Technology Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence

Final Protocol

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1. Title of the project:

INTRABEAM® Photon Radiotherapy System for the adjuvant treatment of early breast cancer.

HTA reference 12/69/01

2. Name of TAR team and 'lead'

TAR team: Southampton Health Technology Assessments Centre (SHTAC), University of Southampton

Project 'lead' contact details:
Dr Joanna Picot
Senior Research Fellow
Southampton Health Technology Assessments Centre (SHTAC)
University of Southampton
1st Floor, Epsilon House
Enterprise Road
Southampton Science Park
Southampton SO16 7NS
Tel: 023 8059 5921
Fax: 023 8059 5662
Email: j.picot@soton.ac.uk

3. Plain English Summary

Breast cancer is the most common cancer in women in England and Wales, with over 10,000 deaths reported in 2012. There are a number of genetic and environmental risk factors, but increasing age is the strongest risk factor with over 80% of new diagnoses of breast cancer in England in women aged over 50 years. Staging is based on a number of characteristics including the size of the tumour, and whether the cancer has spread to lymph nodes (glands) near the breast, or beyond the breast and surrounding tissue. It is suggested that the majority of women are diagnosed with early stage disease (Stage I or II), where the cancer cells are either completely contained within the milk ducts or have not spread beyond the breast or the lymph glands around the affected breast.

There has been an increase in survival rates in recent years and estimates suggest that approximately 95% of women survive 1 year and 83% survive 5 years. The increase is

attributable to earlier detection as well as improved breast cancer treatment. Initial treatment for early breast cancer entails surgery to remove the tumour followed by additional treatment which can include radiotherapy, hormone therapy or chemotherapy. The National Institute for Health and Care Excellence (NICE) recommends whole breast radiotherapy which is delivered after surgery, and generally involves daily treatment for 3-5 weeks, with a possible boost for a further 1-2 weeks for those at high risk of a local recurrence. Recently, a new type of radiotherapy treatment has become available, known as the INTRABEAM® Photon Radiotherapy System. This mobile device can be used at the time of surgery to deliver high dose, low energy radiation to the breast tissue after the tumour has been removed and offers an alternative to weeks of conventional whole breast radiotherapy. Given these developments in breast cancer therapy, it is important for NICE to consider the INTRABEAM radiotherapy system as a treatment option in women diagnosed with early breast cancer.

This review will assess the available studies to enable NICE to make evidence-informed policy recommendations for the treatment of early breast cancer following surgery. In addition, an overall estimate will be made of the benefit to patients in relation to how much treatment costs, taking into account any effect on patients' quality of life. This will allow NICE to determine whether treatment represents an efficient use of health service money.

4. Decision problem

The aim of this assessment is to assess the clinical and cost-effectiveness of the INTRABEAM Photon Radiotherapy System for the adjuvant treatment of early breast cancer during surgical removal of the tumour.

4.1. Background

Breast cancer epidemiology

Breast cancer is the most common cancer in women in England and Wales with 44,092 new diagnoses in 2011.[1;2] It accounts for about a third of all cancers in women.[3] Breast cancer is rare in men (314 new diagnoses[1;2] in England and Wales in 2011) accounting for less than 0.25% of cancers in men in 2011.[1;2] In England in 2011 the age standardised rates of breast cancer incidence per 100,000 population were 124.8 for women and 0.9 for men,[1] and in Wales 123.3 for women and 0.5 for men.[2]

Breast cancer risk is influenced by a combination of genetic and environmental factors with the strongest risk factor being increasing age. Over 80% of new diagnoses of breast cancer in England are in women aged over 50 years[1] and in men aged over 60 years.[1] For women between the ages of 50 and 69 years, who are invited for screening, 56% of breast cancers

diagnosed in the UK in 2007 were screen detected.[4] Although there are no regularly published data on stage of breast cancer at diagnosis[5] evidence suggests that the majority (at least 80%) of women are diagnosed with early disease (Stage I or Stage II).[6]

