Australian Government

Department of Health

Application Form

(New and Amended Requests for Public Funding)

(Version 2.5)

Note: This is a request to change the current MBS listing from interim to permanent for this indication

SIR-Spheres Y-90 resin microspheres for the treatment of:

- **hepatic metastases which are secondary to colorectal cancer and are not suitable for resection or ablation, used in combination with systemic chemotherapy using 5-fluorouracil (5FU) and leucovorin.**

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant):
Corporation name: Sirtex Medical Limited
ABN: REDACTED
Business trading name: REDACTED

Primary contact name: REDACTED

Primary contact numbers
Business: REDACTED
Mobile: REDACTED
Email: REDACTED

Alternative contact name: REDACTED

Alternative contact numbers
Business: REDACTED
Mobile: REDACTED
Email: REDACTED

2. (a) Are you a consultant acting on behalf of an Applicant?

☐ Yes
☒ No

(b) If yes, what is the Applicant(s) name that you are acting on behalf of?

Insert relevant Applicant(s) name here.

3. (a) Are you a lobbyist acting on behalf of an Applicant?

☐ Yes
☒ No

(b) If yes, are you listed on the Register of Lobbyists?

☐ Yes
☐ No
☒ n/a

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

4. Application title

SIR-Spheres Y-90 resin microspheres for the treatment of hepatic metastases which are secondary to colorectal cancer and are not suitable for resection or ablation, used in combination with systemic chemotherapy using 5-fluorouracil (5FU) and leucovorin.

5. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

SIR-Spheres Y-90 resin microspheres are used to treat patients with hepatic metastases secondary to colorectal cancer (CRC) in the absence of extrahepatic metastases, when the hepatic metastases are not amenable to surgery or radiofrequency ablation. They may be used in combination with systemic chemotherapy or hepatic arterial chemotherapy (HAC). SIR-Spheres Y-90 resin microspheres are also used to treat primary non-resectable, non-ablatable hepatocellular carcinoma (HCC); however, this indication is not as common as colorectal liver metastases (CLM) in Australia.

6. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

SIR-Spheres Y-90 resin microspheres (Selective Internal Radiation Spheres) are yttrium-90 resin microspheres that are implanted into malignant liver tumours for the purpose of selectively delivering high doses of ionising radiation to the tumour. They are injected into the hepatic artery by means of a trans-femoral catheter or a permanently implanted hepatic artery port with a catheter. Following injection, the SIR-Spheres Y-90 resin microspheres become concentrated in the microvasculature of the liver tumours, where they have a local radiotherapeutic effect. As tumours within the liver derive their blood supply almost exclusively from the hepatic artery, the SIR-Spheres Y-90 resin microspheres are preferentially delivered in greater amounts to the tumour rather than to the normal liver parenchyma, which is supplied by both the hepatic artery and the portal vein. Following decay of the yttrium-90, the inert resin microspheres remain implanted in the tissue.

7. (a) Is this a request for MBS funding?

☒ Yes
☐ No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

☒ Amendment to existing MBS item(s)
☐ New MBS item(s)

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

MBS Items 35404, 35406 and 35408

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

i. ☐ An amendment to the way the service is clinically delivered under the existing item(s)
ii. ☐ An amendment to the patient population under the existing item(s)
iii. ☐ An amendment to the schedule fee of the existing item(s)
iv. ☐ An amendment to the time and complexity of an existing item(s)
v. ☐ Access to an existing item(s) by a different health practitioner group
vi. ☐ Minor amendments to the item descriptor that does not affect how the service is delivered
vii. ☐ An amendment to an existing specific single consultation item
viii. ☐ An amendment to an existing global consultation item(s)
ix. ☒ Other (please describe below):

The service currently has interim MBS listing under Items 35404, 35406 and 35408. This application is for permanent MBS funding.

