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External Assessment Group Report

Cost comparison evaluation process

Selective internal radiation therapy with QuiremSpheres for treating unresectable advanced hepatocellular carcinoma (Partial review of TA688)

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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 Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Eleonora Uphoff wrote the background (Section 2), critique of the decision problem (Section 3) and contributed to the critiques of the systematic review and clinical effectiveness evidence (Section 4).
Joseph Lord wrote the critique of the cost comparison (Section 5) and cost comparison results (Section 6).
Sumayya Anwer contributed to the background (Section 2), critique of the decision problem (Section 3) and critiques of the systematic review and clinical effectiveness evidence (Section 4).
Melissa Harden reviewed the systematic review searches and wrote sections of the report pertaining to the searches.
Mark Baker provided clinical expert advice relating to the mechanism of actions of selective internal radiation therapies and their use in the NHS.
Matthew Walton oversaw the review of the cost comparison and the report as a whole.
Sarah Nevitt oversaw the review of the clinical effectiveness evidence, wrote, and commented on drafts of the report as a whole.

Note on the text

All commercial-in-confidence (CIC) data have been [redacted]

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List of abbreviations

AE	Adverse event
AG	Assessment Group
BCLC	Barcelona Clinic Liver Cancer
Bq	becquerel
CI	confidence interval
CIC	commercial-in-confidence
CON	confidential
CR	complete response
CRD	Centre for Research and Dissemination
CS	company submission
CT	computed tomography
CTT	conventional transarterial therapy
EAG	Evidence Assessment Group
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
HCC	hepatocellular carcinoma
^{166}Ho	holmium-166
HRQoL	health-related quality of life
ICER	Incremental Cost Effectiveness Ratio
IPG	Intervention Procedure Guideline
IQR	interquartile range
ITT	intention-to-treat
MDT	Multi-Disciplinary Team
MRI	Magnetic Resonance Imaging
MTA	Multiple Technology Appraisal
NICE	National Institute for Health and Care Excellence
NIH	National Institute for Health
NMA	Network Meta-Analysis
NR	not reported
ORR	objective response rate
OS	overall survival
PAS	Patient Access Scheme
PET-CT	Positron emission tomography with computed tomography
PFS	progression-free survival
PLLA	poly-L-lactic acid
PR	partial response
PS	performance status
PVI	portal vein invasion
PVT	portal vein thrombosis
QALY	Quality-adjusted life year
REILD	radioembolization-induced liver disease
RCT	randomised controlled trial
SIRT	Selective Internal Radiation Therapy
SLR	systematic literature review
SPECT	single-photon emission computerised tomography
TACE	transarterial chemoembolization
TAE	transarterial embolization
TARE	transarterial radioembolization
^{99m}Tc-MAA	technetium-macroaggregated albumin
TTP	time-to-progression
^{90}Y	yttrium-90

EXTERNAL ASSESSMENT REPORT: COST COMPARISON EVALUATION PROCESS

1 EXECUTIVE SUMMARY

1.1 Summary of the decision problem

The company's decision problem broadly aligns with the final scope issued by the National Institute for Health and Care Excellence (NICE).

The population specified in the NICE scope for the current appraisal is adults with unresectable advanced hepatocellular carcinoma (HCC) with Child-Pugh grade A liver impairment when conventional transarterial therapies (CTTs) are inappropriate, which was the population that selective internal radiation therapy (SIRT) treatments SIR-Spheres® and TheraSphere® were recommended for in TA688.[1]

The population considered in the clinical and economic evidence for the indicated population within TA688 was more inclusive in terms of Barcelona Clinic Liver Cancer (BCLC) staging, with both intermediate (BCLC B) and advanced (BCLC C) included. Clinical advice to the evidence assessment group (EAG) and company in intervening TA666 of atezolizumab with bevacizumab,[2] suggested that BCLC B patients not amenable to locoregional therapies (i.e., CTT) are not easily clinically distinguishable from BCLC C patients and thus atezolizumab with bevacizumab was recommended for both BCLC B and BCLC C patients.

The EAG considers that the relevant indicated population for this current appraisal should be primarily determined by ineligibility for surgical resection or CTT, i.e., adult patients who are not eligible for CTT *or* surgical resection *and* have BCLC B *or* BCLC C HCC with Child-Pugh grade A liver impairment are relevant to the decision problem. This reflects the company's proposed position of QuiremSpheres and aligns with how SIR-Spheres and TheraSphere are currently used within NHS clinical practice according to clinical advice to the EAG.

1.2 Summary of the clinical evidence

The clinical evidence in the company submission (CS) focuses on three prospective single arm studies (HEPAR Primary, 31 treated patients; Jena Clinical Experience, 14 treated patients; RETOUCH, 15 treated patients) and one retrospective single arm study (RECORD, 55 treated patients) of QuiremSpheres®.

The company have conducted a naïve visual comparison of treatment estimates of QuiremSpheres and comparators (six studies of SIR-Spheres or TheraSphere). The EAG considers that this approach is acceptable given the anticipated observational nature of the relevant studies. The EAG considers that an additional three comparator studies (SIR-Spheres or TheraSphere) provide relevant outcome data for a cohort of patients the majority of whom align with the population relevant to the decision problem and that the cohort recruited to the RETOUCH study is not reflective of the relevant population. Therefore, the EAG includes three QuiremSpheres studies and nine comparator studies in a naïve comparison.

The EAG considers that there is no evidence of any important differences in terms of overall survival (OS), progression free survival (PFS) or objective response rate (ORR) between QuiremSpheres and SIR-Spheres or TheraSphere. There is also no evidence of any important differences in the safety profile of QuiremSpheres compared to SIR-Spheres or TheraSphere. Health-related quality of life (HRQoL) data available are too limited to draw any meaningful comparisons between QuiremSpheres and comparators.

1.3 Summary of the cost comparison evidence

The company's cost comparison analysis assumes equivalence of QuiremSpheres in terms of overall health outcomes as well as healthcare resource use, treatment and administration costs including dose-verification imaging and adverse event costs relative to the comparator technologies SIR-Spheres and TheraSphere. Therefore, only the acquisition costs of the technologies (i.e. the cost per SIRT procedure performed) are included in the cost comparison analysis. The EAG considers this approach to be appropriate and it is plausible that the addition of QuiremSpheres, using ^{99m}Tc-MAA (technetium-macroaggregated albumin) work-up product, as an alternative to SIR-Spheres or TheraSphere could be cost-neutral in this position.

1.4 EAG critique of cost comparison approach to this technology assessment

The EAG considers that a cost comparison approach is an appropriate method to assess this technology. The technical characteristics presented and clinical advice to the company and to the EAG suggest that it is reasonable to consider QuiremSpheres as a technical variant to SIR-Spheres and TheraSphere.

NICE requires that for acceptance of the cost comparison case, sufficient evidence in support of similarity between the intervention and comparator technologies, in terms of overall health outcomes must be presented. The EAG considers that these conditions have broadly been met given the circumstances, and that there is no evidence of any difference in health outcomes or safety profiles between QuiremSpheres and SIR-Spheres or TheraSphere.

Uncertainties remain, relating to low quality evidence provided by observational, retrospective, and non-comparative studies, heterogeneity of study and patient characteristics across studies and generalisability of results of the studies of SIRTs which include patients who would not be eligible to receive SIRT treatment in NHS clinical practice.

The availability of QuiremSpheres is not expected to change the clinical pathway for treating advanced unresectable HCC, as the proposed position of QuiremSpheres is as an alternative SIRT treatment alongside SIR-Spheres or TheraSphere.

Since the appraisal of SIR-Spheres and TheraSphere within TA688, the immunotherapy combination atezolizumab with bevacizumab has been recommended for treating advanced or unresectable HCC, replacing sorafenib as the first-line standard of care for this population in the NHS. The EAG considers that there is insufficient robust clinical effectiveness evidence available to inform a cost-effectiveness analysis of QuiremSpheres compared to SIR-Spheres or TheraSphere, or to atezolizumab with bevacizumab, the current standard of care in NHS practice for treating unresectable or advanced HCC.

2 BACKGROUND

2.1 Introduction

This Evidence Assessment Group (EAG) report is a critique of the company's submission (CS) from Terumo which informs the National Institute for Health and Care Excellence's (NICE's) part review of health technology guidance TA688 'Selective internal radiation therapies for treating hepatocellular carcinoma', published in March 2021.[1]

The Multiple Technology Appraisal (MTA) of selective internal radiation therapies (SIRTs) for hepatocellular carcinoma (HCC) included the appraisal of evidence from SIR-Spheres® (manufactured by Sirtex), TheraSphere® (manufactured by Boston Scientific), and QuiremSpheres® (manufactured by Terumo, and Quirem Medical before its acquisition by Terumo in 2020), for early, intermediate, and advanced HCC. After appraisal by the University of York assessment group (AG), the NICE committee recommended SIR-Spheres and TheraSphere for treating unresectable advanced HCC for people with Child-Pugh grade A liver impairment when conventional transarterial therapies (CTTs) are inappropriate. Although clinical trial data were limited, and compared SIRTs only to sorafenib (the standard of care at the time), the committee recommended SIR-Spheres and TheraSphere on the basis of cost savings and potentially reduced side effects. QuiremSpheres was not recommended as it was considered less effective and costlier than sorafenib.

The CS for the current appraisal reports on the clinical effectiveness and cost comparison of SIRT with QuiremSpheres within its marketing authorisation for treating unresectable advanced HCC. Comparators are the previously recommended SIR-Spheres and TheraSphere. QuiremScout®, a product which uses the same microspheres for the workup procedure of QuiremSpheres, which was included within the cost of QuiremSpheres for TA688, is not included as part of the current appraisal.

The company performed an update of the systematic literature review of SIRT for HCC conducted to inform TA688. In the CS, evidence is presented from four single-arm studies on QuiremSpheres (two unpublished, and all conducted subsequent to the submission of evidence for TA688), and six comparator studies (two of which were included within TA688). Updated costs for QuiremSpheres are also presented.

Two clinical experts, a consultant hepatologist and a Principal Clinical Scientist (medical physicist), advised the EAG during the writing of this report. Clarification on some aspects of the CS were requested from the company by the EAG via NICE on 30th January 2023, and a response was received by the EAG on 14th of February 2023.

2.2 Epidemiology and staging of HCC

Epidemiology of HCC in England, including common causes, is described in the CS (Section B1.3, pp. 12-13). The Barcelona Clinic Liver Cancer (BCLC) staging system, which is used to establish prognosis and enable the selection of appropriate treatment based on underlying liver dysfunction, Eastern Cooperative Oncology Group (ECOG) performance status (PS) and cancer stage, is also presented in the CS (Figure 1, p. 13).

In 2017, 79% of patients diagnosed with HCC in England were men and 21% were women,[3] with most cases occurring in adults over the age of 60. In the HCC BRIDGE study, the mean age of diagnosis of patients across Europe was 65 and 72% were classed as having Child-Pugh grade A liver impairment at diagnosis, indicating normal liver function.[4]

An audit of 11 UK centres between January 2018 and August 2020 reported on patients with advanced HCC suitable for systemic therapy, as determined in a Multi-Disciplinary Team (MDT) meeting and with a subsequent assessment in a local clinic.[5] Out of 361 patients with Child-Pugh grade A liver impairment, 82% were men and the median age at assessment was 68. Cirrhosis, identified by the EAG's clinical advisor as a key predictor of prognosis, was present in 66% of patients. Most patients experienced some limitations to their daily activities; 21% with ECOG PS 0, 62% with ECOG PS 1 and 17% with ECOG PS 2. 57% of patients had received no prior treatments and 34% of patients had received prior CTT therapies of transarterial chemoembolization (TACE) or transarterial embolization (TAE).

2.3 Description of SIRT treatment

2.3.1 Clinical pathway

Since the MTA of QuiremSpheres, SIR-Spheres, and TheraSphere for HCC (TA688) began in 2019, the clinical pathway for patients with advanced HCC has changed. The combination of immunotherapies, atezolizumab with bevacizumab, has been recommended by NICE for treating advanced or unresectable HCC only for adults who have not had previous systemic treatment and have Child-Pugh grade A liver impairment and an ECOG PS of 0 or 1 (TA666)[2]. This replaced sorafenib as the first-line systemic therapy in the NHS. Durvalumab with tremelimumab has also been shown to be superior to sorafenib in terms of overall survival (OS) for patients with unresectable HCC;[6] however, durvalumab with tremelimumab is yet to undergo NICE appraisal so is not yet available for patients in the NHS.[7]

The clinical pathway of care in HCC is described in the CS (pp. 13-15, Figure 1, and Figure 2). CS, Figure 1 outlines proposed treatment strategies for different BCLC stages of HCC. It should be noted

that SIRTs, including QuiremSpheres, are not represented on this figure and the availability of systemic treatments for NHS patients is subject to NICE recommendation.