There were 10,311 deaths of women, and 62 deaths of men from breast cancer in England and Wales in 2012.[7] The UK age-standardised mortality rate from breast cancer for women 2008-2010 was 25.3 per 100,000 population.[8] For women diagnosed with breast cancer during 2004-2006 and followed up to 2011 the 1-year survival rate was 94.7% and the 5-year survival 83.3%.[9] Between 2002 and 2006 a statistically significant annual increase in 1-year survival of 0.3% and in 5-year survival of 0.9% was observed.[9] The rise in survival estimates has been due to earlier detection and improved treatment for breast cancer in women.[3]

Breast cancer diagnosis and staging

The 2009 NICE Guideline 'Early and locally advanced breast cancer: diagnosis and treatment'[10] provides recommendations for breast cancer diagnosis. Diagnosis is made after triple assessment consisting of a clinical assessment, mammography and/or ultrasound imaging, and core biopsy and/or fine needle aspiration cytology.[10] A multidisciplinary team should review and discuss the test results and if a cancer diagnosis is pathologically confirmed the team will suggest a treatment plan.

A breast cancer can be described and classified according to a variety of characteristics. This information is essential for deciding what local and systemic treatments may be required and provides information about prognosis (see *Breast cancer progression and prognosis* below). Key aspects include histological description, grade ranging from low to high, stage based on the Tumour Node Metastases (TNM) classification (see Table 1 and Table 2), oestrogen receptor alpha (ER) status and human epidermal growth factor receptor 2 (HER2) status,[10] and DNA profile. Much of the information required can only be obtained from samples taken during surgical removal of the primary tumour.

Treatment of early breast cancer is the focus of this assessment, however it should be noted that there is no internationally agreed single definition of early breast cancer (e.g. in terms of TMN stage). There are two major categories of early breast cancer: in situ disease predominantly in the form of ductal carcinoma in situ (DCIS) and invasive cancer.[10] For invasive cancer to be categorised as early breast cancer the tumour should not have spread beyond the breast or the lymph nodes (which remain mobile) in the armpit ipsilateral to (on the same side as) the affected breast.[11]

Table 1: Stage of breast cancer using the TNM classification[11;12]

STAGE	TNM (see Table 2)
Stage 0	Tis N0 M0
Stage I	T1 N0 M0
Stage IIa	T1 N1 M0 or T2 N0 M0
Stage IIb	T2 N1 M0 or T3 N0 M0
Stage IIIa	T2 N2 M0 or T3 N1 M0 or T3 N2 M0
Stage IIIb	T4 N0 M0 or T4 N1 M0 or T4 N2 M0
Stage IIIc	any T N3 M0
Stage IV	any T any N M1

[a] ductal carcinoma in situ

Table 2: TNM classification scheme[11;12]

Tumour stage		Nodal stage		Distant metastasis	
Tis	Tumour in situ	N0	No regional lymph node metastasis	M0	No distant metastasis
T1	Tumour < 2 cm diameter	N1	Mobile regional lymph node metastasis	M1	Distant metastasis
T2	Tumour 2 - 5 cm diameter	N2	Fixed regional lymph node metastasis		
T3	Tumour > 5 cm diameter	N3	Supraclavicular lymph node metastasis		
T4	Tumour fixed to skin/chest wall or inflammatory cancer				

Breast cancer progression and prognosis

The natural history of breast cancer is variable and incompletely understood.[13] Evidence from screening studies suggests that some screen detected breast cancers may regress spontaneously,[14] and natural history may vary according to a variety of factors, for example genotype,[15] hormone receptor status,[16] and race.[17] The heterogeneous nature of breast cancer has an impact when trying to provide a prognosis. The Nottingham Prognostic Index (NPI)[18] is a tool commonly used to determine breast cancer prognosis. It combines information on the size of the tumour, the number of lymph nodes involved and the histological grade resulting in an overall score, with a higher score indicating a worse prognosis. The NPI cannot be used for DCIS. Other models have been developed which aim to more accurately

predict outcome by including alternative indicators and/or more explanatory factors, for example, Predict[19] and the Galway Index of Survival (GAINS).[20]

Breast cancer current treatment options

Surgery is usually the first treatment option for early breast cancer (DCIS and invasive breast cancer). Preoperative assessment of the breast and axilla determines the size of the primary tumour relevant to the volume of breast and this information is used to decide whether wide local excision of the tumour ('WLE' or 'lumpectomy') is possible, allowing breast conserving surgery (BCS) instead of mastectomy. Patients who have a mastectomy can have immediate breast reconstruction (carried out at the same time as the mastectomy) or delayed breast reconstruction.