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

i. ☐ A new item which also seeks to allow access to the MBS for a specific health practitioner group
ii. ☐ A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
iii. ☐ A new item for a specific single consultation item
iv. ☐ A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

☐ Yes
☒ No

(g) If yes, please advise:

n/a

8. What is the type of service:

☒ Therapeutic medical service
☐ Investigative medical service
☐ Single consultation medical service
☐ Global consultation medical service
☐ Allied health service
☐ Co-dependent technology
☐ Hybrid health technology

9. For investigative services, advise the specific purpose of performing the service *(which could be one or more of the following)*:

i. ☐ To be used as a screening tool in asymptomatic populations
ii. ☐ Assists in establishing a diagnosis in symptomatic patients
iii. ☐ Provides information about prognosis
iv. ☐ Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
v. ☐ Monitors a patient over time to assess treatment response and guide subsequent treatment decisions
vi. ☐ Is for genetic testing for heritable mutations in clinically affected individuals and, when also appropriate, in family members of those individuals who test positive for one or more relevant mutations (and thus for which the Clinical Utility Card proforma might apply)

10. Does your service rely on another medical product to achieve or to enhance its intended effect?

☐ Pharmaceutical / Biological
☒ Prosthesis or device
☐ No

11. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

☐ Yes
☐ No
☒ n/a

(b) If yes, please list the relevant PBS item code(s):

n/a

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

☐ Yes (please provide PBAC submission item number below)

☐ No
☒ n/a

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

Trade name: n/a
Generic name: n/a

12. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

☒ Yes
☐ No

If yes, please provide the following information (where relevant):
Billing code(s): SE001
Trade name of prostheses: SIR-Spheres Y-90 resin microspheres
Clinical name of prostheses: yttrium-90 resin microspheres
Other device components delivered as part of the service: Delivery apparatus is PVC tubing, ABS stopcocks, acrylic holders and stainless steel needles with PE hubs.

(b) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

☐ Yes
☐ No
☒ n/a

(c) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

☐ Yes
☒ No

(d) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

n/a

13. Please identify any single and / or multi-use consumables delivered as part of the service?

Single use consumables: Biocompatible microspheres 20-60mm (microns) in diameter containing yttrium-90. Delivery apparatus is PVC tubing, ABS stopcocks, acrylic holders and stainless steel needles with PE hubs.
Multi-use consumables: n/a

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

14. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:

Type of therapeutic good: Medical device
Manufacturer's name: Sirtex Medical Limited
Sponsor's name: Sirtex Medical Limited

(b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

☐ Class III
☒ AIMD
☐ N/A

15. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

☐ Yes (If yes, please provide supporting documentation as an attachment to this application form)
☒ No

(b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

☒ Yes (if yes, please provide details below)
☐ No

ARTG listing, registration or inclusion number: 149332
TGA approved indication(s), if applicable: For the treatment of malignant liver tumours of primary or secondary origin that are not suitable for resection or ablation.
TGA approved purpose(s), if applicable: Intended for the treatment of inoperable liver cancer.

16. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

☐ Yes (please provide details below)
☐ No
☒ n/a

Date of submission to TGA: n/a
Estimated date by which TGA approval can be expected: n/a
TGA Application ID: n/a
TGA approved indication(s), if applicable: n/a
TGA approved purpose(s), if applicable: n/a

17. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?

☐ Yes (please provide details below)
☐ No
☒ n/a

Estimated date of submission to TGA: n/a
Proposed indication(s), if applicable: n/a
Proposed purpose(s), if applicable: n/a

PART 4 – SUMMARY OF EVIDENCE

18. **Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only).** ***Please do not attach full text articles, this is just intended to be a summary.***

	Type of study design*	**Title of journal article or research project (including any trial identifier or study lead if relevant)**	**Short description of research (max 50 words)****	**Website link to journal article or research (if available)**	**Date of publication*****
1.	Randomized Phase III Trial	SIRFLOX: Randomized Phase III Trial Comparing First-Line mFOLFOX6 (Plus or Minus Bevacizumab) Versus mFOLFOX6 (Plus or Minus Bevacizumab) Plus Selective Internal Radiation Therapy in Patients With Metastatic Colorectal Cancer	SIRFLOX was a randomized, multicentre trial designed to assess the efficacy and safety of adding selective internal radiation therapy (SIRT) using yttrium-90 resin microspheres to standard fluorouracil, leucovorin, and oxaliplatin (FOLFOX)–based chemotherapy in patients with previously untreated metastatic colorectal cancer.	Listed on Pubmed Authors: van Hazel GA, Heinemann V, Sharma NK, Findlay MP, Ricke J, Peeters M, Perez D, Robinson BA, Strickland AH, Ferguson T, Rodríguez J, Kröning H, Wolf I, Ganju V, Walpole E, Boucher E, Tichler T, Shacham-Shmueli E, Powell A, Eliadis P, Isaacs R, Price D, Moeslein F, Taieb J, Bower G, Gebski V, Van Buskirk M, Cade DN, Thurston K, Gibbs P.	J Clin Oncol. 2016 May 20;34(15):1723-31.