The company's proposed position for QuiremSpheres in NHS clinical practice is described in response to clarification question A1 as an alternative to SIR-Spheres and TheraSphere, for patients with intermediate stage HCC (BCLC stage B) when TACE is not feasible or inappropriate; defined as those with a combination of large tumours (>6 cm), a large number of tumour nodules (≥ 7), and bilobar, multifocal tumours (response to clarification question A7a). QuiremSpheres is also positioned for patients with BCLC stage B HCC when diffuse, infiltrative, extensive bilobar liver involvement is present, or for patients with advanced HCC (BCLC stage C) as an alternative to systematic therapy (response to clarification question A1). The company have also indicated a role for QuiremSpheres in treating advanced stage HCC with portal invasion and no extrahepatic spread (response to clarification question B7). The company's proposed position of QuiremSpheres is outlined in Table 1.

Table 1 Proposed position of QuiremSpheres in NHS clinical practice

HCC BCLC stage	Patient / Tumour characteristics	Recommended first-line treatment	Potential role for QuiremSpheres?
Very early stage (0)	No role for QuiremSpheres		
Early stage (A)	No role for QuiremSpheres		
Intermediate stage (B)	Meeting liver transplant criteria	Transplant	No
	Well defined nodules, preserved portal flow, selective access.	TACE	No
	Diffuse, infiltrative, extensive bilobar liver involvement. No portal invasion. No extrahepatic spread.	Atezolizumab with Bevacizumab	Yes, if Child-Pugh grade A (normal liver function).
Advanced stage (C)	Portal vein invasion and/ or extrahepatic spread.	Atezolizumab with Bevacizumab	Yes, if Child-Pugh grade A (normal liver function).
Terminal stage (D)	No role for QuiremSpheres.		

Abbreviations: TACE: transarterial chemoembolization.

2.3.2 Case for cost comparison: mechanism of action

The NICE guide to the methods of technology appraisal states that "for the acceptance of a cost comparison case, evidence in support of similarity between the intervention and comparator technologies, in terms of overall health outcomes, must be presented."[8]

Evidence to support similarity of QuiremSpheres with SIR-Spheres and TheraSphere presented in the CS includes:

- A comparison of the technical characteristics and mechanisms of action of the SIRTs, including a description of the technical advantages of QuiremSpheres (CS, Section B.1.3, pp11-19)
- Clinical Expert Validation (CS, pp. 62-65)
- Dutch health technology assessment agency (Zorginstituut) guidance[9] and NICE Intervention Procedure Guidelines (IPGs) for SIRTs (CS, p12)
- Naïve comparisons of clinical effectiveness outcomes (OS, PFS and ORR) and safety from studies of QuiremSpheres, SIR-Spheres, and TheraSphere (CS, Section B.3.9)

2.3.2.1 Technical characteristics and mechanisms of action of SIRTs

During a SIRT procedure, radioactive forms of chemical elements (yttrium-90 for SIR-Spheres and TheraSphere, and holmium-166 for QuiremSpheres) are administered into the hepatic artery via a catheter as microspheres (microscopic beads) to deliver radiation to the tumour tissue. Microspheres remain in the capillary bed of the liver tumour(s), from where radiation is emitted in higher doses to tumour tissue than to healthy liver issue.

Table 2 describes the technical specifications, mechanisms of action and treatment procedures associated with QuiremSpheres, SIR-Spheres and TheraSphere, supplementing the information presented in the CS (Table 2, Table 3 and Section B.1.3) with additional information submitted by the companies for TA688.[1]

QuiremSpheres uses poly-L-lactic acid (PLLA) microspheres containing holmium-166(^{166}Ho), whereas SIR-Spheres and TheraSphere use resin and glass microspheres respectively containing yttrium-90 (^{90}Y). While the therapeutic mode (i.e. tumour cell death induced by beta radiation) is the same, QuiremSpheres allow for potentially better visualisation of the microspheres using single-photon emission computed tomography due to its gamma emission (compared to bremsstrahlung imaging for ^{90}Y). ^{166}Ho is also paramagnetic, allowing for imaging of the microspheres via magnetic resonance imaging (MRI) technology.

Table 2 Characteristics of QuiremSpheres, SIR-Spheres and TheraSphere (adapted from CS Table 3, pp18-19)

Characteristics	QuiremSpheres	SIR-Spheres	TheraSphere
TECHNICAL CHARACTERISTICS			
Isotope	^{166}Ho	^{90}Y	^{90}Y
Half-life	26.8 hours	64.1 hours	64.1 hours
Time to 90% of dose deposited	4 days	11 days	11 days
Activity per microsphere	200-400 Bq	50 Bq	2500 Bq
Penetration range in soft tissue	max 8.7 mm, mean 2.5 mm	max 11 mm, mean 2.5 mm	max 11 mm, mean 2.5 mm
Radiation emitted	Beta radiation (therapeutic mode of action); gamma radiation (post-treatment evaluation	Beta radiation (therapeutic mode of action)	Beta radiation (therapeutic mode of action)
Material of microsphere	PLLA (biodegradable)	resin (non-biodegradable)	glass (non-biodegradable)
Mean diameter of microsphere	25-35 µm	20-60 µm	20-30 µm
Typical number of microspheres administered (x million)	20-30	40-60	1.2-8
TREATMENT PROCEDURE			
Work-up imaging surrogate	^{99m}Tc-MAA or ^{166}Ho (QuiremScout)	^{99m}Tc-MAA	^{99m}Tc-MAA
Work-up imaging technology	SPECT/CT	SPECT/CT	SPECT/CT
Product supplied	Patient specific vials (up to 3 vials) ordered following work-up. Available in all increments with 2 decimals. No preparation needed	Mother vial Requires preparation of patient specific dose	Patient specific vial ordered following work-up. Available in 0.5 GBq increments between 3 GBq-20 GBq. No preparation needed
Calculation of required dose	Standard dosimetry or based on dose simulation using QuiremScout® or ^{99m}Tc-MAA.	Standard dosimetry or based on dose simulation using ^{99m}Tc-MAA.	Standard dosimetry or based on dose simulation using ^{99m}Tc-MAA.
Post-treatment imaging	SPECT/CT or MRI	SPECT/CT or PET-CT	SPECT/CT or PET-CT
Hospital visit(s) required	Minimum one day hospital appointment for work up and separate day / visit for treatment	Minimum one day / visit hospital appointment for work up and treatment	Minimum one day hospital appointment for work up and separate day/ visit for treatment

Abbreviations: Bq: becquerel; CT: computed tomography; ^{166}Ho: Holmium-166; MRI: magnetic resonance imaging; PET-CT: positron emission tomography- computed tomography; PLLA: poly-L-lactic acid; SPECT: single-photon emission computed tomography; ^{99m}Tc-MAA: ^{99m}Tc-macroaggregated albumin; ^{90}Y: Yttrium-90.

The company consider the possibility of MRI imaging to be a technical advantage of QuiremSpheres (CS, p16). Clinical advice to the EAG is that imaging using MRI for work-up and post-treatment may result in improved images of radiation and may have advantages for dosimetry during work-up; however, logistically, SPECT-CT more likely to be the preferred option dependent on the capacity of the treatment centre.

The difference in radioactive isotope means QuiremSpheres differs from the SIR-Spheres and TheraSphere with regards to its half-life, time taken to deposit 90% of the dose, and penetration range into tissue. There are also differences between the three SIRTs in the size and number of microsphere beads administered (Table 2).

Clinical advice to the EAG is that the lower maximum penetration rate is due to the lower beta-energy emitted by ^{166}Ho compared to ^{90}Y. This lower penetration range of QuiremSpheres in soft tissue may mean it is less likely to damage healthy liver tissue, but it may also affect the ability of the radiation to effectively reach all tumour tissue.

The number of microspheres per administration is higher for SIR-Spheres and lower for TheraSphere compared to QuiremSpheres (Table 2). Clinical advice to the EAG is that a higher number of microspheres may lead to a better, more uniform delivery of the radiation, whilst a lower number of microspheres may reduce the risk of vascular stasis and thus allow subsequent SIRT procedures.

Prior to administering any SIRT, a work-up procedure is required for treatment planning, to occlude vessels which may carry microspheres away from the liver, and to determine patient eligibility for the full SIRT procedure; a high level of lung shunt or extra-hepatic uptake would contraindicate SIRT. The work-up also allows a more exact calculation of the patient-specific treatment dose for eligible patients compared to standard dosimetry.

The work-up procedure of QuiremSpheres and TheraSphere are patient-specific, meaning that a personalised dose is ordered following dosimetry calculations based on imaging and delivered to the treatment centre. For SIR-Spheres, the dose is prepared on site upon receipt of a mother vial, which means that in principle, the work-up and treatment could be completed in one visit.[10]

However, clinical advice to the EAG is that it is very unlikely that work-up and SIRT treatment would be completed in a single visit on a single day for any of the SIRTs due to the complexity of the work-up, the number of procedures and departments involved in the work-up, dose preparation, and administration of SIRTs, and the potential risk of wastage if a patient cannot received a treatment ordered in advance. In practice, a patient would likely undergo the SIRT procedure several days after work-up, depending on availability of the radiology suite at the treatment centre.

Clinical advice to the EAG is that the shorter half-life of ^{166}Ho, meaning that the therapeutic radiation level within the spheres drops sooner, has advantages as highlighted by the company in the CS (p17) but this may also have practical disadvantages in the event of any delays to the delivery of a patient-specific dose for the SIRT procedure following work-up.

Work-up procedures are performed with a surrogate marker (^{99m}Tc-macroaggregated albumin [^{99m}Tc-MAA]) injected into the hepatic artery using the same catheter position as would be used for a SIRT procedure. The work-up procedure for QuiremSpheres can also be performed using a lower dose of ^{166}Ho (QuiremScout) rather than a ^{99m}Tc-MAA based surrogate marker, but this is not being proposed as part of the current appraisal.

For two of the studies[11, 12] of QuiremSpheres submitted for the current appraisal, all patients received work-up with QuiremScout prior to treatment with QuiremSpheres. In the Jena Clinical Experience study[13], both QuiremScout and ^{99m}Tc-MAA were used for work-up, but the proportions of each surrogate marker used were not reported and in the RECORD study[14], QuiremScout was used in 63.7% of patients and ^{99m}Tc-MAA in 36.3% of patients. The company state that the choice between QuiremScout and ^{99m}Tc-MAA in these studies is based on hospital preference and access to the products and that there were no significant differences in the visually graded targets of the work-up products used for therapy decision (response to clarification question A8).

2.3.3.2 Clinical expert validation and HTA guidance

The company provide clinical expert validation of similarity of clinical efficacy and adverse events between QuiremSpheres and ^{90}Y SIRTs, and the anticipated position of QuiremSpheres in the clinical pathway as an alternative to ^{90}Y SIRTs (CS, pp. 64-65). The Dutch Zorginstituut reassessed the evidence for QuiremSpheres for HCC in 2022[9], after publication of the HEPAR Primary study[11]. They concluded that, whilst there are technical differences between the three SIRTs, the limited evidence available appears to suggest that clinical outcomes are comparable and that holmium-166 microspheres are a “technical variant” of ^{90}Y microspheres.

Clinical advice to the EAG agrees with the clinical expert validation provided to the company and that QuiremSpheres can be considered as a ‘technical variant’ of SIR-Spheres and TheraSphere due to the similar administration methods and same therapeutic mode of action. However, the emission of gamma-radiation and the implications for imaging are technical differences which could provide technical advantages or practical disadvantages for QuiremSpheres. The company also provide clinical expert validation regarding the feasibility of ‘switching’ current patients currently receiving ^{90}Y SIRTs to QuiremSpheres (CS, p65). Clinical advice to the EAG suggests that a choice between QuiremSpheres and ^{90}Y SIRTs or switching patients currently receiving ^{90}Y SIRTs to QuiremSpheres may not be necessary in NHS practice and that if approved, treatment centres may offer both

QuiremSpheres and ^{90}Y SIRTs, with the choice between SIRTs made based on clinician preference and familiarity with a specific SIRT.

The company refer to two published NICE Interventional Procedure Guidelines (IPGs) of SIRT for unresectable primary intrahepatic cholangiocarcinoma and unresectable colorectal metastases in the liver[15, 16] and one IPG in development of SIRT for neuroendocrine tumours that have metastasised to the liver.[17] These IPGs do not make any distinction between the clinical effectiveness of QuiremSpheres, SIR-Spheres and TheraSphere. The EAG notes that NICE recommends SIRTs for these indications only under special arrangements, such as for research, due to limited evidence of effectiveness and safety and considers that these IPGs do not provide supportive evidence of similarity between QuiremSpheres and the ^{90}Y SIRTs for the population outlined in the NICE scope for the current appraisal.

2.3.3.3 EAG commentary on mechanism of action of SIRTs

There are differences between QuiremSpheres, SIR-Spheres and TheraSphere in terms of technical characteristics, work-up, imaging and administration. While some of these differences may offer technical advantages for QuiremSpheres as described by the company (CS, pp. 16-17), the EAG is not aware of any evidence that these technical advantages translate into improved clinical outcomes for patients. Furthermore, these differences may also result in some practical disadvantages of QuiremSpheres, as described by the clinical advisors to the EAG.