After surgical removal of the primary tumour, the information on prognostic and predictive factors obtained by histological examination, the outcome of tests for ER and HER2 status, and other patient and tumour characteristics are used by the breast cancer multidisciplinary team to plan subsequent treatment. Recommendations for a range of breast cancer treatment options are described by the 2009 NICE guideline 'Early and locally advanced breast cancer: diagnosis and treatment'[10] and these are summarised in Table 3.

Whole breast radiotherapy (RT) is the standard of care for all patients (as per the 2009 NICE guideline[10]) delivered either within 4-6 weeks of surgery or 4-6 months later following completion of cytotoxic therapies. This is typically given over 3-5 weeks, and may be followed by a 'boost' dose to the tumour bed in patients considered to be at a higher risk of local recurrence.

Table 3: Non-surgical treatment options for early breast cancer

Adjuvant treatment		
Radiotherapy	whole breast radiotherapy following breast conserving surgery	
	post-mastectomy radiotherapy to chest wall	e.g. if at high risk of local recurrence
	boost to tumour bed following breast conserving surgery	e.g. if at high risk of local recurrence
Systemic therapy for metastatic disease	endocrine therapy	e.g. tamoxifen or aromatase inhibitor for ER positive tumours only
	chemotherapy	e.g. anthracycline containing regimens, docetaxel
	biological therapy	e.g. trastuzumab
May need assessment and treatment for bone loss		
Primary systemic therapy		
chemotherapy	Before surgery e.g. to shrink tumour before surgery, to observe response in the primary tumour before its surgical removal	
endocrine therapy		

4.2. Definition of the intervention

The INTRABEAM Photon Radiotherapy System (Carl Zeiss) has a miniature, electronic, high dose rate, low energy X-Ray source (XRS) which is used to deposit high-dose radiation directly to a tumour or tumour bed.[21] In the USA, INTRABEAM gained FDA approval in 1997, and in Europe was awarded CE certification in 1999.[22] Because INTRABEAM uses a low energy XRS the system does not have to be contained within the kind of specially designed room that is required for high energy radiation sources (e.g. linear accelerators).[21] This means that INTRABEAM can be used to deliver intraoperative radiation therapy (IORT) in an ordinary operating theatre at the time of surgery. In addition, the system is mobile so it can be moved between different operating theatres.

The XRS component of the device has a 10cm long probe[21] and one of a variety of applicators of different sizes can be attached to this depending on the size of the resection cavity. A set of eight spherical applicators is available with diameters from 1.5 to 5.0 cm[22] for irradiating the tumour bed after lumpectomy. Once the tumour has been removed, an appropriately sized spherical applicator is selected and positioned within the resection cavity. The tissue adjacent

to the resection cavity is then irradiated by the INTRABEAM device for 20-30 minutes.[21] A characteristic of the low-energy X-rays produced by the INTRABEAM device is that the maximum dose of radiotherapy is delivered to the tissues at the surface of the cavity, but because the dose attenuates steeply as tissue depth increases, peripheral healthy tissue is spared.[22] As a result, the surface of the tumour bed typically receives 20 gray (Gy) in this single fraction treatment.[22] After this treatment the incision is closed. The design of the INTRABEAM equipment ensures that the tissue most at risk of developing a local recurrence, i.e. comprising the wall of the resection cavity adjacent to the resected tumour, receives the largest dose of irradiation.

4.3. Place of the intervention in the treatment pathway(s)

INTRABEAM has been used in patients with early breast cancer to deliver IORT to the cavity wall resulting from lumpectomy for treatment of the primary tumour. Patients at low risk of recurrence do not need to receive any further local treatment. Patients with a higher risk of recurrence (e.g. histopathology showing invasive lobular carcinoma, extensive intraductal component, grade 3, node involvement, close margins) may go on to receive an additional course of external beam radiotherapy to the whole breast but without a tumour bed boost because the INTRABEAM device has already delivered therapy directly to the tumour bed. Other adjuvant treatments e.g. endocrine therapy, chemotherapy, biological therapy, may also be given if indicated. Alternatively if INTRABEAM is not used at the time of lumpectomy, and the primary tumour histopathology shows clear margins, IORT can be delivered to the resulting cavity wall within 30 days of the lumpectomy as an additional procedure. Adjuvant treatments may then follow.

