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The clinical and cost effectiveness of the INTRABEAM® Photon Radiotherapy System for the adjuvant treatment of early breast cancer

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Contribution of authors

Jo Picot (Senior Research Fellow) project managed the study, developed the research protocol, contributed to drafting the background section, assisted in the development of the search strategy, assessed studies for inclusion, extracted data from and quality assessed the included study (clinical effectiveness), synthesised evidence, and drafted and edited the final report.

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Jackie Bryant (Principal Research Fellow) assisted with the development of the research protocol, assessed studies for inclusion, extracted data from and quality assessed included studies (cost-effectiveness & QoL), and drafted the report.

ABSTRACT

Background: Initial treatment for early breast cancer is usually either breast conserving surgery (BCS) or mastectomy. After BCS whole breast external beam radiotherapy (EBRT) is the standard of care. A potential alternative to post-operative EBRT is intraoperative radiation therapy delivered by the INTRABEAM® Photon Radiotherapy System (Carl Zeiss UK) to the tissue adjacent to the resection cavity at the time of surgery.

Objective: To assess the clinical and cost-effectiveness of INTRABEAM for the adjuvant treatment of early breast cancer during surgical removal of the tumour.

Methods: Systematic reviews of clinical effectiveness, health-related quality of life and cost-effectiveness were conducted. Electronic bibliographic databases, including MEDLINE, EMBASE and The Cochrane Library, were searched to March 2014 for English-language articles. Bibliographies of articles, systematic reviews, clinical guidelines and the manufacturer's submission were also searched. The advisory group was contacted to identify additional evidence. Two reviewers independently screened titles and abstracts for eligibility. Inclusion criteria were applied to full texts of retrieved papers by one reviewer and checked by a second reviewer. Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer. Differences in opinion were resolved through discussion at each stage. Clinical effectiveness studies were included if they were in people with early operable breast cancer. The intervention was the INTRABEAM system compared against EBRT, and study designs were randomised controlled trials. Controlled clinical trials could be considered if data from available RCTs were incomplete. A cost-utility decision analytic model was developed to estimate the costs, benefits and cost-effectiveness of INTRABEAM compared to EBRT for early operable breast cancer.

Results: One non-inferiority randomised controlled trial (TARGIT-A) met the inclusion criteria for the review. The review found that local recurrence was slightly higher following INTRABEAM than EBRT but the difference did not exceed the 2.5% non-inferiority margin providing INTRABEAM was given at the same time as BCS. Overall survival was similar with both treatments. Statistically significant differences in complications were wound seroma requiring more than three aspirations (more frequent in the INTRABEAM group) and an RTOG toxicity score of grade 3 or 4 (less frequent in the INTRABEAM group). Cost-effectiveness analysis indicates that INTRABEAM is less expensive but also less effective than EBRT because it is associated with lower total costs but fewer total QALYs

Limitations: The base case result from the model is subject to uncertainty because the disease progression parameters are largely drawn from the single available RCT. The RCT median follow-up of two years five months may be inadequate, particularly as participants with local recurrence are small. The model is particularly sensitive to this parameter.

Conclusions and implications: A significant investment in INTRABEAM equipment and staff training (clinical and non-clinical) would be required to make this technology available across the

NHS. Longer term follow-up data from the TARGIT-A trial and analysis of registry data are required as results are currently based on a small number of events and economic modelling results are uncertain.

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Background

Breast cancer is the most common cancer in women in England with 41,523 new diagnoses in 2011. Earlier detection and improved treatment for breast cancer in women has led to a rise in survival with 3-year net survival in early breast cancer of 99.3% (TMN stage 1 disease) and 92.4% (TMN stage 2 disease).

The focus of this assessment is the treatment of early breast cancer. Definitions vary but for the purposes of this assessment includes early invasive cancer where the tumour has not spread beyond the breast or the lymph nodes (which remain mobile) in the armpit on the same side as the affected breast. The first treatment option for early breast cancer is usually surgery, which may be wide local excision of the tumour [breast conserving surgery (BCS)] instead of mastectomy. Post-operative whole breast external beam radiotherapy (EBRT) is the standard of care for all patients with early invasive breast cancer after BCS, because it substantially reduces the risk of recurrence and moderately reduces the risk of breast cancer death.

A potential alternative to post-operative EBRT is treatment with the INTRABEAM® Photon Radiotherapy System (Carl Zeiss UK). The INTRABEAM device can be used to deliver intraoperative radiation therapy to the tissue adjacent to the resection cavity in an ordinary operating theatre at the time of surgery.

Objectives

To assess the clinical and cost-effectiveness of INTRABEAM for the adjuvant treatment of early breast cancer during surgical removal of the tumour.

Methods

Data sources

Electronic resources including MEDLINE, EMBASE, The Cochrane Library and Web of Science were searched for published studies and ongoing research from inception to March 2014 for English language articles. Bibliographies of included articles, systematic reviews, clinical guidelines and the manufacturer's submission to NICE were also searched for additional studies. An advisory group was contacted to identify additional published and unpublished evidence.

Study selection

Titles and abstracts were screened for eligibility by two reviewers independently. Inclusion criteria were applied to full texts by one reviewer and checked by a second reviewer. Inclusion criteria were as follows:

- *Intervention*: INTRABEAM device with or without post-operative EBRT

- *Comparator*: EBRT delivered by linear accelerator
- *Population*: People with early operable breast cancer. People with a local recurrence were excluded. For the systematic review of health-related quality of life (HRQoL) the population was not limited to early stage breast cancer.
- *Outcomes*: Overall survival; disease-free survival; ipsilateral local recurrence; adverse effects of treatment; HRQoL, cost-effectiveness (expressed in units such as life-years gained or quality-adjusted life years, or in monetary units).
- *Study design*: Randomised controlled trials (good-quality controlled clinical trials could be considered if the data from RCTs were incomplete) for the review of clinical effectiveness; full cost-effectiveness analyses, cost utility analyses and cost benefit analyses for the systematic review of cost-effectiveness; primary research studies based in the UK, Europe, Northern America and Australasia for the systematic review of QoL.

Abstracts or conference presentations were eligible for inclusion only if sufficient details were presented.

Data extraction and quality assessment

Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer. Differences in opinion were resolved by discussion at each stage.

Data synthesis

Data were synthesised through narrative reviews with full tabulation of the results of included studies.

Economic model

A cost-utility decision analytic model was developed to estimate the costs, benefits and cost-effectiveness of INTRABEAM compared to EBRT for early operable breast cancer. The intervention effects and characteristics of the modelled patient population were obtained from RCT data identified by the clinical effectiveness systematic review. The perspective of the analysis was that of the NHS and Personal Social Services in the UK. A lifetime (40 year) horizon was used to estimate costs and benefits from each treatment. Future costs and benefits were discounted at 3.5% per annum and the outcomes were reported as the cost saved per QALY lost.

Results

Systematic review of clinical effectiveness:

From 655 records screened, 44 references were retrieved for consideration. One non-inferiority RCT, the TARGIT-A trial which evaluated whether INTRABEAM treatment was no worse than EBRT, met the inclusion criteria. The trial was judged to be at a low risk of bias. Results were reported for the whole trial population (n=3,451) and separately for the pre-pathology stratum (n= 2,298 randomisation to INTRABEAM or EBRT prior to wide local excision of the primary tumour) and the post-pathology stratum (n=1,153 randomisation after initial surgery to either INTRABEAM as a

second procedure or EBRT). Median follow-up was two years five months, with 35% of participants achieving median follow-up of five years.

Local recurrence:

Local recurrence in the conserved breast (primary outcome) for the whole trial population was higher in the INTRABEAM group than the EBRT group (3.3% versus 1.3%) however the absolute difference in 5-year risk of local recurrence did not exceed the 2.5% non-inferiority margin. A similar result was observed for the prepathology stratum. In the post-pathology stratum the non-inferiority margin was exceeded and non-inferiority was not established.

Overall survival:

Overall survival (secondary outcome) for the whole trial population did not differ statistically significantly between INTRABEAM and EBRT arms (3.9% versus 5.3%, p=0.099). Rates of breast cancer deaths were similar but there were significantly fewer non-breast cancer deaths in the INTRABEAM group compared to the EBRT group. In the pre-pathology stratum lower overall mortality was observed in the INTRABEAM group because there were significantly fewer non-breast cancer deaths. In the post-pathology stratum overall mortality, breast cancer and non-breast cancer mortality were similar between treatment groups.

Complications:

Wound seroma requiring more than three aspirations occurred more frequently in the INTRABEAM group (2.1% versus 0.8%, p=0.012 whereas an RTOG toxicity score of grade 3 or 4 was less frequent in the INTRABEAM group (0.5% versus 2.1%, p=0.002). These were the only statistically significant differences in complications.

HRQoL sub-study

One small single-centre sub-study n=88 did not identify any statistically significant differences in QoL measures between the study arms.

Systematic review of cost-effectiveness:

From 184 citations screened ten references were retrieved for consideration. Three publications were included, two on the same economic model. Outcomes from both models suggested that INTRABEAM was a cost-effective option when compared to EBRT. In one model the ICER for INTRABEAM dominated EBRT being both cheaper and more effective. In the other model the costs per QALY for EBRT compared with INTRABEAM ranged from $89,234/QALY to $108,735/QALY depending on the difference in whole breast irradiation rates.

Systematic review of HRQoL:

From 939 records screened 65 studies were retrieved for consideration. Nine studies were included which provided EQ-5D data for five of seven health states potentially relevant for the independent model.

Manufacturer's economic evaluation:

The manufacturer's submitted model indicates that INTRABEAM is associated with higher QALYs and lower costs with the incremental analysis showing dominance of INTRABEAM over EBRT. A PSA showed INTRABEAM had a 100% probability of being cost effective, at both the £20,000 and £30,000 thresholds.

Independent economic evaluation:

The assessment group's model finds INTRABEAM to be less expensive but also less effective than EBRT because it is associated with lower total costs but fewer total QALYs. The base case ICER to replace EBRT with IORT is £1,596 saved per QALY lost. INTRABEAM is therefore not cost-effective compared to EBRT at a willingness-to-pay of £20,000 per QALY. The PSA indicates that EBRT has a greater probability than INTRABEAM of being cost-effective at the £20,000 and £30,000 per QALY willingness-to-pay thresholds. INTRABEAM has a higher probability of being cost-effective than EBRT at thresholds of around £5,000 per QALY or less. Deterministic sensitivity analysis finds four parameters where the difference between upper and lower values causes a switch in the treatment option which is considered cost-effective at the £20,000 per QALY threshold. The parameters to which the model is most sensitive are the probability of any other recurrence assumed for EBRT and INTRABEAM, the beta coefficient for the time to local recurrence (INTRABEAM) and the probability of death from breast cancer (INTRABEAM).

Discussion

Systematic reviews and an economic evaluation have been carried out independent of any vested interest. A de novo economic model was developed following recognised guidelines and systematic searches were conducted to identify data inputs for the model. The base case result is subject to uncertainty because the disease progression parameters are largely drawn from the single available RCT. This RCT has a median follow-up of two years five months, which may be inadequate particularly as numbers of participants experiencing a local recurrence in the prepathology stratum are small. The model is particularly sensitive to this parameter.

Conclusions

A significant investment in INTRABEAM equipment and staff training (clinical and non-clinical) would be required to make this technology available across the NHS. Longer term follow-up data from the TARGIT-A trial and analysis of registry data are required as results are currently based on a small number of events and economic modelling results are uncertain.

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Plain English Summary

Breast cancer is the most common cancer in women in England. In early stage breast cancer the tumour has not spread beyond the breast or armpit lymph glands on the same side as the affected breast. Initial treatment may be breast conserving surgery (BCS) (removal of the tumour but keeping an intact breast) or mastectomy (total removal of the breast). After BCS a three-week course of external beam radiotherapy (EBRT) reduces the risk of breast cancer returning in the affected breast (local recurrence). A new radiotherapy approach is single treatment radiotherapy delivered using the INTRABEAM® Photon Radiotherapy System. We used standard systematic methods to identify all the current evidence comparing EBRT with INTRABEAM and one study, the TARGIT-A trial was included. Local recurrence was slightly higher following INTRABEAM than EBRT providing INTRABEAM was given at the same time as BCS, but the likelihood of dying from breast cancer was similar with both treatments. INTRABEAM patients more frequently experienced fluid pockets that were drained more than three times but radiation therapy toxicity was less frequent than with EBRT. In our economic model, INTRABEAM was less expensive but also less effective than EBRT. The results from the model changed when different estimates for treatment effects (e.g. local recurrence, probability of death from breast cancer) were tested. The longer term effects of INTRABEAM are not known and further research on this is needed.

LIST OF ABBREVIATIONS

BCS	Breast conserving surgery
BRCA1 and BRCA2	Breast cancer genes 1 and 2
CCT	Controlled clinical trial
CDSR	Cochrane Database of Systematic Review
CI	Confidence interval
CPCI	Conference Proceedings Citation Index
CRD	Centre for Reviews and Dissemination
DARE	Database of Abstracts of Reviews of Effectiveness
DCIS	Ductal carcinoma in situ
DNA	Deoxyribonucleic Acid
EBRT	external beam radiotherapy
EG	Excellent or good
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life - 5 Dimensions
ER	Estrogen receptor alpha
GAINS	Galway Index of Survival
GP	General Practitioner
Gy	Gray
HDC	High dose chemotherapy
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IORT	intraoperative radiation therapy
IQR	Interquartile range
ITT	Intention-to-treat
LENT SOMA	Late Effects in Normal Tissues Subjective, Objective, Management and Analytic
Linac	Linear accelerator
LRR	Local recurrence rate
MS	Manufacturer's submission
MTA	Multiple Technology Appraisal
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NOS	Not otherwise specified
NPI	Nottingham Prognostic Index
NST	No special type
OR	Odds ratio
PgR	Progesterone-receptor
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	Quality Adjusted Life Year
QLQ-BR23	QoL questionnaire - Breast Cancer Module
QLQ-C30	QoL questionnaire - C30
QoL	Quality of life
RCT	Randomised controlled trial
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group

SCIE	Science Citation Index Expanded
SD	Standard deviation
SE	Standard error
SHTAC	Southampton Health Technology Assessments Centre
SLNB	Sentinel lymph node biopsy
TARGIT	**TARG**eted **I**ntraoperative radio**T**herapy
TNM	Tumour Node Metastases
UK	United Kingdom
VAS	Visual analogue scale
WB	Whole breast
WHO ICTRP	World Health Organisation international clinical trials research platform
WLE	Wide local excision
XRS	X-ray source

1 BACKGROUND

1.1 Description of underlying health problem

Breast cancer is the most common cancer in women in England with 41,523 new diagnoses in 2011.[1] It accounts for about a third of all cancers in women[2] but is rare in men, accounting for less than 0.25% of cancers in 2011 (303 new diagnoses in England in 2011).[1] Consequently the primary focus of this report is breast cancer in women, and where data are presented for men this is clearly indicated.

Breast cancer aetiology

Breast cancer, in common with all other cancers, is caused by DNA mutations that disrupt the normal maintenance of cellular identity, growth and differentiation.[3] The majority of breast and other cancers develop from somatic mutations[3;4] resulting from errors in processes such as DNA replication, DNA modification, or DNA repair[4;5] which in turn may be influenced by environmental and/or dietary factors.[6] A small proportion of cancer types arise from inheritable single-gene disorders,[3] for example BRCA1 and BRCA2 are genes associated with inheritable breast cancer.[4;7-9]

There are two main forms of breast cancer: non-invasive, where the cancer cells have not spread; and invasive, where the breast cancer cells can potentially spread to the surrounding breast tissue, or beyond. Approximately 10% of newly diagnosed breast cancer cases are non-invasive, the majority of these non-invasive cancers (approximately 90%) being ductal carcinoma in situ (DCIS).[10] In DCIS, cancer cells have developed inside milk ducts but have not yet developed the ability to spread beyond the ducts. DCIS is usually identified following a mammogram as it rarely forms a lump. The remaining 90% of newly diagnosed breast cancer cases are various types of invasive breast cancer.

When breast cancer is diagnosed information is gathered to describe and classify it according to a variety of characteristics. Much of the information required can only be obtained from samples taken during surgical removal of the primary tumour. Key aspects include:[11]

- histological type (e.g. invasive ductal carcinoma, invasive lobular carcinoma)
- histological grade ranging from low (slow growing) to high (fast growing)
- stage based on the Tumour Node Metastases (TNM) classification (see Table 1 and Table 2)
- oestrogen receptor alpha (ER) status
- human epidermal growth factor receptor 2 (HER2) status
- DNA profile

This information is essential for deciding what local and systemic treatments may be required and provides information about prognosis. The focus of this assessment is the treatment of early breast cancer, however it should be noted that there is no internationally agreed single definition of early

breast cancer (e.g. in terms of TNM stage). Typically however early breast cancer would be classified as TMN Stage I or Stage II (either IIa or IIb) with potentially some stage III tumours (those for which treatment could be curative).

Table 1: Stage of breast cancer using the TNM classification[12;13]

STAGE	TNM (see Table 2)
Stage 0	Tis[a] 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] DCIS. M - Metastases, N - Node, T - Tumour

Table 2: TNM classification scheme[12;13]

Tumour stage		Nodal stage		Distant metastasis	
Tis [a]	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				

[a] DCIS, M - Metastases, N - Node, T - Tumour

The aim of treatment for early breast cancer is to provide a cure. As already stated there are two major categories of early breast cancer: non-invasive (in situ) disease - predominantly in the form of ductal carcinoma in situ (DCIS), and invasive cancer.[11] 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.[13] Once an invasive cancer has spread to distant sites (which may occur after initial treatment with curative intent) it is no longer curable but can be treated to control symptoms.

Breast cancer epidemiology

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] For the period 2008-2010 the age-standardised rate for women in England was 125.7 (95% CI 125.0 to 126.4).[14] The strongest risk factor for breast cancer is increasing age and consequently 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] Other important risk factors include obesity, alcohol consumption and lack of physical activity which are estimated to be linked to about 18.5% of UK female breast cancer cases.[15]

There were 9,702 deaths of women, and 64 deaths of men from breast cancer in England in 2011.[16] The UK age-standardised mortality rate from breast cancer per 100,000 women in 2008-2010 was 25.3 (95% CI 25.0 to 25.6).[14] For women diagnosed with breast cancer during 2004-2006 and followed up to 2011 the age-standardised 1-year survival rate for all breast cancers was 94.7% and the 5-year survival was 83.3%.[17] 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.[17] The rise in survival estimates has been due to earlier detection and improved treatment for breast cancer in women.[2] An analysis of survival by stage at diagnosis for women in the UK diagnosed with invasive breast cancer (DCIS was excluded) during 2000-2007[18] reported 1-year and 3-year net survival as shown in Table 3.