Clinical advice to the EAG is that technical differences in half-life, penetration range, size and number of microspheres, work-up product and imaging technology are unlikely to significantly impact on clinical outcomes. Therefore, the EAG considers that it is reasonable to consider QuiremSpheres as a technical variant to SIR-Spheres and TheraSphere.

The EAG emphasises that the use of QuiremScout is associated with an additional procurement cost, which does not form part of the QuiremSpheres procedure for the present cost comparison. The QuiremSpheres procedure under cost comparison for the current appraisal must be assumed to use the ^{99m}Tc-MAA work-up product.

The EAG critique of the naïve comparisons of clinical effectiveness outcomes and safety from studies of QuiremSpheres, SIR-Spheres, and TheraSphere is provided in section 4.

3 CRITIQUE OF THE DECISION PROBLEM IN THE COMPANY'S SUBMISSION

The company's decision problem broadly aligns with the final scope issued by NICE (Table 3). The EAG comments below on the definition of the population within the NICE scope and the outcome data provided in the CS and in response to clarification.

Table 3 Summary of the decision problem (adapted from CS Table 1, pp7-8)

	Final NICE scope	Company's decision problem	EAG comments
Population	Adults with unresectable advanced HCC with Child-Pugh grade A liver impairment when CTT are inappropriate.	Same as final scope issued by NICE.	The EAG considers that the relevant population is adult patients who are not eligible for CTT or surgical resection and have BCLC B or BCLC C HCC with Child-Pugh grade A liver impairment. Clinical evidence provided in CS and in clarification reflects a broader population than the relevant population defined above
Intervention	QuiremSpheres	Same as final scope issued by NICE.	No concerns.
Comparators	SIR-Spheres and TheraSphere.	Same as final scope issued by NICE.	No concerns.
Outcomes	• 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.	Same as final scope issued by NICE.	The outcomes in the CS are appropriate and match the scope with the following exceptions: • No clinical effectiveness results are provided for 'rates of liver transplant or surgical resection' The EAG considers this to be appropriate. • Limited data presented for health-related quality of life, therefore equivalence of QuiremSpheres with comparators in terms of this outcome is very uncertain
Economic analysis	Cost comparison	Same as final scope issued by NICE.	No concerns.

Abbreviations: BCLC: Barcelona Clinic Liver Cancer; CTT: conventional transarterial therapies; EAG: Evidence Assessment Group; HCC: hepatocellular carcinoma.

3.1 Population

The population specified in the NICE scope for the current appraisal is adults with unresectable advanced HCC with Child-Pugh grade A liver impairment when CTT are inappropriate, which was the population that SIR-Spheres and TheraSphere were recommended for in TA688.

The trial and economic evidence considered in the Assessment Group (AG) report for TA688 was based on a population defined as patients:

- with unresectable intermediate (BCLC B) or advanced (BCLC C) HCC.
- who are ineligible for any CTT.
- who have no extrahepatic disease.

The resulting indicated population in the TA688 FAD is restricted to advanced HCC, presumably to align with the guidance for sorafenib, the main comparator to the SIRT treatments in TA688, which is indicated for advanced HCC only (TA474).[18] Therefore, the population defined in the TA688 AG report is more inclusive in terms of BCLC staging than implied in the resulting guidance and the scope for the current appraisal, but also excludes those with extrahepatic disease who would be eligible for systemic therapies. In intervening TA666 of atezolizumab with bevacizumab,[2] conducted since the MTA for TA688 began, the guidance includes ‘advanced *or* unresectable HCC', and is inclusive of patients 'not amenable to locoregional therapies', i.e. CTT. Clinical advice to EAG and company within TA666 suggested that BCLC B patients not amenable to locoregional therapies are not easily clinically distinguishable from BCLC C patients. Furthermore, it was not possible to present separate incremental cost-effectiveness ratios (ICERs) by subpopulation in TA666.

Whilst not in alignment with the population sorafenib is recommended for in TA474, it was accepted in TA666 that sorafenib and lenvatinib were standard of care in this BCLC B CTT-ineligible population, and thus atezolizumab with bevacizumab was recommended for both BCLC B and BCLC C patients.

The EAG, therefore, considers that the relevant indicated population for this current appraisal should be primarily determined by ineligibility for surgical resection or CTT. The EAG considers that clinical evidence for SIRT treatment in adult patients who are not eligible for CTT or surgical resection and have BCLC B or BCLC C HCC with Child-Pugh grade A liver impairment is relevant to the current decision problem.

The EAG acknowledges that the eligibility of a patient for CTT is based on multiple factors and therefore a CTT-ineligible population may be difficult to define or to identify retrospectively within a clinical study. The company defines, according to the Asia-Pacific Primary Liver Cancer Expert Consensus Statements,[19] that TACE is inappropriate for tumours which are large in size (> 6cm) and/or large in number (≥ 7 nodules), or large in number and bilobar multifocal (response to clarification question A7a).

The EAG notes that a wider range of HCC patients are included in the studies of QuiremSpheres, SIR-Spheres and TheraSphere than would be relevant to the current decision problem. The implication is that a substantial proportion of patients within some of the studies would not receive SIRT treatment in NHS practice. This introduces uncertainty into the clinical effectiveness results for QuiremSpheres and also into the comparative clinical effectiveness of QuiremSpheres compared to SIR-Spheres and TheraSphere. Further discussion is provided in Section 4.2.1.

3.2 Outcomes

No clinical effectiveness results are data are provided for the outcome rates of liver transplant or surgical resection. The company and the EAG consider that surgical resection is not a relevant outcome for a population with unresectable HCC. Clinical advice to the AG during TA688 was 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. The company agree with this clinical advice (response to clarification question C3), and clinical advice to the EAG for this current appraisal is that rate of transplant is not a relevant outcome for this population.

Very limited data are available for health-related quality of life (HRQoL) from the studies of QuiremSpheres and of SIR-Spheres and TheraSphere included in the CS (Table 13 and response to clarification question A12). The EAG therefore considers that the case for equivalence of HRQoL outcomes for QuiremSpheres compared to SIR-Spheres and TheraSphere to be very uncertain (see Section 4.3.4).

4 SUMMARY OF THE EAG'S CRITIQUE OF CLINICAL EFFECTIVENESS EVIDENCE SUBMITTED

4.1 Critique of the methods of the literature review

4.1.1 Summary of systematic literature review (SLR) conducted for TA688

The SLR conducted by the AG to inform TA688 identified studies including patients with early, intermediate, and advanced stage HCC treated with SIRTs and relevant comparators, in line with the NICE scope for TA688. The SLR included 26 comparative studies of SIR-Spheres and/or TheraSphere and one non-comparative study of QuiremSpheres.[20] A network meta-analysis (NMA) of patients with unresectable HCC who are ineligible for CTTs was performed with two RCTs comparing SIR-Spheres to sorafenib (SARAH[21], SIRveNIB[22]), an RCT comparing sorafenib and lenvatinib[23] and two retrospective studies comparing SIR-Spheres and Therasphere.[24, 25] No comparisons of QuiremSpheres to other therapies, direct or indirect, could be made in TA688.

4.1.2 SLR conducted for the current appraisal

The clinical effectiveness SLR conducted by the company to inform the current appraisal is outlined in response to clarification questions A2 and A3.

4.1.2.1 Searches

An EAG critique of the clinical effectiveness searches is provided in Appendix 1, Table 11.

The search strategies for the identification of studies on the clinical effectiveness of QuiremSpheres, SIR-Spheres and TheraSphere for treating unresectable advanced HCC were not supplied in the CS nor in the clarification response. Therefore, it was not possible for the EAG to check and verify the strategies used for the identification of the evidence for the clinical effectiveness SLR.

The company supplied a description of the searches in their response to clarification question A2. The company partially updated the searches from the previous SLR of SIRT treatments for HCC conducted to inform TA688[26] to identify any studies in the MEDLINE database, published between 25th January 2019 and 1st December 2023. As the company only searched MEDLINE, relevant studies in other databases and resources would not have been identified by this approach. In addition, inappropriate limits were applied to the search of MEDLINE which further reduced the comprehensiveness of the search: a limit to English language studies only, and a further restriction to those studies with available full text. Searches for unpublished studies, ongoing studies and grey literature were not reported. Therefore, the EAG cannot be certain that all potentially relevant studies, both published and unpublished, were identified in the company searches.

4.1.2.2 Study selection

Eligibility criteria and study selection methods used by the company in the SLR are outlined in response to clarification questions A2 to A4.

The company have selected studies with the aim of conducting a naïve visual comparison of treatment estimates of QuiremSpheres and comparators (SIR-Spheres and TheraSphere). The EAG considers that this approach is acceptable given the anticipated observational nature of the relevant studies. The EAG agrees that a mixed treatment comparison using formal synthesis methods, such as an unanchored matching adjusted indirect comparison would be subject to great uncertainty and would not provide any meaningful evidence in addition to a naïve comparison. Nonetheless, a treatment comparison, whether via synthesis or a naïve visual comparison should include all relevant evidence to the decision problem. The EAG considers that study selection has not been conducted[27] nor reported[28] according to systematic review standards.

Selection criteria provided are ambiguous, such as the cohort must be of a 'reasonable size' and the study must be of an 'appropriate design for allowing comparison with available data for QuiremSpheres' without further defining sample sizes that would be considered reasonable or designs that would be considered appropriate (response to clarification question A2).

The company PRISMA flowchart (response to clarification question A3b) indicates that out of 120 studies which 'met broad inclusion criteria,' 108 studies were excluded at full text screening. A list of these 108 studies has not been provided by the company, therefore the EAG is unable to verify the relevance of these studies to the decision problem (Table 3).

The remaining 12 studies identified in the company search were 'included in the final evaluation' for the naïve comparison. Two unpublished QuiremSpheres studies (RECORD[14] and RETOUCH[12]) and the two RCTs comparing SIR-Spheres to sorafenib (SARAH[21] and SIRveNIB[22]) which were included in TA688 were also included in this final evaluation. These four studies identified from other sources are not reflected on the PRISMA flowchart (response to clarification question A3b). Out of these 16 studies evaluated, the company excluded six comparator studies[29-35] identified in the search (response to clarification question A3c) and included four QuiremSpheres studies[11-14], four SIR-Spheres studies[21, 22, 36, 37] and two TheraSphere studies[34, 38] in the naïve comparisons (CS, Section B3.9).

The EAG has assessed eligibility of the 16 studies considered for inclusion in the naïve comparison according to the population, intervention, comparators, and outcomes outlined in the decision problem (Table 3). The company and EAG assessments of eligibility are presented in

Table 4; see Appendix 2, Table 12 and Table 13 for further details of patient baseline characteristics and

Table 14 for clinical effectiveness results extracted by the EAG from the QuiremSpheres and comparator studies.

Table 4 Company and EAG eligibility assessment for naïve comparison of QuiremSpheres and comparators (SIR-Spheres and TheraSphere)

Trial	SIRT interventions	Source	Included in naïve comparison		EAG comments on eligibility
			Company	EAG*	
Reinders 2022 (HEPAR Primary)[11]	QuiremSpheres	Company SLR; study known to the company	Yes	Yes	The majority of the cohort aligns with the relevant population (all treated patients BCLC stage B or C, 90% Child-Pugh grade A liver impairment). Cirrhosis was present in 65% of the cohort, which is lower than would be expected in NHS clinical practice according to the clinical advice. Relevant outcome data are reported (OS, ORR and AEs).
Drescher 2023 (Jena Clinical Experience) [13]	QuiremSpheres	Company SLR; study known to the company	Yes	Yes	The majority of the HCC cohort (n=14) aligns with the relevant population (78% of patients BCLC stage B or C, and 93% Child-Pugh grade A liver impairment). Five patients (36%) received active treatment after QuiremSpheres, which suggests they would not have been eligible for SIRT in the NHS (2 received TACE, 1 resection, and 2 liver transplantations). Relevant outcome data are reported (OS, PFS, ORR and AEs).
RECORD[14]	QuiremSpheres	Unpublished study known to the company	Yes	Yes	The majority of the HCC cohort aligns with the relevant population (78% of patients BCLC stage B or C, and 65.5% Child-Pugh grade A liver impairment). BCLC stage was missing for 13% of patients and 34.5% of patients had Child Pugh grade B or C liver impairment so would not have been eligible for SIRT in the NHS. In the full cohort, treatment was intended to be palliative in only 66.4% of the cases. Relevant outcome data are reported (OS, PFS, ORR and AEs).
RETOUCH[12]	QuiremSpheres	Unpublished study known to the company	Yes	NO*	The majority of the cohort does not align with the relevant population (73% of patients BCLC stage A and 80% with solitary tumours, QuiremSpheres used as downstaging or bridging-therapy).
Vilgrain 2017 (SARAH)[21]	SIR-Spheres	Included in TA688	Yes	Yes	The majority of the cohort aligns with the relevant population (96% of patients BCLC stage B or C, and 87.9% Child-Pugh grade A liver impairment). Relevant outcome data are reported (OS, PFS, ORR and AEs).
Chow 2018 (SIRveNIB)[22]	SIR-Spheres	Included in TA688	Yes	Yes	The majority of the cohort aligns with the relevant population (all patients BCLC stage B or C, and 90.0% Child-Pugh grade A liver impairment and 'not amenable to curative treatment modalities.' Relevant outcome data are reported (OS, PFS, ORR and AEs).
Frantz 2021 (RESiN)[36]	SIR-Spheres	Company SLR	Yes	Yes	The majority of the cohort aligns with the relevant population (74% of patients BCLC stage B or C, and 99% Child-Pugh grade A liver impairment). A small proportion of patients (4.5%) received treatment with the intend of bridging (if BCLC stage A) or downstaging to transplant (if BCLC stage B), and 0.8% received resection after treatment with SIR-Spheres. Relevant outcome data are reported (OS, PFS, ORR and AEs).
Helmberger 2021 (CIRT)[37]	SIR-Spheres	Company SLR	Yes	Yes	BCLC stage not reported. Majority of the cohort Child-Pugh grade A liver impairment (80.9%). After treatment with SIR-Spheres, 8.1% of patients with HCC received TACE, and 3.3% resection or ablation. Relevant outcome data are reported (OS and AEs).

