National Institute for Health and Care Excellence

Health Technology Evaluation

Selective internal radiation therapy with QuiremSpheres for treating unresectable advanced hepatocellular carcinoma (Partial review of TA688) [ID6376]

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Terumo	We deem the evaluation and proposed evaluation route appropriate	Thank you for your comment. No action is needed.
	Sirtex Medical	A cost-comparison methodology would not be appropriate for this evaluation, as the intervention and comparator technologies have not been demonstrated to be similar in terms of overall health outcomes – which is an essential prerequisite for this form of appraisal to be valid. In fact, it has been previously noted in several published NICE documents that Holmium-166 based SIRT should be treated as a distinct technology to Yttrium-90 based SIRT, due to these products containing very different radionuclides. In the original appraisal, (TA688) to which this partial review relates, QuiremSpheres received a negative recommendation, with the AG noting in section 3.33 that:	Thank you for your comments. The cost comparison approach should be used for technologies likely to provide similar or greater health benefits at similar or lower cost than comparator(s) recommended in

Section	Stakeholder	Comments [sic]	Action
		"the technologies used different beads to give treatment, and QuiremSpheres used a different isotope to the other SIRTs. It agreed that these differences might result in different effectiveness and adverse event profiles, to an unknown extent." This position is further reinforced in section 10.3 of the TA688 assessment report: *"…QuiremSpheres uses a different work-up procedure and different radioactive isotope and therefore it is plausible that QuiremSpheres may have differential effectiveness when compared with SIR-Spheres and TheraSphere".* Finally, QuiremSpheres was also treated as a separate technology in the 2020 NICE IPG of SIRT for unresectable colorectal carcinoma, again due to the fact that the product uses a different radionuclide with distinct radiological properties to Yttrium-90: *"There are different types of microspheres used. There are also different types of radionuclides used, but the evidence discussed by the committee only included studies using yttrium."* It is clear that any decision to assume similarity of overall health outcomes across the three SIRT products in this partial review is contradictory to the scientific opinion adopted on this matter in previous NICE decisions. Sirtex agrees with the previous NICE statements quoted above, which clearly support the position that Holmium-166 SIRT and Yttrium-90 SIRT should be treated as independent technologies, due to the inherent dissimilarity of the two radionuclides. Sirtex assert that these differences should preclude any assumption of similar health outcomes between the two products without the further support of robust clinical evidence. The two tables below list some of the major physical and radiological differences between the QuiremSpheres and SIR-Spheres. Some of these	published NICE guidance for the same population. For technologies evaluated using cost comparison, conclusions on the similarity of health benefits will be based on a pragmatic view of all available evidence for the technology compared with the relevant comparator(s). Clinical, technological, biological, or pharmacokinetic evidence can be used to support such a conclusion. The Review of TA688 concluded that QuiremSpheres for treating hepatocellular carcinoma should be re-evaluated, likely as a cost comparison evaluation with other SIRT technologies for the population they

<table>
<tr><th>Section</th><th>Stakeholder</th><th>Comments [sic]</th><th>Action</th></tr>
<tr><td></td><td></td><td>differences have already been demonstrated to have direct effects on the in vivo behaviour of the products and/or their associated clinical outcomes, but for the majority of the factors the clinical relevance remains unknown thus far.
Physical differences
<table>
<tr><th></th><th>Number of spheres per treatment</th><th>Mean Sphere diameter</th><th>Material</th><th>Density</th></tr>
<tr><td>SIR-Spheres</td><td>40-60 million</td><td>20-60 micron</td><td>Resin</td><td>1.1 g/mL</td></tr>
<tr><td>Quirem Spheres</td><td>15-30 million</td><td>25-35 micron</td><td>Polylactic acid</td><td>1.4 g/mL</td></tr>
</table>
Radiological differences
<table>
<tr><th></th><th>Radionuclide (stable decay product)</th><th>Mean activity per sphere</th><th>Radioactive half-life</th><th>Radiation emission profile</th><th>Dosimetry validation</th><th>Mean energy of β emissions</th><th>Maximum tissue penetration of β emissions</th></tr>
<tr><td>SIR-Spheres</td><td>Yttrium-90</td><td>50 Bq</td><td>64.1 hours</td><td>Pure beta emitter</td><td>Method validated across several RCTs</td><td>0.935 MeV</td><td>11 mm</td></tr>
</table></td><td>were recommended for in TA688.
No action is needed.</td></tr>
</table>