Table 3: Age-standardised survival in the UK[a] by invasive breast cancer stage at diagnosis

TNM Stage	1-year net survival (95% CI)	3-year net survival (95% CI)
TNM Stage 1	100% (100 to 100)	99.3% (99.2 to 99.4)
TNM Stage 2	99.2% (99.2 to 99.3)	92.4% (92.2 to 92.7)
TNM Stage 3	90.9% (90.5 to 91.4)	70.7% (69.9 to 71.5)
TNM Stage 4	53.0% (52.0 to 54.0)	27.9% (26.9 to 28.9)

[a] Data for these analyses (which excluded DCIS) came from five of the eight regional cancer registries because these had stage data for at least 50% of registered patients: Northern Ireland; Wales and the Northern and Yorkshire Cancer Registry and Information Service; Eastern Cancer Registration and Information Centre; Oxford Cancer Intelligence Unit; West Midlands Cancer Intelligence Unit. The study defined net survival as the survival of cancer patients, after controlling for other causes of death.

Breast cancer diagnosis

In England the main routes to diagnosis for the majority of breast cancer cases are via the NHS Breast Cancer Screening Programme or urgent (two week wait) referrals from a GP due to a suspicion of cancer. The breast cancer screening programme targets women aged 50-69 years (with extension from 47 to 73 ongoing and expected to be completed after 2016). For 2006-2008 just over 50% of breast

cancer cases in the 50-69 years age group were diagnosed through screening whereas in other age groups (under 50 years and 70 years and older) over 50% of cases were diagnosed through the urgent GP referral route.[19] Breast cancer screening aims to detect cancers at an early stage when they are too small to cause changes to the breast that can be observed or felt. In England in 2011-12, 40.7% (6,403) of all the breast cancers detected by screening were invasive but small (less than 15mm in diameter).[20] For breast cancers detected via routes other than screening there are no regularly published data on stage of breast cancer at diagnosis,[21] however evidence suggests that the majority (at least 80%) of women are diagnosed with early disease (Stage I or Stage II) whatever their route to diagnosis.[22]

The 2009 NICE Guideline 'Early and locally advanced breast cancer: diagnosis and treatment'[11] 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.[11] 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.

Breast cancer natural history and prognosis

The natural history of breast cancer is variable and incompletely understood.[23] If left untreated, a typical invasive breast cancer might progress in the following manner. Initially the breast cancer cells multiply thereby increasing the size of the tumour,[24] and as the tumour proliferates the risk that metastatic cells will be generated increases.[25] A key route for metastatic spread of breast cancer cells is via the lymphatic system. If a breast cancer spreads, the primary place it spreads to is often the first lymph node (or nodes) receiving direct lymphatic drainage from the tumour.[24;25] This lymph node is called the sentinel lymph node.[26] The tumour can also spread to more distant lymph nodes and to systemic sites via the bloodstream (e.g. bone, lung, liver, brain). It is also possible for tumour cells to metastasise via the vascular system directly to systemic sites.[25] However, not all breast cancers metastasise. Evidence from screening studies suggests that some screen detected breast cancers may regress spontaneously,[27] and natural history may vary according to a variety of factors, for example genotype,[28] hormone receptor status,[29] and race.[30]

The heterogeneous nature of breast cancer natural history has an impact when trying to provide a prognosis and tools have been developed which aim to predict invasive breast cancer outcome. For example, the Nottingham Prognostic Index (NPI)[31] (Table 4) is a tool that combines information on the size of the tumour, the number of lymph nodes involved and the histological grade to produce an overall score, with a higher score indicating a worse prognosis. Other models have been developed which aim to more accurately predict outcome by including alternative indicators and/or more explanatory factors, for example, Predict[32] and the Galway Index of Survival (GAINS).[33] The

program Adjuvant! enables prognostic estimates of outcome either with or without therapy to be produced based on estimates of individual patient prognosis and data on the efficacy of a range of adjuvant therapy options.[34]

Table 4: The Nottingham Prognostic Index[35]

NPI = (T x 0.2) + L + G		
T = tumour size in cm		
L = lymph node stage, either 1 (0 lymph nodes involved), 2 (1-3 nodes), or 3 (> 3 nodes)		
G = histological grade, either 1, 2, or 3		
Score	**Prognostic Group**	**10-year survival[a]**
2.08–2.4	Excellent,	96%
2.42 to ⩽3.4	Good,	93%
3.42 to ⩽4.4	Moderate I	81%
4.42 to ⩽5.4	Moderate II	74%
5.42 to ⩽6.4	Poor	50%
6.5–6.8	Very poor	38%

[a] The 10 year breast cancer specific survivals are based on data from 2238 patients treated for breast cancer in 1990-1999 inclusive[35]

Impact of breast cancer

Psychological distress, chiefly in the form of anxiety, may be experienced by women from the initial diagnostic procedures for a suspected breast cancer,[36] through all stages of treatment and beyond.[37;38] In addition to psychological aspects women may experience a range of physical problems for example arm and breast symptoms and/or lymphedema,[39;40] and fatigue.[40]

An analysis of patients' free text comments from the Cancer Patient Reported Outcome Measures (PROMs) Survey in England[41] identified a range of issues that may affect patients diagnosed with breast cancer. These included poor body image following breast surgery, ongoing problems following surgery such as pain and lymphedema and problems associated with other non-surgical treatments for example hot flushes related to hormone treatments, burns following radiotherapy, and neuropathy during and following chemotherapy. In addition some patients found that existing comorbidities such as arthritis and osteoporosis were exacerbated by their treatment. Some survey respondents highlighted that during and/or following treatment a lack of energy affected their everyday life and some found they had cognitive problems and memory loss. Both during treatment and after treatment some patients suffered from feelings of depression, loneliness and isolation. A continuing fear of

recurrence was also an issue for some. Other problems highlighted by the survey were social and financial issues for example relating to employment and obtaining insurance.

The impact of breast cancer for the NHS is likely to increase across all facets of the breast cancer care pathway in the future. This is because the population of England is both growing in size and ageing which will lead to increasing rates of breast cancer given that the strongest risk factor for breast cancer is age.

1.2 Current service provision

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 (removal of the breast). Patients who have a mastectomy can have immediate breast reconstruction (carried out at the same time as the mastectomy) or delayed breast reconstruction.

Preoperative assessment of the axilla includes ultrasound to determine whether morphologically abnormal lymph nodes are present. If abnormal lymph nodes are identified, ultrasound-guided needle biopsy is offered to obtain a tissue sample for testing. If there is no evidence of lymph node involvement on ultrasound, or the ultrasound-guided needle biopsy outcome is negative, lymph node clearance is not performed during BCS. Instead the NICE guideline 'Early and locally advanced breast cancer: diagnosis and treatment'[11] recommends sentinel lymph node biopsy (SLNB) as the preferred technique (SLNB was undertaken for 84% of invasive breast cancers identified during breast cancer screening between April 2011 and March 2012[42]). The tissue from SLNB has typically been analysed using postoperative histopathology with a five to 15 day wait for results. If macrometastases (tumour deposits with at least one dimension over 2mm) are identified a second operation takes place to remove the remaining axillary lymph nodes (axillary lymph node dissection).[43] In August 2013, NICE recommended whole lymph node analysis using the RD-100i OSNA system as an option for detecting sentinel lymph node metastases. This analysis is carried out during breast surgery, takes approximately 30 to 45 minutes, and means that if the result is positive for metastases (cytokeratin-19 gene expression identified which is a marker associated with breast cancer) axillary lymph node dissection can be completed during the initial surgery removing the need for a second operation.[43] The Advisory Group for this assessment indicated that there are 22 RD-100i OSNA system currently in use in the UK and use is increasing.

After surgical removal of the primary tumour (and axillary lymph nodes if indicated), the information on prognostic and predictive factors obtained by histological examination, the outcome of tests for

estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status, and other patient and tumour characteristics are used by the breast cancer multidisciplinary team to consider options for adjuvant therapy for all patients with early breast cancer. Decisions regarding adjuvant therapy are made following discussion with the patient.[44] Adjuvant chemotherapy or radiotherapy should start as soon as clinically possibly and within 31 days of being 'fit to treat' after surgery.[45;46]

Data from the NHS Breast Screening Programme Audit 2011-2012[42] indicates that in practice some trusts are struggling to meet this 31 day standard for radiotherapy. Overall, 57% of women received radiotherapy within 60 days and 92% within 90 days of their final surgery.[42] Advice from the Advisory Group for this assessment suggested that the figures for symptomatic cancer (i.e. not screen detected) were likely to be similar and that meeting the 31 day goal for adjuvant chemotherapy may also be difficult.

The range of recommended breast cancer treatment options described by the 2009 NICE guideline 'Early and locally advanced breast cancer: diagnosis and treatment'[11] are summarised in Table 5.

Table 5: Non-surgical treatment options for early breast cancer

Adjuvant treatment	Treatment options	Comments
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
	radiotherapy to nodal areas	e.g. if four or more involved axillary lymph nodes
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		

After breast conserving surgery whole breast external beam radiotherapy (EBRT) substantially reduces the risk of recurrence (15.7% absolute reduction in 10-year risk of any first recurrence) and moderately reduces the risk of breast cancer death (3.8% absolute reduction in 15-year risk of breast cancer death) for patients with early invasive breast cancer.[47] Therefore post-operative whole breast EBRT is the standard of care for all patients with early invasive breast cancer after breast conserving therapy (as per the 2009 NICE guideline[11]). EBRT works by directing a beam, or multiple beams, of radiation through the skin directly at the tumour and surrounding cancer cells to destroy them. The radiation beam is generated by an instrument, known as a linear accelerator (linac), which is capable of producing high energy x-rays or electrons. The most common types of external radiotherapy use photon beams (as x-rays).[48] From the patient's perspective, external radiotherapy is similar to having an x-ray, only the radiation is more intense. 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 Gray (Gy) in 15 fractions.[11] The 15 fractions are typically delivered to patients by hospital radiotherapy departments at short (10-15 minute) treatment sessions each day, Monday to Friday, with a rest at the weekends. The course is usually given for three weeks but may last longer. This course of radiotherapy can be followed by a 'boost' dose (for example 12 Gy in four fractions, 10 Gy in five fractions, or 16 Gy in eight fractions) to the tumour bed over a further one to two weeks in patients considered to be at a higher risk of local recurrence (e.g. aged under 40 years, grade 3 disease and lymph node positive).[11] 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 five weeks.[49] For patients with apparently localised DCIS treated with BCS there is a 25% risk of a local recurrence over 10 years if there is no further therapy and half of the recurrences will be of invasive cancer.[11] Unfortunately there is no reliable way to identify the patients who will not be at risk of local recurrence.[50] Therefore adjuvant radiotherapy should be offered to all patients with DCIS following BCS alongside a discussion of the potential benefits and risks.[11]

The treatment schedule described above can be difficult for some women to undertake (e.g. if they live a long way from their nearest treatment centre, if they have caring responsibilities, if they are elderly and/or disabled). Whole breast radiotherapy may also be associated with short term adverse effects (e.g. skin soreness/redness, tiredness, nausea) and long term adverse effects (e.g. changes to breast size and texture/feel, lung or heart problems), and can be impossible to deliver effectively in patients unable to lie flat, or in those unable to raise the shoulder on the side receiving treatment.

When chemotherapy is indicated EBRT is nearly always given when chemotherapy has been completed and after a gap of 2-3 weeks that minimises overlapping and/or enhancing toxicities. For

patients who require biological therapy or endocrine therapy this is typically received concurrently with EBRT.

Radiotherapy is viewed as a cost-effective treatment. The total spend on radiotherapy (not limited to breast cancer) has been estimated to comprise just 5% of the estimated total NHS spend on cancer care.[45]

1.3 Description of technology under assessment

The INTRABEAM Photon Radiotherapy System (Carl Zeiss UK) 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.[51] In the USA, INTRABEAM gained US Food and Drug Administration (FDA) approval in 1997, and in Europe was awarded CE certification in 1999.[52] 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).[51] 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 with care between different operating theatres.

The XRS component of the device has a 10cm long probe[51] and one of a variety of applicators of different shapes and sizes can be attached to this depending on the anatomical site being treated. For breast cancer a set of eight reusable spherical applicators is available with diameters from 1.5 to 5.0 cm.[52] An applicator is chosen for irradiating the tumour bed after lumpectomy depending on the size of the resection cavity. The INTRABEAM Technical Specifications state that the dose is usually entered by one person (usually a physicist) and must be checked by a doctor who verifies the dose planning and confirms it by entering a password.[52] The tissue adjacent to the resection cavity is then irradiated by the INTRABEAM device for typically 20-30 minutes.[51] 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.[53] As a result, the surface of the tumour bed typically receives 20 Gy in this single fraction treatment.[53] 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.

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 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, will also be given if indicated.

Six centres in the UK (four in London, one in Winchester, one in Dundee) are known to have used the INTRABEAM device to treat breast cancer but it is not clear if all these centres are currently using the equipment. In addition to these six centres information received from the Advisory Group for this assessment suggests that Liverpool and Harlow have purchased the equipment for neurosurgical and breast use respectively. Ten other NHS Trusts have expressed an interest in purchasing the device and private providers may also have or be intending to purchase the INTRABEAM device.

The device manufacturer has indicated that the cost of the INTRABEAM device in the UK is £435,000. This cost includes a set of spherical applicators, each of which would need replacing at a cost of £3,170 per applicator after 100 treatments. A fully inclusive service contract for maintenance of the device would cost £35,000 annually. Additionally there are associated consumable costs, for example X-drapes radio-protection shields (pack of 10 costs £1,041, sufficient for five treatments), sterile plastic drapes (pack of five £95.00, sufficient for five treatments).

2 DEFINITION OF THE DECISION PROBLEM

2.1 Decision problem

In line with the scope[54] of the NICE appraisal this assessment will consider the intraoperative use of the INTRABEAM Radiotherapy System as an alternative to post-operative EBRT to the whole breast, and as a boost during breast conserving surgery before EBRT is provided. Its use for local recurrence will not be considered.

The comparator for this review is EBRT delivered by linear accelerator.

The population of patients included within this assessment is people with early operable breast cancer who are eligible for wide local excision of the tumour followed by whole breast radiotherapy. If the cancer has spread to the regional lymph nodes the metastasis remains mobile (not fixed to other structures). Although there is no single definition of early breast cancer a common definition is disease that is confined to the breast and draining nodes for which treatment could be curative. The majority of people with early breast cancer are therefore likely to have tumours classified as TNM Stage I or Stage II (either IIa or IIb) but some with stage III tumours could also be considered to have early breast cancer using this definition. People with a local recurrence are excluded from the assessment. The NICE scope that underpins this assessment did not identify any relevant subgroups for consideration.

As specified in the NICE scope,[54] the following outcome measures are included in the decision problem:

- overall survival
- disease-free survival
- ipsilateral local recurrence
- adverse effects of treatment
- health-related quality of life (HRQoL)

2.2 Overall aims and objectives of assessment

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.

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

3 METHODS

The a priori methods for systematically reviewing the evidence of clinical effectiveness and cost-effectiveness are described in the research protocol (Appendix 1), which was sent to our expert advisory group for comment. None of the comments we received identified specific problems with the methods of the review which has been undertaken following the general principles outlined in 'Systematic Reviews: CRD's guidance for undertaking reviews in health care'.[55] The methods outlined in the protocol are briefly summarised below.

3.1 Identification of studies

The search strategies were developed and tested by an experienced information scientist. The strategies were designed to identify all relevant clinical effectiveness studies of the INTRABEAM Photon Radiotherapy System for people with early operable breast cancer. Separate searches were conducted for the economic evaluation (Section 5) to identify studies of cost-effectiveness and HRQoL.

The following databases were searched for published studies and ongoing research from inception to March 2014: 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). Searches were limited to randomised controlled trials (RCTs) and controlled clinical trials (CCTs) for the assessment of clinical effectiveness. Although searches were not restricted by language, only full texts of English-language articles were retrieved during the study selection process.

Bibliographies of included articles, systematic reviews and clinical guidelines were also searched. The manufacturers' submission to NICE was searched for any additional studies that met the inclusion criteria. Members of our advisory group were asked to identify additional published and unpublished evidence. Further details including search dates for each database and an example search strategy can be found in Appendix 2.

3.2 Inclusion and exclusion criteria

The inclusion and exclusion criteria were derived from the final scope[54] issued by NICE.

Study design

- For the systematic review of clinical effectiveness randomised controlled trials (RCTs) were eligible for inclusion. If the data from available RCTs were incomplete (e.g. absence of data on outcomes of interest) evidence from good-quality controlled clinical trials was eligible for consideration.
- For the systematic review of cost-effectiveness full economic evaluations (cost-effectiveness, cost utility or cost benefit analyses) reporting on both measures of costs and consequences were eligible for inclusion.
- For the systematic review of HRQoL primary research studies based in the UK, Europe, Northern America and Australasia were eligible for inclusion.
- Abstracts or conference presentations of studies were eligible for inclusion only if sufficient details were presented to allow an appraisal of the methodology and the assessment of results to be undertaken.
- Case series, case studies, narrative reviews, editorials and opinions were excluded as were non-English language studies. Systematic reviews and clinical guidelines were used only as a source of references.

Intervention(s)

- INTRABEAM Photon Radiotherapy System with or without post-operative EBRT

Comparator(s)

- EBRT delivered by linear accelerator

Population

- For the systematic review of clinical effectiveness people with early operable breast cancer (as defined by the trials)
- For the systematic review of HRQoL people with breast cancer (not limited to early stage breast cancer)
- People with a local recurrence were excluded.

