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Australian Government

Department of Health

MEDICAL SERVICES ADVISORY COMMITTEE

Application 1429

Applicant Submitted Protocol

For

Targeted Intraoperative Radiotherapy

For Early-Stage Breast Cancer

(Xoft[®] Axxent[®])

Regional Health Care Group

6th June 2016

1. Title of application

Targeted Intraoperative Radiotherapy for Early-Stage Breast Cancer (Xoft® Axxent®).

2. Purpose of application

Please indicate the rationale for the application and provide one abstract or systematic review that will provide background.

Background

The purpose of the targeted intraoperative radiotherapy (IORT) technique is to accurately target the tissues where there is the highest risk of cancer recurrence. IORT is a form of partial breast irradiation involving the application of localized radiotherapy to the tissues surrounding a breast cancer in the operating theatre after surgical removal of the tumour (breast-conserving surgery, partial mastectomy or lumpectomy). IORT can also be applied as a second procedure at some time after surgery.

An earlier application by Carl Zeiss for inclusion of IORT in the Medical Benefits Schedule has previously been considered and approved as part of the MSAC process which resulted in the IORT technique using the Zeiss IntraBeam being listed in the Medical Benefits Schedule. The events that resulted in the outcome are as follows:

- Application No. 1189 for Targeted Intraoperative Radiotherapy (IORT) for early breast cancer submitted by Carl Zeiss
- February 2014 - Proposed protocol for consideration by PASC submitted by Carl Zeiss
- March 2014 – Proposed protocol released for comment
- April 2014 – Final protocol unratified by PASC
- November 2014 – Public Summary Document with Ministerial recommendations supporting the inclusion of IORT into the Medical Benefits Schedule released by MSAC
- October 2015 – Publication of new IORT MBS item numbers

Rationale for the Application

The rationale for the application is to facilitate the inclusion of the the Xoft® Axxent® treatment device to the existing MBS items numbers for IORT by demonstrating that the Relative Biological Effectiveness (RBE) of intraoperative radiotherapy (IORT) delivered using the Xoft® Axxent® treatment device is in all respects identical to intraoperative radiotherapy (IORT) delivered using the Zeiss IntraBeam treatment device.

Therefore, the proposed protocol does not seek to introduce new MBS items, rather an amendment to the existing descriptors for MBS items 15900 and 31516. The requested amendments are as follows:

15900	<p>BREAST, MALIGNANT TUMOUR, targeted intraoperative radiotherapy, using an Intrabeam® or Xofig® Axxent® device, delivered at the time of breast-conserving surgery (partial mastectomy or lumpectomy) for a patient who:</p> <p>a) is 45 years of age or more; and b) has a T1 or small T2 (less than or equal to 3cm in diameter) primary tumour; and c) has an histologic Grade 1 or 2 tumour; and d) has an oestrogen-receptor positive tumour; and e) has a node negative malignancy; and f) is suitable for wide local excision of a primary invasive ductal carcinoma that was diagnosed as unifocal on conventional examination and imaging; and g) has no contra-indications to breast irradiation</p> <p>Fee: \$250.00 Benefit: 75% = \$187.50</p>
31516	<p>BREAST, MALIGNANT TUMOUR, complete local excision of, with or without frozen section histology when targeted intraoperative radiotherapy (using an Intrabeam® or Xofig® Axxent® device) is performed concurrently, if the requirements of item 15900 are met for the patient (Anaes.) (Assist.)</p> <p>Fee: \$867.00 Benefit: 75% = \$650.25</p>

Alternatively, varying the existing descriptors for MBS items 15900 and 31516 to make them more consistent with the therapeutic treatment (T-IORT) rather than a particular device would also be acceptable. In this instance, the requested amendments are as follows:

15900	<p>BREAST, MALIGNANT TUMOUR, targeted intraoperative radiotherapy, delivered at the time of breast-conserving surgery (partial mastectomy or lumpectomy) for a patient who:</p> <p>a) is 45 years of age or more; and b) has a T1 or small T2 (less than or equal to 3cm in diameter) primary tumour; and c) has an histologic Grade 1 or 2 tumour; and d) has an oestrogen-receptor positive tumour; and e) has a node negative malignancy; and f) is suitable for wide local excision of a primary invasive ductal carcinoma that was diagnosed as unifocal on conventional examination and imaging; and g) has no contra-indications to breast irradiation</p> <p>Fee: \$250.00 Benefit: 75% = \$187.50</p>
31516	<p>BREAST, MALIGNANT TUMOUR, complete local excision of, with or without frozen section histology when targeted intraoperative radiotherapy is performed concurrently, if the requirements of item 15900 are met for the patient (Anaes.) (Assist.)</p> <p>Fee: \$867.00 Benefit: 75% = \$650.25</p>

3. Population and medical condition eligible for the proposed medical services

Provide a description of the medical condition (or disease) relevant to the service.

Early stage breast cancer - which is the same population group and evidence for the intervention already considered by MSAC as part of application 1189.

Define the proposed patient population that would benefit from the use of this service. This could include issues such as patient characteristics and /or specific circumstances that patients would have to satisfy in order to access the service.

Patient suitability for IORT delivered using the Xoft® Axxent® treatment device is the same as IORT delivered using the Zeiss IntraBeam device, namely:

- aged over 45 years
- pathologically documented invasive ductal breast cancer
- T1 or small T2 tumours (less than or equal to 3cm, histologic Grade 1 or 2)

- are estrogen-receptor positive
- are node negative
- suitable for wide local excision for invasive ductal carcinoma that is unifocal on conventional examination and imaging)
- have no contraindication to breast irradiation

Indicate if there is evidence for the population who would benefit from this service i.e. international evidence including inclusion / exclusion criteria. If appropriate provide a table summarising the population considered in the evidence.

The evidence for this application is primarily based on the following published papers, two of which have already been evaluated by MSAC as part of application 1189.