<table>
<tr><th>Section</th><th>Stakeholder</th><th>Comments [sic]</th><th>Action</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Quirem Spheres</td><td>Holmium-166</td><td>300 Bq</td><td>26.8 hours</td><td>Mixed gamma + beta emitter</td><td>No validation of method in an RCT setting</td><td>0.665 MeV</td><td>8.7 mm</td></tr>
</table>

SIRT health outcomes, either before or after the original publication of TA688. Furthermore, Sirtex is not aware of any randomised or even non-randomised comparative trial data for QuiremSpheres against any comparator in HCC. It appears that the most robust source of clinical evidence for QuiremSpheres in HCC is the “HEPAR-Primary” study, a “nonrandomized, noncomparative, open-label early phase II study.” This study included only 31 patients, of which just nine were BCLC stage C (and hence relevant to this partial TA review), and the clinical outcomes associated with this nine-patient subgroup were not independently reported.

Further to these observations, Sirtex is confident that it would not be possible to conduct any sufficiently robust indirect comparison to demonstrate similar overall health outcomes to the level of certainty necessary for a cost-comparison approach to be appropriate. In short, the most critical prerequisite for a cost comparison case cannot be met, and therefore Sirtex suggest instead that an independent STA of QuiremSpheres for HCC would be the most appropriate alternative appraisal method.
</td><td></td></tr>
<tr><td></td><td>Boston Scientific</td><td>Literature review has not established safety and efficacy of Ho -166 (Terumo’s QuiremSpheres) when compared to NICE adopted Y-90 SIRT technology for advanced HCC.</td><td>Thank you for your comments.

The cost comparison approach should be</td></tr>
</table>

Section	Stakeholder	Comments [sic]	Action
			used for technologies likely to provide similar or greater health benefits at similar or lower cost than comparator(s) recommended in published NICE guidance for the same population. For technologies evaluated using cost comparison, conclusions on the similarity of health benefits will be based on a pragmatic view of all available evidence for the technology compared with the relevant comparator(s). Clinical, technological, biological, or pharmacokinetic evidence can be used to support such a conclusion. No action is needed.

Section	Stakeholder	Comments [sic]	Action
Wording	Terumo	Yes	Thank you for your comment. No action is needed.
	Sirtex Medical	Yes, the wording of the remit reflects the issues that would need to be considered.	Thank you for your comment. No action is needed.
	Boston Scientific	An economic analysis suggests that TheraSphere may be cost-saving relative to both SIR-Spheres and QuiremSpheres (Eastwood et al Health Technol Assess. 2020)	Thank you for your comment. No action is needed.
Timing Issues	Terumo	N/A	Thank you for your comment. No action is needed.
	Sirtex Medical	No comment	-
	Boston Scientific	No comment	-
Any additional comments on the draft remit	Terumo	We would like to request that the title is modified to add Selective Internal Radiation Therapy (SIRT) so that the title is replaced by: Selective Internal Radiation Therapy (with QuiremSpheres) for treating unresectable advanced hepatocellular carcinoma (Partial review of TA688) [ID6376]. This would be more in line with the previous appraisal as well as the terminology used in the NHS.	Thank you for your comment. The title has been updated to 'Selective Internal Radiation Therapy with QuiremSpheres for treating unresectable advanced hepatocellular

Section	Stakeholder	Comments [sic]	Action
			carcinoma (Partial review of TA688).'
	Boston Scientific	No comment	-