Outcomes

Studies were included if they reported on one or more of the following outcomes:

- overall survival
- disease-free survival
- ipsilateral local recurrence
- adverse effects of treatment
- HRQoL
- cost-effectiveness (expressed in natural units such as life-years gained (cost-effectiveness analysis), quality-adjusted life years (cost-utility analysis), or in monetary units (cost-benefit analysis)

3.3 Inclusion screening process

Studies were selected for inclusion through a two-stage process. Literature search results (titles and, if present, abstracts) identified by the search strategy were screened independently by two reviewers to identify all citations that potentially met the inclusion/exclusion criteria detailed above. Full manuscripts of selected citations which appeared potentially relevant were obtained. These were assessed by one reviewer against the inclusion/exclusion criteria using a flow chart and checked independently by a second reviewer before a final decision regarding inclusion was agreed. At each stage any disagreements were resolved by discussion, with the involvement of a third reviewer when necessary.

3.4 Data extraction process

Data were extracted by one reviewer using a standardised data extraction form and each data extraction was checked for accuracy by a second reviewer. Discrepancies in the extracted data were resolved by discussion, with involvement of a third reviewer when necessary.

3.5 Critical appraisal strategy

The risk of bias of the included clinical effectiveness studies was assessed using criteria devised by the Cochrane Collaboration.[56] Criteria were applied by one reviewer and checked by a second reviewer with any disagreements resolved by consensus and involvement of a third reviewer where necessary. The methodological quality of included cost-effectiveness studies was assessed using criteria adapted by the review authors from checklists for appraising economic evaluations by Drummond and colleagues.[57] The economic evaluation included in the manufacturer's submission to NICE was assessed using criteria adapted by the review authors from checklists for appraising

economic evaluations by Drummond and colleagues[57] supplemented with additional criteria for critical appraisal of model-based evaluations by Philips and colleagues.[58] For the systematic review of HRQoL the included studies were assessed against a critical appraisal checklist adapted by the review authors from common themes found in other published assessment forms for HRQoL studies.[59-62]

3.6 Method of data synthesis

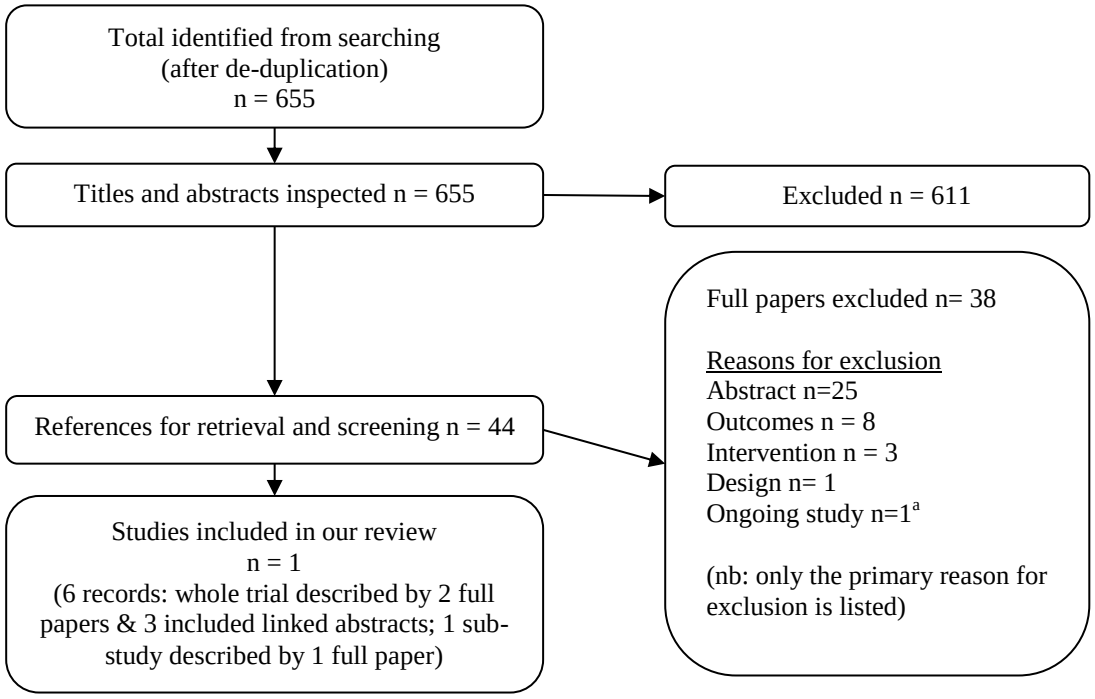
Clinical effectiveness, cost-effectiveness and HRQoL data were synthesised through narrative reviews that included critical appraisal of study methods, critical assessment of data used in any economic models and tabulation of the results of included studies.

4 CLINICAL EFFECTIVENESS

4.1 Results

4.1.1 Quantity and quality of research available

Titles and, where available, abstracts of a total of 655 citations were screened and full copies of 44 references were obtained. Of these 38 were excluded after inspection of the full article (see Appendix 3). The most common primary reason for exclusion was that the reference was an abstract containing insufficient details to allow appraisal of methodology and/or results (n=25), eight records were excluded chiefly because the outcome was not relevant to the review, an incorrect intervention was the key reason for excluding three records, one record was excluded on the basis of study design and one record was for an ongoing study (see section 4.3 for ongoing studies). One RCT, the TARGIT-A trial, met the inclusion criteria for the review (Figure 1). The primary and secondary outcomes for the whole trial population were described by two full papers and three linked abstracts. Five sub-studies of the TARGIT-A trial were identified which report outcome data from participants at just one or two centres. Four of these sub-studies were excluded from this systematic review on the grounds of outcome (see Appendix 3). One sub-study has been included which reports data on HRQoL from patients at one TARGIT-A trial centre.[63] Table 6 provides a summary description of the TARGIT-A study publications included in the clinical effectiveness systematic review.



[a] Ongoing studies are summarised in Section 4.3

Figure 1: Flow chart for the identification of studies

Table 6: Publications included in the clinical effectiveness review

Author	Study	Details
Vaidya *et al*., 2010[64]	TARGIT-A trial	Initial results of local recurrence and complications, n=2232
Vaidya *et al*., 2014[65]	TARGIT-A trial	Updated longer-term results of local recurrence, complications and survival, n=3451
Welzel *et al*., 2013[63]	TARGIT-A trial sub-study One centre (Germany)	Quality of life outcome n=88

Overview of the TARGIT-A trial

The key characteristics of the TARGIT-A trial[64;65] are shown in Table 8Table 7 with further details in the data extraction form (Appendix 4Appendix 4). The TARGIT-A trial is the pivotal trial evaluating the concept of delivering a single dose of targeted IORT at the time of surgery using the mobile INTRABEAM Photon Radiotherapy System (Carl Zeiss UK).

Design

The TARGIT-A trial is an international, multicentre, non-inferiority RCT that recruited participants in 33 centres in 11 countries including the UK (6 centres), Europe (17 centres in six countries), the USA (7 centres), Canada (1 centre) and Australia (2 centres). The trial evaluated IORT using the INTRABEAM device compared to conventional whole breast EBRT. The planned follow up for trial participants is at least 10 years.[66] Median follow-up achieved for the most recent 2014 publication[65]is 2 years 5 months.

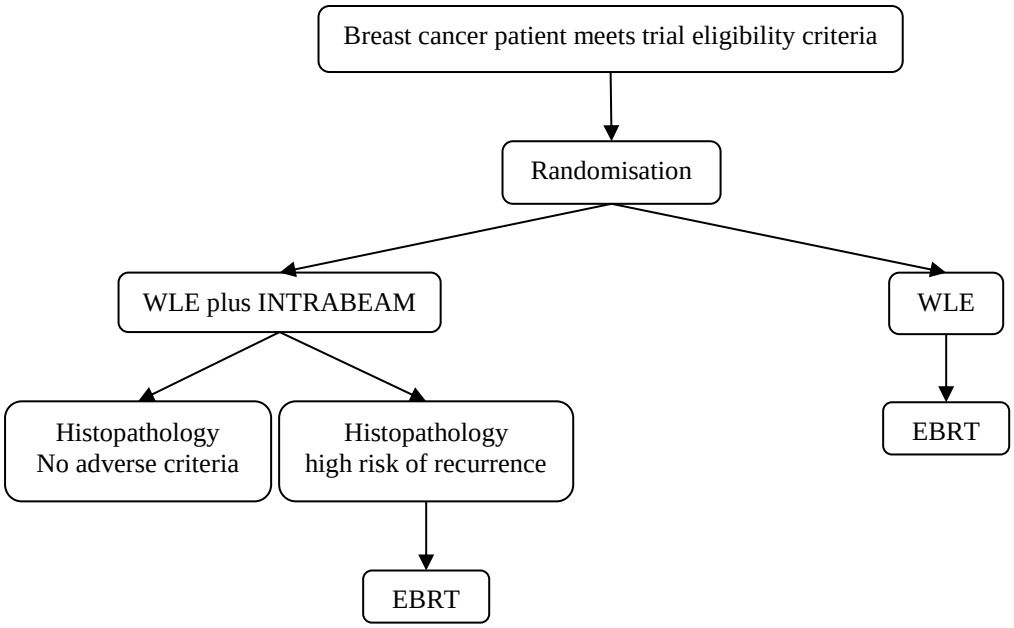
As a non-inferiority trial the RCT sought to determine whether INTRABEAM treatment was no worse than EBRT. The pre-stated non-inferiority margin was an absolute difference of 2.5% in the primary end point (local recurrence) between groups. The 2.5% non-inferiority margin was chosen at the trial outset because it seemed clinically acceptable to both clinicians and patients.[64] However, it should be noted that when the non-inferiority margin was chosen the estimated local recurrence rate (based on the literature available in 1999) was 6% and since then recurrence rates have reduced. Two patient preference studies[67;68] suggest that patients would be willing to accept an increase in the risk of local recurrence for the convenience of INTRABEAM treatment but it should be noted that these studies were conducted in countries where EBRT is typically delivered over 5-6 weeks and it is not known whether patient preference would be similar in England where EBRT is typically delivered over 3 weeks.

The trial randomised participants in three strata: pre-pathology, post-pathology and contralateral breast cancer. In the initial 2010 publication,[64] pre-pathology entry accounted for two thirds of patients, post-pathology approximately 30% and contralateral breast cancer patients less than 4%. It is not clear whether these proportions were maintained in the additional patient numbers reported in the updated 2014 publication.[65] The baseline stratification data show differences between centres in the number of patients entering the trial according to the three timings of delivery strata, particularly pre-pathology and post-pathology (see Appendix 4 for further details). Patients who entered the trial in the pre-pathology stratum were randomised to either INTRABEAM or EBRT prior to wide local excision of the primary tumour (Figure 2, upper panel). The trial was pragmatic in that if participants randomised to INTRABEAM were subsequently found to have unfavourable pathological features (unexpected lobular carcinoma, extensive intraductal component, positive margins at first excision), and hence were at high risk of recurrence elsewhere in the breast, they received EBRT in addition (i.e. INTRABEAM + EBRT, approximately 15% of INTRABEAM patients). The protocol also allowed for post-pathology entry of patients whereby patients underwent initial surgery and then, providing no unfavourable pathological features were identified, were randomised in a second stratum to receive INTRABEAM delivered as a second procedure or EBRT (Figure 2, lower panel). Post-pathology entrants to the trial were randomised within 30 days after lumpectomy and the median time between initial lumpectomy and post-pathology INTRABEAM treatment was 37 days. The timing of INTRABEAM delivery was not specified in the intervention description within the NICE scope and therefore the post-pathology participants are included in this systematic review. Additionally, patients with a history of previous contralateral breast cancer were also included and randomised in a third stratum. Treatment for breast cancer in the contralateral breast is not an exclusion criterion for this review and therefore these participants are also judged to meet the criteria for inclusion.

Participants

The TARGIT-A trial was a moderately large trial, recruiting 3,451 women with early breast cancer eligible for breast conserving surgery (2298 to the pre-pathology stratum, 1153 to the post-pathology stratum, as noted above final proportion of contralateral breast cancer patients not reported).[65] Participants had to be 45 years or older and have invasive ductal carcinoma that was unifocal on conventional examination and imaging. The trial protocol specifically defined early invasive breast cancer as T1 and small T2, N0-1, M0.[66] The initial trial publication[64] stipulated the pre-operative diagnosis of lobular carcinoma as a single exclusion criterion, although the trial protocol specified additional exclusion criteria.[66] Furthermore, because the trial was pragmatic, each participating centre had the option to pre-define more restrictive entry criteria than in the core protocol (e.g. age, tumour size, grade, node) and to stipulate local policy for the delivery of EBRT.

PRE-PATHOLOGY STRATUM



POST-PATHOLOGY STRATUM

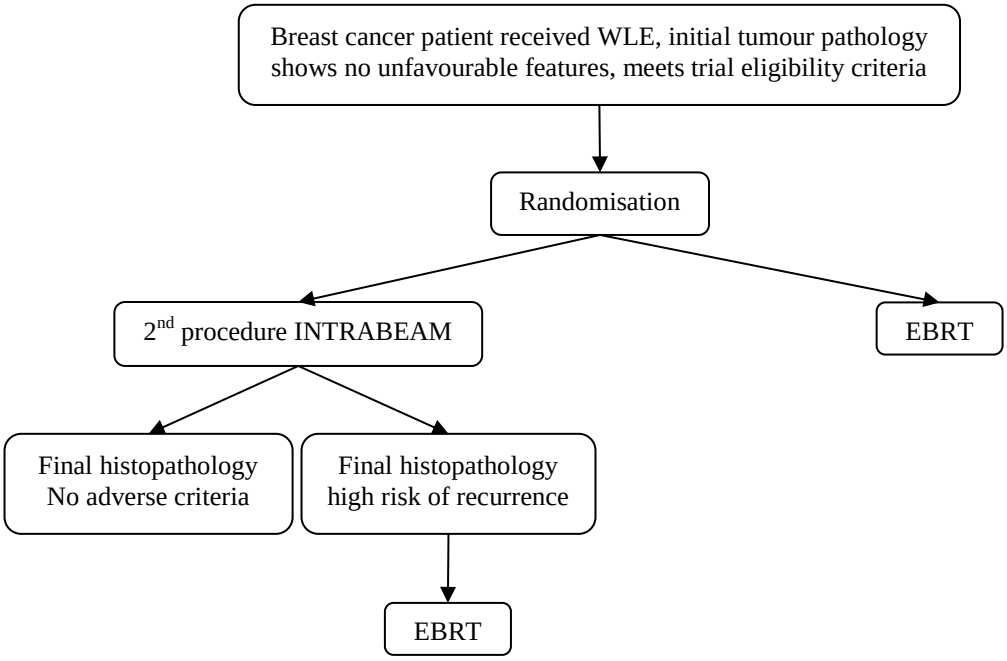


Figure 2: Flow diagram for the two main trial strata: pre-pathology and post-pathology.

The majority of women (77%) were aged between 51 and 70 years. Approximately one third of participants had a grade 1 tumour and around half had grade 2, whilst only 15% had a grade 3 tumour. The publications[64;65] did not specify the grading system used but it is likely to have been the standard Bloom-Richardson system[69] or the Nottingham system[70] which is modification of the Bloom-Richardson system. In the majority of women, cancer tumour sizes were small (87% <2cm) and with

good prognosis - nodes were uninvolved (84%), oestrogen-receptor status and progesterone-receptor status were positive (93% and 82% respectively).[65] Two thirds of women were receiving hormone therapy as adjuvant systemic treatment whilst around 12% were receiving chemotherapy.[64]

Intervention

INTRABEAM patients received a typical dose of 20 Gy to the surface of the tumour bed (attenuating to 5-7 Gy at 1cm depth).

Comparator

EBRT patients received a typical dose of 40-56 Gy with/without an additional boost to the tumour bed of 10-16 Gy. Trial centres were allowed to stipulate local policy for the delivery of EBRT and therefore there would have been some differences between EBRT delivered at different centres. It is presumed that in UK centres 40 Gy in 15 fractions would have been the likely treatment schedule whereas in some other centres local policy was an alternative schedule, for example 56 Gy in 28 fractions.[63]

Outcomes

The primary outcome of the trial was pathologically confirmed local recurrence in the conserved breast. In the initial 2010 paper[64] survival free of recurrence (disease-free survival) was reported but in the 2014[65] paper the data on recurrence are not presented in that format. Secondary outcomes were rates of local toxicity or morbidity which were assessed using a complications form that contained a pre-specified checklist. The timing of the data collection for complications was unclear in the trial publications being described as 'early' in the 2010 paper[64] and 'arising 6 months after randomisation' in the 2014 paper.[65] Complications recorded on the pre-specified checklist were haematoma, seroma, wound infection, skin breakdown, delayed wound healing and Radiation Therapy Oncology Group (RTOG) toxicity grade 3 or 4 (for dermatitis, telangiectasia, pain in irradiated field, or other). Overall survival was reported as a secondary outcome measure in the 2014 updated publication.[65] No data on HRQoL have been published for the whole trial population however one small sub-study[63] is included in this systematic review which reports on HRQoL for 88 participants enrolled at one centre in Mannheim, Germany. HRQoL was assessed by two validated questionnaires of the European Organisation for Research and Treatment of Cancer (EORTC), the QoL questionnaire C30 (QLQ-C30, version 3) and the Breast Cancer Module (QLQ-BR23). Data presented in the initial TARGIT-A trial publication[64] suggest that all the participants enrolled at this centre were randomised to the pre-pathology stratum.

For most outcomes analyses were by ITT, one exception being local recurrence in the conserved breast which, because of the nature of the outcome, could not include women who had undergone a

mastectomy (approximately 2%). For a superiority trial the CONSORT statement[71] states that analysis should be by ITT. The TARGIT-A trial however is a non-inferiority trial. An extension to the consort statement[72] for non-inferiority trials indicates that non-ITT analyses might be desirable and that there would be greater confidence in the results if these were consistent between ITT and non-ITT analyses. Therefore an analysis by treatment received in addition to the ITT analyses presented for the TARGIT-A trial would have been welcome. Outcomes of local recurrence and overall survival were reported for the whole trial population and separately for the pre-pathology and post-pathology strata. Data from participants who received INTRABEAM only and from those who received INTRABEAM with EBRT in addition were analysed together for most outcomes. Median length of follow-up for participants in the initial 2010 publication was not reported although it was stated that maximum follow-up was 10 years.[64] The more recent 2014 publication reported an overall median follow-up of 2 years 5 months, with 2020 (59%) participants reaching a median 4 years and 1222 (35%) reaching a median 5 years.

Funding

The trial was funded primarily by the NIHR Health Technology Assessment (HTA) Programme in addition to funding from a number of academic centres and government bodies.