Study	Targeted intraoperative radiotherapy vs. whole breast radiotherapy: an international, prospective, randomized, non-inferiority phase 3 trial.	Risk-adapted targeted intraoperative radiotherapy vs whole-breast therapy for breast cancer. 5-year results for local control and overall survival from the TARGIT-A randomized trial.	12 month follow-up results of a trial utilizing Xoft® Axxent® to deliver intraoperative radiotherapy for early stage breast cancer
Author	Vaidya <i>et al</i>	Vaidya <i>et al</i>	Ivanov <i>et al</i>
Publication & Date Published	The Lancet online, June 5, 2010	The Lancet online, February 15, 2014 – Vol 383: 603-13	Annals of Surgical Oncology, 2011 – 18: 453-458
Type of Trial	Non-inferiority	5-year risk results	1 year results
Type of Therapy	Targeted intraoperative radiotherapy	Targeted intraoperative radiotherapy	Targeted intraoperative radiotherapy
Comparator	EB-WBRT	EB-WBRT	EB-WBRT
Number of Patients	2,232	3,451	11
Primary Endpoint	Local Recurrence Rates	5-Year Recurrence Rates	Local Recurrence Rates

The referenced clinical evidence substantiating non-inferiority of the proposed intervention (IORT using Xoft® Axxent® IORT treatment system) to EB-WBRT was largely derived using the Zeiss IntraBeam device in the TARGIT-A trial so the protocol submission is based on the

premise that equivalence in Relative Biological Effectiveness (RBE) for comparable applicator sizes has been conclusively demonstrated to be in the order of less than 1% between the two systems when calculated using the Monte Carlo damage simulator.

Since MSAC has already considered and accepted the TARGIT evidence, we believe that this evidence can reasonably apply to both Xoft and Zeiss systems given the marginal difference in Dosimetry and Relative Biological Effectiveness between the two systems.

Evidence of equivalence of Dosimetry and Relative Biological Effectiveness for Zeiss Intrabeam and Xoft® Axxent® is provided in the following studies:

Study	A comparison of the relative biological effectiveness of low energy electronic brachytherapy sources in breast tissue: a Monte Carlo study	Spectral Comparison of the Xoft and Zeiss 50 kVp X-ray Systems	Spectral Comparison of the Xoft and Zeiss 50 kVp X-ray Systems
Author	Shane A. White <i>et al</i>	Linda Kelley <i>et al</i>	A/Professor Prabhakar Ramachandran
Publication	Physics in Medicine and Biology 61 (2016) 383-399	Medical Physics 41, 293 (2014) AAPM Poster AAPM Presentation	Peter MacCallum Cancer Centre QMS. Ref. No. DRO_07.23.01_MRB
Type of Trial	Comparative	Comparative	Comparative
Equipment	XOFT Axxent	XOFT Axxent	XOFT Axxent
Comparator	Zeiss Intrabeam	Zeiss Intrabeam	Zeiss Intrabeam
Conclusion	X-Ray Spectra & RBE Equivalence	X-Ray Spectra Equivalence	Preliminary results X-Ray Spectra Equivalence

Provide details on the expected utilisation, if the service is to be publicly funded.

The expected utilisation of this service will be estimated based on:

- The current incidence of breast cancer treated with breast-conserving surgery (partial mastectomy or lumpectomy);
- The percentage of these patients who currently have external beam whole breast radiation therapy (EB-WBRT).
- The percentage of these patients who would have access to IORT in the short and long-term.

The claims on the following MBS Item numbers give some indication of the potential population.

31512

BREAST, MALIGNANT TUMOUR, complete local excision of, with or without frozen section histology (Anaes.) (Assist.)

Fee: \$650.15 Benefit: 75% = \$487.65

There were 7,947 claims in the 2014-15 Financial Year for MBS Item 31512.

15221

RADIATION ONCOLOGY TREATMENT, using a single photon energy linear accelerator with or without electron facilities - each attendance at which treatment is given - 1 field - treatment delivered to primary site (breast)

Fee: \$59.65 Benefit: 75% = \$44.75 85% = \$50.75

There were 474 claims in the 2014-15 Financial Year for MBS Item 15221.

15236

RADIATION ONCOLOGY TREATMENT, using a single photon energy linear accelerator with or without electron facilities - each attendance at which treatment is given - 2 or more fields up to a maximum of 5 additional fields (rotational therapy being 3 fields) - treatment delivered to primary site (breast)

The fee for item 15221 plus for each field in excess of 1, an amount of \$37.95

There were 21,376 claims in the 2014-15 Financial Year for MBS Item 15236.

15251

RADIATION ONCOLOGY TREATMENT, using a dual photon energy linear accelerator with a minimum higher energy of at least 10MV photons, with electron facilities - each attendance at which treatment is given - 1 field - treatment delivered to primary site (breast)

Fee: \$59.65 Benefit: 75% = \$44.75 85% = \$50.75

There were 23,839 claims in the 2014-15 Financial Year for MBS Item 15251.

15266

RADIATION ONCOLOGY TREATMENT, using a dual photon energy linear accelerator with a minimum higher energy of at least 10MV photons, with electron facilities - each attendance at which treatment is given - 2 or more fields up to a maximum of 5 additional fields (rotational therapy being 3 fields) - treatment delivered to primary site (breast)

The fee for item 15251 plus for each field in excess of 1, an amount of \$37.95

There were 267,820 claims in the 2014-15 Financial Year for MBS Item 15266.

15900

BREAST, MALIGNANT TUMOUR, targeted intraoperative radiotherapy, using an Intrabeam® device, delivered at the time of breast-conserving surgery (partial mastectomy or lumpectomy) for a patient who: a) is 45 years of age or more; and b) has a T1 or small T2 (less than or equal to 3cm in diameter) primary tumour; and c) has an histologic Grade 1 or 2 tumour; and d) has an oestrogen-receptor positive tumour; and e) has a node negative malignancy; and f) is suitable for wide local excision of a primary invasive ductal carcinoma that was diagnosed as unifocal on conventional examination and imaging; and g) has no contra-indications to breast irradiation

Fee: \$250.00 Benefit: 75% = \$187.50

There were 0 claims in the October 2015 to February 2016 period for MBS Item 15900.

31516

BREAST, MALIGNANT TUMOUR, complete local excision of, with or without frozen section histology when targeted intraoperative radiotherapy (using an IntraBeam® device) is performed concurrently, if the requirements of item 15900 are met for the patient (Anaes.) (Assist.)

Fee: \$867.00 Benefit: 75% = \$650.25

There were 0 claims in the October 2015 to February 2016 period for MBS Item 31516.