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Terumo	The treatment options listed (surgical resection and liver transplantation, radiotherapy, and systemic treatments) should also include ablation and trans-arterial therapies (such as transarterial chemoembolization, TACE)	Thank you for your comment. Ablation and locoregional transarterial therapies were added to the list of available treatments.
	Sirtex Medical	The background information acknowledges that QuiremSpheres received a negative recommendation in the original appraisal but provides no explanation as to why this decision was taken and does not mention any new evidence that warrants a re-evaluation. Sirtex therefore consider the background information provided to be incomplete, as it is unclear why this re-evaluation is now being undertaken. The background information also fails to mention the significantly increased resources required for use of QuiremSpheres relative to SIR-Spheres. This is important context to include, as any recommendation for use of QuiremSpheres would have significant NHS budget and workload impacts: Use of QuiremSpheres is inherently more resource-intensive than use of SIR-Spheres, due to the combination of inherent radiological differences between the products as described above, and because of improvements made to Sirtex logistical systems since the publication of the original appraisal:	Thank you for your comments. The conclusion of Review of TA688 was added to the rational to re-evaluate QuiremSpheres. The background information section is just a brief overview. A full review of the evidence will be conducted by the

Section	Consultee/ Commentator	Comments [sic]	Action
		• The entire SIR-Spheres workup and administration process now requires only a single hospital admission, with no mandatory minimum length of stay. I.e. patients are commonly discharged on the same day (day-case) or subsequent day after the implantation procedure. (Pollock et al. Adv Ther. 2023;40:294–309) • QuiremSpheres still require either three separate hospital admissions (workup; implantation; post-implantation imaging), or 1-2 more lengthy admissions with multiple night's stay between procedural steps. For these reasons, the overall resource use associated with QuiremSpheres is significantly greater than that associated with SIR-Spheres: In the Pollock et al article cited above, it was estimated that just by moving from two separate hospital admissions to one for SIR-Spheres administration, a cost saving of £2,842 per patient could be realised. There are also significantly increased costs associated with the 'workup' procedure for QuiremSpheres relative to the two comparators. Both comparator products utilise 99mTechnetium labelled macroaggregated albumin (99mTc-MAA) as an inactive surrogate for SIRT microsphere deposition during the workup process. In the original TA688 assessment report, the cost of 99mTc-MAA was estimated at £74 per workup procedure. In contrast, the QuiremSpheres workup procedure requires mandatory usage of a specialist product known as "QuiremScout" instead of 99mTc-MAA. In the original TA688 assessment report the acquisition cost of QuiremScout is quoted as £5,178.32. This significant additional cost therefore needs to be considered in any overall estimation of QuiremSpheres resource usage.	evidence review group. The full cost of the QuiremSpheres treatment, including workup, will be considered by the committee. No action is needed.
	Boston Scientific	See comments above.	Thank you for your comment. No action is needed.

Section	Consultee/ Commentator	Comments [sic]	Action
Population	Terumo	Yes	Thank you for your comment. No action is needed.
	Sirtex Medical	Yes, Sirtex agree with the population as defined.	Thank you for your comment. No action is needed.
	Boston Scientific	No comment	Thank you for your comment. No action is needed.
Subgroups	Terumo	No	Thank you for your comment. No action is needed.
	Sirtex Medical	No comment	-
	Boston Scientific	No comment	-
Comparators	Terumo	Yes	Thank you for your comment. No action is needed.
	Sirtex Medical	A meaningful cost-comparison analysis between the intervention and the proposed comparators cannot be achieved with the data currently available: 1. As previously acknowledged by NICE, “QuiremSpheres used a different isotope to the other SIRTs. It agreed that these differences might result in different effectiveness and adverse event profiles, to an unknown extent.”	Thank you for your comments. he cost comparison approach should be used for technologies

Section	Consultee/ Commentator	Comments [sic]	Action
		2. There are significant physical and radiological differences between QuiremSpheres and SIR-Spheres, primarily relating to the different radionuclide used in QuiremSpheres: Holmium-166 produces a lower energy β emission with a lower depth of tissue penetration, compared to the β emissions from Yttrium-90. Holmium-166 also decays more than twice as rapidly as Yttrium-90, meaning treatment is delivered over a significantly shorter time period, and SIR-Spheres also delivers more than twice as many microspheres as QuiremSpheres on average – which is likely to result in enhanced tumour coverage. The clinical relevance of these important differences has not been established, yet they are significant enough differences that assumption of similar health outcomes should not be made without the support of direct clinical evidence. 3. To the best of Sirtex's knowledge there are still no data available that directly compare health outcomes associated with the intervention to the proposed comparators. If additional data has been provided to NICE in confidence by the manufacturer of the intervention, Sirtex is obviously unable to comment on any impact of this data on comparator selection.	likely to provide similar or greater health benefits at similar or lower cost than comparator(s) recommended in published NICE guidance for the same population. For technologies evaluated using cost comparison, conclusions on the similarity of health benefits will be based on a pragmatic view of all available evidence for the technology compared with the relevant comparator(s). Clinical, technological, biological, or pharmacokinetic evidence can be used to support such a conclusion. The Review of TA688 concluded that QuiremSpheres for treating hepatocellular carcinoma should be re-