In line with the scope of the NICE appraisal this assessment will consider the use of INTRABEAM as an alternative to whole breast radiation and as a boost before whole breast radiation is provided. Its use if a local recurrence occurs will not be considered.

4.4. Comparator(s)

The comparator for this review is external beam radiotherapy delivered by linear accelerator. External beam therapy works by directing a beam, or multiple beams, of radiation through the skin directly at the tumour and surrounding cancer cells. The radiation beam is generated by an instrument, known as a linear accelerator (linac), which is capable of producing high energy x-rays, cobalt irradiation or particle beams such as protons or electrons. The most common types of external radiotherapy use photon beams (either as x-rays or gamma rays).[23] From the patient's perspective, external radiotherapy is similar to having an x-ray, only the

radiation is more intense. Conventional whole breast external beam radiotherapy is provided after surgery and the procedure itself is painless. In the UK a hypofractionated regimen is standard practice, with NICE guidelines recommending that patients with early invasive breast cancer who have undergone breast conserving surgery receive 40 Gy in 15 fractions.[10] The 15 fractions are typically delivered one a day, Monday to Friday, for 3 weeks with a rest at the weekends. A schedule of alternate weekdays, Monday, Wednesdays and Fridays for 5 weeks[24] is little used in practice. Both of these courses of radiotherapy can be followed by a boost to the tumour bed over a further 1-2 weeks for those patients with a high risk of local recurrence (e.g. aged under 40 years, grade 3 disease and lymph node positive).[10] Boost schedules include 12 Gy in 4 fractions, 10 Gy in 5 fractions and 16 Gy in 8 fractions. In many other parts of the world standard practice for whole breast radiotherapy is 50 Gy in 25 fractions given daily (Monday to Friday) over 5 weeks.[25]

4.5. Population and relevant subgroups

The population of patients included within this assessment are people with early operable breast cancer. As described above (Section 4.1), people with early breast cancer form the majority of new breast cancer diagnoses. Early operable breast cancer includes people with DCIS and those with invasive early breast cancer. The invasive early breast cancer may have spread to the regional lymph nodes but if so the metastasis remains mobile. Although there is no single definition of early breast cancer the majority of people with early breast cancer are likely to have tumours classified as Stage I or Stage II (either IIa or IIb). People with a local recurrence are excluded from the assessment.

4.6. Key factors to be addressed

As specified in the NICE scope, the following outcome measures are included in the decision problem:

- overall survival
- progression-free survival
- ipsilateral local recurrence
- adverse effects of treatment
- health-related quality of life

Other intra-operative techniques have not been included as comparators in the NICE scope because they are not currently in use in clinical practice. These techniques are also not included as interventions alongside INTRABEAM because their use was not considered sufficiently comparable.

5. Report methods for synthesis of evidence of clinical effectiveness

A systematic review of the evidence for clinical effectiveness and cost-effectiveness will be undertaken following the general principles outlined in 'Systematic Reviews: CRD's guidance for undertaking reviews in health care'.[26]

5.1. Search strategy

A search strategy will be developed and tested by an experienced information scientist. The strategy will be designed to identify all relevant clinical effectiveness studies of the INTRABEAM Photon Radiotherapy System for people with early operable breast cancer. Separate searches will be conducted for the economic evaluation section of the MTA as described below (Section 6).

A draft search strategy for Medline is shown in Appendix 9.1. This will be adapted for other databases. The following databases will be searched: The Cochrane Library including the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Central Register of Controlled Trials, CRD (University of York) Database of Abstracts of Reviews of Effectiveness (DARE), the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database; Medline (Ovid); Embase (Ovid); Medline In-Process and Other Non-Indexed Citations (Ovid); Web of Science with Conference Proceedings: Science Citation Index Expanded (SCIE) and Conference Proceedings Citation Index - Science (CPCI) (ISI Web of Knowledge); Biosis Previews (ISI Web of Knowledge); Zetoc (Mimas); NIHR-Clinical Research Network Portfolio; Clinical Trials.gov, Current Controlled Trials and WHO ICTRP (international clinical trials research platform).