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.*

**** If the publication is a follow-up to an initial publication, please advise.*

19. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). ***Please do not attach full text articles, this is just intended to be a summary.***

	Type of study design*	Title of research (including any trial identifier if relevant)	Short description of research (max 50 words)**	Website link to research (if available)	Date***
1.	RCT Phase III Open-label	FOXFIRE (ISRCTN83867919)	Patients with unresectable, liver-dominant mCRC who have not received previous chemotherapy for advanced disease (UK) SIRT using SIR-Spheres Y-90 resin microspheres plus FOLFOX (± bevacizumab or cetuximab) vs FOLFOX (± bevacizumab or cetuximab)		Q3 2017
2.	RCT Phase III Open-label	FOXFIRE Global (NCT01721954)	Patients with unresectable, liver-dominant mCRC who have not received previous chemotherapy for advanced disease (Global) SIRT using SIR-Spheres Y-90 resin microspheres plus FOLFOX (± bevacizumab or cetuximab) vs FOLFOX (± bevacizumab or cetuximab)		Q3 2017

** Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment.*

****Date of when results will be made available (to the best of your knowledge).*

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

20. List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):

The Royal Australian and New Zealand College of Radiologists (RANZCR). Please see web site http://www.insideradiology.com.au/sirt-hp/

21. List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):

The Royal Australian and New Zealand College of Radiologists (RANZCR). Oncology society?

22. List the relevant consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):

Bowel Cancer Australia (https://www.bowelcanceraustralia.org/selective-internal-radiation-therapy)

23. List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:

None

24. Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):

Name of expert 1: REDACTED

Telephone number(s): REDACTED

Email address: REDACTED

Justification of expertise: REDACTED

Name of expert 2: REDACTED

Telephone number(s): REDACTED

Email address: REDACTED

Justification of expertise: REDACTED

Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.

PART 6 – POPULATION (AND PRIOR TESTS), INDICATION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

25. Define the medical condition, including providing information on the natural history of the condition and a high level summary of associated burden of disease in terms of both morbidity and mortality:

Colorectal metastases of the liver (CRC) is the most common cancer after non-melanomatous skin cancer and the third most common cause of cancer death reported to Australian cancer registries. In 2001, CRC accounted for 14.5 per cent of all new cases of cancer and 13.1 per cent of cancer deaths (excluding non-melanocytic skin cancer) (AIHW & AACR 2004). In 2001, premature death from CRC was responsible for an estimated 29 768 person-years of life lost before the age of 75, making it second only to lung cancer for this measure of disease burden (AIHW & AACR 2004).

Approximately 50 per cent of patients with CRC will develop liver metastases within 5 years and 20 per cent of patients will already have liver metastases at the time of primary diagnosis (COSA & CAN 1999). If untreated, liver metastases from CRC show a very poor prognosis, with a median survival of 19 to 21 months, and no patients surviving 5 years (Liu et al. 2003).

26. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:

Patients with hepatic metastases secondary to colorectal cancer which are not suitable for resection or ablation. *See answer to Q27 for investigative tests.*

27. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):

- Blood test samples ('liver function tests') can be taken to see how well the liver is working and can be used to monitor patients for the early detection of secondary cancer
- A chest x-ray may be taken to determine if the cancer has spread to the lungs
- A CT scan to create a cross sectional, 3D image of the tumour(s) and surrounding tissues and organs.
- Liver biopsy
- A CT scan can be combined with a PET scan to show where there are any cell changes in the body, and whether the cancer has spread
- Magnetic resonance imaging (MRI) to show the tumour(s) in great detail and look at the blood supply to the liver
- Ultrasound

PART 6b – INFORMATION ABOUT THE INTERVENTION

28. Describe the key components and clinical steps involved in delivering the proposed medical service:

Selective Internal Radiation Therapy (SIRT) normally comprises two procedures:

Preparation or "work-up"

In preparation for the angiogram: blood tests to evaluate the kidney function and blood clotting.

Angiogram to prepare the liver for SIRT. During the angiogram a small amount of dye (or contrast medium) is injected through a catheter (a thin plastic tube) inserted into an artery. The dye travels down the catheter into the liver and highlights the vessels.

The work-up procedure for SIRT is normally done on an outpatient basis.