Van Thai 2021[35]	SIR-Spheres	Company SLR	No	YES*	The majority of the cohort aligns with the relevant population (all patients BCLC stage B or C, 94% Child-Pugh grade A liver impairment and 'unsuitable for radical treatments [surgery, liver transplantation, or percutaneous ablation] or chemoembolization as a result of the presence of PVT or extensive tumour burden'). Relevant outcome data (OS, ORR and AEs) are reported.
Casáns-Tormo 2023[30]	SIR-Spheres TheraSphere	Company SLR	No	YES*	The majority of the cohort aligns with the relevant population (all patients Child-Pugh grade A liver impairment, 92% BCLC stage B or C, 83% SIRT treatment palliative, median tumour size 63 [range 9-150]) and relevant outcome data (OS, ORR and AEs) are reported.
Hur 2023[31]	SIR-Spheres TheraSphere	Company SLR	No	YES*	All patients have advanced HCC with PVT. The company have indicated a role for QuiremSpheres in this population. Relevant outcome data are reported (OS, PFS, ORR and AEs).
Garin 2020 (DOSISPHERE-01)[38]	TheraSphere	Company SLR	Yes	Yes	All patients BCLC stage B or C, 79% of patients Child-Pugh grade A5 liver impairment (remaining 21% grade A6 or B7). One of the inclusion criteria was 'not amenable to surgery or local ablative treatment'. Relevant outcome data are reported (OS, PFS, ORR and AEs).
Lam 2022 (TARGET)[34]	TheraSphere	Company SLR	Yes	Yes	The majority of the cohort aligns with the relevant population (87.0% of patients BCLC stage B or C, 89.5% of patients Child-Pugh grade A liver impairment).
Makary 2023[29]	^{90}Y SIRTs	Company SLR	No	No	Agree with company reason for exclusion; 77% of the cohort could be downstaged to or maintained within the Milan criteria which does not reflect the relevant population for this appraisal.
Dhondt 2022[32]	TheraSphere	Company SLR	No	No	Agree with company reason for exclusion; the study includes patients who are eligible for CTT.
Salem 2021[33]	TheraSphere	Company SLR	No	No	Agree with company reason for exclusion; the study includes patients who are eligible for CTT.

*Indicates a different judgment to the company of study eligibility for inclusion in the naïve comparison

Abbreviations: AEs: adverse events; BCLC: Barcelona Clinical Liver Cancer; CTT: conventional transarterial therapies; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PVT: portal vein thrombosis; SIRT: selective internal radiation therapies; SLR: systematic literature review, TACE: transarterial chemoembolization; ^{90}Y: yttrium-90.

The patient populations recruited to the 16 studies are broader than the population the EAG deems relevant for the decision problem (Section 3.1). The company further describes the relevance of the patient cohorts recruited to the four QuiremSpheres studies to the population defined in the decision problem (response to clarification question A7a and A7b). The EAG acknowledges the difficulty of assessing eligibility of the patient cohorts, particularly in terms of suitability for CTT which is determined by multiple factors (Section 2.3.1). Therefore, the EAG has adopted an inclusive approach and has included all studies of QuiremSpheres and comparators in which the majority of patients receiving SIRT align with the relevant population, or where outcome data for the relevant population are presented separately.

The EAG also considers studies which report relevant outcome data in any format to be eligible for inclusion in the naïve comparison. While studies which report the same summary statistics (e.g., median and 95% confidence intervals [CIs] for OS and PFS) may be more readily comparable in a visual format such as a forest plot, studies which provide alternative summary statistics for relevant outcomes (e.g., mean OS or PFS) should also be included in the naïve comparison. Therefore, the EAG has included three studies of comparators that were excluded by the company (Casáns-Tormo 2023[30], Hur 2023[31], Van Thai 2021[35]) in which the majority of patients receiving SIRT align with the relevant population, and relevant outcome data are reported. The EAG has also excluded one of the QuiremSpheres studies (RETOUCH[12]) from the naïve comparison, in which the majority of patients receiving SIRT did not align with the relevant population (Table 4).

4.2 Included studies

4.2.1 Patient and disease characteristics

Study characteristics and patient baseline characteristics of the four QuiremSpheres studies included by the company are presented in CS (Table 8 and Table 9 respectively). Patient baseline demographic characteristics and disease characteristics in the three QuiremSpheres studies and nine comparator studies included in the EAG naïve comparisons are presented in Appendix 2, Table 12 and Table 13.

Patients recruited into the studies of QuiremSpheres, ranging from a median age of 66.2 years[14] to 73 years[11, 13], were on average slightly older than patients recruited into the studies of comparators, ranging from a mean or median age of 59.4 years [31] to 66.3 years[21]. Cohorts recruited to the studies of QuiremSpheres and of comparators were majority male (67.8% to 93%) and where reported, cirrhosis, an important prognostic factor in HCC, was present in the majority of patients (65% to 97%). Of note, the QuiremSpheres HEPAR Primary study[11] recruited the lowest proportion of patients with cirrhosis (65%), which is lower than would be expected in NHS clinical practice, according to clinical advice to the EAG.

The proportion of patients with portal vein thrombosis (PVT) or invasion (PVI) present, a characteristic which contraindicates CTT, was variable across studies ranging from 10.9%[14] to 100%[31]. In most studies of QuiremSpheres and of comparators, the majority of the cohort had an ECOG PS of zero, indicating no restrictions in daily activities, with the exceptions of comparator studies DOSISPHERE-01[38] (48% with ECOG PS 0) and van Thai[35] (14% with ECOG PS 0). Despite the majority of the cohort aligning with the relevant population of the decision problem, the combination of restrictions to daily activities (85.6% of the cohort with ECOG PS 1 or 2), cirrhosis (97%), and PVT (63%) present suggests a worse prognosis for the cohort recruited to the van Thai study[35] compared to the other studies of QuiremSpheres and comparators.

Across all studies, the majority of the cohort were classified as having Child-Pugh grade A liver impairment at diagnosis (normal liver function) and were intermediate (BCLC stage B) or advanced (BCLC stage C) HCC and would therefore potentially be eligible to receive SIRT treatment with QuiremSpheres in NHS clinical practice within the position proposed by the company (Table 1).

All except one study[30] included a minority (up to 30.9%[14]) of patients with Child Pugh score B7 indicating mild to moderate liver damage and three studies[14, 37 36] included one or two patients with Child-Pugh grade C liver impairment, indicating severe liver damage which may limit treatment options. Two QuiremSpheres studies[13, 14] and two comparator studies[36 34] included between 5.5% and 19% of patients with early stage HCC (BCLC stage A) and one QuiremSpheres study[14] included 3.6% of patients with very early stage HCC (BCLC stage 0). One comparator study included 7% of patients with end-stage HCC (BCLC stage D)[36] and one comparator study did not report BCLC stages[37]. All of these patients within these studies would likely not be eligible to receive SIRT treatment in the NHS (Table 1), which limits the generalisability of the results of these studies to NHS clinical practice.

Where reported, a minority of patients included in the studies had received prior treatments including systemic therapies, TACE, resection, and radiotherapies. The distribution of tumour involvement (unilobar vs bilobar) and the number of tumours present (one or multiple tumours, including over ten up to an uncountable number of tumours) varied greatly across the studies. The impact of these variations in patient baseline characteristics on the treatment effect estimates should be considered when drawing conclusions from the naïve comparisons of the QuiremSpheres studies to the comparator studies.

4.2.2 Quality assessment

Quality assessment of the four QuiremSpheres studies is presented in CS, Table 11, and Appendix D1.3. Quality assessment of the four of the comparator studies[34, 36-38] are presented in response to clarification question A6. The company refer to the quality assessment conducted of the SARAH[21] and SIRveNIB[22] studies within TA688.

The EAG believes that the company used the National Institute of Health (NIH) Quality Assessment Tool for before-after studies with no control group[39] for the quality assessments presented in CS Appendix D.1.3 and in response to clarification question A6 (rather than the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies as described in response to clarification question A5). The company did not use a specific tool for the quality assessments presented in CS, Table 11 (response to clarification question A5).

The EAG considers that aside from general limitations associated with observational evidence from single arm studies without control groups[27], the main limitations of the QuiremSpheres studies and the studies of SIR-Spheres and TheraSphere are the generalisability of the populations in these studies to patients who would receive SIRT treatment in NHS practice (Section 4.2.1), small sample sizes of some of the studies and the exclusion of data from patients lost to follow-up in some of the studies. The EAG has not performed a formal quality assessment of the three additional studies included within the EAG naïve comparisons[30, 31, 35], but considers that these studies are associated with similar limitations as those included in the company naïve comparison.

4.3 Clinical effectiveness evidence for QuiremSpheres

Table 7 of the CS describes four QuiremSpheres studies submitted as evidence by the company:

- The HEPAR Primary Study, a multi-centre, interventional, non-randomized, non-comparative, early Phase II trial[11]
- RETOUCH, a prospective, non-randomized, single-center pilot study[12]
- RECORD, a real-world, multicenter, retrospective registry[14]
- Jena Clinical Experience, a prospective single center observational study[13]

CS, Sections B3.2 to B 3.5 summarise the design, characteristics, and methodology of four QuiremSpheres studies and Section B.3.6 describes the clinical effectiveness results of these studies.

The company's naïve visual comparison of treatment effect estimates from QuiremSpheres studies and comparator studies is presented in Section B.3.9 of the CS. The company conclude that the results of the naïve comparison demonstrate that the OS, PFS and ORR outcomes for patients receiving QuiremSpheres are similar to those for patients receiving SIR-Spheres or TheraSphere.

The EAG does not consider the RETOUCH study[12] to be eligible for inclusion in the naïve comparison of QuiremSpheres and comparators (see Section 4.1.2.2). Appendix 2, Table 14 presents OS, PFS and ORR results extracted by the EAG from the QuiremSpheres studies and comparator studies included in the EAG naïve comparison. Figure 1 and

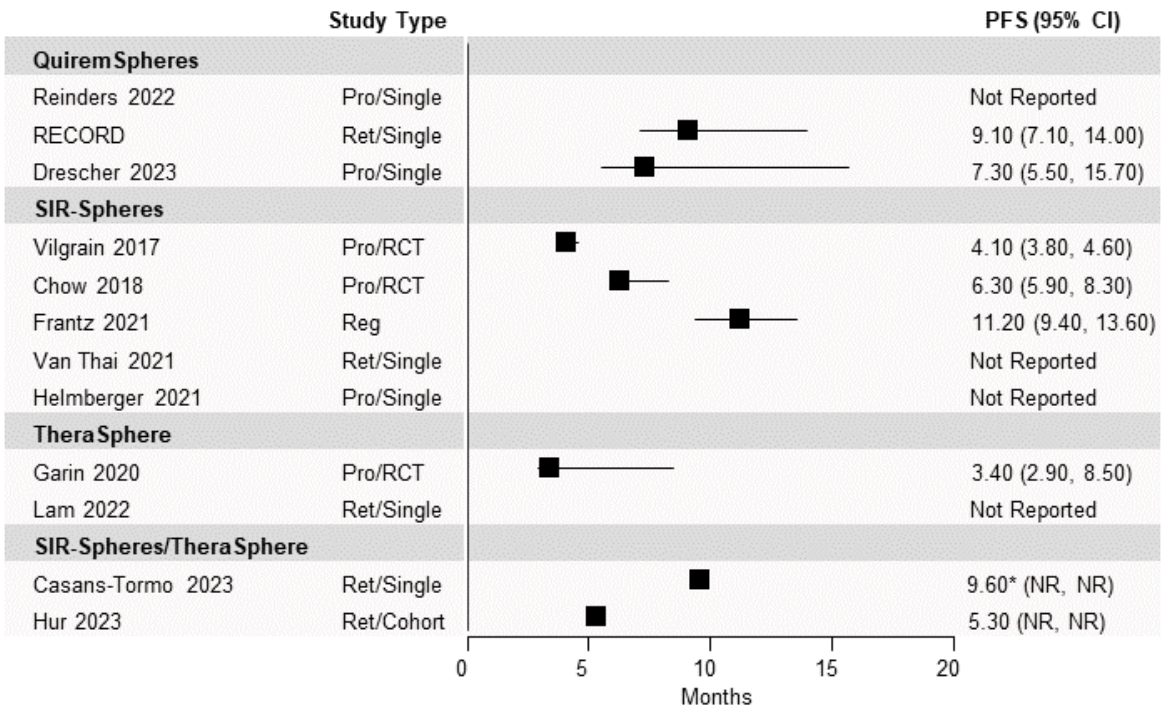

Figure 2 also visually display OS and PFS results of the EAG naïve comparison.

