Final Research Protocol
Selective internal radiation therapies (SIRT) for treating hepatocellular carcinoma

Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence (HTA 17/109/19)

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1 Title of the project

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

2 Name of TAR team and project 'lead'

TAR team: Centre for Reviews and Dissemination/Centre for Health Economics (CRD/CHE) Technology Assessment Group, University of York.

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3 Plain English summary

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer; there were 3,235 men and 1,690 women diagnosed with HCC in England in 2016.[1] Around 90% of HCCs are associated with a known underlying cause, most frequently chronic viral hepatitis B or C or excessive alcohol intake, which can cause cirrhosis (scarring of the liver). One-third of patients with cirrhosis will develop HCC during their lifetime.[2]

There is a range of treatments for HCC and treatment choice is dependent on the location and stage of the cancer and liver function. The Barcelona Clinic Liver Cancer (BCLC) staging system is used to establish prognosis (likely outcome) and enable the selection of appropriate treatment. Early stage HCC (BCLC stage A) may be treated with surgery (resection or liver transplant) or percutaneous thermal ablation in an attempt to cure the disease. Treatment options for intermediate stage disease (BCLC stage B) include interventional radiology procedures such as transarterial embolisation (TAE), transarterial chemoembolisation using lipiodol mixed with chemotherapeutic agents (TACE) or transarterial chemoembolisation using drug-eluting beads with doxorubicin or cisplatin (DEB-TACE).

Advanced stage disease (BCLC stage C) is generally treated with systemic therapy, with anti-cancer drugs such as sorafenib, lenvatinib or regorafenib (for patients who have previously had sorafenib). Best supportive care is offered to patients when chemoembolisation or systemic therapy is not available or appropriate, including patients with terminal stage disease (BCLC stage D).

Selective internal radiation therapies (SIRT) deliver radiation to liver tumours via microspheres that are injected into the hepatic artery. This appraisal will assess the clinical and cost effectiveness of SIRT for treating patients with unresectable early, intermediate or advanced stage HCC. The SIRT technologies to be appraised are TheraSphere, SIR-Spheres and QuiremSpheres. TheraSphere comprises glass microspheres containing yttrium-90, SIR-Spheres comprises resin microspheres containing yttrium-90 and QuiremSpheres comprises polyester microspheres containing holmium-166.

4 Decision problem

4.1 Background

Liver cancer is the fifth most common cancer and the second most frequent cause of cancer-related death globally. HCC is the most common type of liver cancer, representing around 90% of primary liver cancers.[2] There were 3,235 men and 1,690 women diagnosed with HCC in England in 2016.[1] Around 90% of HCCs are associated with a known underlying aetiology, most frequently chronic viral hepatitis B or C or excessive alcohol intake, which can cause cirrhosis. One-third of patients with cirrhosis will develop HCC during their lifetime.[2]

There is a range of treatments for HCC and treatment choice is dependent on the location and stage of the cancer and liver function. The BCLC staging system is used to establish prognosis and enable the selection of appropriate treatment. Patients are classified into five stages (0, A, B, C and D) according to tumour burden, liver function and performance status. The European Association for the Study of the Liver (EASL) Clinical Practice Guidelines for the management of hepatocellular carcinoma summarise treatment recommendations according to BCLC classification.[2] The recommendations, modified slightly to reflect entry criteria to pivotal clinical trials of chemoembolisation and systemic therapies, are summarised in Table 1 below.

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	Chemoembolisation (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

Current NICE guidance includes a technology appraisal on sorafenib for the treatment of advanced HCC (TA474) recommending sorafenib as an option for people with Child-Pugh grade A liver impairment. A technology appraisal on lenvatinib for untreated advanced HCC (TA551) recommends lenvatinib as an option for people with Child-Pugh grade A liver impairment and an ECOG performance status of 0 or 1. A recent technology appraisal on regorafenib for treating advanced unresectable HCC (TA555) recommends regorafenib as an option for people who have had sorafenib and have Child-Pugh grade A liver impairment and an ECOG performance status of 0 or 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. TheraSphere comprises glass microspheres impregnated with yttrium-90, SIR-Spheres comprises resin microspheres containing yttrium-90 and QuiremSpheres comprises polyester microspheres containing holmium-166. The most likely place 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. NICE interventional procedures guidance 460 states that current evidence on the efficacy and safety of SIRT for primary HCC is adequate for use with normal arrangements. However, uncertainties remain about its comparative effectiveness relative to transarterial and systemic therapeutic options.[3]

4.2 Purpose of the decision to be made

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

4.3 Clear definition of interventions

Three SIRT interventions will be considered within this assessment: TheraSphere, SIR-Spheres and QuiremSpheres.