Section	Consultee/ Commentator	Comments [sic]	Action
			evaluated, likely as a cost comparison evaluation with other SIRT technologies for the population they were recommended for in TA688. No action is needed.
	Boston Scientific	No comment	-
Outcomes	Terumo	Yes	Thank you for your comment. No action is needed.
	Sirtex Medical	All of the outcomes listed are appropriate, however the relative importance of the different outcomes listed is unclear - the scoping document does not explicitly state which of these outcomes are considered necessary to demonstrate sufficient similarity. For example, if similar response rates could be demonstrated between treatments but overall survival data were not available, would this be considered sufficient demonstration of similarity of health outcomes or not?	Thank you for your comment. For technologies evaluated using cost comparison, conclusions on the similarity of health benefits will be based on a pragmatic view of all available evidence for the technology compared with the relevant comparator(s). Clinical, technological,

Section	Consultee/ Commentator	Comments [sic]	Action
			biological, or pharmacokinetic evidence can be used to support such a conclusion. No action is needed.
	Boston Scientific	No comment	-
Equality	Terumo	No equality issues identified	Thank you for your comment. No action is needed.
	Sirtex Medical	No comment	-
	Boston Scientific	No comment	-
Other considerations	Terumo	No other considerations	Thank you for your comment. No action is needed.
	Sirtex Medical	No comment	-
	Boston Scientific	1. Lack of data There are no studies or publications that allow for an accurate comparison to the established SIR-Spheres and TheraSphere products. QuiremSpheres is still an investigational product that needs to prove equality or superiority.	Thank you for your comments. For technologies evaluated using cost comparison, conclusions on the

Section	Consultee/ Commentator	Comments [sic]	Action
		2. Different radiation properties QuiremSpheres emits both beta and gamma radiation, whereas SIR-Spheres and TheraSphere are pure beta emitters. Quirem claims the shorter half-life is beneficial but provides no satisfactory scientific or clinical evidence. Moreover, there may be additional safety considerations and protocols required with regards to patient treatment pathway and release when using QuiremSpheres compared to the pure beta-emitting products. In summary, QuiremSpheres lacks the strong evidence base, cost efficiency data, and imaging capabilities to justify direct comparison or use over established SIR-Spheres and TheraSphere currently. More data is needed to determine if claimed benefits translate to better patient outcomes.	similarity of health benefits will be based on a pragmatic view of all available evidence for the technology compared with the relevant comparator(s). Clinical, technological, biological, or pharmacokinetic evidence can be used to support such a conclusion. No action is needed.
Questions for consultation	Terumo	QuiremSpheres is a technical variation of SIR-Spheres and Therasphere and can be used as an alternative option. QuiremSpheres will fit in the same pathway as SIR-Spheres and Therasphere, as SIRT treatments. We fully support the cost-comparison route as it is very relevant to this appraisal.	Thank you for your comment. No action is needed.
	Sirtex Medical	No comment	-
	Boston Scientific	No comment	-

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft scope	Sirtex Medical	No	Thank you for your comment. No action is needed.
	Boston Scientific	1. Challenging production/supply chain - QuiremSpheres requires patient-specific dose activation in a reactor, which could make scaling up production challenging. The organic PLLA carrier material also seems less stable than resin. This could lead to higher production costs that may not be justified by any added benefit. 2. Imaging capabilities - Terumo has an open trial investigate MRI -guided Ho-166 radioembolization. The outcome of this study could shed light on the effectiveness and usefulness of MRI guided SIRT with QuiremSpheres. Additionally, implementing MRI-guided procedures would require significant investment and training that may not be benefitting patients or providers.	Thank you for your comments. A full review of the evidence will be conducted by the evidence review group. The full cost of the QuerimSpheres treatment will be considered by the committee. No action is needed.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

None.