The study designs, the range of follow-up, and how the extent of follow-up was reported, varied across the QuiremSpheres studies and comparators studies. The comparability of OS and PFS results from studies with shorter follow-up, such as the RECORD study[14] of QuiremSpheres with a median of 7.1 months follow-up to longer term comparator registry studies RESiN[36] and CIRT[37] with two to four years of follow-up, must be considered when making naïve comparisons.

4.3.1 Overall survival (OS)

The estimates for median OS vary between 14.7 and 22.1 months for QuiremSpheres, and between 9.9 months and 28.2 months for comparator studies. Notably, the three RCTs of comparator treatments, SIR-Spheres (SARAH, [21] SIRveNIB[22]) and TheraSphere (DOSISPHERE-01[38]), showed the lowest median OS ranging from 9.9 to 11.3 months (Figure 1).

4.3.2 Progression free survival (PFS)

The estimates for median PFS were 8.8 months and 9.1 months for QuiremSpheres, PFS was not reported for in the HEPAR Primary study.[11] Where reported, median PFS ranged from 3.4 months to 10.6 months (for patients with Child-Pugh grade A liver impairment and intermediate BCLC stage B HCC[36]). Similar to OS, the PFS values observed in the three RCTs are amongst the lowest (

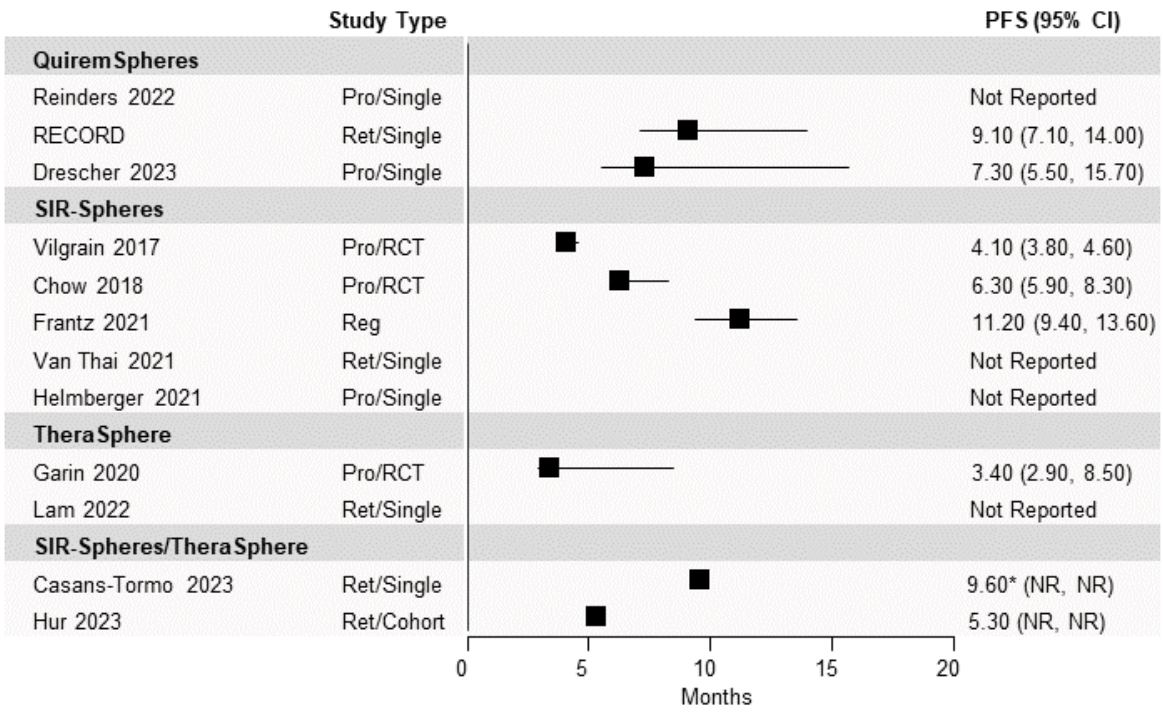

Figure 2). The EAG notes that the definition of progression events and censoring approaches varied across studies and different criteria were used to assess progression (RECIST 1.1 or mRECIST). These differences must be considered when making naïve comparisons of PFS treatment effect estimates.

4.3.3 Objective response rate

Response was evaluated using RECIST 1.1 criteria or mRECIST criteria. The mRECIST criteria were developed for HCC due to limitations of conventional RECIST guidelines which measure tumour size as an indicator of response.[40] However, the mRECIST criteria which consider target and non-target lesion response as well as liver response, and occurrence of new lesions may also have limitations and 'response' as indicated by mRESIST criteria may not correlate with with overall survival.[11]

The EAG considers that due to the difference in definitions of 'complete' and 'partial' response according to the two criteria,[40] ORR rates calculated using the two different criteria are not comparable. Specifically, ORR rates calculated using mRECIST criteria are generally higher than those calculated using RECIST 1.1. This is particularly evident from the results of the TARGET study,[34] where both criteria were used.

Restricting to ORR rates calculated using the mRECIST criteria only; ORR rates ranged from 53% to 84% for QuiremSpheres and from 54.7% to 69.2% for comparators. It should also be noted when making naïve comparisons that ORR rates are calculated at different time points and based on numbers of evaluable patients, which varied across the studies.

4.3.4 Health-related quality of life (HRQoL)

CS, Table 13 reports HRQoL results from the HEPAR Primary study[11] (median and IQR of EORTC QLQ C30 Global Health Status score) and from comparator studies SARAH[21] (mean and standard deviation EORTC QLQ C30 Global Health Status score) and SIRveNIB [22](mean and 95% CI of EQ 5D score). Additional results relating to EORTC QLQ C30 functional and symptom scales from the HEPAR Primary study[11] are provided in CS, Figure 5. The EAG considers that the available HRQoL data is too limited to draw meaningful comparisons between QuiremSpheres and comparators.

4.4 Adverse events

Adverse events (AEs) for reported in the HEPAR Primary[11] and RETOUCH[12] studies of QuiremSpheres are presented in Section B.3.10 of the CS (Table 14 and Table 15).

In the HEPAR Primary study, the most commonly observed grade 1/2 AEs were fatigue (54% of patients), abdominal pain (19%) and ascites (29%). Of the 19 serious AEs that occurred, 4 events (in 3 patients) which were deemed to be related or possibly related to treatment: 2 patients experienced spontaneous bacterial peritonitis (of which one case was fatal), and one patient experienced radiation-induced cholecystitis and cholangitis. In RETOUCH, grade 1/2 fever (observed in 20% of patients) and grade 1/2 fatigue (in 27% of the patients) were the most commonly observed AEs.

A comparison of AEs reported in the HEPAR Primary[11] and RETOUCH[12] studies to AEs reported in the SARAH[21] and SIRveNIB[22] RCTs of SIR-Spheres and the DOSISPHERE RCT[38] personalised versus standard dosimetry with TheraSphere are presented in CS, Table 16. The EAG considers that the types and frequency of AEs reported within the interventional studies of QuiremSpheres are in line with those reported in the interventional studies of SIR-Spheres and TheraSphere.

The EAG acknowledges that recording of AEs differs in observational and retrospective designed studies to the prospective recording within interventional studies and that rates of AEs reported across differing study designs may not be directly comparable. Nonetheless, observational studies such as registry studies often provide extended follow-up of patients compared to interventional studies to monitor for delayed or longer-term AEs. The EAG summarises the AEs reported in the observational and retrospective studies of QuiremSpheres and comparators.

Within the retrospective RECORD study of QuiremSpheres[14], 5 (3.4%) patients experienced at least one AE of special interest, including gastric ulceration in 3 patients (2.1%). Three of the five fatal AEs were considered related to device or procedure: one case of cholecystitis (related to procedure and device), one case of renal failure (related to the procedure), and one case of radioembolization induced liver disease (REILD) (related to the procedure and potentially related to the device).

Limited AE data were reported in the Jena Clinical Experience study[13] of QuiremSpheres; significant deterioration of liver function in two patients which may have been related to the procedure, and three cases of periprocedural abdominal pain.

A retrospective study of SIR-Spheres[35] reported gastrointestinal disorders and constitution symptoms at a similar rate to the interventional studies of SIRT, as well as one case of radiation pneumonitis. The retrospective TARGET study of TheraSphere also reported Grade 3 and 4 gastrointestinal and liver disorders, and constitutional symptoms at a similar rate to the interventional studies of SIRT. One retrospective study of SIRT (SIR-Spheres or TheraSphere)[31] reported treatment related AEs including gastrointestinal disorders and liver disorders as well as two cases of radiation pneumonitis and six cases of REILD. Another retrospective study of SIRT[30] reported limited adverse data for the entire study cohort which also included patients with liver metastases and cholangiocarcinoma.

Retrospective registry studies RESiN[36] and CIRT[37] of SIR-Spheres, reported Grade 3 and 4 liver and gastrointestinal disorders, constitution symptoms and AEs attributed to procedure at a similar rate to the interventional studies of SIRT. Three cases of REILD were reported in the CIRT registry study.[37]

Considering all of the relevant evidence, the EAG agrees with the company conclusion that the adverse event profile of QuiremSpheres when used to treat HCC is very similar to the adverse event profiles of SIR-Spheres and TheraSphere for treating HCC.

4.5 Summary

The EAG considers that there is no evidence of any important differences in terms of OS, PFS, ORR or adverse events between QuiremSpheres and SIR-Spheres or TheraSphere. However, uncertainty in the comparisons remains due to:

- Differences in study designs and distributions of patient baseline characteristics across the studies of QuiremSpheres, SIR-Spheres and TheraSphere.
- Limitations associated with observational, retrospective, and non-comparative evidence, as well as small sample sizes and losses to follow-up within some studies.
- The generalisability of the results of the QuiremSpheres and comparator studies all of which include patients who would not be eligible to receive SIRT treatment in NHS clinical practice.
- HRQoL data available is too limited to draw meaningful comparisons.

Although no robust, high quality, comparative evidence is available for QuiremSpheres, nor to inform direct or indirect treatment comparisons between QuiremSpheres, SIR-Spheres, and TheraSphere, the EAG believes that these interventions are likely to be broadly similar in terms of overall health outcomes and that the case for a cost comparison has been met.

5 SUMMARY OF THE EAG'S CRITIQUE OF COST COMPARISON EVIDENCE SUBMITTED

The EAG's critique of the economic evidence submitted by the company assumes that the clinical evidence provided is sufficient to support a case for the similarity in terms of overall health outcomes of QuiremSpheres compared to SIR-Spheres and TheraSphere (see Section 4).

The EAG considers a comparison of the costs of QuiremSpheres with SIR-Spheres and TheraSphere within the scope of NICE's part-review of TA688. The following critique focusses on addressing the question of whether QuiremSpheres is likely to be cost-saving or -neutral relative to SIR-Spheres and TheraSphere, although, it should be noted that these options may not represent the current standard of care in the population relevant to the decision population (see Section 2.3.1 and Section 3.1).

The evidence presented by the company sought to address the committee's concerns which led to QuiremSpheres not being recommended for routine use in TA688, namely, that QuiremSpheres lacked clinical evidence and was associated with higher costs than the other two SIRT technologies. The additional costs of QuiremSpheres were driven primarily by the use of the proprietary QuiremScout work-up, which does not form part of the QuiremSpheres procedure for the purposes of this cost comparison. With the omission of QuiremScout, the company argue that all remaining resource use remains equivalent to approved SIRT technologies. The CS therefore largely comprises a comparison with the committee's preferred assumptions for SIR-Spheres and TheraSphere in TA688.

5.1 Summary of costs and assumptions

The company present a cost comparison analysis which assumes equivalence of QuiremSpheres in terms of costs and resource use relative to the comparator technologies. Under the assumption that QuiremSpheres is a clinically equivalent 'technical variant' of the ^{90}Y SIRTs, the company argue that there are no differences in resource use across the three technologies, and thus only the relative acquisition costs are relevant to the cost comparison.