1) TheraSphere (manufactured by BTG) is a CE marked class III active medical device comprising glass microspheres containing yttrium-90. Each milligram contains between 22,000 and 73,000 microspheres, each with a mean diameter of 20-30µm. TheraSphere is available in doses ranging from 3 GBq to 20 GBq of yttrium-90.[4]
2) SIR-Spheres (manufactured by Sirtex) is a CE marked class III active medical device comprising resin microspheres containing yttrium-90. Each vial contains 40-80 million microspheres, with a median diameter of 32.5 µm (range 20-60µm) and a dose of 3 GBq of yttrium-90 ± 10%.[5]
3) 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. The mean diameter is 30µm (97% between 15-60µm).[6]

SIRT (also called transarterial radioembolisation) is a complex intervention that delivers radiation to liver tumours via microspheres that are injected into the hepatic artery via a catheter from the femoral artery. Patients undergo preliminary angiography of the hepatic artery, and protective coiling of extrahepatic branches to reduce extrahepatic radiation uptake if necessary. For TheraSphere and SIR-Spheres, ^{99m}Tc-macroaggregated albumin is used as a surrogate and injected into the hepatic artery using the same catheter position chosen for the scheduled SIRT session. Calculation of the dose to the tumour, adjacent liver, hepato-pulmonary shunt fraction and tracer distribution are evaluated with macroaggregated albumin single-photon emission CT imaging. For QuiremSpheres, unlike yttrium-90, holmium-166 microspheres can be visualised with SPECT and MR imaging even at low concentrations, therefore, a lower dose of holmium-166 is used for evaluating dose distribution, rather than a surrogate, which may mean more accurate results. Severe lung shunting and extrahepatic uptake contraindicate the SIRT procedure. When SIRT is not contraindicated, patients are readmitted for the SIRT procedure, which is performed in a lobar, sectorial or segmental approach according to tumour size and location.[2]

4.4 Place of the interventions in the treatment pathway

- TheraSphere is indicated for the treatment of hepatic neoplasia.
- SIR-Spheres is indicated for the treatment of inoperable liver tumours.
- QuiremSpheres is indicated for the treatment of unresectable liver tumours.

SIRT is most likely to be used in patients with intermediate (BCLC stage B) or advanced (BCLC stage C) stage HCC as a non-curative option. However, patients with advanced stage disease are more likely to have more limited liver function, so may be less able to tolerate transarterial therapies. There may also be a role for SIRT as a bridging therapy for patients awaiting transplant (BCLC stage A) or as downstaging therapy for patients whose tumours are slightly too large to meet the liver transplant/resection criteria, as an alternative to transarterial chemoembolisation.

NICE IPG460 states that current evidence on the efficacy and safety of SIRT for primary HCC is adequate for use with normal arrangements. However, uncertainties remain about its comparative effectiveness and clinicians are encouraged to enter eligible patients into trials comparing the procedure against other forms of treatment. Clinicians are also advised to enrol all patients into the UK SIRT registry (launched in 2013).[3]

4.5 Relevant comparators

SIRT interventions (TheraSphere, SIR-Spheres and QuiremSpheres) may be compared against each other, against embolisation/chemoembolisation therapies (TAE, TACE and DEB-TACE) or, for people for whom any transarterial therapies are inappropriate, against established clinical management without SIRT, such as systemic therapy (sorafenib, lenvatinib and regorafenib) or best supportive care.

4.6 Population and relevant subgroups

The population under consideration is 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.

If evidence allows, the following subgroups will be considered:

People with unresectable HCC for whom treatments for downstaging to resection or transplantation or as a bridge to transplantation are considered appropriate treatment options.

People with unresectable HCC with portal vein thrombosis/involvement.

4.7 Key factors to be addressed

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) chemoembolisation therapies, (iii) systemic therapy, and (iv) best supportive care.

5 Methods for investigation of clinical evidence

A systematic review of the clinical effectiveness evidence will be undertaken following the general principles outlined in CRD's guidance on undertaking systematic reviews[7] and reported according to the general principles of the PRISMA statement.[8] The research protocol will be registered on PROSPERO, the international prospective register of systematic reviews in health and social care (http://www.crd.york.ac.uk/prospero/).