Table 7: Key characteristics of the TARGIT-A trial[64;65]

Study	Methods	Key inclusion/exclusion criteria	Key participant characteristics[a]	Outcomes
Vaidya *et al*., 2010[64] and 2014[65] TARGIT-A trial (**TARG**eted **I**ntraoperative radio**T**herapy) *N^{o} centres*: 33 (6 in UK) *Countries*: 11 (Europe, USA, Canada, Australia) *Sponsor*: Academic and government bodies	*Design*: International, multicentre, non-inferiority RCT *Intervention*: Targeted intraoperative radiotherapy – Targit (INTRABEAM device) Dose: typically 20 Gy to surface of tumour bed attenuating to 5-7 Gy at 1cm depth. *Comparator*: Whole breast external beam radiotherapy – EBRT Dose: typically 40-56 Gy +/- boost of 10-16 Gy. *Other interventions used*: Adjuvant systemic treatment as appropriate. Participants in the INTRABEAM group with unfavourable pathological features found subsequently (e.g. lobular carcinoma) received EBRT in addition after INTRABEAM.	*Inclusion criteria*: • Women with early breast cancer • Aged ≥ 45 years • Suitable for wide local excision for invasive ductal carcinoma that was unifocal on conventional examination and imaging *Exclusion criterion*: • Pre-operative diagnosis of lobular carcinoma	*Reported in updated 2014 paper (n=3451):*[65] • Age (years): ≤50: INTRABEAM 9%, EBRT 7% 51-60: INTRABEAM 31%, EBRT 32% 61-70: INTRABEAM 45%, EBRT 47% >70: INTRABEAM 15%, EBRT 15% • Tumour grade 1: INTRABEAM 35%, EBRT 37% 2: INTRABEAM 50%, EBRT 48% 3: INTRABEAM 15%, EBRT 15% Unknown: INTRABEAM 11%, EBRT 13% • Tumour size (cm) ≤1: INTRABEAM 39%, EBRT 39% 1.1-2: INTRABEAM 48%, EBRT 48% >2: INTRABEAM 12%, EBRT 14% Unknown: INTRABEAM 10%, EBRT 12% • Nodes involved 0: INTRABEAM 83%, EBRT 85% 1-3: INTRABEAM 14%, EBRT 14% >3: INTRABEAM 3%, EBRT 2% Unknown: INTRABEAM 9%, EBRT 11% • Lymphovascular invasion Absent: INTRABEAM 87%, EBRT 88% Present: INTRABEAM 13%, EBRT 12% Unknown: INTRABEAM 10%, EBRT 12%	*Primary outcome*: Local recurrence[64;65] *Secondary outcomes*: • Local toxicity or morbidity (complications);[64;65] • Overall survival (breast cancer and non-breast cancer deaths)[65] Reported in sub-studies: • Persistent pain[73] • Toxicity[74] • Quality of life[63] • Cosmetic outcomes[75]

	N^o participants: n = 3451[65] INTRABEAM, n= 1721 EBRT, n= 1730 *Received allocated treatment:* INTRABEAM, n= 1571[b]/1721 EBRT, n= 1590/1730 *Follow-up*: Median 2 years & 5 months (IRQ 12-52 months)		• ER status: ER +ve: INTRABEAM 92%, EBRT 94% ER –ve: INTRABEAM 8%, EBRT 7% Unknown: INTRABEAM 9%, EBRT 12% • PgR status: PgR +ve: INTRABEAM 81%, EBRT 82% PgR –ve: INTRABEAM 19%, EBRT 18% Unknown: INTRABEAM 12%, EBRT 14% *Additional characteristics reported only in 2010 paper (n=2232):*[64] • Tumour type [c] Invasive ductal carcinoma: INTRABEAM 95%, EBRT 94% Invasive lobular carcinoma: INTRABEAM 4%, EBRT 4% Mixed: INTRABEAM 3%, EBRT 3% Unknown: INTRABEAM 4%, EBRT 4% • Ductal carcinoma in situ Absent: INTRABEAM 50%, EBRT 49% Present: INTRABEAM 50%, EBRT 49% Unknown: INTRABEAM 4%, EBRT 4% • Adjuvant therapy Hormone: INTRABEAM 65%, EBRT 67% Chemotherapy: INTRABEAM 10%, EBRT 13% Other: INTRABEAM 4%, EBRT 4% Unknown: INTRABEAM 9%, EBRT 8%	

EBRT, external beam radiotherapy; ER, oestrogen-receptor; IQR, interquartile range; PgR, progesterone-receptor. [a]The denominator for each category is the number of known cases; the denominator for 'unknown' percentages is the number of randomised patients; additionally, percentages are rounded so may not add up to 100%. [b]Of the 1571 who received INTRABEAM, 1332 (85%) received INTRABEAM only and 239 (15%) received INTRABEAM + EBRT. [c] Numbers reported in the paper do not sum to the given denominator and consequently the reported percentages sum to more than 100%.

Quality assessment of TARGIT-A trial

Overall, the methodological quality of the TARGIT-A trial was judged to be good with a low risk of bias. Table 8 shows the judgements of risk of bias in the various domains. For the HRQoL sub-study the assessment of selection bias and reporting bias for the main trial was judged to apply. For the remaining criteria it was judged that the HRQoL sub-study could potentially differ from the main trial and therefore separate assessments were conducted (Table 8). Overall the sub-study was judged to be at a high risk of bias due to the lack of blinding and it is not clear how representative the results are for the total trial population because the sub-study represents only about 2.5% of the overall trial population. Therefore the sub-study results should be interpreted with caution.

Randomisation schedules which were generated by computer and held securely in two centres, with requests for randomisation made by phone or fax, meant that the risk of selection bias was low.

Due to the nature of the interventions, it was not feasible to blind the patients or investigators in the trial which could potentially introduce performance bias. However, given that the main trial outcomes (recurrence and survival) were objective measures, it was deemed unlikely that patients or investigators were influenced by the lack of blinding and thus performance bias was judged to be low. Similarly, for the main trial although not all outcome assessors were blinded, the risk of detection bias was judged to be low because the main trial outcomes (recurrence and survival) were objective measures. For the sub-study[63] the lack of patient and investigator blinding led to a judgement of a high risk of performance bias and detection bias was judged as unclear due to a lack of information.

The risk of attrition bias (differences between groups in withdrawals from the study) was deemed to be low in the TARGIT-A trial. There was a low proportion of withdrawals and this appeared similar between treatment groups (0.5% INTRABEAM, 1.6% EBRT).[65] Similar numbers of patients in the two treatment groups received their allocated treatment (91% INTRABEAM, 92% EBRT)[65] and all randomised patients were included in an intention-to-treat (ITT) analysis for most outcomes. However as noted above (Overview of Targit-A trial, Outcomes) an additional analysis by treatment received would have been desirable. The sub-study[63] was deemed to be at low risk of attrition bias because only one patient was reported as lost to follow-up.

The risk of bias due to selective reporting was deemed low as all outcomes specified in the trial protocol[66] were reported in either the original or updated publication.[64;65] No other sources of bias in the total trial

population were identified. The sub-study[63] used a retrospective questionnaire without reporting baseline measurements and was therefore deemed to be at unclear risk of other sources of bias.

Table 8: Assessment of risk of bias

Cochrane criteria for assessment of risk of bias in RCTs[56]	**Judgement[a]**	**Support for Judgement**
Selection bias		
Random sequence generation	Low risk	Computer-generated randomisation schedules
Allocation concealment	Low risk	Central allocation
Performance bias		
Blinding of participants and personnel in the TARGIT-A trial	Low risk	Neither patients nor investigators were blinded. However, outcomes of mortality and recurrence were unlikely to be influenced by lack of blinding.
Blinding of participants and personnel in the HRQoL substudy	High Risk	As part of the TARGIT-A trial neither patients nor investigators were blinded and the outcome could potentially be influenced by the lack of blinding.
Detection bias		
Blinding of outcome assessment in the TARGIT-A trial	Low risk	Some investigators and teams were not blinded and it is not clear whether all the analyses were performed unblinded. However, outcomes of mortality and recurrence are objective measures and hence unlikely to be influenced by lack of blinding.
Blinding of outcome assessment in the HRQoL substudy	Unclear risk	No information reported for this sub-study
Attrition bias		
Incomplete outcome	Low risk	Low proportion of withdrawals and participants not receiving

data addressed in the TARGIT-A trial		allocated treatment (reasons similar between groups). Analyses by ITT.
HRQoL sub-study	Low risk	Reason for loss of one participant given.
Reporting bias		
Selective reporting	Low risk	The protocol is available online[66] http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0007/51892/PRO-07-60-49.pdf and specifies all outcomes including relapse-free survival and overall survival (as secondary outcomes).
Other bias		
Other sources of bias in the TARGIT-A trial	Low risk	None evident.
Other sources of bias in the HRQoL substudy	Unclear risk	Retrospective questionnaire with no baseline QoL measurement.

[a]'Low risk', 'high risk' or 'unclear risk' of bias

4.1.2 Assessment of effectiveness

The majority of the results presented in the following section are the most recent data for the TARGIT-A trial reported in the updated publication by Vaidya and colleagues 2014.[65] Results are presented for ipsilateral local recurrence (Section 4.1.2.1), overall survival (Section 4.1.2.2), and morbidity and toxicity (Section 4.1.2.3). The main trial outcome data are supplemented with some morbidity data from the initial trial publication (Vaidya and colleagues 2010[64]). The TARGIT-A trial presented outcomes of recurrence and survival for the whole trial population, and separately for the pre-pathology and post-pathology strata. The separate analysis of these two strata was prespecified. No data were presented from the third stratum (participants with a history of previous contralateral breast cancer) and no data on HRQoL have been published for the whole trial population. However limited data on the secondary outcome of quality of life (section 4.1.2.4) are provided by a sub-study at one trial centre.[63]

4.1.2.1 Ipsilateral local recurrence

Local recurrence in the conserved breast was the primary outcome in the TARGIT-A trial. Recurrence was defined as a recurrent tumour in the ipsilateral breast and was confirmed pathologically by clinical examination and cytology or biopsy.[66] The most recent data from the 2014[65] publication are shown,

which were not expressed in terms of disease-free survival. Results are presented in Table 9 and Table 10 and show data for the whole cohort and for the two pre-specified randomisation strata (pre-pathology and post-pathology) representing the different timings in delivery of INTRABEAM therapy. The trial authors also report results separately for the mature cohort (participants previously reported in the initial publication in 2010[64]) and the earliest cohort (which excludes participants enrolled in the last four years of the study) in order to 'assess stability over time'[65] (Table 10). However there has been criticism of this approach[76] because all patients included in the earliest cohort are also included in and account for just over half of the mature cohort and are included again in the whole cohort representing approximately a third of this. The assessment team and the advisory group for this assessment also have concerns about the approach taken. For the INTRABEAM arm, data from participants who received INTRABEAM only and from those who received INTRABEAM and EBRT were analysed together.

By nature of the outcome, the recurrence data do not include women who underwent mastectomy (n=76). Statistical significance levels were set at $p<0.01$ for recurrence. The rationale for setting $p<0.01$ for recurrence but $p<0.05$ for survival (Section 4.1.2.2) is not provided.

As can be seen in Table 9, the 5-year risk for local recurrence in the conserved breast in the whole cohort of patients was higher in patients receiving INTRABEAM compared to EBRT but the absolute difference did not exceed the pre-stated non-inferiority margin of 2.5% (3.3% vs 1.3% respectively, absolute difference 2.0%, $p=0.042$). With the statistical significance level set at $p<0.01$ for recurrence the difference between groups was not statistically significant. Similarly, in the pre-pathology stratum (INTRABEAM delivered at the time of BCS), the absolute difference in recurrence did not exceed the 2.5% non-inferiority margin (2.1% INTRABEAM vs 1.1% EBRT, absolute difference 1.0%, $p=0.31$) and the difference between groups was not statistically significant. However, in the post-pathology stratum (INTRABEAM delivered after BCS as a secondary procedure), although the difference between groups was not statistically significant (and the analysis may not have been powered to detect a difference) the 5-year local recurrence was higher in INTRABEAM patients with the difference being larger than the pre-defined non-inferiority margin of 2.5% (5.4% INTRABEAM vs 1.7% EBRT, absolute difference 3.7%, $p=0.069$). Therefore INTRABEAM has been shown to be non-inferior to EBRT for the whole group and for the pre-pathology stratum but not for participants in the post-pathology stratum (based on a non-inferiority margin of 2.5%).

Table 9: Ipsilateral local recurrence at five years

Local recurrence Events/N; 5-year cumulative risk % (95% CI)[65]	**INTRABEAM**	**EBRT**	**Absolute difference in Kaplan-Meier estimate at 5-years; p-value**
Whole group (n=3375)[a]	23/1679 3.3% (2.1-5.1)	11/1696 1.3% (0.7-2.5)	12 (2.0%); p=0.042
Pre-pathology stratum (n=2234)[a]	10/1107 2.1% (1.1 to 4.2)	6/1127 1·1% (0.5 to 2.5)	4 (1.0%); p=0.31
Post-pathology stratum (n=1141)[a]	13/572 5.4% (3.0 to 9.7)	5/569 1.7% (0.6 to 4.9)	8 (3.7%), p=0.069

[a] Patients who had undergone a mastectomy were not included in the analysis of local recurrence (n= 76 mastectomies in the whole group, n=64 in the pre-pathology stratum, n=12 in the post-pathology stratum).

The data on recurrence were used to generate a non-inferiority statistic ($p_{non\text{-}inferiority}$) for the absolute difference in the binomial proportions of ipsilateral local recurrence (Table 10). INTRABEAM was shown to be non-inferior to EBRT for the whole cohort (absolute difference in binomial proportions 0.72%, (90% CI 0.2 to 1.3), $p_{non\text{-}inferiority} <0.0001$) and for all pre-pathology patients (absolute difference in binomial proportions 0.37%, (90% CI -0.2 to 1.0), $p_{non\text{-}inferiority} <0.0001$). However, non-inferiority was not established for the post-pathology patients (absolute difference in binomial proportions 1.39%, (90% CI 0 to 2.8), $p_{non\text{-}inferiority} = 0.0664$).

The non-inferiority statistic was also reported separately for two cohorts of participants within the trial which had longer follow-up. As already noted the stated aim of these analyses was to 'assess stability over time'[65] but participants in the earliest cohort are also included in the mature cohort and whole trial population and there are concerns about this approach. Therefore the results should be interpreted cautiously. For the mature cohort which comprised participants previously reported on in 2010,[64] the results reflect those of the 'All patients' analyses. For the earliest cohort which had a median follow-up of five years, non-inferiority results for the pre-pathology and post-pathology strata reflect those of the 'All patients' analyses but non-inferiority is not established for the whole trial earliest cohort (absolute difference in binomial proportions 1.14% (90% CI -0.1 to 2.4), $p_{non\text{-}inferiority} = 0.0400$) because the significance level is set at $p<0.01$ for local recurrence. It is worth noting that the number of local recurrence events in the earliest cohort (median follow-up five years) was 23 events for the whole trial, just nine of which occurred in pre-pathology participants.

Table 10: $P_{non\text{-}inferiority}$ for ipsilateral local recurrence

Local recurrence[65]	Median follow-up	Events, n	Absolute difference (90% CI) in the binomial proportions[a] of ipsilateral local recurrence (INTRABEAM minus EBRT)	Z score	$p_{non\text{-}inferiority}$
Whole trial: All patients	2 years 5 months	34	0.72% (0.2 to 1.3)	-5.168	<0.0001
Mature cohort [b]	3 years 7 months	32	1.13% (0.3 to 2.0)	-2.652	0.0040
Earliest cohort [c]	5 years	23	1.14% (-0.1 to 2.4)	-1.750	0.0400
Pre-pathology: All patients	2 years 4 months	16	0.37% (-0.2 to 1.0)	-5.954	<0.0001
Mature cohort [b]	3 years 8 months	14	0.6% (-0.3 to 1.5)	-3.552	0.0002
Earliest cohort [c]	5 years	9	0.76% (-0.4 to 2.0)	-2.360	0.0091
Post-pathology: All patients	2 years 4 months	18	1.39% (0.2 to 2.6)	-1.503	0.0664
Mature cohort [b]	3 years 7 months	18	2.04% (0.3 to 3.8)	-0.429	0.3339
Earliest cohort [c]	5 years	14	1.8% (-1.2 to 4.8)	-0.382	0.3511

The prespecified non-inferiority margin was 2.5% and the significance level was set at $p<0.01$.

[a] Binomial proportion = number of recurrences/number of patients; [b] Mature cohort = 2232 participants previously reported on in 2010[64] (pre-pathology n=1450, post-pathology n=782). Numbers of participants in the mature cohort who received mastectomy and who are therefore excluded from the analysis of local recurrence were not reported; [c] Earliest cohort n=1222 excludes participants enrolled in the last four years of the study (pre-pathology n=817, post-pathology n=405). Numbers of participants in the earliest cohort who received mastectomy and who are therefore excluded from the analysis of local recurrence were not reported.

The absolute differences in the 5-year Kaplan-Meier estimates of percentage with local recurrence in the conserved breast were calculated and presented as a figure in the trial publication[65] for the pre-pathology stratum only. Data were estimated from the figure using Engauge digitizing software (Appendix 4). The Kaplan-Meier estimates were consistent across the three cohorts with increasing median follow-up, with absolute differences in percentage with local recurrence in the conserved breast of 1.1 (whole cohort), 1.1 (mature cohort) and 1.0 (earliest cohort).

4.1.2.2 Overall survival

Overall survival was a secondary outcome in the TARGIT-A trial and was reported in the more recent 2014 publication.[65] Overall survival was defined as the time interval between randomisation and death[66] and included breast cancer deaths and non-breast cancer deaths. Statistical significance levels were set at $p<0.05$ for survival. As already noted the rationale for setting $p<0.05$ for survival but $p<0.01$ for recurrence is not provided.

There were no statistically significant differences in overall mortality between women who received INTRABEAM compared to those who received EBRT (3.9% vs 5.3% respectively, difference -1.4%, p=0.099) (Table 11). When mortality was split into breast cancer and non-breast cancer deaths, rates of breast cancer death were similar between the two treatments (2.6% vs 1.9%, p=0.56), but there were significantly fewer non-breast cancer deaths in the INTRABEAM group compared to the EBRT group (1.4% vs 3.5% respectively, p=0.0086).