Lack of claims for MBS items 15900 and 31516 can be attributed to the fact that the benefit was only listed on the MBS schedule from 1st October 2015 and there is currently only one Zeiss IntraBeam device in operation in Australia at Sir Charles Gardiner Hospital.

It is anticipated that claims on MBS item numbers 15900 & 31516 will increase as more equipment enters the market and the technology and IORT technique gain acceptance as a viable alternative to EB-WBRT.

4. Intervention – proposed medical service

Provide a description of the proposed medical service.

The administration of local radiotherapy to the tumour bed using the Xofig®Axxent® IORT treatment system following surgical removal of early stage breast cancer.

Following lesion excision, the balloon applicator of the Xofig®Axxent® system is inserted into the surgical cavity and inflated with saline to the volume determined using a cavity evaluation device. To prevent skin burns, an Ultrasound unit is used to verify that the distance from the skin surface to the balloon applicator surface is greater than 1cm. Shielding of critical structures is achieved by the placement of stainless steel shields into the surgical site.

The x-ray source is then inserted into the applicator for delivery of a 20Gy single fraction prophylactic treatment. The treatment time is dependent on the size of the applicator but ranges between 8-15 minutes.

Following radiation delivery, the balloon applicator is deflated and withdrawn and the wound is closed in the usual fashion to achieve a good cosmetic result.

The procedural aspects of treatment delivery for the Xofig®Axxent® and Zeiss IntraBeam IORT systems are very similar, as are the costs, and whilst not widely reported in the literature, the use of intraoperative ultrasound for determining adequate applicator to skin distance to prevent skin burns is widespread and is considered to be the standard of care for IORT regardless of treatment device. The requirement for intraoperative US is clearly cited in application 1189.

The major difference between the two systems is shorter treatment delivery times for the same dose with the Xofig®Axxent® mainly due to the fact that the the Xofig®Axxent® utilizes a higher x-ray tube current than the Zeiss IntraBeam.

If the service is for investigative purposes, describe the technical specification of the health technology and any reference or “evidentiary” standard that has been established.

This service is not for investigative purposes

Indicate whether the service includes a registered trademark with characteristics that distinguish it from any other similar health technology.

This service includes the use of a registered trademarked device, Axxent[®] Electronic Brachytherapy (eBx[®]) System[®] by Xoft[®]. Xoft[®] is a subsidiary of iCAD Inc.

Indicate the proposed setting in which the proposed medical service will be delivered and include detail for each of the following as relevant: inpatient private hospital, inpatient public hospital, outpatient clinic, emergency department, consulting rooms, day surgery centre, residential aged care facility, patient's home, laboratory. Where the proposed medical service will be provided in more than one setting, describe the rationale related to each.

The proposed setting for the delivery of this service, when provided as part of a breast conserving surgery, is an operating theatre with the patient classified as an inpatient in either a private or public hospital.

Describe how the service is delivered in the clinical setting. This could include details such as frequency of use (per year), duration of use, limitations or restrictions on the medical service or provider, referral arrangements, professional experience required (e.g.: qualifications, training, accreditation etc.), healthcare resources, access issues (e.g.: demographics, facilities, equipment, location etc.).

Patients have only one treatment which is delivered to the tumour bed in a single fraction of targeted radiotherapy immediately following the surgical removal of early stage breast cancer as part of breast-conserving surgery, partial mastectomy or lumpectomy surgical procedures.

The dose delivered to the tumour bed is approximately 20Gy. The treatment time is dependent on the size of the balloon applicator but ranges between 8-15 minutes

Prior to the first T-IORT treatment delivery, all service providers must undertake appropriate training and achieve certification in treatment delivery and radiation safety. Service providers include:

- (i) Breast surgeons
- (ii) Radiation oncologists
- (iii) Medical physicists

IORT is delivered by a radiation oncologist. A medical physicist is also required in order to calibrate the device.

The Axxent[®] Electronic Brachytherapy (eBx[®]) System is very portable consisting only of a single control unit on wheels (similar to a mobile x-ray unit). Consequently, given the mobility of the device and the ability to deliver IORT without special 'shielding', it has the potential to be used in any operating theatre that is suitable for breast conserving surgery.

The relative low cost of Axxent[®] Electronic Brachytherapy (eBx[®]) System, compared to the linear accelerator required to deliver EB-WBRT, makes it possible to provide this proposed service in more geographically remote locations.

5. Co-dependent information (if not a co-dependent application go to Section 6)

Please provide detail of the co-dependent nature of this service as applicable

This is not a co-dependent service

6. Comparator – clinical claim for the proposed medical service

Please provide details of how the proposed service is expected to be used, for example is it to replace or substitute a current practice; in addition to, or to augment current practice.

It is intended that the Xofig[®]Axxent[®] IORT treatment device be used as a direct substitute or alternative for the Zeiss Intrabeam treatment device (primary comparator) covered under MBS item numbers 15900 (Intraoperative Radiotherapy) and 31516 (operations General).

However, due to the fact that there is currently limited availability of IORT treatment delivery systems in Australia, the vast majority of patients undergoing breast conserving surgery for early stage breast cancer would still be treated post-operatively with whole breast external beam radiotherapy EB-WBRT.

As a consequence, the Xofig[®]Axxent[®] IORT treatment device can also be used as an alternative to the practice of EB-WBRT (secondary comparator). EB-WBRT is delivered using a linear accelerator in an out-patient setting. The cost of this service is covered by a combination of MBS fee, the Radiation Oncology Health Programme Grant (ROHPG) and the Medicare (outpatient) Safety Net (EMSN).

In contrast, the proposed IORT service is delivered in an inpatient setting using equipment not covered by the ROHPG and as part of a current surgical procedure.

MSAC has already assessed and accepted the comparative efficacy and safety of IORT delivered with the Zeiss Intrabeam system vs EB-WBRT as part of application 1189.

7. Expected health outcomes relating to the medical service

Identify the expected patient-relevant health outcomes if the service is recommended for public funding, including primary effectiveness (improvement in function, relief of pain) and secondary effectiveness (length of hospital stays, time to return to daily activities).