5.1 Search strategy

A comprehensive search will be undertaken to systematically identify clinical effectiveness literature relating to TheraSphere, SIR-Spheres and QuiremSpheres within their licensed indications for HCC. In addition, a search for comparator therapies will be undertaken, in order to strengthen the network of evidence on SIRT.

5.1.1 Search strategy for selective internal radiation therapy (SIRT) studies

Searches of electronic databases and resources will be undertaken to identify studies of TheraSphere, SIR-Spheres and QuiremSpheres. A draft search strategy has been developed in Ovid MEDLINE (see Appendix 12.1). The strategy includes terms for HCC combined with terms for the SIRT interventions, limited to studies from the year 2000 onwards. Scoping searches 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 will not be restricted by language or study design. This strategy will be adapted to run on the other databases and resources listed below.

The following databases will be searched: MEDLINE, MEDLINE In-Process, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, the Science Citation Index, Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database.

In addition, information on studies in progress, guidelines, unpublished research or research reported in the grey literature will also be sought by searching a range of relevant resources including: Conference Proceedings Citation Index - Science, ProQuest Dissertations & Theses A&I,

PROSPERO, NICE website, NHS Evidence, ClinicalTrials.gov, WHO International Clinical Trials Registry portal and the EU Clinical Trials Register.

Company websites, company submissions and relevant systematic reviews will also be hand-searched to identify further relevant studies and clinical advisors will be consulted.

The searches described above will be used to identify studies on the cost-effectiveness as well as the clinical effectiveness of SIRT interventions. The archive of the NHS Economic Evaluations Database and EconLit will be searched in addition to the resources listed above.

5.1.2. Search strategy for comparator therapies

A search for literature on comparator therapies will be undertaken, in order to strengthen the network of evidence on SIRT. Ideally, comprehensive literature searches will be undertaken using the following resources: MEDLINE, MEDLINE In-Process, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL and the Science Citation Index. A draft search strategy has been developed in Ovid MEDLINE combining terms for HCC with terms for the comparator therapies listed in Section 5.2.4 (see Appendix 12.2). Retrieval will be restricted to randomised controlled trials with a clinically appropriate date limitation, published in any language.

However, in view of time and resource limitations, it may be necessary to search existing relevant systematic reviews and network meta-analyses for RCTs of comparator therapies in the first instance, then undertake update searches, using the resources listed above.

Clinical advisors will also be consulted for additional relevant RCTs of comparator therapies.

5.2 Inclusion and exclusion criteria

Inclusion criteria have been defined in line with the final scope provided by NICE and are outlined below. Studies will be initially assessed for relevance using titles and abstracts. One reviewer will examine titles and abstracts with a second reviewer checking 10% of records. Full manuscripts of any titles/abstracts that may appear relevant will be obtained where possible and the relevance of each study assessed independently by two reviewers according to the criteria outlined below. Any discrepancies will be resolved through consensus and, where necessary, a third reviewer will be consulted. Where possible, relevant foreign language studies will be translated and included in the reviews.

5.2.1 Study design

Randomised controlled trials (RCTs) will be included in the clinical effectiveness review. However, where RCT evidence is insufficient to address the decision problem, non-randomised comparative

studies (including retrospective studies) and non-comparative studies of SIRT will be considered for inclusion. The evidence will be scoped before deciding what level of evidence will be included for data extraction and quality assessment.

5.2.2 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, will be included in the review. Studies of people with secondary liver metastases or other types of liver cancer (such as cholangiocarcinoma) will not be included unless they also include people with primary HCC and results are reported separately for people with HCC.

5.2.3 Interventions

The interventions under consideration are the selective internal radiation therapies TheraSphere, SIR-Spheres and QuiremSpheres.

Where there is evidence on combined treatments (e.g. SIRT plus sorafenib), we will consider these for inclusion.

5.2.4 Comparators

SIRT interventions (TheraSphere, SIR-Spheres and QuiremSpheres) may be compared against each other, against chemoembolisation therapies (TAE, TACE and DEB-TACE) or, for people for whom any transarterial embolisation therapies are inappropriate, against established clinical management without SIRT, such as systemic therapy (sorafenib, lenvatinib and regorafenib) or best supportive care.