Implant of SIR-Spheres Y-90 resin microspheres®

A second angiogram is performed to implant the SIR-Spheres Y-90 resin microspheres® (SIRT). The catheter used during the angiogram is then guided by the interventional radiologist through the artery and placed close to the tumours in the liver. The purpose of the angiogram this time is to implant the SIR-Spheres Y-90 resin microspheres®. SIR-Spheres Y-90 resin microspheres® are then infused through a catheter into the liver. This whole procedure may take about 60 minutes.

For this procedure, the patient is admitted to hospital.

Source: http://www.insideradiology.com.au/

29. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

SIR-Spheres Y-90 resin microspheres (Selective Internal Radiation Spheres) are yttrium-90 resin microspheres that are implanted into malignant liver tumours for the purpose of selectively delivering high doses of ionising radiation to the tumour.

30. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

It was a new approach for this patient sub-group when interim listed on the MBS in 2006 - patients with hepatic metastases secondary to colorectal cancer which are not suitable for resection or ablation.

31. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):

Patient sub-group - patients with hepatic metastases secondary to colorectal cancer which are not suitable for resection or ablation. To be claimed once in the patient's lifetime only.

32. If applicable, identify any healthcare resources or other medical services that would need to be delivered at the same time as the proposed medical service:

Used in combination with systemic chemotherapy using 5-fluorouracil (5FU) and leucovorin.

33. If applicable, advise which health professionals will primarily deliver the proposed service:

The service must be performed by a specialist or consultant physician recognised in the specialties of nuclear medicine or radiation oncology.

34. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

n/a

35. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

The service must be performed by a specialist or consultant physician recognised in the specialties of nuclear medicine or radiation oncology.

Patients must have a referral from an oncologist to the interventional radiologist.

36. If applicable, advise what type of training or qualifications would be required to perform the proposed service as well as any accreditation requirements to support service delivery:

The service must be performed by a specialist or consultant physician recognised in the specialties of nuclear medicine or radiation oncology.

Sirtex provides a robust training programme, the SIR-Spheres Y-90 resin microspheres Microspheres Training, Evaluation and Certification (TEC) Programme, for institutions or new users that want to start or re-start a SIR-Spheres Y-90 resin microspheres service. The training programme is designed to instruct new physicians and healthcare professionals in the clinical use of SIR-Spheres Y-90 resin microspheres and to help an institution to build a sustainable, high-quality SIR-Spheres Y-90 resin microspheres programme.

37. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select all relevant settings):

- ☒ Inpatient private hospital
- ☒ Inpatient public hospital
- ☒ Outpatient clinic
- ☐ Emergency Department
- ☐ Consulting rooms
- ☐ Day surgery centre
- ☐ Residential aged care facility
- ☐ Patient's home
- ☐ Laboratory
- ☐ Other – please specify below

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

See answer to Q28 - Preparation or "work-up" carried out in outpatient setting. Implant of the SIR-Spheres Y-90 resin microspheres® carried out in inpatient setting.

38. Is the proposed medical service intended to be entirely rendered in Australia?

- ☒ Yes
- ☐ No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

39. Nominate the appropriate comparator(s) for the proposed medical service, i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):

According to the Assessment Report for MSAC Application 1082, both systemic chemotherapy and hepatic arterial chemotherapy (HAC) have been identified as comparators.

According to SIRFLOX (a randomized, multicentre trial) selective internal radiation therapy (SIRT) using yttrium-90 resin microspheres was added to standard fluorouracil, leucovorin, and oxaliplatin (FOLFOX)–based chemotherapy and compared to the comparator of standard fluorouracil, leucovorin, and oxaliplatin (FOLFOX)–based chemotherapy in patients with previously untreated metastatic colorectal cancer.

40. Does the medical service that has been nominated as the comparator have an existing MBS item number(s)?

☒ Yes (please provide all relevant MBS item numbers below)
☐ No

41. Define and summarise the current clinical management pathways that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards including health care resources):

Only palliative care.

42. (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?