The expected health outcomes are anticipated to be the same as for the Zeiss Intrabeam, namely:

- The primary health outcome (effect) is the prevention of the local recurrence of breast cancer.
- Secondary health outcomes are comparable overall survival rates, improved cosmesis and reduced toxicity.
- Other outcomes include a reduced time spent in the hospital setting by the patient and a more rapid return to daily activities

Evidence of equivalence of Dose Distribution and Relative Biological Effectiveness for Zeiss Intrabeam and Xofig[®]Axxent[®] demonstrating that the two technologies are interchangeable in a clinical environment is supported by the following studies:

Study	A comparison of the relative biological effectiveness of low energy electronic brachytherapy sources in breast tissue: a Monte Carlo study	Spectral Comparison of the Xoft and Zeiss 50 kVp X-ray Systems	Spectral Comparison of the Xoft and Zeiss 50 kVp X-ray Systems
Author	Shane A. White <i>et al</i>	Linda Kelley <i>et al</i>	A/Professor Prabhakar Ramachandran
Publication	Physics in Medicine and Biology 61 (2016) 383-399	Medical Physics 41, 293 (2014) AAPM Poster AAPM Presentation	Peter MacCallum Cancer Centre QMS. Ref. No. DRO_07.23.01_MRB
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Comparator	Zeiss Intrabeam	Zeiss Intrabeam	Zeiss Intrabeam
Conclusion	X-Ray Spectra & RBE Equivalence	X-Ray Spectra Equivalence	Preliminary results X-Ray Spectra Equivalence

In addition to the above referenced studies, The Peter MacCallum Cancer Centre has access to a Xoft[®]Axxent[®] IORT treatment device and is presently conducting a Physics study comparing the x-ray spectra and dose distribution of the Xoft[®]Axxent[®] IORT and Zeiss Intrabeam treatment devices for similar applicator sizes.

The primary outcome of this study is to demonstrate comparable x-ray spectra and dose distribution characteristics for the Xoft[®]Axxent[®] IORT device as compared to the Zeiss Intrabeam device thereby demonstrating that the two technologies are interchangeable in a clinical environment.

The results of this study are expected to be available prior to the August PASC meeting.

Describe any potential risks to the patient.

The potential risks to the patient are anticipated to be the same as for the Zeiss Intrabeam, namely:

- IORT may cause redness and soreness of the skin of the breast, tenderness or painful sensations within the breast, or redness of the skin of the breast, and firmness of the breast tissue at the surgical site. These side effects gradually disappear after treatment has finished, but may also continue for several months. The feeling of firmness tends to be greatest between the third and sixth month post-surgery, and decline thereafter.
- Participants who received IORT in the TARGIT-A Trial were observed to have a slightly high risk of fluid formation at the lumpectomy site than those who received standard whole breast radiation therapy. This fluid was easily managed with aspiration (drainage) using a needle and was not associated with an increased risk of infection.
- Complications arising from IORT have been demonstrated in the TARGIT-A Trial. These complications include swelling (edema), scarring, skin ulceration, radiation-

induced tissue death (fat necrosis), and delayed wound healing. Some of these treatments may limit the ability of physical examination and mammograms to evaluate the breast for a cancer recurrence and may require that the patient undergo additional studies to evaluate the breast.

Specify the type of economic evaluation.

Cost minimization analysis for IORT as tabled in Public Summary Document for application 1189 has already been considered and accepted by MSAC. Anecdotal evidence suggests that the overall cost of treatment delivery, as well as the intervention and outcomes for the Xoft®Axxent® IORT treatment device and the Zeiss IntraBeam treatment device are very similar, so it is reasonable to assume that the costs will be the same so no further economic evaluation needs to be conducted.

8. Fee for the proposed medical service

Explain the type of funding proposed for this service.

As a service rendered in an in-patient setting, the type of funding proposed for this service is a fee for the providers.

Please indicate the direct cost of any equipment or resources that are used with the service relevant to this application, as appropriate.

- A depreciation cost for the capital used to acquire the IORT treatment delivery system
- Cost per procedure for balloon applicators, drapes, etc
- Maintenance and x-ray source contract

Provide details of the proposed fee.

The proposed fee for this service is identical to the recently introduced item numbers for IORT, specifically:

15900	<p>BREAST, MALIGNANT TUMOUR, targeted intraoperative radiotherapy, using an IntraBeam® device, delivered at the time of breast-conserving surgery (partial mastectomy or lumpectomy) for a patient who:</p> <p>a) is 45 years of age or more; and b) has a T1 or small T2 (less than or equal to 3cm in diameter) primary tumour; and c) has an histologic Grade 1 or 2 tumour; and d) has an oestrogen-receptor positive tumour; and e) has a node negative malignancy; and f) is suitable for wide local excision of a primary invasive ductal carcinoma that was diagnosed as unifocal on conventional examination and imaging; and g) has no contra-indications to breast irradiation</p> <p>Fee: \$250.00 Benefit: 75% = \$187.50</p>
31516	<p>BREAST, MALIGNANT TUMOUR, complete local excision of, with or without frozen section histology when targeted intraoperative radiotherapy (using an IntraBeam® device) is performed concurrently, if the requirements of item 15900 are met for the patient (Anaes.) (Assist.)</p> <p>Fee: \$867.00 Benefit: 75% = \$650.25</p>