In order to strengthen the network of evidence on SIRT, chemoembolisation therapies (TAE, TACE and DEB-TACE), systemic therapies (sorafenib, lenvatinib and regorafenib) and best supportive care may be compared against each other using RCT evidence. The evidence will be scoped and criteria for inclusion will be developed. RCTs will be assessed for quality and key outcome data will be extracted, based on requirements for the model.

5.2.5 Outcomes

The outcome measures to be considered include:

- Overall survival
- Progression-free survival
- Time-to-progression
- Response rates

- Rates of liver transplant or surgical resection
- Adverse effects of treatment
- Health-related quality of life
- Time on treatment/number of treatments provided

5.3 Data extraction strategy

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

5.4 Quality assessment strategy

The methodological quality of the included studies will be assessed using criteria relevant to the study design. RCTs will be assessed using a modified version of the Cochrane risk of bias tool.[9] Quality assessment tools for other study designs will be developed using relevant criteria such as those outlined in CRD's guidance on undertaking systematic reviews.[7] Quality assessment will be undertaken by one reviewer and all data will be independently checked by a second reviewer. Any disagreements will be resolved through consensus and, where necessary, a third reviewer will be consulted. Details of the quality of the included studies will be presented in descriptive tables and their impact on the reliability of results will be considered.

5.5 Methods of analysis/synthesis

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

Where the data allow, a network meta-analysis (NMA) using Bayesian statistical methods with software such as R or winBUGS will be undertaken in order to estimate the relative effectiveness of the different treatments. Results will be 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 will be assessed. The results of the NMA will feed into the economic model described in Section 6.

6 Methods for investigation of Cost effectiveness

6.1 Cost-effectiveness review

Comprehensive searches (with no language or study design restriction) will be undertaken to identify studies of the cost-effectiveness of TheraSphere, SIR-Spheres, and QuiremSpheres for the treatment of HCC using the search strategy described in Section 5.1.1. Any identified studies will be used to guide the development of a *de novo* economic model for this appraisal, with the aim of identifying important structural assumptions, highlighting key areas of uncertainty and outlining the potential issues of generalising from the results of existing models.

A broad range of studies will be considered in the assessment of cost-effectiveness including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) for the treatment of HCC will be included in the review of economic literature. Additional hand-searching of related NICE technology appraisals for the treatment of HCC (TA 474, 551 and 555) will also be undertaken.

The quality of the cost-effectiveness studies will be assessed according to a checklist updated from that developed by Drummond *et al*.[10] This checklist will reflect the criteria for economic evaluation detailed in the methodological guidance developed by the National Institute for Health and Care Excellence (NICE).[11] This information will be tabulated and summarised within the text of the report.

Information will be extracted and assessed for relevance to the present decision problem, including:

- the comparators,
- study population,
- main analytic approaches (e.g. patient-level analysis/decision-analytic modelling),
- primary outcome specified for the economic analysis,
- details of adjustment for quality of life,
- direct costs and indirect costs,
- estimates of incremental cost-effectiveness and
- approaches to quantifying decision uncertainty (e.g. deterministic/probabilistic sensitivity analysis).

It is anticipated that a separate search will be undertaken to identify published studies reporting utility estimates in HCC patients which i) directly estimate EQ-5D utility values; and ii) establish the

relationship between generic measures of utility (in particular, the EQ-5D) and quality of life measures (such as the EORTC QLQ-HCC1, FACT-HEP, FHSI and QOL-LC) including mapping studies.

6.2 Development of a new decision-analytic model

A new decision-analytic model will be developed to estimate the cost-effectiveness of TheraSphere, SIR-Spheres, and QuiremSpheres for the treatment of HCC.

Where data permits, the comparators included will be consistent with the final NICE scope. The model will be developed in accordance with the NICE reference case. The model will have a time horizon sufficiently long to reflect differences in costs and outcomes between the interventions being compared. All costs will be considered from the perspective of the National Health Services and Personal Social Services. Both costs and quality-adjusted life years (QALYs) will be discounted at 3.5% per annum.

Where sufficient data permits analysis, the cost-effectiveness assessment will also explore the sequential and adjunctive use of SIRT therapies with other comparator therapies. However, it is envisaged that, due to limitations in existing data, such analyses are likely to be exploratory in nature.