The company present resource assumptions agreed upon in TA688 in the CS (Table 18, pp61-62). The company assume that resource use items such as proportion of work-ups leading to SIRT, mean number of work-ups required, and mean number of SIRT procedures, are equivalent to the modelled values for SIR-Spheres and TheraSphere in the TA688 AG model. The company note that the only cost differences in the assumptions agreed upon in TA688 were the price of the technologies.

The company did not perform a systematic literature review to identify relevant cost-effectiveness evidence against SIR-Spheres and TheraSphere, but the company describe how, to their knowledge, no economic studies have been published comparing QuiremSpheres to comparators (response to

clarification question B1). The EAG have also identified no such studies following a limited online search for cost-effectiveness studies of the named QuiremSpheres technology, appearing to confirm that there have been no more relevant analyses published since TA688.

5.2 EAG critique of cost comparison analysis

The EAG critiques the key assumptions of the company analysis described above related to verifying the assumed equivalence of QuiremSpheres with comparators according to the following parameters:

- Acquisition costs
- Healthcare resource use
- Treatment costs
- Adverse event costs

Given that comparator acquisition costs inclusive of Patient Access Scheme (PAS) discount are unknown to company, and the PAS applied to QuiremSpheres may be subject to change, we consider the appropriateness of the company's analysis which is based solely on acquisition costs. To allow us to consider only the relative acquisition costs of each technology in the cost comparison (in line with the company's analysis), the EAG considers the plausibility of equivalence between the technologies in terms of each of these key aspects of resource use (excluding acquisition costs) relative to the accepted values in TA688, making use of any available trial evidence made available following TA688.

5.2.1 Acquisition costs

The acquisition costs of the technologies as confirmed by the manufacturers are presented in Table 5.

Table 5 Acquisition prices of QuiremSpheres, SIR-Spheres, and TheraSphere

Technology	Price	Source
QuiremSpheres	[redacted]	Company submission
SIR-Spheres	£8,000	Sirtex
Therasphere	£20,000	Boston Scientific

The company have proposed a [redacted] The EAG notes that there are confidential pricing arrangements in place for both comparator technologies, which are not known to the company. Details of all confidential commercial arrangements for QuiremSpheres, SIR-Spheres, and TheraSphere are provided in the confidential appendix to this report. These prices were correct as of 9th February 2024. The acquisition costs discussed in the CS and the EAR include only the proposed pricing arrangements for QuiremSpheres.

The company state that the company's proprietary Q-suite dosimetry software will be provided free of charge by Terumo as part of the hospital start-up process (response to clarification question B4); they also state that the Q-suite software is not required for administration of QuiremSpheres, and that standard software packages can be used to calculate personalised QuiremSpheres dosing.

5.2.2 Healthcare resource use

The original AG model developed for TA688 relied on a number of key resource use parameters for SIRT. The company, as part of this appraisal, assume that QuiremSpheres is equivalent to comparators in terms of these key resource use parameters in line with the committee's preferred assumptions in TA688 (Table 18, pp61-62).

The assumption of equivalence of resource use parameters for QuiremSpheres with SIR-Spheres and TheraSphere was made in TA688 due to the lack of study data available for QuiremSpheres at that time. The EAG considers that any data collected in the intervening years should now be used to support the assumption of equivalent resource use. For example, if QuiremSpheres were more likely than the comparators to require repeat procedures to achieve full coverage of the liver, it may be inappropriate to consider only acquisition costs in the cost comparison without adjustment for the rate of repeat procedures. The company provided resource use data from the four QuiremSpheres studies submitted as evidence for this current appraisal in response to clarification question B2 (Table 6).

Table 6 Comparison of trial resource use values to MTA values

Resource use parameter	TA688 value (SARAH [n=237*])	HEPAR Primary (n=41*)	Jena Clinical Experience (n=20*; HCC: n=14*)	RETOUCH (n=20*)	RECORD (n=157*; HCC: n=55*)
Proportion of work-ups leading to SIRT	**81.4% (184/226)**	96.6% (31/32)	NR	75% (15/20)	97.7% (167/171) (entire population)
Mean number of work-ups per patient	**1.09**	NR	NR	1.13	1.25 (HCC population)
Mean number of SIRT procedures per patient	**1.28**	NR	1.5 (HCC population)	1.13	1.14 (entire population) 1.22 (HCC population)

*assigned to receive SIRT
Abbreviations: HCC: hepatocellular carcinoma; MTA: multiple technology appraisal; NR: Not reported; SIRT: selective interval radiation therapy.

The EAG consider the QuiremSpheres study data provided to be broadly similar to the accepted values in TA688. As might be expected due to the small sample sizes it is not possible to conclude equivalence with any certainty. However, on the basis of the information available, the EAG are satisfied that these parameters of healthcare resource use are unlikely to be significantly different across QuiremSpheres and the comparators.

5.2.3 Treatment costs

The company assumes that the costs incurred by QuiremSpheres are equivalent to the values applied in the AG model developed as part of TA688 for the two comparators, comprising work-up costs and procedure costs (CS, Table 18, pp. 61-62). The costs applied in the company's analysis are described in Table 7.

Table 7 Treatment costs

Treatment costs	Company value (TA688)	Source
Work-up costs	£860.32	Based on values elicited from the Christie NHS Foundation Trust using micro-costing approach
SIRT procedure costs	£2,790.00	NHS reference costs for 2017-18 for YR57Z - average cost of 'Percutaneous, Chemoembolisation, or Radioembolisation, of Lesion of Liver'
Total	**£3,650.32**	

The company's position in TA688 was that QuiremSpheres required the use of the QuiremScout work-up procedure. The list price of QuiremScout was £4,372, which drove the higher total costs of QuiremSpheres compared to all other treatment strategies and contributed to the negative committee decision. QuiremScout has not been proposed by the company as part of the present cost comparison, instead assuming that all patients use ^{99m}Tc-MAA work-up product.

Same-day vs multi-day procedure

In response to the scope for this appraisal,[41] Sirtex Medical describe how due to improvements to logistical set-up following the publication of TA688, the entire SIR-Spheres work-up and administration process now requires only a single hospital admission where patients are commonly discharged on the same day or a subsequent day. Sirtex also argue that QuiremSpheres would require either three separate hospital admissions (work-up, implantation, post-implantation imaging), or 1-2 lengthy admissions. As a result, QuiremSpheres may result in the health system incurring greater costs associated with the procedure compared with SIR-Spheres.

The company state in the CS (p. 59) that the complete work-up and SIRT procedure can be performed either in a single day or across multiple days. They describe how in HEPAR I and HEPAR II studies,[42, 43] a same-day procedure was used but described how additional costs may be incurred (related to additional hospital admissions) if the procedure were to be administered over multiple days. The company stated that they anticipated that a multi-day procedure would be used in line with current clinical practice in the NHS (response to clarification question B3).

Clinical advice to the EAG confirms that SIRT technologies used in current NHS practice are most likely to be administered according to a multi-day procedure as imaging and dosimetry and radio-pharmacy would take most of the day and would not necessarily be less resource-intensive than if a

patient were invited back another day for the SIRT procedure. The EAG consider it unclear which of the single- and multi-day procedure approaches are typically less resource intensive from an NHS perspective, and that it is likely that they incur similar costs on average. There may, however, be a patient preference for the full procedure to be done in a single day, particularly in cases where the treatment centre is a long distance from home. Conversely, as a single day procedure would necessarily begin very early and end very late, it is likely that hotel stays would be required and therefore there may be preference among some patients for multiple hospital visits, separated by several days, which would allow patients to return home in between procedures.

The EAG are satisfied that QuiremSpheres would likely be equivalent in terms of treatment costs compared to comparators.

5.2.4 Dose verification imaging

In the CS (p16), the company describe how an advantage of QuiremSpheres is that SPECT-CT and high-resolution MRI can be used for dose verification. The company state that this differs from PET-CT currently used in clinical practice for ^{90}Y SIRT. They argue that the use of SPECT-CT offers benefits in the form of more accurate and flexible use across clinical settings. As a result, the EAG considered whether the different imaging technologies may result in different costs for QuiremSpheres against comparators. The latest NHS reference costs (21/22 – total Healthcare Resource Group (HRG)) are presented in Table 8 for each of the procedure codes provided by the company in response to clarification question B6.

Table 8 NHS reference costs for SPECT-CT, MRI and PET-CT

Procedure	Value – NHS 21/22 reference costs (total HRG)
RN05A: SPECT-CT of Two or Three Areas, 19 years and over	£659
RD01A: MRI Scan of One Area, without Contrast, 19 years and over	£197
RN02A: PET-CT of Two or Three Areas, 19 years and over	£703

Abbreviations: HRG: Healthcare Resource Group; MRI: Magnetic Resonance Imaging, PET-CT: Positron Emission Tomography with Computed Tomography; SPECT-CT: Single Photon Emission Computed Tomography with Computed Tomography

The costs associated with SPECT-CT appear slightly less than the equivalent cost for PET-CT. MRI costs appear significantly less than the other procedures. However, clinical advice to the EAG suggests that due to the demand for MRI at most treatment centres, it would typically be unlikely to be made available for the purpose of dose verification where SPECT-CT is available. Due to inconsistencies in the data described by the company in their clarification response, the EAG prefers the 'Total HRG' cost rather than the more granular data from nuclear medicine/diagnostic imaging. The EAG consider that any cost differences as a result of different dose verification imaging techniques are likely to be inconsequential.

5.2.5 Adverse event costs

The original AG model incorporated costs associated with management of adverse events (AEs) derived from previous TAs (2018 cost year) and weighted them according to AE incidence rates from the SIR-Spheres arm of the SARAH trial. This resulted in a total cost applied to each technology of £477.69 which is the value applied by the company in this analysis.

The equivalence of QuiremSpheres to comparators in terms of AEs is discussed further in Section 4.4**Error! Reference source not found.**. The EAG consider that it is reasonable to assume that adverse event costs are broadly equivalent between QuiremSpheres and the comparators.

5.3 Summary

Under the assumption that the clinical evidence presented is sufficient to demonstrate similarity in terms of overall health outcomes of QuiremSpheres compared to the other SIRT technologies, the EAG consider it plausible that the addition of QuiremSpheres in this position could be cost-neutral. As a result, the EAG consider it appropriate to compare only the acquisition costs of the technologies. In order for this to be the case inclusive of acquisition costs, currently available PAS discounts for TheraSphere and SIR-Spheres will have to be accounted for.

6 COMPANY AND EAG COST COMPARISON RESULTS

The following section details the results of the company's base case and the EAG's preferred base case (Table 9). All comparator acquisition costs are based on list prices, while the proposed PAS price for QuiremSpheres is inclusive of PAS. This analysis does not consider the use of QuiremScout in the workup procedure and assumes that all patients use ^{99m}Tc-MAA work-up product.

Given that the company assumed that QuiremSpheres is equivalent in terms of healthcare resource use and adverse event costs, the only relevant costs for the purpose of the cost comparison are the acquisition costs of the SIRT technologies themselves. The results in Table 9 (exclusive of PAS discounts) indicate that at list price, TheraSphere is the most costly option. The analysis inclusive of PAS prices is presented in the confidential appendix to this report.

Table 9 Company base case results (adapted from CS, Table 19)

Technologies	Acquisition cost (£)
QuiremSpheres*	[redacted]
TheraSphere	£20,000
SIR-Spheres	£8,000

*performed with ^{99m}Tc-MAA work-up (i.e., excl. QuiremScout)

6.1 EAG-preferred base case

The EAG accepts the company's assumptions included in their base case analysis; namely the equivalence of QuiremSpheres in terms of costs except acquisition costs.

7 EQUALITIES AND INNOVATION

The company does not present any equality issues (CS section B.1.4).

Clinical advice to the EAG is that SIRT can only be performed at specialist treatment centres which have clinical expertise combined with departments of nuclear medicine and interventional radiology. It is therefore likely that patients would only receive QuiremSpheres or ^{90}Y SIRTs in larger hospitals, which may impede access for those living further away from these specialist centres.

EAG critique of the "Technical advantages of QuiremSpheres supporting the unmet need" (CS, pp. 16-17) is provided in Section 2.3.2.1.

8 EAG COMMENTARY ON THE ROBUSTNESS OF EVIDENCE SUBMITTED BY THE COMPANY

8.1 Conclusions

The EAG considers that the case for a cost comparison approach for SIRT with QuiremSpheres for treating unresectable advanced HCC has been met.

Although there are technical differences between the SIRTs, for example in the radioactive isotope, the size and number of spheres, and the workup and imaging requirements, there is no evidence to suggest that these differences would have an impact on clinical outcomes. This view is supported by two clinical advisors consulted by the EAG, and the EAG considers that it is reasonable to consider QuiremSpheres as a technical variant to SIR-Spheres and TheraSphere.