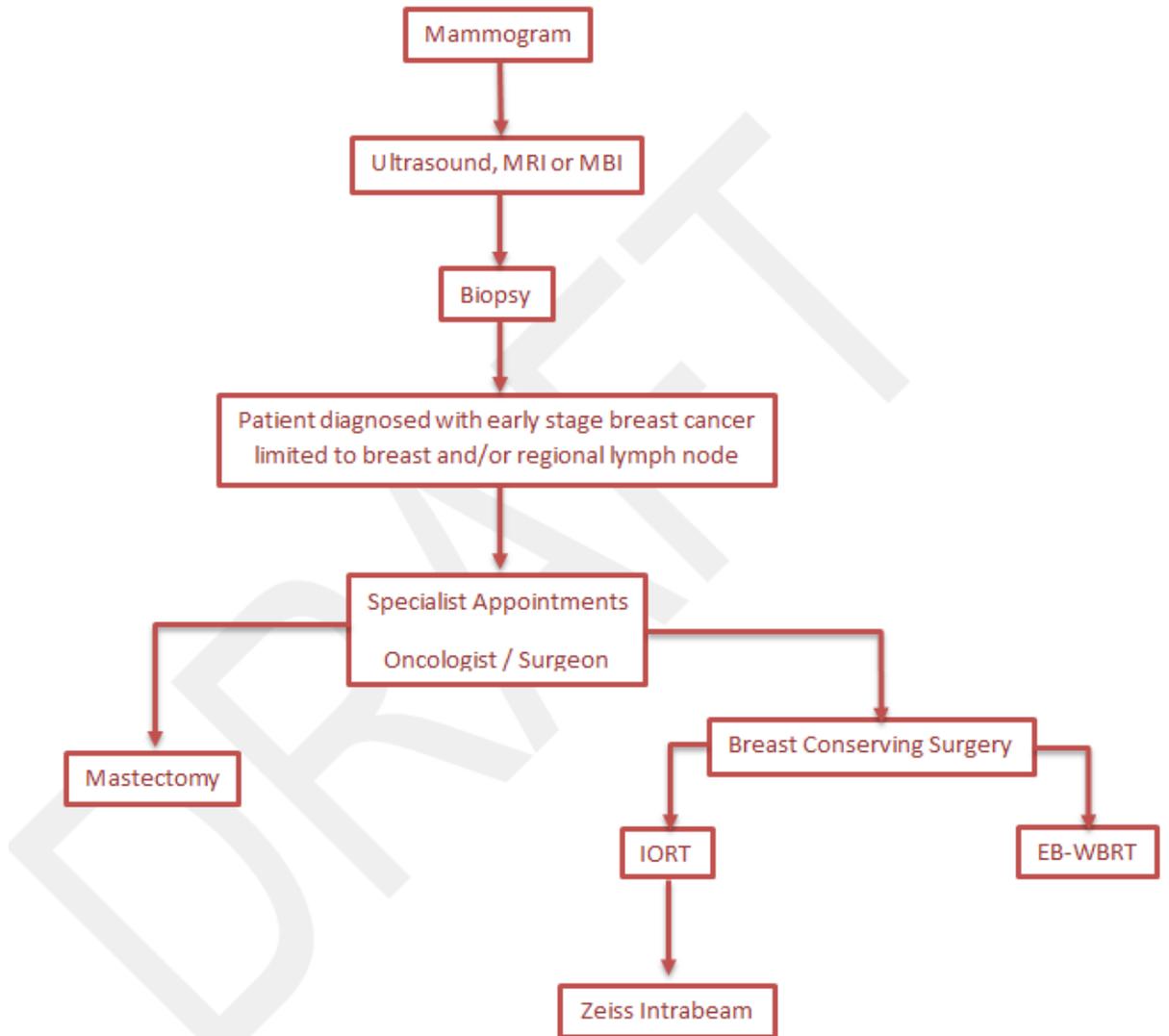
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The proposed fee does not include the cost of the equipment, and is solely based on the professional and operating costs of providing the service. Further, we confirm that ROHPG's are not being sought for the Xoft® Axxent® device.

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9. Clinical Management Algorithm - clinical place for the proposed intervention

Provide a clinical management algorithm (e.g.: flowchart) explaining the current approach (see (6) Comparator section) to management and any downstream services (aftercare) of the eligible population/s in the absence of public funding for the service proposed preferably with reference to existing clinical practice guidelines.



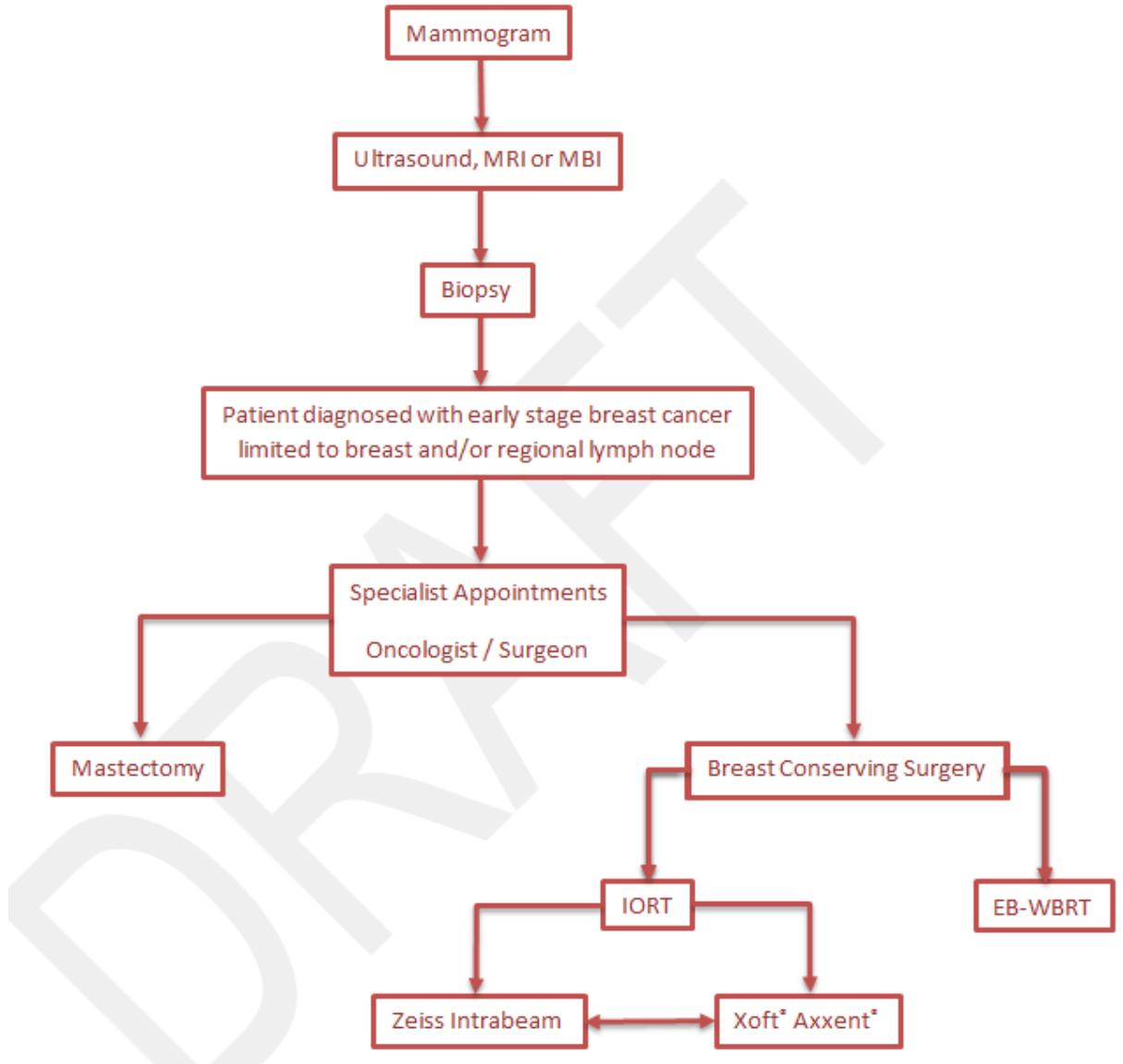
NBCC Recommended follow-up schedule

	1-2 Years	3-5 Years	After 5 Years
History & Exam	Every 3 months	Every 6 months	Every year
Mammography (& adjunctive imaging if indicated)	At 6-12 months after radiotherapy for conserved breast	Every year	Every year