The specific objectives of the cost-effectiveness analysis are:

- To develop a *de novo* model that appropriately characterises patients' care, subsequent disease progression and the impacts of alternative therapies on HCC, in a way that is clinically valid.
- To populate this model using the most appropriate data. This is likely to be identified systematically from published literature, routine data sources and potentially using data elicited from relevant clinical experts.
- To relate initial and intermediate outcomes (such as resection rates) to final health outcomes, expressed in terms of QALYs. This is necessary in order to provide decision makers with an indication of the health gain achieved by each intervention, relative to its additional cost, in units that permit comparison with other uses of health service resources.
- To estimate the cost-effectiveness of each of the therapies based on an assessment of long-term NHS and Personal Social Service costs and quality-adjusted survival.
- To characterise the uncertainty in the data used to populate the model and to present the uncertainty in these results to decision makers. A probabilistic model will be developed which requires that each input in the model is entered as an uncertain, rather than a fixed parameter. Using Monte Carlo simulation, this *parameter uncertainty* is translated into uncertainty in the overall results. The purpose of their analysis is to characterise the decision uncertainty i.e. to

provide an estimate of the probability that a decision to fund a particular technology is a wrong decision. This will be presented using cost-effectiveness acceptability curves which show the probability that each intervention is cost-effective conditional on a range of possible threshold values which NHS decision makers attach to an additional QALY.

- To use scenario analyses to explore the sensitivity of the cost-effectiveness results to changes in the structural assumptions of the model (e.g. excluding the costs associated with the work-up phase for SIRT), and the time horizon over which the treatments are assessed. A number of one- and two-way sensitivity analyses around key parameter values will also be explored, with the upper and lower limits determined by the range of likely values for the parameter (e.g. the 95% CI). Results will be presented in a tornado diagram. These will determine which sources of uncertainty have the greatest impact on the cost-effectiveness results.

The specific details of the data to be used to populate the model will have to await the development of the structure, the systematic searches of the literature and the company submissions. Preliminary thoughts on an appropriate model structure and potential issues with parameterisation of the model are detailed below.

Model structure

We anticipate that the model structure will be driven by the available data, and is likely to encapsulate a number of sub-models for each stage of the disease, given that SIRT is to be appraised at multiple points in the treatment pathway. For later stages of HCC (BCLC-C), we anticipate developing a similar three state partition survival (PartSA) model commonly used in the previous NICE technology appraisals for sorafenib, regorafenib and lenvatinib, based on the progression-free survival and overall survival data. For earlier stages, a more flexible model may be appropriate. For example, a hybrid approach based on a decision-tree to capture the initial response period and a longer-term Markov model to estimate longer term outcomes. It is anticipated that the model will be developed in Microsoft Excel.

Parameterisation

From a preliminary review of the literature, the clinical effectiveness review is likely to identify these outcome measures in a range of formats. Where possible and appropriate, time to event data (overall survival, progression-free survival) will be used, specific for each treatment arm. However, it may be that the review and associated syntheses provide estimates of short-term response only (i.e. probability of response, probability of being downstaged, success as a bridge-to-transplant, etc.). If this is the case, estimates of the longer-term prognosis for patients may use observational evidence

relevant to clinical practice in England. Data from the SIRT registries may be used directly in this regard, or as a validation tool.

The presence of any additional data gaps identified during the development of the model may necessitate further searches. A number of key issues identified in previous NICE technology appraisals may require targeted searches or acquisition of observational data to resolve. An initial review suggests these may include:

- Resource use, which has been identified as an important driver of cost-effectiveness and has historically been based on elicitation exercises completed with a limited number of clinical experts;
- Scheduling and dosing of treatments, which was identified being subject to considerable uncertainty with respect to systemic agents, with mismatches observed between pivotal trial data and routine use.
- Drug wastage, which was identified as an important driver of cost in recent appraisals of systemic therapies;
- Utility values, in previous appraisals values adopted have been based upon trial-derived utility data, however, these were noted to be inconsistent with clinical judgments about the health-related quality of life of patients with progressive disease.
- Relevance of effectiveness, differences between the UK population and those recruited to the trials have been noted in previous appraisals. In particular, concerns have been raised about the generalisability of using data from patients recruited from Asia-Pacific regions who have a different disease profile to UK patients.