In the pre-pathology stratum (INTRABEAM delivered at the time of BCS), overall mortality was slightly lower in the INTRABEAM group (4.6% vs 6.9% for INTRABEAM and EBRT respectively, difference -2.3%, no p-value was reported). When split into causes of death, the same pattern was observed as for the whole cohort where deaths attributable to breast cancer were similar between the two treatments (3.3% vs 2.7% for INTRABEAM and EBRT respectively, p=0.72), but there were significantly fewer non-breast cancer deaths in the INTRABEAM group (1.3%) compared to the EBRT group (4.4%, p=0.016). When INTRABEAM was delivered after BCS as a delayed procedure (post-pathology stratum), rates of overall mortality, breast cancer and non-breast cancer mortality were similar between treatment groups (see Table 11).

Table 11: Breast cancer and non-breast cancer deaths at five years

Mortality[65] **Events/N;** **5-year cumulative risk %** **(95% CI)[65]**	**INTRABEAM**	**EBRT**	**Absolute difference;** **p-value**
Overall mortality:			
All patients (n=3451)	37/1721 3.9% (2.7 to 5.8)	51/1730 5.3% (3.9 to 7.3)	-14 (-1.4%); p=0.099
Pre-pathology stratum (n=2298)	29/1140 4.6% (1.8 to 6.0)	42/1158 6.9% (4.3 to 9.6)	-13 (-2.3%); p=NR
Post-pathology stratum (n=1153)	8/581 2.8% (1.3 to 5.9)	9/572 2.3% (1.0 to 5.2)	-1 (0.5%); p=NR
Breast cancer mortality:			
All patients (n=3451)	20/1721 2.6% (1.5 to 4.3)	16/1730 1.9% (1.1 to 3.2)	p=0.56
Pre-pathology stratum (n=2298)	17/1140 3.3% (1.9 to 5.8)	15/1158 2.7% (1.5 to 4.6)	p=0.72
Post-pathology stratum (n=1153)	3/581 1.2% (0.4 to 4.2)	1/572 0.5% (0.1 to 3.5)	p=0.35
Non-breast cancer mortality:			
All patients (n=3451)	17/1721 1.4% (0.8 to 2.5)	35/1730 3.5% (2.3 to 5.2)	p=0.0086
Pre-pathology stratum (n=2298)	12/1140 1.3% (0.7 to 2.8)	27/1158 4.4% (2.8 to 6.9)	p=0.016
Post-pathology stratum (n=1153)	5/581 1.58% (0.62 to 3.97)	8/572 1.76% (0.7 to 4.4)	p=0.32

NR, not reported.

For non-breast cancer mortality which was statistically significantly different between the INTRABEAM and EBRT groups, Vaidya and colleagues[65] detailed the causes of death. These included other types of cancer, cardiovascular causes and other causes. Details can be found in the data extraction form in Appendix 4.

The absolute differences in the 5-year Kaplan-Meier estimates of percentage overall mortality were calculated and presented in the published paper for the pre-pathology stratum only (as with local recurrence, Section 4.1.2.1) for the three cohorts with increasing median follow-up. As noted in section 4.1.2.1 there are concerns about the approach taken and therefore the results should be interpreted cautiously. The Kaplan-Meier estimates were similar across the three cohorts, with absolute differences in percentage mortality of -2.3 (whole cohort), -2.6 (mature cohort) and -2.2 (earliest cohort) (the data extracted from the published figure is available in Appendix 4. These data and the absolute differences in the 5-year Kaplan-Meier estimates of percentage with local recurrence in the conserved breast (Section 4.1.2.1) were presented together in the 2014 trial publication[65] to demonstrate the relationship between local recurrence and mortality whereby women receiving INTRABEAM experience more local recurrences but fewer deaths compared to those receiving EBRT.

4.1.2.3 Morbidity and toxicity

Complications, in the form of local toxicity and morbidity, were reported as secondary outcomes. The initial publication by Vaidya and colleagues, 2010[64] reported early complications but did not specifically define 'early', though the trial protocol[66] stipulated that the period of serious adverse event observation extended from the time of registration onto the trial until 90 days after the completion of randomised treatment. The more recent TARGIT-A publication (Vaidya and colleagues, 2014[65]), reported complications arising six months after randomisation.

As can be seen in Table 12, the incidence of any early complication was similar in the two treatment groups. Clinically significant complications were also similar between groups with the exception of two. Wound seroma requiring more than three aspirations occurred more frequently in women receiving INTRABEAM than in those receiving EBRT (2.1% vs 0.8% respectively, p=0.012), whilst conversely an RTOG toxicity score of grade 3 or 4 was less frequent in the INTRABEAM group compared to the EBRT group (0.5% vs 2.1%, p=0.002).[64] Separate data were not reported for the categories of dermatitis, telangiectasia, pain in irradiated field, or other that contributed to the RTOG toxicity grade 3 or 4 outcome. A member of the Advisory Group for this assessment indicated that the clinical impact for patients with grade 3 or 4 toxicity is much greater than for those with a seroma requiring several aspirations.

The incidence of complications arising six months after randomisation (reported by the 2014 publication[65]) was lower in both treatment groups, although it is not clear whether these complications occurred in any of the same patients who were reported in the 2010 publication[64] as having clinically significant

complications. There appeared to be no differences between treatment groups in any single defined wound-related complication (Table 12) (p-values were not reported), nor for total complications (1.1% INTRABEAM vs 0.9% EBRT, p=0.599). The incidence of radiotherapy-related complications (RTOG toxicity score of grade 3 or 4) remained higher in women receiving EBRT (0.8%) compared to those receiving INTRABEAM (0.2%), but the difference between the groups was no longer statistically significant (p=0.29).

Table 12: Toxicity and morbidity

Early[a] complications	**INTRABEAM (n=1113)**	**EBRT (n=1119)**	**p-value**
No. of complications per patient:[64]			
0	917/1113 (82.4%)	946/1119 (84.5%)	NR
1	151/1113 (13.6%)	139/1119 (12.4%)	NR
2	29/1113 (2.6%)	27/1119 (2.4%)	NR
3	11/1113 (1.0%)	5/1119 (0.4%)	NR
4	3/1113 (0.3%)	0/1119	NR
5	2/1113 (0.2%)	0/1119	NR
6	0/1113	3/1119 (0.3%)	NR
Any complication[a]	196/1113 (17.6%)	174/1119 (15.5%)	$\chi 2$ 1.74, p=0.19[b]
Clinically significant complications:[a64]	**INTRABEAM (n=1113)**	**EBRT (n=1119)**	**p-value**
Haematoma needing surgical evacuation	11/1113 (1.0%)	7/1119 (0.6%)	0.338
Seroma needing >3 aspirations	23/1113 (2.1%)	9/1119 (0.8%)	0.012
Infection needing i.v. antibiotics or surgical intervention	20/1113 (1.8%)	14/1119 (1.3%)	0.292
Skin breakdown or delayed wound healing[c]	31/1113 (2.8%)	21/1119 (1.9%)	0.155
RTOG toxicity grade 3 or 4[d]	6/1113 (0.5%)	23/1119 (2.1%)	0.002
Major toxicity[e]	37/1113 (3.3%)	44/1119 (3.9%)	0.443

Wound-related complications arising 6 months after randomisation:[65]	**INTRABEAM (n=1721)**	**EBRT (n=1730)**	**p-value**
Haematoma/seroma needing >3 aspirations	4/1721 (0.2%)[f]	2/1730 (0.1%)[f]	NR
Infection needing i.v. antibiotics or surgery	12/1721 (0.7%)[f]	9/1730 (0.5%)[f]	NR
Skin breakdown or delayed wound healing	3/1721 (0.2%)[f]	5/1730 (0.3%)[f]	NR
Total	19/1721 (1.1%)	16/1730 (0.9%)	0.599
Radiotherapy-related complications:[65]			
RTOG toxicity grade 3 or 4	4/1721 (0.2%)	13/1730 (0.8%)	0.029

NR, not reported; RTOG, Radiation Therapy Oncology Group. Data are number of patients (%). [a]The 2010 paper[64] does not indicate the time period over which these complications arose but the 2014[65] paper describes them as 'early complications'. [b]TARGIT vs EBRT for no complications vs any number of complications, degree of freedom = 1. [c]Some patients in first three rows could be included in the 4th row. [d]No patient had grade 4 toxicity. [e]Defined as skin breakdown or delayed wound healing and RTOG toxicity grade of 3 or 4. [f]Percentages calculated by reviewer.

4.1.2.4 Sub-study reporting quality of life for participants at one trial centre

No data on HRQoL have been published for the whole trial population, however Welzel and colleagues[63] have assessed quality of life retrospectively in one small sub-study of 88 participants enrolled at one centre in Mannheim, Germany. The initial TARGIT-A trial publication[64] indicates that all the participants enrolled at this centre were randomised to the pre-pathology stratum. Quality of life was assessed by using two validated questionnaires of the EORTC, the QLQ-C30 (version 3) and the QLQ-BR23. Participants (n=88) were asked to report on their situation in the last week. These participants represent 2.5% of the total TARGIT-A trial population. The results of both an ITT analysis and an as-treated analysis (with a threshold for significance of $p < 0.01$ in both cases) are presented in Table 13. The as-treated analysis removes five participants from the INTRABEAM group and moves four of them to the EBRT group because this was the treatment received, with the fifth (who refused EBRT) not contributing data. The ITT analysis did not identify any statistically significant differences in QoL measures (global health status, restrictions in daily activities, general pain, breast or arm symptoms) reported by the INTRABEAM arm in comparison to the EBRT arm. The as-treated analyses were not presented in the same way as the ITT analysis. For the as-treated analyses the results for the

INTRABEAM arm were reported separately for those who received INTRABEAM therapy only and those who received INTRABEAM + EBRT with statistical comparisons of INTRABEAM only vs EBRT, INTRAEAM only vs INTRABEAM + EBRT, and EBRT vs INTRABEAM + EBRT being reported. Thus a statistical comparison between the original randomised groups is not reported. For the comparison of the INTRABEAM only group with the EBRT treated group the as treated analyses showed a statistically significant benefit of INTRABEAM for the restrictions in daily activities, general pain, breast symptoms and arm symptoms, but there was no statistically significant difference in the global health status subscale. When comparing the INTRABEAM only group with the INTRABEAM + EBRT group the only statistically significant difference in the reported QoL measures was for breast symptoms. No statistically significant differences were reported for comparisons of QoL measures between the INTRABEAM + EBRT and the EBRT groups. These data should be interpreted cautiously due to their non-randomised nature and the small numbers involved. The breast and arm symptoms most commonly reported by participants were moderate or severe pain in the arm or shoulder, difficulty in raising/moving arm sideways and pain in area of affected breast. No statistically significant differences between groups were reported for the as treated analysis of frequency of symptoms.

Table 13: QoL outcomes

ITT analysis, QoL outcome, mean (SD)	**INTRABEAM n=46 (IORT n=30, INTRABEAM + EBRT n=16)**	**EBRT n=42**	**p-value**[a]
Global health status[b]	61.6 (21.7) N=46	54.8 (19.9) N=40	0.183
Restrictions in daily activities[b]	72.8 (32.3) N=46	61.8 (29.2) N=41	0.055
General pain[c]	29.3 (32.8) N=46	42.5 (33.0) N=42	0.048
Breast symptoms[c]	17.0 (20.8) N=45	18.1 (20.2) N=42	0.629
Arm symptoms[c]	24.4 (26.7) N=45	31.1 (27.9) N=40	0.279

As-treated analysis, QoL outcome, mean (SD)	**INTRABEAM n=25**	**INTRABEAM + EBRT n=16**	**EBRT n=46**	**p-value**
Global health status[b]	63.6 (24.2)	60.9 (19.9)	52.4 (22.1)	>0.01
Restrictions in daily activities[b]	78.7 (35.2)	NR	60.5 (29.5)	0.007[e]
General pain[c,d]	21.3 (95% CI NR[h] to 54.4)	43.7 (95% CI 11.6 to 75.9)	40.9 (95% CI 8.6 to 73.2)	0.007[e] 0.018[f]
Breast symptoms[c,d]	7.2 (95% CI NR[h] to 20.9)	29.7 (95% CI 6.8 to 52.5)	19.0 (95% CI NR[h] to 39.2)	0.001[e] <0.001[f] 0.021[g]
Arm symptoms[c,d]	15.2 (95% CI NR[h] to 37.2)	32.6 (95% CI 6.8 to 58.4)	32.8 (95% CI 4.2 to 61.5)	0.009[e] 0.011[f]
As-treated analysis, frequency breast/arm symptoms,[i] % moderate/severe	**INTRABEAM n=25**	**INTRABEAM + EBRT n=16**	**EBRT n=46**	**p-value**
Pain in area of affected breast	4% / 0	25% / 13%	11% / 4%	>0.01
Swelling in area of affected breast	0 / 0	7% / 7%	4% / 2%	
Oversensitivity in area of affected breast	4% / 0	20% / 7%	9% / 7%	
Skin problems on or in area of affected breast	4% / 4%	13% / 6%	9% / 4%	
Pain in arm or shoulder	8% / 8%	33% / 20%	18% / 23%	>0.01
Swelling in arm or hand	8% / 4%	6% / 6%	9% / 7%	
Difficulty in raising or moving arm sideways	20% / 0	13% / 7%	24% / 12%	>0.01

NR, not reported. [a] statistical significance was set at 0.01, [b] higher scores are equal to good functioning/good quality of life, [c] higher scores are equal to severe symptoms/worse quality of life, [d] figures estimated from graph (4C) by reviewer using Engauge digitizing software, [e] IORT vs EBRT, [f] IORT vs IORT-EBRT, [g] EBRT vs IORT-EBRT, [h] lower CI not specified on bar chart, [i] reported by patients.

Summary of Clinical Effectiveness

- One RCT[64;65] met the inclusion criteria for the systematic review. It evaluated IORT using the INTRABEAM device compared to conventional whole breast EBRT. In addition to the main trial,[64;65] one substudy reported on participants from an individual trial centre for the outcome of quality of life.[63] Other publications from TARGIT-A were not included.
- The RCT had two randomisation strata. Participants in the pre-pathology stratum were randomised prior to surgery to remove the tumour to INTRABEAM or EBRT. Any participants in the INTRABEAM arm who were subsequently found to have unfavourable pathological features received EBRT in addition (i.e. INTRABEAM + EBRT). Participants in the post-pathology stratum received surgery to remove the tumour and were entered into the trial providing initial histopathology showed no adverse criteria. Participants in the INTRABEAM arm found to have unfavourable pathological features on final histopathology received INTRABEAM + EBRT.
- The quality of the RCT was judged to be good with a low risk of bias.
- Local recurrence in the conserved breast was the primary outcome of the RCT with the pre-stated non-inferiority margin being an absolute difference of 2.5% between groups. Overall survival was a secondary outcome. The median follow-up was two years five months, with 59% of the total study population reaching a median follow-up of four years and 1222 (35%) reaching a median follow-up of five years. Results were presented for the whole trial population, the pre-pathology stratum and the post-pathology stratum.

  Whole trial population

  - Local recurrence for the whole trial population was higher in the INTRABEAM group but the absolute difference in 5-year risk of local recurrence did not exceed the 2.5% non-inferiority margin. Analysis of the non-inferiority statistic for local recurrence indicated that INTRABEAM was non-inferior to EBRT.
  - The difference in overall survival for the whole trial population between women who received INTRABEAM and those who received EBRT was not statistically significant. Analysis of breast cancer and non-breast cancer deaths showed that rates of breast cancer death were similar between the two treatments but there were significantly fewer non-breast cancer deaths in the INTRABEAM group compared to the EBRT group.
  - When considering these results for differences in 5-year risks it should be remembered that median follow-up was just under 2.5 years, 1222 participants had completed five years of follow-up. The initial sample size calculation required 2232 participants be enrolled however this was based on a background 5-year recurrence rate of 6% whereas the observed

recurrence rate in the trial to date is lower than 6% so a smaller sample size could achieve the same statistical power.

Pre-pathology stratum

- Local recurrence for the pre-pathology stratum was higher in the INTRABEAM group but the absolute difference in 5-year risk of local recurrence did not exceed the 2.5% non-inferiority margin. Analysis of the non-inferiority statistic for local recurrence indicated that INTRABEAM was non-inferior to EBRT.
- Overall mortality was slightly lower in the INTRABEAM group because although breast cancer deaths were similar between the two treatments there were significantly fewer non-breast cancer deaths in the INTRABEAM group.
- Participants in the pre-pathology stratum treated with INTRABEAM experienced a 1% increase in local recurrence but this was counterbalanced with a potential 2.3% decrease in overall mortality.
- When considering these results the same issues regarding median length of follow-up apply as noted for the whole trial population. It should also be remembered that 2298 participants were randomised to the pre-pathology stratum.

Post pathology stratum

- Local recurrence in the post-pathology stratum was higher in the INTRABEAM arm and the absolute difference in the 5-year local recurrence exceeded the pre-defined non-inferiority margin of 2.5%. Analysis of the non-inferiority statistic indicated that non-inferiority was not established for the post-pathology patients.
- Overall mortality, breast cancer and non-breast cancer mortality were similar between treatment groups.
- When considering these results the same issues regarding median length of follow-up apply as noted for the whole trial population. In addition it should be remembered that 1153 participants were randomised to the post-pathology stratum.

- Numbers of early complications reported were similar in the two treatment groups. Clinically significant complications were also similar except for wound seroma requiring more than three aspirations which occurred more frequently in the INTRABEAM group whereas an RTOG toxicity score of grade 3 or 4 was less frequent in the INTRABEAM group. Complications arising six months after randomisation appeared similar between the groups and although RTOG toxicity of grade 3 or 4 remained more common among EBRT arm participants the difference between groups was no longer statistically significant.
- Sub-study reporting quality of life for participants at one trial centre

- The outcomes from this sub-study should be treated with some caution because of the risks of bias identified and the small proportion of the overall trial population involved.
- ITT analysis did not identify any statistically significant differences in QoL measures between the study arms.

4.2 SHTAC review of clinical effectiveness in manufacturer submission to NICE

Carl Zeiss UK (INTRABEAM manufacturer) submitted a report and economic model to NICE. The clinical effectiveness evidence has been briefly appraised (Appendix 5). A review of the economic model and cost-effectiveness results included in the manufacturer's submission (MS) can be found in Chapter 5 (Section 5.3).