Bibliographies of related papers will be assessed for relevant studies where possible. The manufacturers' submissions to NICE will be assessed for any additional studies that meet the inclusion criteria. Members of our advisory group will be contacted to identify additional published and unpublished evidence. A comprehensive database of relevant published and unpublished articles will be constructed using Reference Manager software.

All databases will be searched from inception to the present. Searches will be limited to randomised controlled trials (RCTs) and controlled clinical trials (CCTs) for the assessment of clinical effectiveness. All searches will be updated when the draft report is under review, prior to submission of the final report to NICE.

5.2. Inclusion and exclusion criteria

The inclusion and exclusion criteria for intervention, population, comparator, and outcomes have been stipulated in the final scope issued by NICE (Table 4).

Table 4: Inclusion and exclusion criteria for the review of clinical effectiveness

Interventions	INTRABEAM Photon Radiotherapy System with or without external beam radiotherapy
Participants	People with early operable breast cancer (as defined by the trials). People with a local recurrence are excluded.
Comparator	External beam radiotherapy delivered by linear accelerator
Outcomes	Studies will be included if they report on one or more of the following outcomes: • overall survival • ipsilateral local recurrence • adverse effects of treatment • health-related quality of life • cost-effectiveness (such as incremental cost per QALY gained)
Design	The following types of study will be eligible for inclusion: RCTs [If no RCTs are found, or if the data from available RCTs is incomplete (e.g. absence of data on outcomes of interest) evidence from good-quality controlled clinical trials may be considered.] Studies published as abstracts or conference presentations will only be included if sufficient details are presented to allow an appraisal of the methodology and the assessment of results to be undertaken; Systematic reviews and clinical guidelines will be used as a source of references; Case series, case studies, narrative reviews, editorials and opinions will be excluded; Non-English language studies will be excluded

5.3. Screening and data extraction process

Reference screening

Studies will be selected for inclusion through a two-stage process. The titles and abstracts of studies identified by the search strategy will be screened independently by two reviewers to identify all citations that potentially meet the inclusion/exclusion criteria detailed above. Full manuscripts of studies which appear potentially relevant will be obtained. These will be screened by two reviewers and a final decision regarding inclusion will be agreed. At each stage any disagreements will be resolved by discussion, with the involvement of a third reviewer when necessary.

Data extraction

Data will be extracted by one reviewer using a standardised data extraction form (see Appendix 9.2) and will be checked for accuracy by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

5.4. Quality assessment strategy

The quality of included clinical effectiveness studies will be assessed according to criteria based on those devised by the Centre for Reviews and Dissemination (CRD, University of York)[26] and/or the Cochrane Collaboration.[27] The quality of the individual studies will be assessed by one reviewer and checked by a second reviewer with any disagreements resolved by consensus and involvement of a third reviewer where necessary. The quality assessment strategy for cost-effectiveness studies is provided in section 6.1.

5.5. Methods of data analysis/synthesis of clinical effectiveness data

Clinical effectiveness data will be synthesised through narrative review with tabulation of the results of included studies. Where data are of sufficient quality and homogeneity the results from individual studies will be synthesised through meta-analysis to estimate a summary measure of effect on relevant outcomes. If a meta-analysis is appropriate it will be performed using specialised software such as Cochrane Review Manager 5 (RevMan) and presented using forest plots and tabular forms. If direct evidence is lacking, we will consider appropriate methods of indirect comparisons.[28]

6. Report methods for synthesis of evidence of cost-effectiveness

The cost-effectiveness of the INTRABEAM Photon Radiotherapy System for the adjuvant treatment of early operable breast cancer will be assessed through two stages: a systematic

review of cost-effectiveness studies and the development of a decision analytic economic model.