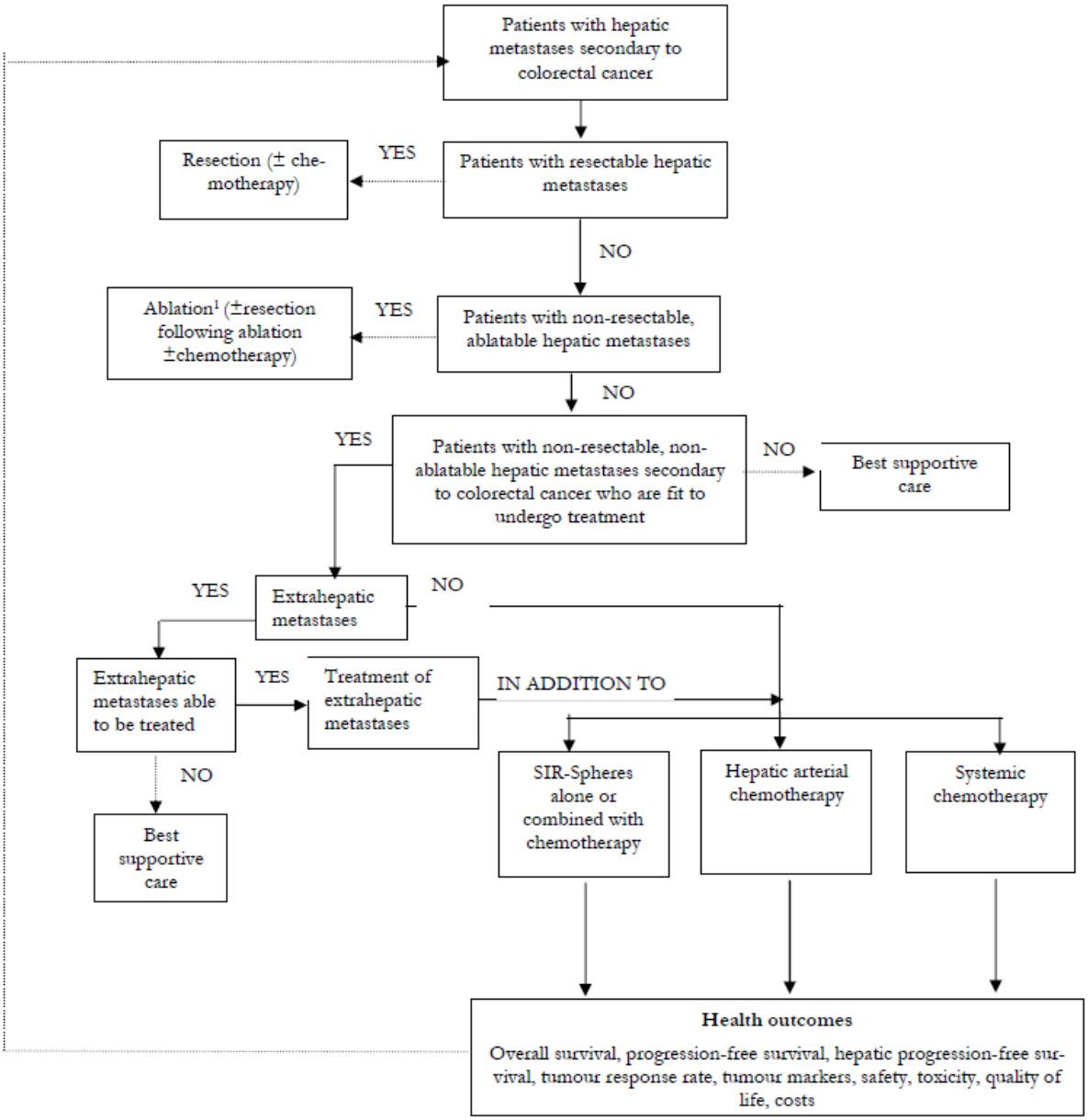
☒ Yes
☐ No

(b) If yes, please outline the extent of which the current service/comparator is expected to be substituted:

Selective internal radiation therapy (SIRT) using yttrium-90 resin microspheres is added to standard fluorouracil, leucovorin, and oxaliplatin (FOLFOX)–based chemotherapy in patients with previously untreated metastatic colorectal cancer.

43. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service including variation in health care resources (Refer to Question 39 as baseline):

Flow chart of SIR-Spheres Y-90 resin microspheres® treatment (page 96 of Assessment Report for MSAC Application 1082)



[1]Ablation: Radiofrequency ablation (RFA), cryoablation, microwave ablation or laser ablation

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

44. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

Selective internal radiation therapy (SIRT) used in combination with systemic chemotherapy using 5-fluorouracil (5FU) and leucovorin, in patients with liver-dominant or liver only metastatic colorectal cancer, significantly delayed disease progression in the liver.