The manufacturer did not conduct a formal systematic review of the clinical effectiveness evidence. Although databases searched and the dates of searches were specified no information is provided to indicate how the results of this search were screened to identify relevant studies, no detailed inclusion or exclusion criteria were presented and there is no quality assessment of the included studies. The manufacturer did not report searching for any ongoing studies but information is included from conference proceedings.

The MS contains a narrative summary of the single key RCT, the TARGIT-A trial, which is also included in the SHTAC systematic review. However there are two differences in the evidence presented. The MS excludes evidence from the initial TARGIT-A trial publication from 2010[64] reasoning that the 2010 results are expected to be included in the more recent (2014[65]) publication. In contrast the SHTAC systematic review includes evidence on early complications from the 2010 TARGIT-A trial publication[64] since these are not reported by the more recent 2014 trial paper.[65] The second difference in the TARGIT-A trial evidence presented is that the MS includes a cohort study (Tuschy and colleagues 2013[77]) reporting on post-operative complications within the first week following surgery at the TARGIT-A trial centre in Mannheim. This cohort study is excluded from the SHTAC systematic review because it is likely that the data reported are either partially or wholly contained within the early complications reported by the initial TARGIT-A trial publication[64] and furthermore Tuschy and colleagues[77] report no comparable data for the EBRT group.

In addition to evidence from the TARGIT-A RCT the MS also provides a narrative summary of evidence from a further 22 studies (6 reported as conference abstracts) that did not meet the inclusion criteria of the SHTAC review, chiefly on the grounds of study design.

The MS 'Interpretation of clinical evidence' subsections a, b, and c (MS pages 42-46) focuses on the TARGIT-A trial data, and consequently, with just one included trial there is no discrepancy for the key outcomes of recurrence and overall survival between the MS and the SHTAC systematic review.

4.3 Ongoing studies

The clinical effectiveness search and the search for ongoing studies identified one ongoing RCT (TARGIT-B), one prospective single arm study (TARGIT-E) and three registry database studies (TARGIT-R, TARGIT-BQR and TARGIT-US). A brief description of each study is provided in Table 14.

Table 14: Ongoing studies

Title **Database identifier(s)**	**Study type** **Estimated enrolment**	**Summary description of study aims**	**Start date**	**End date** **(Primary end date)**	**Funding &/or Sponsor**
TARGIT-B NCT01792726 HTA 10\104\07	RCT (multicentre, multinational) n=1796	To evaluate whether a tumour bed boost in the form of a single fraction of radiotherapy given intra-operatively and targeted to the tissues at the highest risk of local recurrence is superior (in terms of local tumour control) to standard post-operative external beam radiotherapy boost, after breast conserving surgery in women undergoing breast conserving therapy who have a higher risk of local recurrence.	March 2013	April 2022 (Jan 2022)	HTA
TARGIT-E NCT01299987	Prospective multicentre single arm phase II n=265	To investigate the efficacy of a single intraoperative radiotherapy treatment (based on the protocol of TARGIT-A) within elderly low risk patients which is followed by EBRT only when risk factors are present. In presence of risk factors postoperative EBRT will be added according to international guidelines.	January 2011	Nov 2025 (Nov 2015)	Sponsor University Hospital Mannheim
TARGIT-R ISRCTN91179875	Registry database (multicentre, multinational) n not provided	To monitor the long-term effectiveness and safety of TARGIT treatment in women who receive TARGIT outside of a clinical trial. Recruitment start mid-2013 continuing to at least mid-2015.	July 2013	July 2023	Royal Free Charity (UK)
TARGIT-BQR NCT01440010	Registry database (Germany) n=1000	A quality control registry collecting data on local recurrence rate, toxicity and overall survival. For women with breast cancer receiving TARGIT with the INTRABEAM system as an advanced boost followed by shortened EBRT.	September 2011	not provided	Sponsor University Hospital Mannheim
TARGIT-US NCT01570998	Registry Trial (USA) n=755	A pragmatic registry trial (modelled on TARGIT-A) to continue the use of intraoperative radiotherapy for a select population of women, and to follow outcomes of local and regional control, toxicity and morbidity.	May 2012	not provided (Jan 2015)	Sponsor University of California, San Francisco

5 ECONOMIC ANALYSIS

The aim of this section is to assess the cost-effectiveness of the INTRABEAM Photon Radiotherapy System for the adjuvant treatment of early operable breast cancer.

The economic analysis comprises:

- A systematic review of the literature on the cost-effectiveness of the INTRABEAM Photon Radiotherapy System for the adjuvant treatment of early operable breast cancer;
- A systematic review of studies of the HRQoL of patients with breast cancer;
- A review of the INTRABEAM manufacturers' submission to NICE;
- an independent economic model and cost-effectiveness evaluation (the SHTAC model).

5.1 Systematic review of existing cost-effectiveness evidence

The methods and inclusion criteria considered for this review of economic evaluations are presented in Section 2.1 and details of the search strategy are documented in Appendix 2.

A total of 184 citations were identified through the systematic searches. Following examination of titles and abstracts, ten potentially relevant papers were retrieved for a more detailed inspection. Of these, seven papers were excluded; some for more than one reason. The primary reasons for exclusion were: full economic evaluation was not conducted in four studies; two studies were abstracts with insufficient details to allow an appraisal of the methodology and results; and one study was excluded because the intervention was not INTRABEAM (for details, see list of excluded studies in Appendix 6). A summary of the selection process and the reasons for exclusion is presented in Figure 3.

Three publications were eligible for inclusion, two of which reported the same economic model: Alvarado and colleagues[78] reported a full economic evaluation based on the trial results of TARGIT-A, and Esserman and colleagues[79] assessed the level of confidence of the TARGIT-A trial results and the impact of early and late adoption of the trial results. The remaining study by Shah and colleagues[80] conducted an economic evaluation based on TARGIT-A and the Electron Intraoperative Radiotherapy (ELIOT) trial, however the analysis based on ELIOT trial is not relevant to this systematic review. Characteristics of the included studies[78-80] are shown in Table 15 and discussed in more detail subsequently. The full data extraction forms are shown in Appendix 7.

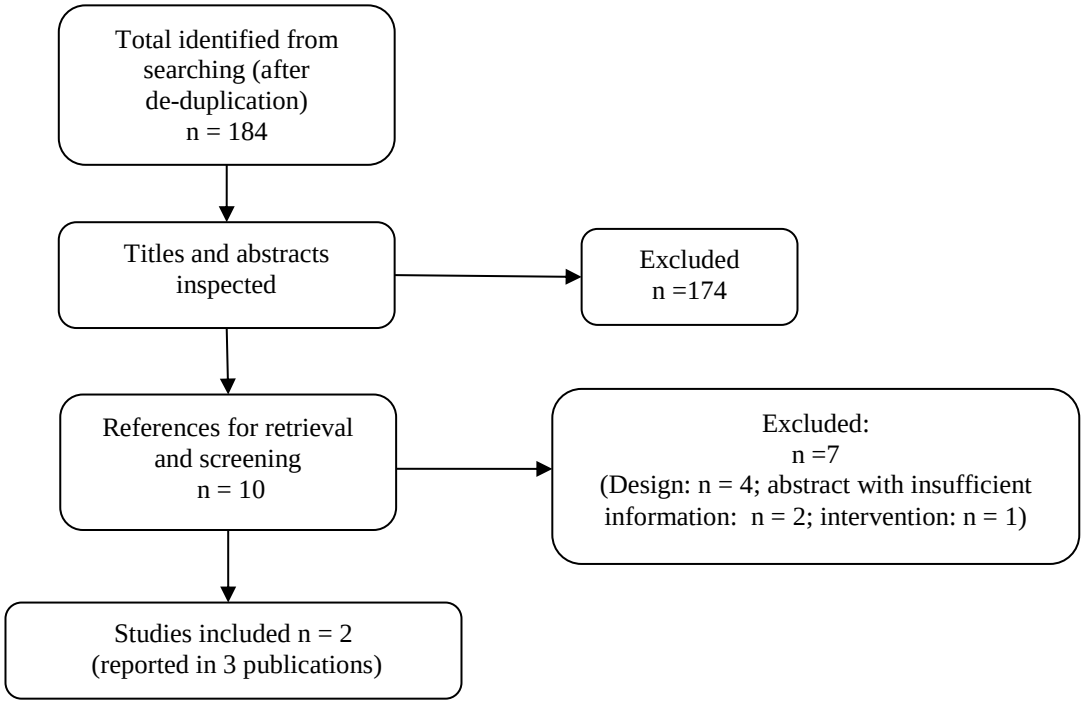


Figure 3: Flow chart of identification of studies for inclusion in the review of cost effectiveness

Table 15 Characteristics of included economic evaluations

Author	**Alvarado et al.[78;79]**	**Shah et al.[80]**
Publication Year	2013, 2014	2014
Country	USA	USA
Funding source	Not stated	Not stated
Study type	Cost utility analysis	Cost utility analysis; Cost minimisation analysis
Perspective	Societal	Societal
Study population	Women with early breast cancer included in TARGIT-A trial	Women with early breast cancer as included in TARGIT-A trial
Intervention(s)	INTRABEAM	INTRABEAM
Comparator(s)	6-week EBRT with a standard 33 fractions	Whole Breast Irradiation (EBRT)
Intervention effect	Kaplan-Meier estimate of local recurrence in the conserved breast at 4 years: 1.2% (95% CI: 0.53 – 2.71) for INTRABEAM and 0.95% (95% CI: 0.39 – 2.31) for EBRT (TARGIT-A trial).	Local recurrence rates 3.3% for INTRABEAM and 1.3% for EBRT (TARGIT-A trial).
Currency base	US Dollars 2011	Not stated
Model type, health states	A Markov decision-analytic model with 6 health states based on the TARGIT-A trial.	Not reported explicitly, analyses were based on reimbursement models.
Time horizon	10 year	Not clearly stated, assumed to be 10 years
Baseline cohort	Women aged ≥55 years with early breast cancer defined as stage I-IIA ER+	TARGIT-A trial: Women with early-stage ductal breast cancer who were ≥45 years
Base case results	Costs: INTRABEAM $28,879; 6-week EBRT $34,070. LY: INTRABEAM 8.38240; 6-week EBRT 8.38257. QALY: INTRABEAM 7.66020; 6-week EBRT 7.65994.	ICERs for local recurrence: range $1782 to $2172 for EBRT based on difference in whole breast irradiation rates (15% - 21%). Costs per QALY for EBRT compared with INTRABEAM: range $89,234/QALY to $108,735/QALY depending on the

	ICER: 6-week EBRT dominated.	difference in whole breast irradiation rates.

ER+: Estrogen Receptor Positive; ICER: Incremental cost-effectiveness ratio; IORT: Intraoperative Radiation Therapy; WB-EBRT: Whole-Breast External Beam Radiation Therapy; CI: Confidence Interval; TARGIT: Targeted Intraoperative Radiotherapy; ELIOT: Electron Intraoperative Radiotherapy; IORT: Intraoperative radiation therapy; QALY: Quality Adjusted Life Years.

Critical appraisal of the economic evaluations

The included cost-effectiveness studies were assessed against a critical appraisal checklist (Table 16) which appraised the quality of the studies and their generalisability to the UK.

Both studies clearly defined the decision problem and used the relevant intervention and comparator for the purpose of this review, although the number of fractions used in the comparator arm of EBRT was not relevant to UK practice (a standard of 33 fractions was used by Alvarado and colleagues,[78] whereas standard UK practice is 15 fractions over three weeks; the number of fractions was not reported by Shah and colleagues[80]). The patient groups of interest as well as the perspective of the studies (societal) were stated. However, as the studies were based in the USA they are not generalisable to the UK NHS setting. It is to be noted that the TARGIT-A trial, on which both the economic evaluations were based, included pre-pathology and post-pathology patients. The study type and modelling methodology adopted by Alvarado and colleagues[78] are appropriate for the decision problem in this review. Shah and colleagues,[80] on the other hand, do not describe the methodology but do state that the methodologies are described elsewhere.

The study by Alvarado and colleagues[78;79] was transparent with respect to the information on model inputs and the assumptions used. Health state specific costs and utilities were populated from published literature, although it was unclear if systematic reviews were conducted to inform these parameters. Both direct and indirect costs were reported.[78;79] The utilities associated with the health states in the base case model were obtained via standard gamble technique in the source study.[81] Health outcomes were reported in terms of QALYs and life years gained. A ten year time horizon was used; this is considered inappropriate as risk of local recurrence continues over a lifetime. A series of one-way and two-way sensitivity analyses were conducted to assess uncertainty. In addition, scenario analysis of the 3-week accelerated EBRT schedule of 16 fractions was performed. Although the results of the one-way sensitivity analyses favoured INTRABEAM over EBRT in the treatment of patients with early stage breast cancer, the robustness of the results still remains questionable as probabilistic sensitivity analysis (PSA) was not conducted. The external validity of the economic model was assessed by comparing the

findings with the published results of TARGIT-A, as well as against an online tool for adjuvant therapy and published cost-effectiveness evidence in the disease area using EBRT as one of the comparator arms. The results of the base case model were comparable with these sources.

Shah and colleagues[80] reported that all assumptions and methodology adopted in the analyses were based on and consistent with previously published articles, references of which were obtained and examined by the Assessment Group (AG). The methodologies adopted to estimate reimbursement costs as well as the assumptions used in cost estimations were adequately described in the references provided. The study reported health outcomes in terms of QALYs. The time horizon for the analysis was not clearly stated but based on the estimation of mean utility by reimbursement technique it was assumed to be ten years. No sensitivity or validation checks were reported, thus raising questions about the robustness of the results presented.

Table 16: Critical appraisal checklist for economic evaluations (based on Drummond and colleagues[57])

Item	**Alvarado and colleagues 2013**[78;79]	**Shah and colleagues 2014**[80]
1. Is the decision problem (including interventions compared and patient group) relevant to the UK?	Y	Y
2. Is the setting comparable to the UK?	N	N
3. Is the analytical and modelling methodology appropriate?	Y	Y
4. Are all the relevant costs and consequences for each alternative identified?	Y	Y
5. Are the data inputs for the model described and justified?	Y	Y
6. Are health outcomes measured in QALYs?	Y	Y
7. Is the time horizon considered appropriate?	N	?
8. Are costs and outcomes discounted?	Y	N
9. Is an incremental analysis performed?	Y	N
10. Is uncertainty assessed?	Y	N

Y – yes, N – no, ? – unclear

Description and results of the published economic evaluations

Alvarado and colleagues[78]

Modelling approach

Alvarado and colleagues[78] developed a Markov decision analytic model in TreeAge software to assess the cost-effectiveness of INTRABEAM compared to EBRT based on the results of the TARGIT-A trial. The analysis was conducted over a 10 year time horizon with annual model cycles. Patients' transition through the model was clearly stated. The six health states were:

- Disease-free status post breast conserving surgery (BCS)
- Disease-free following local recurrence + salvage mastectomy
- Disease-free following local recurrence + salvage lumpectomy
- Metastases
- Death due to other causes
- Death due to metastatic breast cancer

All patients entering the model were assumed to be in a healthy state without evidence of the disease, having initially undergone breast conserving surgery and allocated radiation treatment. Patients with local recurrence who initially received EBRT were treated with salvage mastectomy followed by immediate reconstruction. However, patients with local recurrence who had initially received INTRABEAM also had the option of salvage lumpectomy followed by EBRT. Patients could die due to any other causes at any time in the model, although death resulting from breast cancer was possible only for those women who had metastatic breast cancer. 14.1% of women with INTRABEAM received an additional five weeks (28 fractions) of EBRT. Costs and benefits were discounted at 3% per annum. Costs were expressed in US $ and the price year was 2011.

Assumptions

Alvarado and colleagues[78] incorporated the following assumptions to inform the cost-utility model:

- Local recurrence rates were assumed to progress linearly over 10 years. This is a strong assumption and should be treated with caution.
- For women treated with INTRABEAM followed by EBRT, it was assumed that they incurred the same local recurrence rates as those who had INTRABEAM alone.

Estimation of effectiveness

Alvarado and colleagues[78] sourced inputs for 10-year local recurrence rates and probabilities from one publication. Data for the 4-year local recurrence rates from the TARGIT-A trial[64] were converted to

annual transitional probabilities and projected over a 10-year period. The Kaplan-Meier estimate of local recurrence in the conserved breast at four years was estimated to be 1.2% (95% CI: 0.53 – 2.71) for the INTRABEAM arm and 0.95% (95% CI: 0.39-2.31) in the EBRT arm.

Estimation of QALYs

Alvarado and colleagues[78] stated that where possible, health state utilities were obtained via standard-gamble preferences. These were sourced from a 1998 publication, which evaluated HRQoL in breast cancer patients treated with lumpectomy and radiotherapy.[81] The utilities for INTRABEAM, 6-week EBRT, and INTRABEAM followed by 5-week EBRT, were assumed to be the same, at 0.92. The utility associated with salvage mastectomy was valued at 0.82; and that of salvage mastectomy followed by EBRT at 0.87. Patients with metastatic breast cancer were assigned a value of 0.70.

Estimation of costs

A societal perspective was adopted for the analyses, including both direct and indirect costs. Direct costs included by Alvarado and colleagues[78] were costs of the physician, facility fees for various surgical and radiotherapy therapy treatments and costs of the metastatic health state. Surgical and treatment costs were estimated using Medicare reimbursements, and the costs associated with the metastatic states were sourced from published literature. The intervention costs were reported as: INTRABEAM: $5547; 6-week EBRT: $10,464; INTRABEAM followed by 5-week EBRT: $13,640; and 3-week EBRT: $6,640.

Indirect costs were derived from published data and were estimated as follows: INTRABEAM followed by 5-week EBRT: $1244; 6-week EBRT: $1467; and 3-week EBRT: $667.

Cost effectiveness results

For the base case analysis, Alvarado and colleagues[78] found that INTRABEAM resulted in a QALY gain of 0.00026 and cost $5191 less than 6-week EBRT. Therefore the ICER of INTRABEAM dominated 6-week EBRT as it was cheaper and more effective. One-way and two-sensitivity analyses, conducted to check uncertainty in the base case model prediction, further supported the base case results. External validity of the model was assessed; the predicted 4-year recurrence rate of INTRABEAM in the model was similar to that in TARGIT-A trial and the predicted 10 year overall survival in the model compared with the results of an online tool of an adjuvant therapy and a published cost-effectiveness model.