The evidence on the effectiveness of QuiremSpheres and comparators submitted in the CS is of low quality, high heterogeneity, and is limited in terms of its application to NHS clinical practice. The evidence for QuiremSpheres comes from four relatively small single-arm studies. None of the QuiremSpheres or comparator studies are based within UK healthcare settings, and all of the studies include patients who would not be eligible to receive QuiremSpheres (or other SIRTs) within the NHS currently or under the company's proposed position of QuiremSpheres.

Despite the lack of robust, high-quality evidence, there are no clear differences between the OS, PFS and ORR estimates between QuiremSpheres and comparators, nor any evidence of differences between the safety profiles of QuiremSpheres, SIR-Spheres and TheraSphere.

The EAG considers that there is insufficient robust clinical effectiveness evidence available to inform an updated cost-utility analysis of QuiremSpheres compared to SIR-Spheres or TheraSphere, or to atezolizumab with bevacizumab, the current standard of care in NHS practice for treating unresectable or advanced HCC.

8.2 Areas of uncertainty

Table 10 summarises areas of uncertainty, which could be addressed in future research and through monitoring of the use of SIRTs in UK clinical practice.

Table 10 Outstanding areas of uncertainty

No.	Issue	Description	Report section
1	Technical equivalence	It is possible that technical differences between the SIRTs impact on clinical outcomes, for example through differences in the dosimetry, imaging, or embolic effect of microspheres. The potential advantages or disadvantages of the QuiremScout workup were not considered as part of this appraisal.	2.3.2
2	Implementation in clinical practice	It is unclear how differences between SIRTs such as the workup, dosimetry, and length / number of hospital visits would affect preferences for one SIRT over another, and any associated costs to the NHS.	2.3.2, 5.2
3	Relevant population	To align with related NICE guidance, and to reflect the current use of SIRT treatment within NHS clinical practice, the EAG considers that the relevant population for this appraisal should be adult patients who are not eligible for CTT or surgical resection and have BCLC B or BCLC C HCC with Child-Pugh grade A liver impairment	3.1
4	Literature review and study selection	Search of the literature appears to be incomplete, and the process of identifying studies lacks transparency; selection criteria were not specific. It is possible relevant recent publications were not included.	4.1
3	Evidence does not match population in scope	No evidence from UK based treatment settings. Patient cohorts of QuiremSpheres studies and comparator studies vary with regard to their fit with the population relevant to the decision problem.	4.2.1
4	Lack of robust evidence	Four relatively small single-arm studies of QuiremSpheres; naïve comparisons made to non-comparative studies of SIR-Spheres and TheraSphere. Heterogeneity of study and patient characteristics, and of outcomes definitions such as response rates and adverse events. Insufficient HRQoL data to allow a meaningful comparison	4.3
5	Resource implications of same-day vs multi-day procedure	The work-up and administration process for SIR-Spheres is plausibly completed by SIRT centres in a single day, whilst this is very unlikely to be possible with QuiremSpheres. The resource implications from an NHS perspective of each approach are uncertain, as is the extent to which a same-day approach has been adopted across the NHS.	5.2.3

Abbreviations: BCLC: Barcelona Center Liver Cancer; CTT: conventional transarterial therapy
HCC: hepatocellular carcinoma; HRQoL: health-related quality of life; SIRT: selective internal radiation therapy

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APPENDICES

APPENDIX 1. SYSTEMATIC LITERATURE SEARCHES

Table 11 EAG appraisal of company searches

Topic	EAG response	Note
Is the report of the search clear and comprehensive?	NO	Search strategies missing from Appendix D of the company submission and not supplied in the company response to the clarification questions A2 and A3.
Were appropriate sources searched?	NO	Search of MEDLINE only.
Was the timespan of the searches appropriate?	YES	Update of a previous review, covering the period 25th January 2019 to 1st December 2023.
Were appropriate parts of the PICOS included in the search strategies?	UNCLEAR	The search strategy run by the company in MEDLINE was not provided, so could not be checked by the EAG.
Were appropriate search terms used?	UNCLEAR	The search strategy run by the company in MEDLINE was not provided, so could not be checked by the EAG.
Were any search restrictions applied appropriate?	NO	Searches were limited to English language articles, therefore language bias is possible. Searches were limited to those studies with full text available.
Were any search filters used validated and referenced?	UNCLEAR	The search strategy run by the company in MEDLINE was not provided, so could not be checked by the EAG.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

APPENDIX 2. STUDIES INCLUDED IN EAG NAÏVE COMPARISON

Table 12 Patient baseline demographic characteristics in QuiremSpheres and comparator studies included in the EAG naïve comparison

Trial	N	SIRT Intervention	Age, years	Male: n (%)	Cirrhosis present: n (%)	ECOG PS: n (%)	PVT / PVI present: n (%)
Reinders 2022 (HEPAR Primary)[11]	31	QuiremSpheres	Median: 73 Range: 44-85	28 (90)	20 (65)	0: 18 (58) 1: 13 (42)	PVT: 6 (19)
RECORD[14]	HCC: 55[a] Total: 146	QuiremSpheres	Median: 66.2 SD: 10.9	99 (67.8)	NR	0: 59 (41) 1: 46 (32); ≥2: 8 (5.5) Unknown: 33 (22.6)	PVT: 6 (10.9)
Drescher 2023 (Jena Clinical Experience)[13]	14	QuiremSpheres	Median: 73 Range: 58-82	13 (93)	12 (86)	NR	NR
Vilgrain 2017 (SARAH)[21]	174[b]	SIR-Spheres	Mean: 66.3 SD: 9.4	158 (90.8)	154 (88.5)	0: 1.09 1:65 (37.4)	PVI: 100 (57.5)
Chow 2018 (SIRveNIB)[22]	130[b]	SIR-Spheres	Mean: 60.9 SD: 11.5	107 (82.3)	NR	0: 106 (81.5) 1: 24 (18.5)	PVT: 30 (23.1)
Frantz 2021 (RESiN)[36]	448[c]	SIR-Spheres	Median: 66 IQR: 61-72	349 (78)	NR	0: 205 (51) 1: 155 (39); ≥2: 41 (10)	PVI: 60 (15)
Van Thai 2021[35]	97	SIR-Spheres	Mean: 64 ± 12.3	90 (92.8)	94 (96.9)	0: 14 (14.4) 1: 71 (73.2); 2: 12 (12.4)	61 (62.9)
Helmberger 2021 (CIRT)[37]	442	SIR-Spheres	NR for HCC	NR for HCC	300 (71.1)	0: 252 (59.7) 1: 136 (32.2); ≥2: 34 (8.1)	PVT: 140 (33.2)
Casáns-Tormo 2023[30]	53	SIR-Spheres (94%) TheraSphere (6%)	Mean: 68 SD: 10	41 (77.4)	NR	NR	NR
Hur 2023[31]	124[d]	SIR-Spheres (% NR) TheraSphere (% NR)	Median: 59.4 IQR: 51.8-68	103 (83.1)	24 (83)	0: 68 (54.8) 1: 54 (43.6); 2: 2 (1.6)	124 (100)
Garin 2020 (DOSISPHERE-01)[38]	28[e]	TheraSphere[d]	Mean: 62.5 SD: 13.1	26 (93)	24 (86)	0: 13 (46) 1: 15 (54)	PVI: 21 (75)
Lam 2022 (TARGET)[34]	209	TheraSphere	Median: 66 Range: 27-87	166 (79.4)	185 (88.5)	0: 135 (64.6) 1: 67 (32.1); ≥2: 7 (3.4)	PVT: 69 (33.0)

[a] Characteristics are presented for the entire study cohort of 146 patients; presence of PVT only presented for 55 patients with HCC, [b] per protocol/treated population, [c] ECOG PS percentages were calculated using a denominator of 401, and a denominator of 397 for PVI, [d] Unmatched cohort [e] characteristics presented for the modified ITT population of the standard dosimetry group
Abbreviations: EAG: evidence assessment group; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HCC: hepatocellular carcinoma; IQR: interquartile range; ITT: intention to treat, NR: not reported; PVI: portal vein invasion; PVT: portal vein thrombosis; SD: standard deviation; SIRT: selective internal radiation therapy

Table 13 Patient baseline disease characteristics in QuiremSpheres and comparator studies included in the EAG naïve comparison

Trial	N	SIRT Intervention	Child-Pugh Classification: n (%)	BCLC stage: n (%)	Prior Treatments: n (%)	Tumour involvement: n (%)	Number of Tumours: n (%)
Reinders 2022 (HEPAR Primary)[11]	31	QuiremSpheres	A (5-6): 28 (90) B7: 3 (10) C: 0 (excluded)	0: 0 (0) A: 0 (0) B: 22 (71) C: 9 (29)	None: 26 (84) Resection: 4 (13) Ablation: 4 (13) TACE: 1 (3)	Unilobar: 14 (45) Bilobar: 17 (55)	1: 4 (13) 2-3: 4 (13) >3: 23 (74)
RECORD[14]	55	QuiremSpheres	A (5-6): 36 (65.5) B7: 17 (30.9) C: 2 (3.6)	0: 2 (3.6) A: 3 (5.5) B: 32 (58.2) C: 11 (20) Unknown: 7 (12.7)	NR	Unilobar: 13 (23.6) Bilobar: 35 (63.6)	NR
Drescher 2023 (Jena Clinical Experience)[13]	14	QuiremSpheres	A (5-6): 13 (93) B7: 1 (7)	A: 2 (14) B: 9[a] (64) C: 3[a] (21)	None: 8 (57) Resection: 4 (29) TACE: 1 (7) Percutaneous Radiation: 1 (7)	NR	NR
Vilgrain 2017 (SARAH)[21]	174[b]	SIR-Spheres	A (5 - 6): 153 (87.9) B7: 20 (11.5) C: 0 (excluded) Unknown: 1 (0.6)	A: 7 (4) B: 53 (30.5) C: 114 (65.5)[c]	NR	Unilobar: 136 (78.2) Bilobar: 38 (21.8)	1: 81 (46.6) ≥2: 93 (53.4)
Chow 2018 (SIRveNIB)[22]	130[d]	SIR-Spheres	A: 117 (90.0) B: 10 (7.7)	A: 0 (excluded) B: 79 (60.8) C: 50 (38.5)	NR	NR	NR
Frantz 2021 (RESiN)[36]	448[e]	SIR-Spheres	A: 70% B: 29% C: <1%	A: 19% B: 59% C: 15% D: 7%	Systemic: 16% TACE: 26% Ablation: 13% Resection: 8% Radiotherapy: 2%	Unilobar: 58% Bilobar: 42%	1: 36% 2-5: 40% 6-10: 3% >10: 21%
Van Thai 2021[35]	97	SIR-Spheres	A: 91 (93.8) B: 6 (6.2) C: 0 (excluded)	A: 0 B: 38 (39.2) C: 59 (60.8) D: 0	None: 78 (80.4) Resection: 5 (5.2) RFA: 3 (3.1) TACE: 9 (9.3) PEI: 2 (2.1)	Unilobar: 81 (83.5) Bilobar: 16 (16.5)	NR
Helmberger 2021 (CIRT)[37]	442	SIR-Spheres	(N= 162) A: 131 (80.9) B: 30 (18.5) C: 1 (0.6)	NR	Systemic: 45 (10) Surgical: 72 (17.1) Ablation: 62 (14.7) TACE: 97 (23.0) Vascular: 15 (3.6) Abdominal radiotherapy: 7 (1.7)	Unilobar: 263 (62.3) Bilobar: 159 (37.7)	1: 110 (26.1) 2-5: 154 (36.5) >10: 55 (13) Uncountable: 80 (19)

Casáns-Tormo 2023[30]	53	SIR-Spheres (94%) TheraSphere (6%)	All Child-Pugh A5 or A6.	B or C: 49 (92.4)	Embolization, TACE or RFA: 27 (51)	Unilobar: 23 (43.3) Bilobar: 30 (56.6)	NR
Hur 2023[31]	124[f]	SIR-Spheres (NR) TheraSphere (NR)	A (5-6): 105 (97.6) B7: 3 (2.4)	NR	NR	Unilobar: 88 (54.0) Bilobar: 36 (29.0)	1: 69 (55.7) 2: 21 (16.9) ≥ 3: 34 (27.4)
Garin 2020 (DOSISPHERE-01)[38]	28[g]	TheraSphere[g]	A5: 22 (79) A6 or B7: 6 (21)	A: 0 (0) B: 3 (10) C: 26 (90)	None: 25 (89) Previous SIRT: 3 (11)	Unilobar: 12 (43) Bilobar: 16 (57)	NR
Lam 2022 (TARGET)[34]	209[d]	TheraSphere	A (5-6): 187 (89.5) B7: 22 (10.5)	A: 27 (12.9) B: 68 (32.5) C: 114 (54.5)	Sorafenib: 21 (10)	Unilobar: 148 (70.8) Bilobar: 61 (29.2)	1: 145 (69.4) 2: 45 (21.5) 3: 14 (6.7) 4-10: 5 (2.4)