Treatment goals of SIRT with SIR-Spheres Y-90 resin microspheres are to: extend overall survival (OS); increase time to progression (TTP) or increase progression-free survival (PFS); downsize liver tumours to potentially curative resection or bridge to transplantation; and relieve symptoms to improve quality of life (QoL).

SIRFLOX, the first large-scale, randomised controlled trial (RCT) of 530 chemotherapy-naive patients with liver-only or liver-dominant metastatic colorectal cancer (mCRC) showed that the addition of SIR-Spheres Y-90 resin microspheres significantly improved median liver PFS by 7.9 months, corresponding to a 31% risk reduction. While there was no improvement in PFS at any site with the addition of SIR-Spheres Y-90 resin microspheres, this is not unexpected with a liver-directed treatment. The addition of SIR-Spheres Y-90 resin microspheres did not adversely affect the delivery of chemotherapy. Furthermore, the safety profile from the addition of SIR-Spheres Y-90 resin microspheres to the mFOLFOX6 chemotherapy regimen in SIRFLOX was as anticipated and manageable, with no unexpected toxicities observed.

45. Please advise if the overall clinical claim is for:

☒ Superiority
☐ Non-inferiority

46. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

Clinical Effectiveness Outcomes: Delayed disease progression in the liver.

Safety Outcomes: Common grade ≥ 3 AEs associated with chemotherapy such as neutropenia, febrile neutropenia, and thrombocytopenia

Justification

SIRFLOX is the largest randomised interventional radiology study ever conducted in oncology. The investigators reported:

- n=530 (n=263 arm A; n=267 arm B) chemotherapy-naïve patients with non-resectable, liver-only or liver-dominant (liver plus lung and/or lymph node metastases) mCRC were randomised to receive either mFOLFOX6 (±bev) (arm A) or mFOLFOX6 (±bev) + SIR-Spheres Y-90 resin microspheres (arm B); bevacizumab (bev) was allowed at investigator's discretion, per institutional practice;
- a majority of patients had poor prognostic factors at baseline; 40% had extra-hepatic metastases in both arms, 46% and 45% had the primary tumour *in situ*, and 89% and 90% had synchronous metastases in arm A and arm B, respectively;
- median overall PFS – the primary endpoint of the study – was 10.2 *vs.* 10.7 months in arm A *vs.* B, respectively (HR: 0.93; 95% CI 0.77–1.12; *P* = 0.429);
- median liver PFS was 12.6 *vs.* 20.5 months in arm A *vs.* B (HR: 0.69; 95% CI 0.55–0.90; *P* = 0.002) by competing risk analysis; SIR-Spheres Y-90 resin microspheres significantly extended PFS in the liver with a 31% risk reduction of progression in the liver;

- median Liver PFS was 12.4 *vs*. 21.1 months in arm A vs. B (HR: 0.64; 95% CI 0.48–0.86; *P* = 0.003) for patients with liver-only metastases, and 12.6 *vs.* 16.7 months (HR: 0.77, 95% CI 0.54–1.09; p=0.147) for those with liver and extra-hepatic metastases;
- median Liver PFS was 10.6 *vs.* 18.9 months in arm A *vs*. B (HR: 0.69; 95% CI 0.50–0.96; *P* = 0.028) for patients with ITT for no bevacizumab, and 12.7 *vs*. 21.0 months (HR: 0.69, 95% CI 0.50–0.94; *P* = 0.018) for those with ITT to receive bevacizumab; SIR-Spheres Y-90 resin microspheres significantly extend PFS in the liver with a 31% reduction in risk of progression in the liver, independent of bevacizumab;
- ORR (PR + CR) was 68.1% *vs.* 76.4% in arm A *vs.* B, respectively (p=0.113); hepatic ORR 68.8% *vs.* 78.7% in arm A *vs.* B (p=0.042), including complete response (CR) rate 1.9% *vs.* 6.0% (p=0.02);
- the liver resection rate was 13.7% v 14.2% in arm A *vs.* B (*P* = 0.857);[7]
- all-causality grade ≥3 adverse events were noted in 73.3% *vs*. 85.4% (NS) of patients in arm A *vs*. B, respectively; grade 5 events occurred in 1.9% *vs.* 3.7% in arm A *vs.* B (NS);
- the investigators concluded that the addition of SIR-Spheres Y-90 resin microspheres to standard chemotherapy failed to improve overall PFS. However, median liver PFS was significantly extended. The addition of SIR-Spheres Y-90 resin microspheres was associated with acceptable toxicity