- Chest X-ray: Only if clinically indicated
- Bone Scan, blood count & biochemistry: Only if clinically indicated

Provide a clinical management algorithm (e.g.: flowchart) explaining the expected management and any downstream services (aftercare) of the eligible population/s if public funding is recommended for the service proposed.

Clinical management algorithm – including proposed service



NBCC Recommended follow-up schedule

	1-2 Years	3-5 Years	After 5 Years
History & Exam	Every 3 months	Every 6 months	Every year
Mammography (& adjunctive imaging if indicated)	At 6-12 months after radiotherapy for conserved breast	Every year	Every year

- Chest X-ray: Only if clinically indicated
- Bone Scan, blood count & biochemistry: Only if clinically indicated

10. Regulatory Information

Please provide details of the regulatory status. Noting that regulatory listing must be finalised before MSAC consideration.

The Xoft[®] Axxent[®] Electronic Brachytherapy (eBx[®]) System is TGA registered under ARTG Certificate Number: DV-2013-MC-14630-1

- Identifier 231951: a-ray generator, therapeutic
- Identifier 231952: x-ray tube
- Identifier 231953: balloon applicator, surgical

11. Decision analytic

Provide a summary of the PICO as well as the health care resource of the comparison/s that will be assessed, define the research questions and inform the analysis of evidence for consideration by MSAC (as outlined in Table 1).

Key Research Question (Technical)

- Can T-IORT delivered using the Xoft[®]Axxent[®] device be considered as having the same Relative Biological Effectiveness as T-IORT delivered using the Intrabeam device?

Key Research Question (Clinical)

- If T-IORT delivered using the Xoft[®]Axxent[®] and Intrabeam device is considered to be non-inferior to EB-WBRT, are the results of the TARGIT-A trial translatable to the anticipated patient outcomes of T-IORT if treatment was delivered using the Xoft[®]Axxent[®] device instead of the Intrabeam device?

Key Evidence (Technical)

The key evidence for the submission will be from:

- (i) A comparison of the relative biological effectiveness of low energy electronic brachytherapy sources in breast tissue: a Monte Carlo study: Shane A White, Brigitte Reniers, Evelyn E C de Jong, Thomas Rusch and Frank Verhaegen. Published in Physics in Medicine and Biology 61 (2016) 383-399.
- (ii) Spectral Comparison of the Xoft and Zeiss 50 kVp X-ray Systems, AAPM Poster: Linda Kelley, Randall Holt and Thomas Rusch
Published in Medical Physics 41, 293 (2014)
- (iii) Spectral Comparison of the Xoft and Zeiss 50 kVp X-ray Systems, AAPM Presentation: Linda Kelley, Randall Holt and Thomas Rusch
- (iv) Spectral Comparison of the Xoft and Zeiss 50 kVp X-ray Systems: Linda Kelley
- (v) Preliminary results of Spectral Comparison of the Xoft and Zeiss 50 kVp X-ray Systems: Associate Professor Prabhakar Ramachandran - Peter MacCallum Cancer Centre. QMS No: DRO_07.23.01_MRB (please contact Prabhakar direct for details)

Key Evidence (Clinical)

Supplementary evidence for the submission will be from:

- (i) Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial.

Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, Flyger HL, Massarut S, Alvarado M, Saunders C, Eiermann W, Metaxas M, Sperk E, Sütterlin M, Brown D, Esserman L, Roncadin M, Thompson A, Dewar JA, Holtveg HM, Pigorsch S, Falzon M, Harris E, Matthews A, Brew-Graves C, Potyka I, Corica T, Williams NR, Baum M; on behalf of the TARGIT trialists' group.
Lancet. 2013 Nov 8. pii: S0140-6736(13)61950-9.

- (ii) Long-term results of targeted intraoperative radiotherapy (Targit) boost during breast-conserving surgery.

Vaidya JS, Baum M, Tobias JS, Wenz F, Massarut S, Keshtgar M, Hilaris B, Saunders C, Williams NR, Brew-Graves C, Corica T, Roncadin M, Kraus-Tiefenbacher U, Sütterlin M, Bulsara M, Joseph D.
Int J Radiat Oncol Biol Phys. 2011 Nov 15;81(4):1091-7.

- (iii) Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial.

Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, Alvarado M, Flyger HL, Massarut S, Eiermann W, Keshtgar M, Dewar J, Kraus-Tiefenbacher U, Sütterlin M, Esserman L, Holtveg HM, Roncadin M, Pigorsch S, Metaxas M, Falzon M, Matthews A, Corica T, Williams NR, Baum M.
Lancet. 2010 Jul 10;376(9735):91-102.

- (iv) Twelve-month follow-up results of a trial utilizing Axxent electronic brachytherapy to deliver Intraoperative Radiation Therapy for early stage breast cancer.

Olga Ivanov, Adam Dickler, Bennett Y. F. Lum, James V. Pellicane, and Darius S. Francescatti.
Annals of Surgical Oncology, 2011 – 18: 453-458

Refer Table 1 for PICO summary

12. Healthcare resources

Using tables 2 and 3, provide a list of the health care resources whose utilisation is likely to be impacted should the proposed intervention be made available as requested whether the utilisation of the resource will be impacted due to differences in outcomes or due to availability of the proposed intervention itself.

