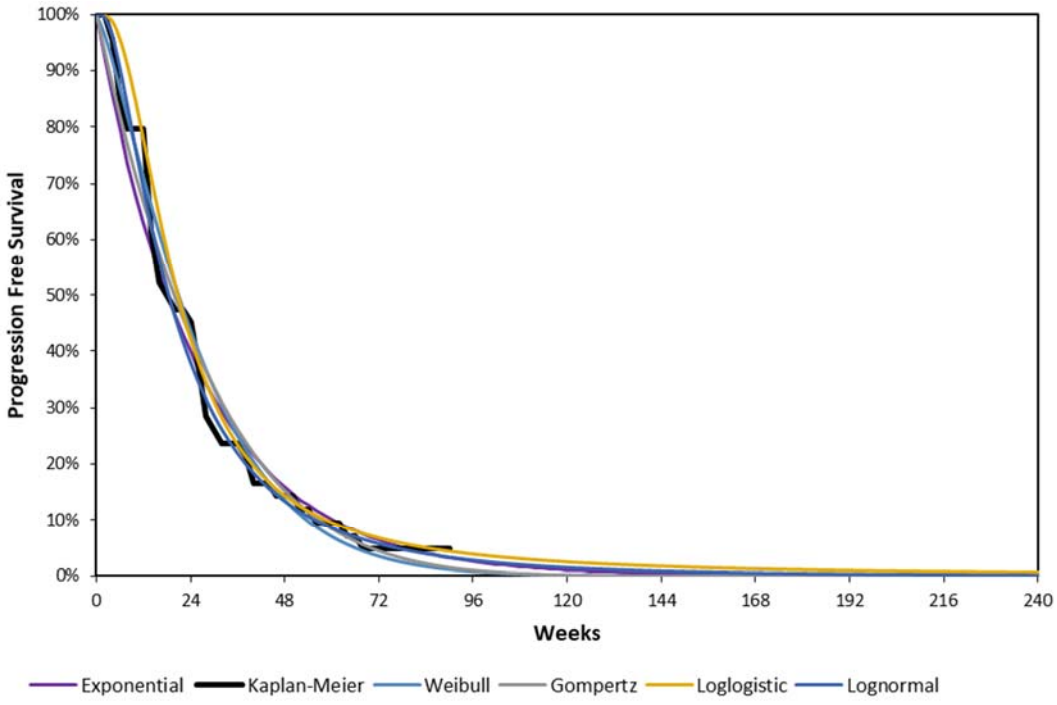


Figure 37: Extrapolation of PFS No MVI subgroup: Sorafenib

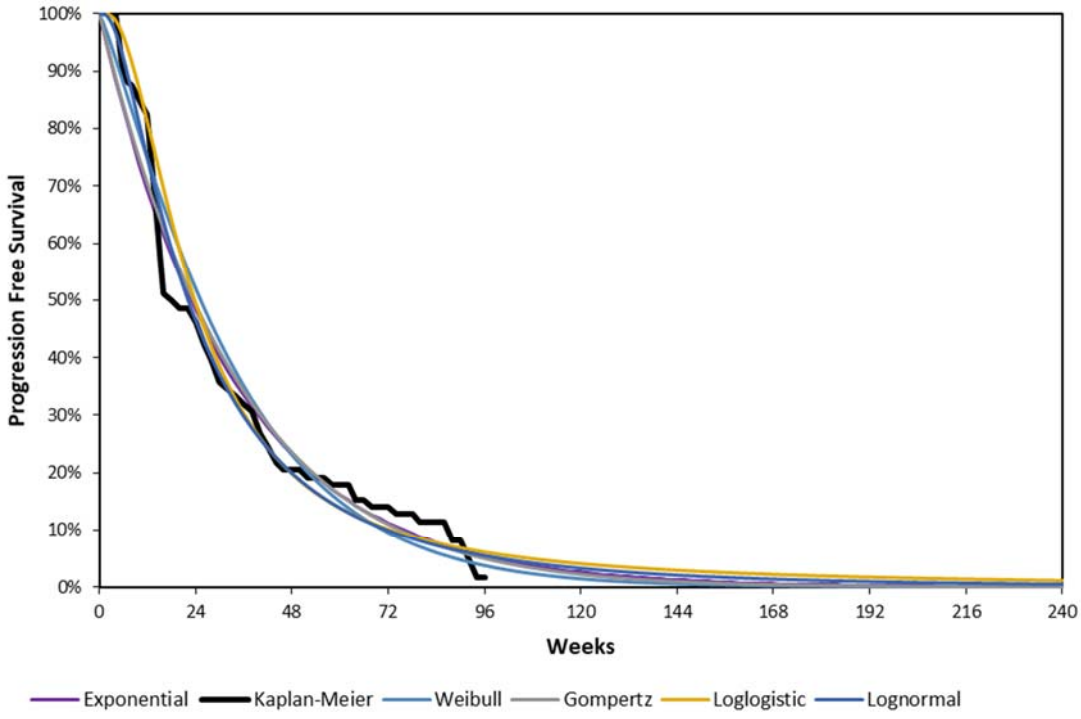


Table 75: Adverse event unit costs

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)