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

47. Estimate the prevalence and/or incidence of the proposed population:

A rough estimate of the number of patients eligible for SIR-Spheres Y-90 resin microspheres for metastatic colorectal cancer (mCRC) is

Colorectal Cancer	**N**	**References**
Incidence of colorectal cancer (CRC) in Australia	15,868	Globocan 2012
15–34% present with Stage IV synchronous mCRC (assume 20%)	3,174	NCCN v2 2016; Van Cutsem 2014; Adam 2012; Mantke 2012; Sadahiro 2013; Khatri 2007; GlobalData 2014;. Van der Geest 2015
44% of synchronous mCRC is confined to the liver and 26% of these receive surgical resection; 40–75% of resected patients get recurrence (assume 70%), of which 38% are liver only, with 50% receiving further surgical resection/ablation	48	Kumar 2014; Pawlik 2005; Nordlinger 2013; Van Cutsem 2014; Fong 1997; Pawlik 2005; Abbas 2011; Nakagawa 2014; Navarro-Freire 2015; Lee 2015
11% of synchronous mCRC have liver + lung mCRC and 13.5% have liver + non-lung mCRC; 35% of these have liver and limited lung or lymph node metastases	269	Kumar 2014; Van der Geest 2015
80% of patients present with Stage I to III CRC, and 17–50% of these develop metachronous metastases (assume 26%)	3,301	NCCN v2 2016; Van Cutsem 2014; Adam 2012; Mantke 2012; Sadahiro 2013; Khatri 2007; GlobalData 2014;. Van der Geest 2015
30% of metachronous mCRC is confined to the liver and 60% of these receive surgical resection; 40–75% of resected patients get recurrence (assume 70%), of which 38% are liver only, with 50% receiving further surgical resection/ablation	475	Kumar 2014; Pawlik 2005; Nordlinger 2013; Van Cutsem 2014; Fong 1997; Pawlik 2005; Abbas 2011; Nakagawa 2014; Navarro-Freire 2015; Lee 2015
9% of metachronous mCRC have liver + lung mCRC and 11% have liver + non-lung mCRC; 36% of these have liver and limited lung or lymph node metastases	240	Kumar 2014; Van der Geest 2015
Number of patients with unresectable liver-only mCRC	1,557	
Number of patients with unresectable liver + limited extra-hepatic mCRC	509	
Total number of patients with unresectable liver ± limited extra-hepatic mCRC	2,066	
85% of mCRC patients receive first-line chemotherapy	1,756	Hind 2005; Zafar 2009; Abrams 2015; GlobalData 2014.
Of these, it is estimated that 63.6% would be suitable for SIRT [1st-line SIRT]	1,117	Sirtex. MSAC submission. 2004
75% of those treated at first line receive second-line chemotherapy	1,317	Hind 2005; Zafar 2009; Abrams 2015; GlobalData 2014.
Of these, it is estimated that 63.6% would be suitable for SIRT [2nd-line SIRT]	838	Sirtex. MSAC submission. 2004
50% of those treated at second line receive third-line chemotherapy	659	Hind 2005; Zafar 2009; Abrams 2015; GlobalData 2014.
Of these, it is estimated that 63.6% would be suitable for SIRT [3rd-line SIRT]	419	Sirtex. MSAC submission. 2004
33% of those treated at third line receive fourth-line chemotherapy	217	Hind 2005; Zafar 2009; Abrams 2015; GlobalData 2014.
Of these, it is estimated that 63.6% would be suitable	138	Sirtex. MSAC submission. 2004

for SIRT [4th-line SIRT]		
Note: SIR-Spheres is currently used as a single treatment at either 3rd or 4th line, with a minority of patients receiving treatment at an earlier stage such as 2nd line; Patients very rarely receive more than a single SIRT treatment		Sirtex. Feedback from oncologists and interventional radiologists in Australia
Maximum estimated patient population	1,117 838 419 217	If SIRT is used at 1st line If SIRT is used at 2nd line If SIRT is used at 3rd line If SIRT is used at 4th line

48. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

Once

49. How many years would the proposed medical service(s) be required for the patient?

Once per lifetime

50. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

103 services (2006/2007) – first year of listing on the MBS

51. Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of 'leakage' to populations not targeted by the service:

Claims on MBS Item 35404 since listing – 1st May 2006

DOSIMETRY, HANDLING AND INJECTION OF SIR-SPHERES for selective internal radiation therapy of hepatic metastases which are secondary to colorectal cancer and are not suitable for resection or ablation, used in combination with systemic chemotherapy using 5-fluorouracil (5FU) and leucovorin

Year	Services
2006/2007	103
2007/2008	169
2008/2009	152
2009/2010	166
2010/2011	178
2011/2012	153
2012/2013	194
2013/2014	191
2014/2015	176
2015/2016	195

PART 8 – COST INFORMATION

52. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

MBS Item 35406: Fee: $813.30 Benefit: 75% = $610.00

MBS Item 35408: Fee: $610.10 Benefit: 75% = $457.60

Prostheses List: SE001 benefit $8,230 - SIR-Spheres Y-90 resin microspheres including Delivery Apparatus

Table 26 Average total cost per patient (page 55 Assessment Report MSAC Application 1082)

Component	SIR-Spheres + 5-FU/LV	5-FU/LV alone
Work-up	$3,337	$1,107
Treatment	$16,947	$1,983
Adverse events	$2,964	$2,136
Follow up	$6,219	$3,062
Total av cost/patient	$29,507	$8,288

53. Specify how long the proposed medical service typically takes to perform:

Approximately 60 minutes

54. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

Current MBS Listings for Selective Internal Radiation Therapy (SIRT)

MBS 35404
DOSIMETRY, HANDLING AND INJECTION OF SIR-SPHERES for selective internal radiation therapy of hepatic metastases which are secondary to colorectal cancer and are not suitable for resection or ablation, used in combination with systemic chemotherapy using 5-fluorouracil (5FU) and leucovorin, not being a service to which item 35317, 35319, 35320 or 35321 applies
The procedure must be performed by a specialist or consultant physician recognised in the specialties of nuclear medicine or radiation oncology on an admitted patient in a hospital. To be claimed once in the patient's lifetime only.
Multiple Services Rule T8.2
Fee: $346.60 Benefit: 75% = $259.95

MBS 35406
Trans-femoral catheterisation of the hepatic artery to administer SIR-Spheres to embolise the microvasculature of hepatic metastases which are secondary to colorectal cancer and are not suitable for resection or ablation, for selective internal radiation therapy used in combination with systemic chemotherapy using 5-fluorouracil (5FU) and leucovorin, not being a service to which item 35317, 35319, 35320 or 35321 applies excluding associated radiological services or preparation, and excluding aftercare
Multiple Services Rule T8.2
(Anaes.) (Assist.)
Fee: $813.30 Benefit: 75% = $610.00

MBS 35408
Catheterisation of the hepatic artery via a permanently implanted hepatic artery port to administer SIR-Spheres to embolise the microvasculature of hepatic metastases which are secondary to colorectal cancer and are not suitable for resection or ablation, for selective internal radiation therapy used in combination with systemic chemotherapy using 5-fluorouracil (5FU) and leucovorin, not being a service

to which item 35317, 35319, 35320 or 35321 applies excluding associated radiological services or preparation, and excluding aftercare
Multiple Services Rule T8.2
(Anaes.) (Assist.)
Fee: $610.10 Benefit: 75% = $457.60

EXPLANATORY NOTES - Selective Internal Radiation Therapy (SIRT) using SIR-Spheres - (35404, 35406 and 35408)
These items were introduced into the Schedule on an interim basis in May 2006 following a recommendation of the Medical Services Advisory Committee (MSAC). Medicare funding for these items is available until May 2011, before which time MSAC will review the results of trials conducted in the intervening period. SIRT should not be performed in an outpatient or day patient setting to ensure patient and radiation safety requirements are met.

PART 9 – FEEDBACK

The Department is interested in your feedback.

55. How long did it take to complete the Application Form?

Approximately five full days

56. (a) Was the Application Form clear and easy to complete?

☐ Yes
☒ No

(b) If no, provide areas of concern:

Example: Q42 (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)? Answer yes / no. This does not make sense.

57. (a) Are the associated Guidelines to the Application Form useful?

☐ Yes
☒ No

(b) If no, what areas did you find not to be useful?

Similar information required for difference questions.

58. (a) Is there any information that the Department should consider in the future relating to the questions within the Application Form that is not contained in the Application Form?

☒ Yes
☐ No

(b) If yes, please advise:

Example: It's standard to identify published papers using authors. This information is not required in the table for Q18. Also, asking where the paper can be found is unusual since the majority of published papers are on Medline.