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The purchase price of the Xofig[®]Axxent[®] IORT treatment device is of course commercially sensitive but anecdotal evidence from treatment centers that have experience with both the Xofig[®]Axxent[®] and Zeiss Intrabeam IORT treatment devices suggest that the overall per patient cost of treatment delivery, taking into account equipment purchase price, ongoing maintenance costs, applicator sterilization costs and consumables is fairly comparable between the two systems.

Furthermore, the clinical procedural aspects of treatment delivery for the two systems are virtually identical, including the need for intraoperative ultrasound to assess the applicator to skin distance (as cited in application 1189), so performing IORT using either the Xofig[®]Axxent[®] or Zeiss Intrabeam device is a cost neutral exercise for all practical purposes.

Considering that the Xofig[®]Axxent[®] IORT treatment device will be used as a direct alternative to the Zeiss Intrabeam treatment device (primary comparator) no additional treatment delivery costs over and above those for the Zeiss Intrabeam device are anticipated.

However, given that there is only one Intrabeam device in clinical operation in Australia at the present time, it is anticipated that the main change in resources will result from the replacement of treatment delivery using EB-WBRT (secondary comparator) with IORT so a rough cost minimization analysis based on IORT vs EB-WBRT (secondary comparator) follows.

Based on the 5 year results for local control and overall survival from the TARGIT-A trial (Vaidya et al. 2014), non-inferiority of IORT as compared to EB-WBRT was only demonstrated for patients treated with IORT concurrent with breast conserving surgery (BCS) so the cost minimization analysis is limited to this scenario.

A rough estimate of the current funding for a typical course of EB-WBRT (50Gy over 25 fractions) delivered using dual photon 3D-CRT linear accelerator is as follows:

<u>MBS Item</u>	<u>Description</u>	<u>MBS per attendance*</u>	<u>HPG per attendance</u>	<u>Number of attendances</u>	<u>Total</u>
MBS15550	Simulation	\$658.60	\$101.94	1	\$760.54
MBS15562	Dosimetry	\$1,120.75	\$107.44	1	\$1,228.19
MBS15251	Treatment	\$59.65	\$55.97	25	\$2,890.50
MBS15266	Treatment (additional fields)	\$173.50		25	\$4,337.50
MBS15705	Verification	\$76.60		8	\$612.80
Total					\$9,830

The overall cost for breast conserving surgery (BCS) was estimated as \$6,025 per patient in public summary document for application 1189 so on the assumption that around 15% of patients undergoing IORT at the time of BCS will receive a supplemental booster course of EB-WBRT based on pathology at the time of surgery, the following estimated cost savings per patient could be achievable when using IORT as opposed to EB-WBRT (secondary comparator).

<u>Treatment</u>	<u>T-IORT</u>	<u>EB-WBRT</u>	<u>Incremental</u>
Breast Conserving Surgery (BCS)	\$6,025	\$6,025	\$0
Targeted Intraoperative Radiotherapy (T-IORT) in conjunction with BCS	\$1,117	\$0	+\$1,117
Additional OR and Physicist time – 30min	\$1,500	\$0	+\$1,500
Supplemental EB-WBRT following Pathology for 15% of patients	\$1,280	\$0	+\$1,280
External Beam Whole Breast Radiotherapy (EB-WBRT)	\$0	\$9,830	-\$9,830
<u>Total</u>	\$9,922	\$15,855	-\$5,933

The inclusion criteria for IORT suggests that only around 20% of patients undergoing breast conserving surgery would be eligible for prophylactic IORT treatment at the time of BCS and this percentage is unlikely to change in the foreseeable future. As a consequence, the following table is an estimate of the number of patients undergoing IORT over the next five years (assuming MBS listing of the Xofig[®]Axxent[®] device), and the potential cost savings to government over the respective financial years.

<u>Description</u>	<u>2017</u>	<u>2018</u>	<u>2019</u>	<u>2020</u>	<u>2021</u>
Estimated total number of BCS Patients based on 5% annual growth of BCS	8170	8578	9006	9456	9929
Estimated number of Radiotherapy treatment centres providing IORT	2	3	5	7	9
Estimated number of IORT procedures based on 5% annual growth of BCS and increased number of Radiotherapy treatment centres providing IORT	204	321	588	947	1461
Estimated Cost Savings to Government	\$1,210,332	\$1,904,493	\$3,488,604	\$5,618,551	\$8,668,113

13. Questions for public funding

Please list questions relating to the safety, effectiveness and cost-effectiveness of the service / intervention relevant to this application, for example:

- Which health / medical professionals provide the service
- Are there training and qualification requirements
- Are there accreditation requirements

The procedural aspects of treatment delivery for the Xofig[®]Axxent[®] and Zeiss IntraBeam IORT systems are the same, namely:

Prior to the first T-IORT treatment delivery, all service providers must undertake appropriate training and achieve certification in treatment delivery and radiation safety. Service providers include:

- (i) Breast surgeons
- (ii) Radiation oncologists
- (iii) Medical physicists

IORT delivered using the Xofig[®]Axxent[®] treatment device is delivered by a radiation oncologist. A medical physicist is also required in order to calibrate the device.

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Table 1 - Summary of PICO to define research question

Technical Research Question

PICO	Comments
Patients	Not Applicable
Intervention	Xoft® Axxent® treatment device – Single Dose
Comparator	Zeiss IntraBeam treatment device – Single Dose
Outcomes	Relative Biological Effectiveness of the Xoft® Axxent® and IntraBeam device to a common reference of Cobalt-60 (Co-60). Relative Biological Effectiveness of the 50kVp spectra of the Xoft® Axxent® device Spectral comparison of the Xoft® Axxent® and IntraBeam 50kVp devices Comparison of the dose distribution in the breast for the Xoft® Axxent® and IntraBeam devices

Clinical Research Question

PICO	Comments
Patients	Patient characteristics should be consistent with the proposed eligible MBS patient population, i.e: 45 years of age or more; has a T1 or small T2 (less than or equal to 3cm in diameter) primary tumour; has an histologic Grade 1 or 2 tumour; has an oestrogen-receptor positive tumour; has a node negative malignancy; is suitable for wide local excision of a primary invasive ductal carcinoma that was diagnosed as unifocal on conventional examination and imaging; and has no contra-indications to breast irradiation.
Intervention	Xoft® Axxent® treatment device – Single Dose
Comparator	Primary comparator: IntraBeam treatment device – Single Dose (as per the intervention arm of TARGIT-A) Secondary comparator: Whole Breast External Beam Radiotherapy (as per the comparator arm of TARGIT-A)
Outcomes	Pathologically confirmed local recurrence in the conserved breast (primary outcome of TARGIT-A trial). Local toxicity or morbidity (secondary outcome of TARGIT-A trial). Overall survival (reported as part of long-term follow-up data reported from the TARGIT-A trial) Patient preference for T-IORT or WB-EBRT.