[a] Conservative assessment as 5 patients are characterised tumour Stage II that can also imply vascular invasion which would make patients BCLC C (CS, Table 9), [b] Per protocol population. [c] 36 patients in the SIRT group had both BCLC C and TACE failure, [d] Treated population, [e] percentages only reported as different denominators are used for each characteristic, [f] Unmatched cohort. [g] characteristics are presented for the modified ITT population of the standard dosimetry group

Abbreviations: EAG: evidence assessment group; ITT: intention to treat; NR: not reported; PEI: Percutaneous ethanol injection therapy, RFA: radiofrequency ablation, SIRT: selective internal radiation therapy, TACE: transarterial chemoembolization,

Table 14 Clinical effectiveness results in studies in QuiremSpheres and comparator studies included in the EAG naïve comparison

Trial	N	SIRT interventions	Follow-up (months)	OS (Median, months)	PFS (Median, months)	Response: n (%) ORR: % and (95% CI[a])
Reinders 2022 (HEPAR Primary) [11]	31	QuiremSpheres	≥6 months: 21 (68%) ≥12 months: 18 (58%) ≥24 months: 11 (35%)	14.9 (95% CI: 10.4-24.9)	NR	mRECIST at 3 months (n=26): CR: 5 (19.2); PR: 9 (34.6) ORR: 53.8 (33.4 -76.6) mRECIST at 6 months (n=19): CR: 7 (36.8); PR: 9 (47.4) ORR 84.2 (60.4 - 96.6)
RECORD [14]	55	QuiremSpheres	Median 7.1 (95% CI 7.4 to 9.3)	14.7 (95% CI: 13.8 – NE)	9.1 (95% CI: 7.1- 14.0)	Mixed mRECIST and RECIST 1.1 at >3 months (n=37): CR+PR=26 ORR: 70.3 (53.0 - 84.1)[b]
Drescher 2023 (Jena Clinical Experience)[13]	14	QuiremSpheres	Median 17.7 (range 0.8 – 58)	22.1 (95% CI: 13.6 – 29.8)	7.3 (95% CI: 5.5-15.7)	mRECIST at 3 months (n=12): CR: 1 (8); PR: 7 (58) ORR: 66.7 (34.9-90.1)
Vilgrain 2017 (SARAH)[21]	174[c]	SIR-Spheres	Median: 27.9 IQR: 21.9-33.6	9.9 (95% CI: 8.0 – 10.7)	4.1 (95% CI: 3.8 – 4.6)	Best response, RECIST 1.1 (n=164): CR: 4 (2.4); PR: 28 (17.1) ORR: 19.5 (13.7 – 26.4)
Chow 2018 (SIRveNIB)[22]	130[d]	SIR-Spheres	≥6 months: 65 (50%) ≥12 months: 22 (17%) ≥24 months: 6 (5%)	11.3 (95% CI: 9.2 - 13.6)	6.3 (95% CI: 5.9-8.3)	Best response, RECIST 1.1 (n=103): CR: 0 (0); PR: 30 (29.1) ORR: 29.1 (20.6 – 38.9)
Frantz 2021 (RESiN)[36]	Child-Pugh A: 151[e]	SIR-Spheres	Up to 48 months	BCLC B (n=132): 21.5 (95% CI: 16.5-25.2) BCLC C (n=19): 21.8 (6.2-N/R)	BCLC B (n=132): 10.6 (95% CI: 9.0 – 15.4) BCLC C (n=19): N/R (3.5-N/R)	NR
Van Thai 2021[35]	97	SIR-Spheres	Median 16.4 (range: 1.8 -62)	Median: 23.9 (95% CI NR)	NR	mRECIST at 3 months (n=87): CR: 10 (11.5); PR: 42 (48.3) ORR: 59.8 (48.7-70.1) mRECIST at 6 months (n=64): CR: 12 (18.8); PR: 23 (35.9) ORR: 54.7 (41.7 – 67.2)
Helmberger 2021 (CIRT)[37]	422	SIR-Spheres	26 (2.5%) with less than 2 years follow-up	16.5 (95% CI: 14.2 – 19.3)	NR	NR

Casáns-Tormo 2023[30]	53	SIR-Spheres (94%) TheraSphere (6%)	Follow-up period was at least 1 year	Mean: 17.7 SD: 12.8	Mean: 9.6[f] SD: 8.9	mRECIST after mean of 3.7 months: CR and PR: NR ORR: 69.2 (95% CI NR)
Hur 2023[31]	124[g]	SIR-Spheres (NR) TheraSphere (NR)	≥12 months: 70 (56%) ≥24 months: 42 (34%)	28.2 IQR: 7.6-91.1	5.3 IQR: 2.4 – 23.3	Best response, mRECIST (n=124): CR: 28 (22.6), PR: 48 (38.7) ORR: 61.3 (52.1 -69.9)
Garin 2020 (DOSISPHERE-01)[38]	29[h]	TheraSphere[h]	27.2 IQR: 33.9-18.7	10.7 (95% CI: 6.0- 16.8)	3.4 (95% CI: 2.9-8.5)	RECIST 1.1 at 3 months (n=28): Investigator Evaluated: CR: 3(11); PR: 7 (25) ORR: 36 (19-56) Centralised Evaluation: CR: 6 (21); PR: 6 (21) ORR: 43 (24-63)
Lam 2022 (TARGET)[34]	209	TheraSphere	Median 13.3 range: 0.6 - 98.0	20.3 (95% CI: 16.7 – 26.4)	NR	mRECIST, ≤ day 180 post SIRT (n=209): CR + PR: 129 (61.7) ORR 61.7 (55.0-68.0) RECIST 1.1, ≤ day 180 post SIRT (n=209): CR + PR: 72 ORR 34.4 (28.3-41.1)

[a] Binomial confidence interval, ORR and 95% CI extracted from study reports or calculated by the EAG based on number of evaluable patients [b] Not used in company in their naïve comparisons as the tumour response was evaluated using a mixture of mRECIST and RECIST 1.1, [c] Per protocol population, [d] Treated population, [e]The results presented here are the stratified results presented for the patients who had a Child-Pugh grade A, and either BCLC B (n=132, 14% treated aiming to downstage to transplant) or C (n=19), [f]PFS was defined as the time until tumour recurrence or disease progression. [g] Unmatched cohort. [h] results are presented for the modified ITT population of the standard dosimetry group

Abbreviations: CR: complete response; EAG: evidence review group, HCC: hepatocellular carcinoma, IQR: Interquartile range; ITT: intention to treat. mRECIST: modified Response Evaluation Criteria in Solid Tumours for HCC, NR: not reported, N/R: not reached, ORR: objective response rate; OS: overall survival; PFS: progression free survival; PR: partial response; RECIST: Response Evaluation Criteria in Solid Tumours, SD: standard deviation, SIRT: selective internal radiation therapy

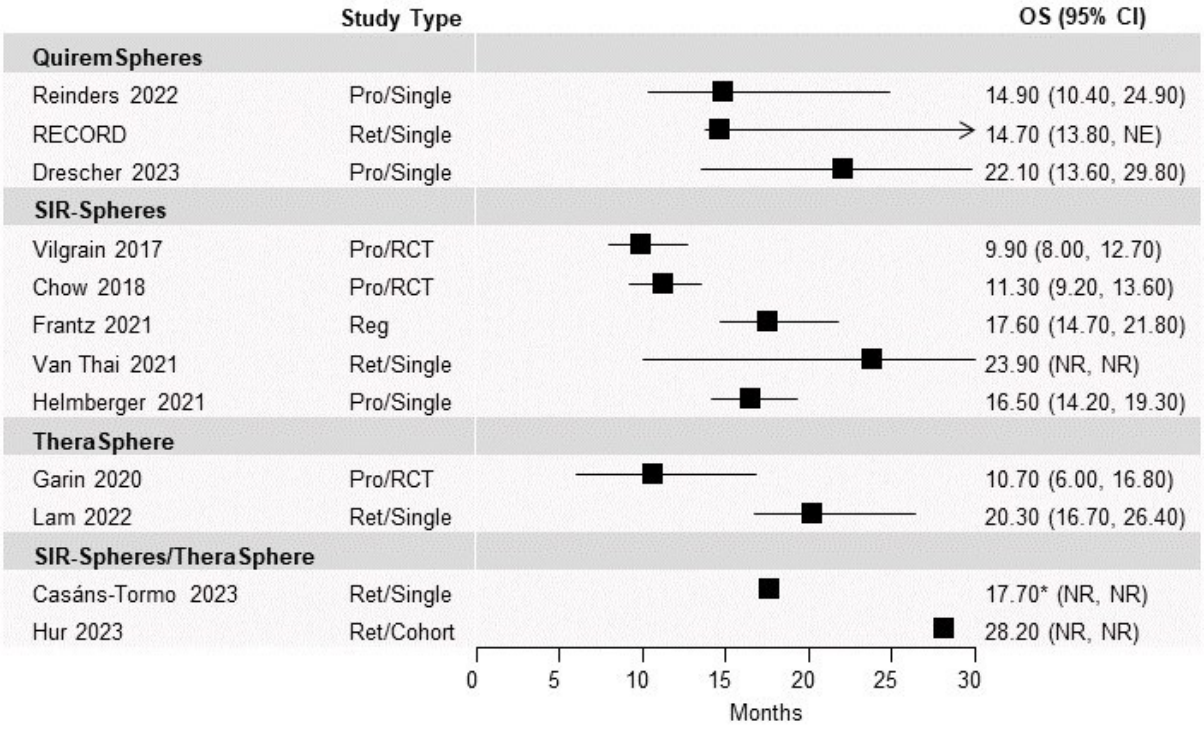

Figure 1 EAG naïve comparison of median OS in QuiremSpheres and comparator studies

Studies report median OS with the exception of Casáns-Tormo 2023[30] which reported mean OS (indicated with an asterisk*)
Abbreviations: CI: confidence interval; OS: overall survival; NE: not evaluable, NR: not reported; Pro: prospective; RCT: randomised controlled trial; Reg: registry data Ret: retrospective; Single: single-arm.

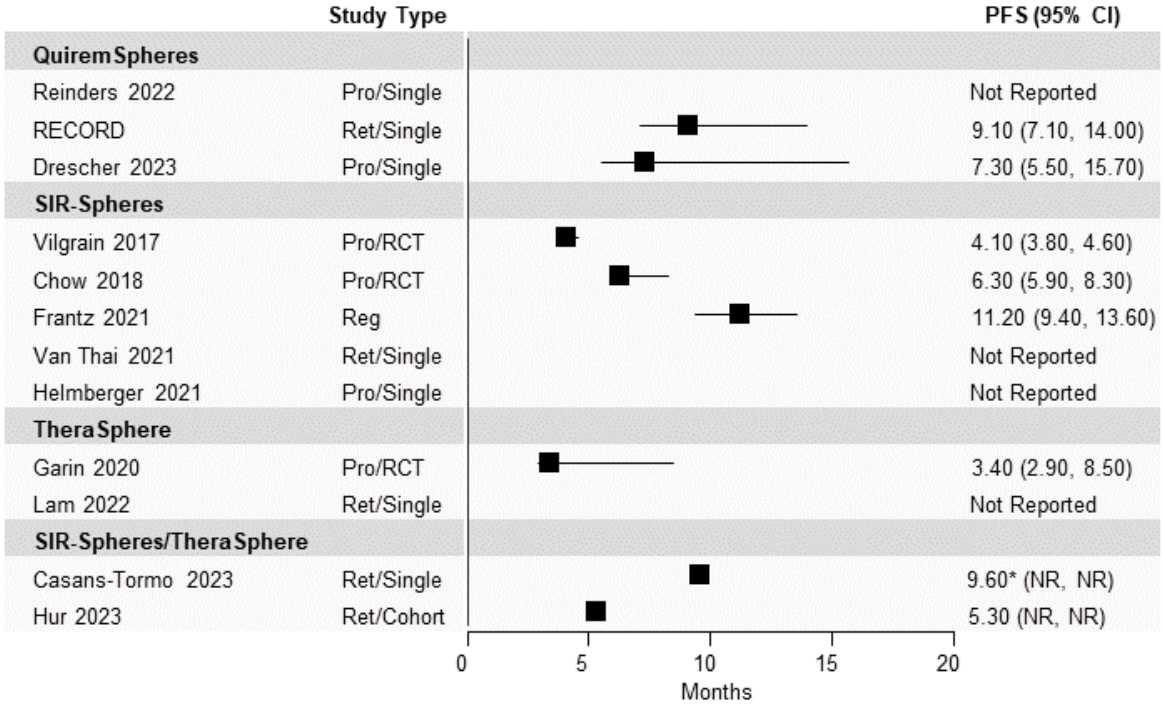

Figure 2 EAG naïve comparison of median PFS in QuiremSpheres and comparator studies

Studies report median OS with the exception of Casáns-Tormo 2023[30] which reported mean OS (indicated with an asterisk*)
Abbreviations: CI: confidence interval; NR: not reported; PFS: progression-free survival; Pro: prospective; RCT: randomised controlled trial; Reg: registry data. Ret: retrospective; Single: single-arm.