Summary of key issues

- The study Alvarado and colleagues[78] was based on US healthcare system; hence it is not generalisable to the UK setting. Further, a societal perspective was adopted which differed from the UK NHS and Personal Social Services (PSS) perspectives.
- The model included results from both pre-pathology and post-pathology patients.
- The number of fractions of EBRT was not relevant to UK practice. The study used the assumption of using EBRT with a standard 33 fractions whereas the current standard UK practice is 15 fractions.
- Uncertainty around the base case results was not fully explored; a very limited number of one-way and two-way sensitivity analyses were conducted; probabilistic sensitivity analysis was not performed.
- The economic analysis was conducted for a time horizon of 10 years which is inappropriate given that risk of local recurrence continues over a lifetime.

Shah and colleagues[80]

Modelling approach

Shah and colleagues[80] analysed the cost-effectiveness of IORT compared with EBRT and accelerated partial-breast irradiation (APBI) through reimbursement models based on the results of two trials, TARGIT-A and ELIOT. The results based on the ELIOT trial were not extracted as the intervention was not eligible for inclusion in this systematic review. The study estimated reimbursement models in four ways:

- Reimbursement only (professional and facility)
- Reimbursement incorporating additional medical costs (e.g. increased operative time with IORT, fraction of IORT patients requiring additional radiation)
- Reimbursement requiring non-medical costs
- Reimbursement incorporating costs associated with recurrences

A cost minimization analysis was also conducted based on the absolute difference in reimbursements by techniques. The ICER analysis provided the increased reimbursement required to use EBRT or APBI compared with IORT per percentage point of improvement in local recurrence. The study, in general, did not adhere to the prescribed modelling techniques advocated by NICE. Costs year and discount rates were not reported.

Assumptions

Shah and colleagues[80] refer to other publications for details about assumptions.[82-85]

Estimation of effectiveness

Shah and colleagues[80] obtained local recurrence rates for both the INTRABEAM and EBRT arms (3.3% for INTRABEAM vs. 1.3% for EBRT) from the TARGIT-A trial.

Estimation of QALYs

The utility values used by Shah and colleagues[80] were obtained from the same source[81] as Alvarado and colleagues[78] as outlined above. A utility of 0.92 was assigned to the 'no recurrence' health state; 0.779 to 'local recurrence'; and 0.685 to the 'other recurrence' health state.

Estimation of costs

A societal perspective was adopted for the analyses, including both direct and indirect costs. Details of the costs (direct and indirect) used in the analysis by Shah and colleagues[80] were described elsewhere. [82-85] A detailed overview of the methods to estimate non-medical costs, follow-up costs, and costs of local recurrence or other recurrence (including salvage mastectomy) was presented. Reimbursement costs for INTRABEAM and EBRT were reported as outlined in **Table 17**. Non-medical costs were reported as $44.96 and $89.92 per day for once-daily and twice-daily treatment schedules respectively. Non-medical costs were estimated as follows:

- Average round-trip travel was 40 miles to the radiation centre (6 cents per mile),
- The time involved was two hours per treatment, including travel of which 30 minutes were spent receiving treatment ($14.78 per hour),
- Patients receiving twice-daily treatment returned to work during the inter-fraction interval.

Table 17: Reimbursement costs for INTRABEAM and EBRT reported by Shah and colleagues[80]

	INTRABEAM	**EBRT**
Total reimbursement	$3094	$11,726
Reimbursement including additional medical costs[a]	$8003 - $8706	$11,726
Reimbursement including medical and nonmedical costs[a]	$8192 - $8971	$12,985
Reimbursement including medical, nonmedical, and recurrence costs (TARGIT)[a]	$9399 - $10,179	$13,122

[a] Range based on differences in EBRT rates (15% - 21%)

Cost effectiveness results

Based on the TARGIT-A trial results, Shah and colleagues[80] reported that the ICERs for local recurrence ranged from $1782 to $2172 for EBRT, based on the difference in whole breast irradiation rates (15% - 21%), when all associated costs were incorporated. The costs per QALY for EBRT compared with INTRABEAM ranged from $89,234/QALY to $108,735/QALY depending on the difference in whole breast irradiation rates. Results from the cost-minimization analysis indicated that the use of INTRABEAM was associated with cost-savings of $3.6-$4.3 million when compared with EBRT.

Summary of key issues

Shah and colleagues[80] reported the results of cost-effectiveness analysis based on reimbursement models. This study also had a number of limitations:

- The study was based in the USA and adopted a societal perspective, which is not generalisable to the UK NHS and PSS setting.
- Limited information was reported on the model approach and assumptions in the included paper, however details on model structure and assumptions were reported elsewhere.
- The time-horizon for the analysis was not clearly stated.
- Although the techniques adopted to estimate costs associated with non-medical, follow-up, local recurrence or other recurrence (including salvage mastectomy) were mentioned, the costs were not reported, except for non-medical costs.
- Sensitivity analysis was not conducted as part of the analysis, thereby raising questions on the robustness of the model predictions.

Summary of cost-effectiveness studies

- Two cost-effectiveness studies, reported in three publications[78-80] were identified.
- Both studies were based on the findings of the TARGIT-A trial.
- Cost-utility analyses were performed to evaluate QALYs, costs and ICERs of INTRABEAM vs EBRT.
- The analyses were conducted for a time horizon of ten years in one study;[78;79] for the other study[80] it is assumed that a similar time horizon was adopted, although this was not clearly stated.
- The quality of utility data used in both the studies is questionable. The source study by Hayman and colleagues[81] was an old publication and more recent data would have been appropriate, such as those identified in section 5.2. It was also not clear whether a systematic approach was adopted to identify this source.

- The perspectives, settings and comparators of both studies were not generalisable to the UK setting.
- Alvarado and colleagues[78] found INTRABEAM to be a more valuable strategy with less cost and greater QALYs than EBRT. Shah and colleagues[80] concluded that whilst INTRABEAM represented a potential cost-saving alternative compared to EBRT, the latter represented a cost-effective modality compared to INTRABEAM when additional medical and non-medical costs were factored in.

5.2 SHTAC systematic review of health related quality of life studies

A systematic review of HRQoL was undertaken, which aimed to identify utility data to populate the planned independent economic model of INTRABEAM for breast cancer discussed in section 5.4.

The methods used to identify studies are described in section 3, although the selection criteria were modified slightly. Firstly, as stated in section 3.2, inclusion was not limited to women with early breast cancer. After considering previous research, such as the TARGIT-A trial (discussed in section 4.1.1) and other cost-effectiveness studies (discussed in 5.1), it was anticipated that the following health states would be of potential relevance for developing an economic model. These health states were then specified *a priori* as eligibility criteria for the systematic review of HRQoL:

- Disease-free after wide local excision (WLE)
- WLE + INTRABEAM
- WLE + External Beam Radiation Therapy (EBRT)
- WLE + INTRABEAM + EBRT
- Mastectomy and reconstruction
- Disease free after local recurrence
- Distant recurrence/metastases

Secondly, although the initial intention was to include studies that reported either preference-based measures of health such as EQ-5D, SF-6D, HUI3; disease-specific measures such as EORTC QLQ BR23, EORTC QLQ C30; or SF36, this resulted in a large number of HRQoL studies of potential relevance. Therefore the selection criteria were narrowed to only those studies that reported patients' quality of life using the EQ-5D measure. The EQ-5D consists of five dimensions of health: mobility, self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression. It is the preferred measure of HRQoL by NICE as it permits comparison of cost-effectiveness (e.g. in terms of QALYs) with other

healthcare interventions to inform decisions about recommended treatments. In addition, it has been widely used and validated in many different patient populations.

The eligibility criteria for the systematic review of QoL are summarised below.

- Participants:
    - Women with breast cancer and meeting any of the health states defined above.
- Intervention/comparator:
    - Radiotherapy; endocrine/hormonal therapy; chemotherapy.
- Outcomes:
    - EQ-5D index [EQ-5D visual analogue scale (VAS) was excluded].
- Design:
    - Primary research studies [mapping studies (which seek to create a mathematical link between two different QoL instruments) were excluded].
    - Studies based in the UK, Europe, Northern America and Australasia.
    - Studies published as abstracts or conference presentations were included only if sufficient details were provided to allow an appraisal of the methodology and assessment of the results.
    - Non-English language studies were excluded.

A total of 939 potentially relevant studies were identified through the systematic searches, the majority of which (874 studies) were excluded based on titles and abstracts. Full papers of the remaining 65 studies were retrieved for further inspection; these studies were first screened to check they met all of the following five selection criteria:

- Breast cancer patients (including metastases)
- Primary research
- EQ-5D
- Published in English language and
- Full paper or abstract with sufficient information available

Any study that did not meet any of the above five criteria was excluded. If studies met all five criteria, they were further screened to check:

- If EQ-5D data were reported for any of the seven health states of interest
- If the geographical origin of the participants was the UK, Europe, North America or Australasia. The geographical locations were limited to these regions due to similar racial compositions.

Studies were included in this review if they met all of the above criteria.

Nine studies met the inclusion criteria. Some studies were excluded for more than one reason; the main reasons for exclusion of the remaining 55 studies were: not primary research (3), abstracts with insufficient details (19), inappropriate participants (9), studies not reporting EQ-5D data (11), and no utility data on any of the seven health states of interest for the purpose of this review (13). A summary of the selection process and the reasons for exclusion are presented in Figure 4 and Appendix 8 respectively.

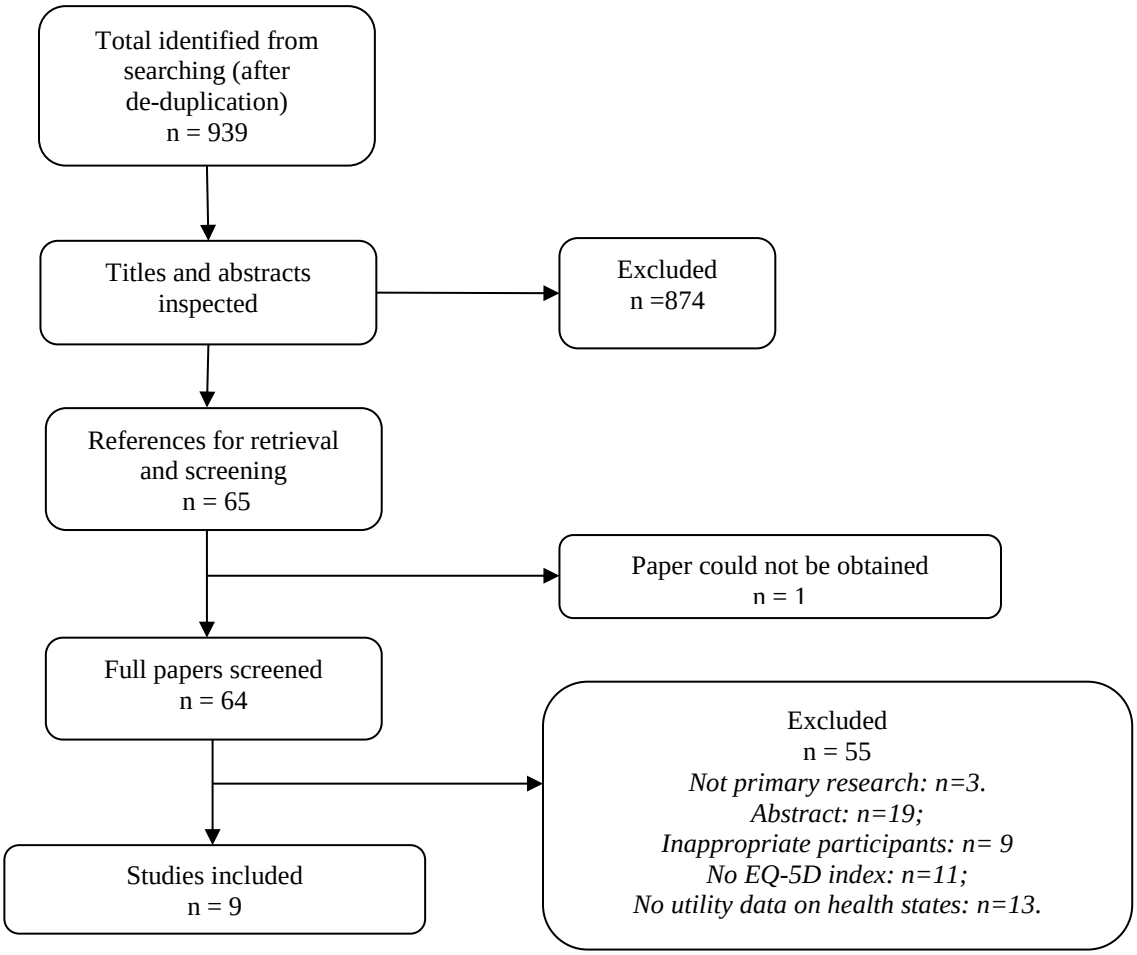


Figure 4: Flow chart of identification of studies for inclusion in the review of QoL

The characteristics of the nine included studies are presented (see Table 18) and discussed according to the health states outlined earlier. The studies were diverse in terms of their aims, comparisons made, patient characteristics and locations. Full data extraction of all the included studies is shown in Appendix 9. The nine studies provided data for five of seven health states potentially relevant for the independent model: disease-free after WLE (one study), WLE+EBRT (three studies), disease-free after local recurrence (one study), mastectomy and reconstruction (two studies), and distant recurrence/metastatic

breast cancer (three studies). No EQ-5D data were identified for the health states WLE+INTRABEAM or WLE+INTRABEAM+EBRT. Of the nine studies, two studies each were based in the UK;[86;87] the USA;[88;89] and Sweden;[90;91] one study each was based in Canada;[92] and Germany;[93] and the remaining study was based on an RCT conducted across the UK and USA.[94]

Table 18 Characteristics of included quality of life studies

Author	**Turnbull et al.**[87]	**Freedman et al.**[88]	**Prescott et al.**[86]	**Serra et al.**[89]	**Conner-Spady et al.**[92]	**Robertson et al.**[90]	**Lidgren et al.**[91]	**Sherrill et al.**[94]	**Hildebrandt et al.**[93]
Publication Year	2010	2010	2007	2012	2005	2012	2007	2008	2014
Country	UK	USA	UK	USA	Canada	Sweden	Sweden	UK and USA	Germany
Study type	RCT	Single cohort study	RCT and a non-randomised cohort	Single cohort study	Two-year longitudinal study	Retrospective descriptive study	Cross sectional observational study	RCT Q-TWiST analysis	Cross-sectional survey
Health state relevant to the SHTAC model	Disease-free after WLE	WLE+EBRT	WLE+EBRT	WLE+EBRT	Mastectomy and immediate reconstruction	Mastectomy and immediate reconstruction	Disease-free after local recurrence; Distant metastases	Distant metastases	Distant recurrence/ metastases
Study population	1625 women with biopsy-proven primary breast cancer	1050 women with early stage breast cancer treated with breast conserving surgery and radiation with or without	253 women with “low risk” axillary node negative breast cancer undergoing breast conserving surgery +	66 women undergoing radiation therapy for breast cancer	52 women with stage II and III breast cancer at high risk of relapse	223 Immediate Breast Reconstruction (IBR) patients with implants	345 women with a previous diagnosis of breast cancer	399 women with advanced or metastatic HER2 + breast cancer who had progressive disease following prior therapy including an anthracycline, a	592 patients with breast (n=497), cervical, endometrium, ovarian or other gynaecological cancer

Author	Turnbull et al.[87]	Freedman et al.[88]	Prescott et al.[86]	Serra et al.[89]	Conner-Spady et al.[92]	Robertson et al.[90]	Lidgren et al.[91]	Sherrill et al.[94]	Hildebrandt et al.[93]
		systemic therapy	endocrine therapy					taxane and trastuzumab	
Study population age	MRI scan: 56.38 yrs (SD 9.67); No MRI scan: 56.59 yrs (SD 10.09)	18 – 44 yrs: 13% 45 – 64 yrs: 68% >64 yrs: 30%	Radiotherapy: 72.3 yrs (SD 5.0); No radiotherapy: 72.8 yrs (SD 5.2)	57 yrs (range: 28-77)	44.7 yrs (SD 8.5)	Mean age at IBR:50 years	57 years (range 28-93) <50 yrs: 26% 50–64 yrs: 52% 65 & older: 22%	59.07 yrs (range: 20.12 – 83.33)	All patients: 59.07 yrs (range: 20.12 – 83.33)
Comparator population	No MRI scan	No comparator	No radiotherapy	No comparator	No comparator	No comparator	No comparator	Capecitabine	No comparator
Interventions	MRI scan	Breast conserving surgery and radiation	Radiotherapy	Guided imagery (GI) (a stress reduction technique)	High dose chemotherapy treatment with autologous blood stem cell transplanta-tion	Immediate Breast Reconstruction	No intervention	Lapatinib combined with capecitabine	No intervention
QoL instrument used	EQ-5D	EQ-5D	EQ-5D	EQ-5D	EQ-5D	EQ-5D	EQ-5D	EQ-5D	EQ-5D

Author	**Turnbull et al.**[87]	**Freedman et al.**[88]	**Prescott et al.**[86]	**Serra et al.**[89]	**Conner-Spady et al.**[92]	**Robertson et al.**[90]	**Lidgren et al.**[91]	**Sherrill et al.**[94]	**Hildebrandt et al.**[93]
Time period where HRQoL instruments administered	Baseline, 8 weeks post randomisation, 6 and 12 months post initial surgery	5 years, 10 years, 15 years	Baseline, 3.5 months, 9 months, 15 months	Prior to start of GI treatment; end of radiation therapy	Pre induction; day 1 third cycle of FAC chemotherapy ; 3 week post HDC; 6 months; 12 months; 18 months; 24 months	Median 4 years post-operatively	Administered once	HRQoL data specific to the different time points of the study were not reported; the study reported only average utility values	Administered once

FAC: Fluorouracil, Adriamycin, and cyclophosphamide; HDC: High Dose Chemotherapy

Critical appraisal of the included studies

A summary of the critical appraisal of the included studies is presented in Appendix 10.