6.1. Systematic review of published cost-effectiveness studies

The sources detailed in Section 5.1 will be used to identify studies of the cost-effectiveness of the INTRABEAM Photon Radiotherapy System for the adjuvant treatment of early operable breast cancer. Studies will be included in the systematic review of cost-effectiveness if they are full economic evaluations (cost-effectiveness, cost utility or cost benefit analyses) that report both measures of costs and consequences. Other inclusion and exclusion will be identical to those of the clinical effectiveness review. The methodological quality of included studies will be assessed using accepted criteria for appraising economic evaluations.[29] Where relevant this will be supplemented with additional criteria for critical appraisal of model-based evaluations.[30] Studies will be synthesised through a narrative review that includes a clear explanation of the assessment process, detailed critical appraisal of study methods, critical assessment of data used in any economic models and tabulation of the results of included studies. Published studies conducted in the UK and adopting an NHS and Personal Social Services (PSS) perspective will be examined in more detail.

Stand alone cost analyses based in the UK NHS will also be searched for. These will not be included in the systematic review, but will be retained as sources of information on resource use and cost associated with INTRABEAM Photon Radiotherapy (including short term and longer term adverse events).

Any economic evaluation included in the manufacturer's submission to NICE will be assessed using the same quality criteria which are used for published economic evaluations, but will be reported separately.

6.2. Methods for estimating quality of life

Relevant health-related quality of life (HRQoL) data, where available, will be extracted from studies included in the clinical and cost-effectiveness systematic reviews. An additional systematic literature search will be conducted specifically for publications reporting HRQoL or health state utility for people with early operable breast cancer, including the impact of INTRABEAM Photon Radiotherapy on this patient group. Studies will be synthesised through a narrative review with tabulation of results of included studies.

Where QoL data are insufficient to calculate utility estimates, data will be derived from the broader literature or estimated from other sources. In accordance with the NICE

methodological guide for technology appraisals,[31] the utility values used in the model will be elicited where possible from the general population using a preference-based method. Where these are not available, utility estimates will be derived from alternative sources and the assumptions made will be explicitly stated.

6.3. Economic modelling

Existing economic models which estimate the cost-effectiveness of the INTRABEAM System which are identified in the systematic review of economic evaluations will be assessed for their quality, relevance and suitability for adoption in the current review. If considered relevant and valid the models will be adapted (if required) and populated with updated (and UK-practice-relevant) clinical and cost parameter values using data identified in our clinical and cost-effectiveness reviews.

If no appropriate economic model is identified in the systematic review of economic evaluations, a decision analytic model will be built *de novo*.

The model structure will be determined by the biological disease process, the main care pathways for patients in the UK NHS and the disease states or events which are most important in determining patients' clinical outcomes, QoL and consumption of NHS or PSS resources. It will be informed by published clinical research evidence and expert opinion, as well as methods adopted in previously published economic evaluations and NICE guidance.

The model perspective will be that of the NHS and PSS, with costs and outcomes discounted at 3.5%. The time horizon will initially be governed by the follow-up data from the included clinical trials. We will investigate extrapolating these data in order to model a lifetime horizon. The incremental cost-effectiveness of the interventions will be estimated in terms of cost per quality-adjusted life year (QALY) gained, as well as the cost per life year gained, if data permit.

Parameter values for the model will be obtained from the best available evidence in the relevant research literature, including our own systematic review of clinical effectiveness. Where required parameters are not available from good quality published studies in the relevant patient group, we may use data from sponsor submissions to NICE or clinical experts' opinion. Searches for additional information regarding model parameters, patient preferences, and other topics will be conducted as required and may include a wider range of study types than the review of clinical effectiveness (including non-randomised studies). Sources for parameter values will be stated clearly.

Adverse effects will be accounted for in the model if these are clearly reported by the trials included in our systematic review of clinical effectiveness. These will be included as an extra cost and, where possible, disutility.

Resource use will be specified and valued from the perspective of the NHS and PSS. Cost data will be derived from local sources, extracted from published sources or from sponsor submissions to NICE, as appropriate.

6.4. Analysis of uncertainty

Uncertainty in the model concerning both the structure and parameters used will be investigated through deterministic sensitivity analyses and scenario analysis. If the data and modelling approach permit, joint parameter uncertainty will be explored by probabilistic sensitivity analysis (PSA). The outputs of any PSA will be presented using plots of the cost-effectiveness plane and cost-effectiveness acceptability curves.