Table 2 - For investigative services

Prior tests	Not Applicable
Reference standard	Not Applicable

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Table 2: List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
Resources provided to identify eligible population										
Specialist Consultation	Specialist	Outpatient	100%	1						
Resources provided to deliver proposed intervention (T-IORT for early breast cancer - Xoft® Axxent®)										
IORT - Xoft® Axxent® As per MBS Item 15900	Radiation Oncologist	Inpatient	100%	1	250.00	0	0	0	0	250.00
IORT - Xoft® Axxent® As per MBS Item 31516	Breast Surgeon	Inpatient	100%	1	867.00	0	0	0	0	867.00
Capital Equipment: Xoft® Axxent® device for treatment delivery	Hospital	Inpatient	100%	1	0	0	0	0	0	0
Consumables such as balloon applicators, sterile drapes, etc	Hospital	Inpatient	100%	1	0	0	0	0	0	0
Resources provided in association with proposed intervention (T-IORT for early breast cancer - Xoft® Axxent®)										

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
Approximately 30 min Physicist time for device calibration	Medical Physicist	Inpatient	100%	1	0	0	0	0	0	0
Approximately 30 min additional operating theatre time	Hospital	Inpatient	100%	1	0	0	0	0	0	0
Intra-operative Ultrasound	Hospital	Inpatient	100%	1	0	0	0	0	0	0
Resources provided to deliver primary comparator (T-IORT for early breast cancer - Zeiss Intrabeam)										
IORT – Zeiss Intrabeam MBS Item 15900	Radiation Oncologist	Inpatient	100%	1	250.00	0	0	0	0	250.00
IORT – Zeiss Intrabeam MBS Item 31516	Breast Surgeon	Inpatient	100%	1	867.00	0	0	0	0	867.00
Capital Equipment: Zeiss Intrabeam device for treatment delivery	Hospital	Inpatient	100%	1	0	0	0	0	0	0
Consumables such as balloon applicators, sterile drapes, etc	Hospital	Inpatient	100%	1	0	0	0	0	0	0

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
Resources provided in association with primary comparator (T-IORT for early breast cancer - Zeiss Intrabeam)										
(e.g., pre-treatments, co-administered interventions, resources used to monitor or in follow-up, resources used in management of adverse events, resources used for treatment of down-stream conditions)										
Approximately 30 min Physicist time for device calibration	Medical Physicist	Inpatient	100%	1	0	0	0	0	0	0
Approximately 30 min additional operating theatre time	Hospital	Inpatient	100%	1	0	0	0	0	0	0
Intra-operative Ultrasound	Hospital	Inpatient	100%	1	0	0	0	0	0	0
Resources provided to deliver secondary comparator (EB-WBRT)										
Simulation MBS Item 15550	Radiation Oncologist	Outpatient	100%	1	658.60	0	101.94	0	0	760.54
Dosimetry MBS Item 15562	Radiation Oncologist	Outpatient	100%	1	1,120.75	0	107.44	0	0	1,228.19
Treatment MBS Item 15251	Radiation Oncologist	Outpatient	100%	25	59.65	0	55.97	0	0	2,890.50

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
Treatment MBS Item 15266	Radiation Oncologist	Outpatient	100%	25	173.50	0	0	0	0	4,337.50
Verification MBS Item 15705	Radiation Oncologist	Outpatient	100%	8	76.60	0	0	0	0	612.80
Resources provided in association with secondary comparator (EB-WBRT)										
Additional Imaging	Specialist	Outpatient	Variable							
Resources used to manage patients successfully treated with the proposed intervention (T-IORT for early breast cancer - Xofig[®] Axxent[®])										
Resource 1										
Resource 2										
Resources used to manage patients who are unsuccessfully treated with the proposed intervention (T-IORT for early breast cancer - Xofig[®] Axxent[®])										
Simulation MBS Item 15550	Radiation Oncologist	Outpatient	100%	1	658.60	0	101.94	0	0	760.54
Dosimetry MBS Item 15562	Radiation Oncologist	Outpatient	100%	1	1,120.75	0	107.44	0	0	1,228.19

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
Treatment MBS Item 15251	Radiation Oncologist	Outpatient	100%	25	59.65	0	55.97	0	0	2,890.50
Treatment MBS Item 15266	Radiation Oncologist	Outpatient	100%	25	173.50	0	0	0	0	4,337.50
Verification MBS Item 15705	Radiation Oncologist	Outpatient	100%	8	76.60	0	0	0	0	612.80
Resources used to manage patients successfully treated with primary comparator (T-IORT for early breast cancer - Zeiss Intrabeam)										
Resource 1										
Resource 2										
Resources used to manage patients who are unsuccessfully treated with primary comparator (T-IORT for early breast cancer - Zeiss Intrabeam)										
Simulation MBS Item 15550	Radiation Oncologist	Outpatient	100%	1	658.60	0	101.94	0	0	760.54
Dosimetry MBS Item 15562	Radiation Oncologist	Outpatient	100%	1	1,120.75	0	107.44	0	0	1,228.19
Treatment	Radiation	Outpatient	100%	25	59.65	0	55.97	0	0	2,890.50

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
MBS Item 15251	Oncologist									
Treatment MBS Item 15266	Radiation Oncologist	Outpatient	100%	25	173.50	0	0	0	0	4,337.50
Verification MBS Item 15705	Radiation Oncologist	Outpatient	100%	8	76.60	0	0	0	0	612.80

* Include costs relating to both the standard and extended safety net.

Table 3: Alternative summary of resources table for state transition models

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per cycle per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other government budgets (PBS, hospitals, etc)	Private health insurer	Patient	Total cost
Health state 1										
Resource 1										
Resource 2										
Health state 2										
Resource 1										
Resource 2										
Health state 3										
Resource 1										
Resource 2										

* Include costs relating to both the standard and extended safety net.