Depending upon the limitations of the available data, it may also be necessary to consider expert elicitation with a sample of UK experts who have experience of using SIRT or relevant comparator therapies. If this is necessary, an interactive elicitation exercise will be designed to generate estimates of the relevant unknown parameters with uncertainty.[12] We will also work with our clinical advisors at the start of the project to identify relevant UK data sources (e.g. British Society of Interventional Radiology SIRT registry) and will make contact with the relevant investigators with a view to securing access to this data should this be required.

6.3 Quality assurance

The economic model developed by the ERG will be subject to a number of quality assurance processes. A health economist not directly involved in the project will check the internal validity of the model, e.g. using pressure tests of parameter values, a formula audit. A clinician with experience

of treatment for HCC will ensure that the analysis is externally valid, i.e. by verifying key assumptions made in the analysis. These processes will be fully documented.

7 Handling the company submission(s)

All data submitted by the companies/sponsors will be considered if received by the TAR team no later than 4 June 2019. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluations included in the company submissions, provided they comply with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model.

Any 'commercial in confidence' data taken from a company submission, and specified as confidential in the checklist, will be highlighted in blue and underlined in the assessment report (followed by an indication of the relevant company name e.g. in brackets). Any 'academic in confidence' data will be highlighted in yellow and underlined. Where comparator PAS are available results will be presented in a confidential appendix, commercial in confidence results will be highlighted in green and underlined.

8 Project stages and timelines

The project will be undertaken over an 8-month period, beginning in January 2019:

Milestone	**Date**
Draft protocol	25 January 2019
Final scope	8 February 2019
Final protocol	15 February 2019
Company submissions	4 June 2019
Progress report	11 June 2019
Draft assessment report	4 August 2019
Final assessment report	4 September 2019

9 Project team

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10 Competing interests of authors

None.

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12 Appendices

Appendix 12.1 – Draft MEDLINE search strategy for SIRT studies

Database: Ovid MEDLINE(R) ALL <1946 to January 25, 2019>
Search Strategy:
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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)

Appendix 12.2 – Draft MEDLINE search strategy for comparator therapies

Database: Ovid MEDLINE(R) ALL <1946 to February 19, 2019>
Search Strategy:
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1 Carcinoma, Hepatocellular/ (77735)
2 Liver Neoplasms/ (137916)
3 ((liver or hepato$ or hepatic$) adj3 (carcinoma$ or cancer$ or neoplas$ or tumour$ or tumor$ or malign$)).ti,ab. (132224)
4 hepatocarcinoma$.ti,ab. (3760)
5 hepatoma$.ti,ab. (27391)
6 or/1-5 (207860)
7 Sorafenib/ (4228)
8 (sorafenib or nexavar).af. (7605)
9 (regorafenib or stivarga).af. (806)
10 (lenvatinib or lenvima).af. (383)
11 or/7-10 (8434)
12 6 and 11 (3564)
13 Chemoembolization, Therapeutic/ (5226)
14 (chemo-emboli$ or chemoemboli$).ti,ab. (7055)
15 (chemoembolotherap$ or chemo-embolotherap$).ti,ab. (4)
16 TACE.ti,ab. (4615)
17 cTACE.ti,ab. (83)
18 (DEBTACE or DEB-TACE).ti,ab. (155)
19 (eluting adj2 bead$).ti,ab. (494)
20 DC bead$.ti,ab. (94)
21 or/13-20 (9667)
22 6 and 21 (7543)
23 Embolization, Therapeutic/ (30052)
24 (emboli$ or embolotherap$).ti,ab. (115876)
25 23 or 24 (124721)
26 (transarterial$ or trans-arterial$ or transcatheter$ or trans-catheter$ or arterial$).ti,ab. (376856)
27 25 and 26 (23919)
28 (bland adj3 (emboli$ or embolotherap$)).ti,ab. (124)
29 TAE.ti,ab. (2165)
30 or/27-29 (24688)
31 6 and 30 (3884)
32 12 or 22 or 31 (12527)
33 randomized controlled trial.pt. (476462)

34 controlled clinical trial.pt. (92918)
35 randomi$.ab. (533423)
36 placebo.ab. (195482)
37 clinical trials as topic.sh. (186059)
38 randomly.ab. (305671)
39 trial.ti. (194369)
40 or/33-39 (1238283)
41 exp animals/ not humans.sh. (4549113)
42 40 not 41 (1140293)
43 32 and 42 (1384)
44 limit 43 to yr="2000 -Current" (1238)