7. Handling the company submission

All data submitted by the manufacturers/sponsors will be considered if received by the assessment team no later than Monday 13th January 2014. Data arriving after this date will not be considered. If the data meet the inclusion criteria for the review they will be extracted and quality assessed in accordance with the procedures outlined in this protocol. Any economic evaluation included in the company submission, provided it complies with the NICE methodological guide for technology appraisals,[31] will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used in the economic model.

Any 'commercial in confidence' data taken from a company submission, and specified as confidential in the checklist, will be highlighted in blue and underlined in the assessment report. Any 'academic in confidence' data will be highlighted in yellow and underlined.

8. Competing interests of authors

None

9. References

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Appendices

9.1. Draft search strategy

1 exp Breast Neoplasms/

2 Carcinoma, Intraductal, Noninfiltrating/

3 ("ductal carcinoma* in situ" or DCIS).tw.

4 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal* or infiltrat* or intraductal* or lobular or medullary or malignan*)).tw.

5 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or dcis or ductal* or infiltrat* or intraductal* or lobular or medullary or malignan*)).tw.

6 exp "Neoplasms, Ductal, Lobular, and Medullary"/

7 (breast or mammar*).tw.

8 6 and 7

9 or/1-5,8

10 intrabeam*.af.

11 Radiosurgery/ or radiosurg*.tw.

12 Radiotherapy, Adjuvant/

13 (radiother* or irradiat* or radiat* or xray or "x-ray").tw.

14 or/12-13

15 "during surg*".tw.

16 "radio* guided surg*".tw.

17 (intraoperativ* or "intra operativ").tw.

18 ("single dose" or "single fraction*").tw.

19 or/15-18

20 14 and 19

21 IORT.tw.

22 (intraoperativ* adj5 radiotherap*).tw.

23 TARGIT*.tw.

24 "tumo?r bed".tw.

25 (boost* or target*).tw.

26 13 and 24 and 25

27 9 and (10 or 11 or 20 or 21 or 22 or 23 or 26)

28 Randomized Controlled Trials as Topic/

29 randomized controlled trial.pt.

30 controlled clinical trial.pt.

31 Controlled Clinical Trial/

32 placebos/

33 random allocation/

34 Double-Blind Method/

35 Single-Blind Method/

36 (random* adj2 allocat*).tw.

37 placebo*.tw.

38 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).tw.

39 crossover studies/

40 (crossover* or (cross adj over*)).tw.

41 Research Design/

42 ((random* or control*) adj5 (trial* or stud*)).tw.

43 Clinical Trials as Topic/

44 random*.ab.

45 or/28-44

46 27 and 45

9.2. Data extraction form

Reviewer 1: **Date:**	**Reviewer 2:** **Date:**	**Version:**	
Reference and design	**Intervention and Comparator**	**Participants**	**Outcome measures**
Study identifier: *Study acronym:* *Study design:* *Country or countries:* *Number of centres:* *Recruitment dates:* *Funding:*	*Intervention*: *Comparator*: *Other interventions used*:	*Number of randomised participants*: n = *Intervention*, n= *Comparator*, n= *Inclusion criteria*: *Exclusion criteria*:	*Primary outcomes:* *Secondary outcomes:* *Method of assessing outcomes:* *Length of follow-up:*
Baseline characteristics	**Intervention n=**	**Comparator n=**	**Comments**
Results			
Primary Outcome	**Intervention n=**	**Comparator n=**	**p-value**
Comments:			
Secondary Outcomes			

Comments:			
Adverse Events			
Comments:			
Methodological comments • *Allocation to treatment groups*: • *Blinding*: • *Comparability of treatment groups*: • *Method of data analysis*: • *Sample size/power calculation*: • *Attrition/drop-out*:			
General comments • *Generalisability*: • *Outcome measures*: • *Inter-centre variability*: • *Conflict of interests*:			

Assess quality of included clinical effectiveness studies according to criteria based on that devised by the Centre for Reviews and Dissemination (CRD, University of York)[26] and/or the Cochrane Collaboration.[27]