The designs of the included studies varied: three were RCTs,[86;87;94] two were single cohort studies,[88;89] one was a longitudinal study,[92] one was a retrospective descriptive study,[90] and two were cross sectional studies.[91;93]

All nine included studies defined the study question and explained the treatment strategies. Across the studies, the study designs as well as the methods of recruiting participants were clearly outlined. The studies were transparent with regard to the information provided for the methodologies applied. One study did not include patients <65 years;[86] another excluded those aged >65 years;[92] and three studies did not state clearly if any individuals relevant to this review were excluded.[89;90;93] One study[90] did not describe participant characteristics. With respect to the sample size, only two studies[87;89] provided an appropriate justification for the study sample size. The response rates to EQ-5D were not reported in two studies [86;93;94] thereby raising questions on the validity of the reported results as a lower response rate could possibly result in biased outcomes. Loss to follow-up was not reported by four studies.[88-90;93]

The included studies were assessed on the basis of their relevance to the NICE reference case. Of the nine included studies, only three[86;87;91] met all of the criteria (see Appendix 9). Five studies did not meet one of the criteria, as valuations of HRQoL were not undertaken from the general UK population.[88-90;93;94] The population characteristics in the remaining study did not match those described in the decision problem as they included women with a poor prognosis (stage II/III).[92]

Of the included studies, only one study reported utility value for disease-free after WLE.[87] This study was UK based and included patients aged ≥18 years. Three studies reported utility values for the WLE+EBRT health state, of which one was based in the UK[86] and two were US based.[88;89] Patients in the study by Freedman and colleagues[88] were over 18 years of age, and those in the study by Serra and colleagues[89] ranged between 28 – 77 years. The UK-based study by Prescott and colleagues[86] excluded women under 65 years; the mean age of the baseline cohort was 72 years. It was observed that the baseline patient characteristics with respect to age differed across the three studies. Freedman and colleagues[88] included women with early-stage breast cancer for their analysis which was similar to the population of interest for the independent model. In addition, they reported outcomes at a longer follow-up of up to 15 years.

The utility values for the health state of mastectomy and immediate reconstruction were reported by two studies.[90;92] Robertson and colleagues[90] conducted a retrospective study based on Swedish breast

cancer patients who had undergone immediate breast reconstruction with implants. Conner-Spady and colleagues,[92] on the other hand, conducted a longitudinal study in Canadian women with stage II and III breast cancer and at high risk of relapse. The study by Robertson and colleagues[90] had advantages over Conner-Spady and colleagues[92] with respect to larger sample size, recent publication date, and longer follow-up period. Further, women aged over 65 years were not included in the Canadian study.[92]

Three studies reported utility associated with distant metastases;[91;93;94] one of which also reported utility associated with disease-free after local recurrence.[91] Sample size ranged from 345[91] to 497.[93] In two of these studies, median age of population were 57 years[91] and 59 years;[93] no information related to age was provided in the other study.[94] Lidgren and colleagues[91] included women with a previous diagnosis of breast cancer, whilst Sherrill and colleagues'[94] focused on those with advanced or metastatic HER2+ breast cancer who had progressive disease. Hildebrandt and colleagues[93] included both male and female patients affected by breast, cervical , endometrium , ovarian, and other gynaecological cancer, and reported data separately for each disease.

Results

The utility values for the potentially relevant health states extracted from the nine included studies are tabulated in Table 19.

Disease-free after WLE

Turnbull and colleagues[87] reported EQ-5D estimates for women with biopsy-proven primary breast cancer who were scheduled for wide local excision. The utility estimates for women randomised to receive an MRI scan group were 0.86 at baseline, 0.78 at eight weeks post randomisation, and 0.80 and 0.81 at six and 12 months post initial surgery, respectively. Those randomised to receive no MRI scan had similar utility estimates to those receiving an MRI scan at baseline and 12 months post initial surgery, but slightly lower values of 0.77 and 0.79 at eight weeks post randomisation and six months post initial surgery, respectively.

WLE+EBRT

Freedman and colleagues[88] reported EQ-5D estimates for women in early stage breast cancer treated by breast conserving surgery and radiotherapy with or without systemic therapy as 0.89, 0.9 and 0.9 at five years, 10 years and 15 years respectively.

Prescott and colleagues[86] included breast cancer patients who had undergone breast-conserving surgery and endocrine therapy to assess the quality of life and cost-effectiveness of omission of postoperative radiotherapy in women with "low-risk" axillary node negative breast cancer (T0-2). For

the radiotherapy arm, reported EQ-5D estimates varied between 0.77 at baseline to 0.74 at 15 months; utility estimates varied between 0.74 at baseline and 0.73 at 15 months for the no-radiotherapy arm. This study did not include patients aged below 65 years.

Serra and colleagues[89] assessed EQ-5D estimates on people undergoing radiotherapy for breast cancer to evaluate the impact of guided imagery (a stress reduction technique). The utility values prior to the start of radiotherapy plus guided imagery therapy and at the end of radiation therapy were reported as 0.88 and 0.86 respectively. One of the disadvantages of this study was that it reported very limited details on the inclusion/exclusion criteria; hence it was not transparent whether any relevant individuals were excluded from the analysis.

Mastectomy and immediate reconstruction

Conner-Spady and colleagues[92] evaluated EQ-5D estimates in Canadian patients with stage II/III breast cancer who were at high risk of relapse and were receiving high dose chemotherapy treatment with autologous blood stem cell transplantation. There was a decrease in HRQoL from pre-induction (0.78) to 3-weeks post high-dose chemotherapy (0.61) and return to baseline levels at eight weeks post high-dose chemotherapy (HDC) (0.79). The EQ-5D estimate at two years was 0.89. In the short term, HRQoL was impacted negatively by treatment but quickly rebounded; no data were available for long-term. EQ-5D estimates specific to different types of surgery: modified radical mastectomy, total mastectomy and segmental surgery were not reported. Patients aged over 65 years were excluded.

Robertson and colleagues[90] presented an audit of all Immediate Breast Reconstruction (IBRs) during the period 2005-08 performed by breast surgeons and investigated post-operative HRQoL in a Swedish setting. The EQ-5D estimate was reported as 0.83. The study did not state clearly if any relevant individuals were excluded; therefore generalisability of the results is unclear.

Disease-free after local recurrence; Distant metastases

In a cross-sectional observational study, Lidgren and colleagues[91] estimated HRQoL for different breast cancer disease states in Swedish women with a previous diagnosis of breast cancer. This study reported EQ-5D estimates for two health states: disease-free after local recurrence and distant metastases. Patients in the first year after a primary breast cancer had EQ-5D estimate of 0.696; EQ-5D estimates in the first year after local recurrence and in the second and following years after both primary breast cancer and local recurrence were same at 0.779; and patients in metastatic disease had an EQ-5D estimate of 0.685.

Sherrill and colleagues[94] conducted a Quality-adjusted time without symptoms of disease or toxicity of treatment (Q-TWiST) analysis in patients with advanced or metastatic HER2 + breast cancer who

had progressive disease following prior therapy including an anthracycline, a taxane and trastuzumab. The study compared the health states of patients receiving combination therapy of lapatinib+capecitabine compared to those receiving capecitabine alone. The EQ-5D estimate associated with relapse health state was reported as 0.41 for the lapatinib+capecitabine arm compared to 0.44 for capecitabine monotherapy arm. However this trial was stopped early before attaining the sample size.

In a cross sectional survey, Hildebrandt and colleagues[93] investigated health utilities as cardinal values of individual's preferences for specific health-related outcomes in women treated in Germany in the fields of gynaecological oncology and mastology to provide local German data. The study found that patients with breast cancer who had primary disease had the highest estimates of QoL as measured by EQ-5D VAS and these declined if the disease was already advanced. However, this difference was not evident from the EQ-5D health index in patients with primary, metastatic, recurrent, or both which had a consistent median value at 0.8870.

When comparing the EQ-5D estimates reported across the potentially relevant health states in breast cancer patients across the studies included in this review, it is observed that there are variations in EQ-5D estimates for similar health states. These differences could be explained by the differences in patient characteristics, country settings, nature of the intervention(s) and comparators(s) used in the treatment of breast cancer patients across different countries, and length of follow-up.

Table 19 EQ-5D values from included studies

Study (country)	Health state	EQ-5D estimates
Turnbull et al.[87] (UK) (COMICE trial)	Disease-free after WLE	MRI scan / No MRI scan Baseline: 0.8667 / 0.8601 8 weeks post randomisation: 0.7791 / 0.7728 6 months post initial surgery: 0.8040 / 0.7935 12 months post initial surgery: 0.8101 / 0.8112
Freedman et al.[88] (USA)	WLE+EBRT	0.89 (95% CI: 0.87 to 0.91) at 5 years, 0.9 (95% CI: 0.86 to 0.94) at 10 years, and 0.9 (95% CI: 0.83 to 1.0) at 15 years
Prescott et al.[86] (UK)	WLE+EBRT	Radiotherapy / No Radiotherapy Baseline: 0.77 / 0.74 3.5 months: 0.78 / 0.76 9 months: 0.76 / 0.72 15 months: 0.74 / 0.73
Serra et al.[89] (USA)	WLE+EBRT	0.88 prior to the start of guided imagery therapy; 0.86 at the end of therapy
Conner-Spady et al.[92] (Canada)	Mastectomy and immediate reconstruction	Pre induction: 0.78; Day 1 third cycle of FAC chemotherapy: 0.75; 3 week post HDC:0.61; 6 months: 0.79; 12 months:0.84; 18 months:0.84; 24 months: 0.89
Robertson et al.[90] (Sweden)	Mastectomy and immediate reconstruction	0.83

Study (country)	Health state	EQ-5D estimates
Lidgren et al.[91] (Sweden)	Disease free after local recurrence; Distant metastases	Patients in their first year after a primary breast cancer: 0.696 (95% CI: 0.634 to 0.747); Patients in first year after a recurrence: 0.779 (CI: 0.700 to 0.849); Patients in their second and following years after primary breast cancer / recurrence: 0.779 (CI: 0.745 – 0.811); Patients with metastatic disease: 0.685 (CI: 0.620 to 0.735).
Sherrill et al.[94] (UK and USA)	Distant metastases	Lapatinib + capecitabine / Capecitabine Toxicity-grade (3/4): 0.60 / 0.59 TWiST: 0.66 / 0.60 Relapse: 0.41 / 0.44
Hildebrandt et al.[93] (Germany)	Distant recurrence/ metastases	**Breast cancer** — **Median** Overall 0.8870 Primary disease 0.8870 Metastatic disease 0.8870 Recurrent disease 0.8870 Both 0.8870

FAC: Fluorouracil, Adriamycin, and cyclophosphamide; HDC: High Dose Chemotherapy; TWiST: Time without symptoms of disease progression or toxicity.

Summary and conclusions of the HRQoL review

The key findings of this systematic review are summarised below:

- Nine studies met the inclusion-criteria of the HRQoL systematic review.
- Two studies study were UK-based; the remaining studies were based in Europe and North America.
- The included studies were diverse with respect to their aims, population of interest, geographical locations, interventions, comparators, study designs, and methodologies adopted.
- The review identified utilities that could be used to inform the independent cost-effectiveness model for five of seven potentially relevant health states: disease-free after WLE; WLE+EBRT; disease free after local recurrence; mastectomy and immediate reconstruction; and distant recurrence.
- The review did not identify any relevant study to populate the utilities for two potentially relevant health states: WLE + INTRABEAM or WLE + INTRABEAM + EBRT.

5.3 Review of evidence submission from Carl Zeiss UK to NICE

A structured data extraction form was used to guide the review of the Carl Zeiss UK submission to NICE (Appendix 5). The MS evaluated the cost-effectiveness of INTRABEAM in early breast cancer patients when compared with radiotherapy usually given in the UK over 3-6 weeks as EBRT. The total costs, QALYs gained and cost-effectiveness associated with the intervention and comparator under consideration in the appraisal were reported in the MS. The perspective adopted in the submission was that of the NHS, capturing direct costs and benefits only. A systematic review of any relevant cost-effectiveness models was not conducted. Very limited information on the model was presented in the main submission document, and whilst further details were contained within the Excel model, these too were limited.

Modelling approach

A multi-state Markov model, developed in Microsoft Excel, was used in the submission. The model used a cohort of breast cancer patients aged 55 years and older, who were disease-free after wide local excision. The economic model was based on the results of the pre-pathology stratum of the TARGIT-A trial[95] with 2298 patients. This was because results were less favourable in post-pathology stratum (4.1.2) and the submission recommended that INTRABEAM be used in pre-pathology patients only (MS p. 3-4).

It was not reported whether the model was constructed *de novo* or adapted from another previously existing model. The model consisted of four health states:

- Disease-free
- Local recurrence treated by mastectomy/lumpectomy
- Non-breast cancer death
- Breast cancer death

Patients in the disease-free state could remain in that state or transition to either local recurrence or non-breast cancer death. Those in the local recurrence state could remain in that state; or die from either non-breast cancer or breast cancer related deaths. The two death states were the absorbing states. The analysis was conducted for a time-period of 20 years with an annual cycle length.

Assumptions

The manufacturer's model made the following assumptions:

- After local recurrence INTRABEAM patients would have salvage lumpectomy
- After local recurrence EBRT patients would have salvage mastectomy. There is also an undocumented assumption that all patients undergoing mastectomy have reconstruction; this is reflected in the high cost of mastectomy.
- The death rate in disease free patients was equal to the general population
- An average of 23 fractions of EBRT per patient was delivered, based on 15-30 fractions in the clinical practice
- All patients were given INTRABEAM concurrent with initial lumpectomy (pre-pathology stratum of TARGIT-A trial)

A few of the model assumptions are not relevant to UK practice. The model assumed that INTRABEAM patients would have salvage lumpectomy after local recurrence; however clinical experts advised that in the UK most patients would have mastectomy after local recurrence instead. Further, the undocumented assumption that all mastectomy patients would have reconstruction is not in line with UK practice, as only around 31% of the patients undergoing mastectomy will have reconstructions as shown in the independent model discussed in Section 5.5. In addition, the assumption of using an average of 23 fractions of EBRT per patient was not appropriate as the current standard UK practice is 15 fractions.

Critical appraisal of model

The manufacturer's economic evaluation was appraised for methodological quality and generalisability to the UK NHS using a checklist adapted from the NICE reference case requirements and the Philips and colleagues[58] checklist (see Table 20). The evaluation met half of the requirements for methodological quality and generalisability; the remaining criteria were either not met or unclear. A brief description is presented below.

Table 20: Critical appraisal checklist of the manufacturer's economic evaluation

(based on Drummond and colleagues[57] and Philips and colleagues[58])

	Item	Carl Zeiss[97]
1	Is there a clear statement of the decision problem?	Yes
2	Is the comparator routinely used in UK NHS?	?[a]
3	Is the patient group in the study similar to those of interest in UK NHS?	?[b]
4	Is the health care system comparable to UK?	Yes
5	Is the setting comparable to the UK?	Yes
6	Is the perspective of the model clearly stated?	Yes
7	Is the study type appropriate?	Yes
8	Is the modelling methodology appropriate?	?
9	Is the model structure described and does it reflect the disease process?	Yes
10	Are assumptions about model structure listed and justified?	No
11	Are the data inputs for the model described and justified?	No
12	Is the effectiveness of the intervention established based on a systematic review?	No
13	Are health benefits measured in QALYs?	Yes
14	Are health benefits measured using a standardised and validated generic instrument?	Yes
15	Are the resource costs described and justified?	No
16	Have the costs and outcomes been discounted?	Yes
17	Has uncertainty been assessed?	?
18	Has the model been validated?	No

Yes / No / ? (unclear)

[a] Different number of EBRT fractions used in the model (23 fractions) than standard UK practice (15 fractions).

[b] Baseline characteristics were not provided.

The manufacturer's evaluation provided a clear statement of the decision problem to be addressed, which appeared to follow the scope for the appraisal issued by NICE. Although the comparator included EBRT, which is routinely used within the NHS, its appropriateness is questionable as the number of EBRT fractions used in the UK practice is 15 compared with 23 fractions used in the model. Six out of 33 centres in the TARGIT-A trial were based in the UK and centres were allowed to follow local policy for EBRT delivery. The MS reported 23 fractions as the average of the range between 15-30 fractions being used in all the countries in the trial, but it was not clear if this was a weighted average of fractions used in the trial or a midpoint. The perspective adopted in the model

was appropriate. Although the MS reported that the analysis was UK based, limited details were provided on the baseline characteristics of the patient population. A Markov modelling methodology was used, which seemed appropriate given the clinical nature of breast cancer. However, the AG considered that the reported model was a simplified structure with only four health states, and that an additional health state for progressed disease would have been appropriate. Another limitation was that a lifetime horizon was not adopted. Patients entering the model were aged 55 years (on average) and followed for 20 years. This time-span might not reflect the entire follow-up period of the disease. Patients transitioned through the health states in annual cycles, which is an appropriate assumption. The model structure was presented diagrammatically but no justification of the key assumptions and description of the data inputs used was provided. Measures of clinical effectiveness were obtained from a single study,[65] however no other relevant trials were identified by the SHTAC systematic review. Benefits for the model were measured in QALYs using standard gamble for measuring utility, although the source study was dated 1997.[96] It was not clear if a systematic review was conducted to identify the study. The model extrapolated local recurrence and survival data beyond five years by tacitly assuming an exponential fit to time to local recurrence; however a the AG considers that a log-normal distribution would be the best fit based upon comparison with external data (section 5.5.1). All benefits and costs were discounted at 3.5% as outlined in NICE guidance. Uncertainty was assessed through PSA; no one-way or scenario analyses were conducted. Finally, no details around model validation were provided.

Estimation of effectiveness

Data on effectiveness for both the intervention (INTRABEAM) and the comparator (EBRT) were derived from a single RCT (TARGIT-A) by Vaidya and colleagues.[65] 5-year cumulative risks reported in the source study were converted to annual probabilities and populated in the model. It was not reported whether a systematic review was conducted to identify the source study; however no other relevant trials were identified by the SHTAC systematic review (section 4.1.1). No adverse events were included in the analysis which was considered appropriate by the AG.

Estimation of QALYs

HRQoL utility values were assigned to patients in the disease free state, those undergoing salvage lumpectomy and those undergoing salvage mastectomy. For the disease free state, a utility value of 0.92 was used; a value of 0.87 was assigned to patients undergoing salvage lumpectomy; and those undergoing salvage mastectomy were assigned a value of 0.82. The MS obtained these values from a single study by Hayman and colleagues published in 1997.[96] No details were provided of the method of deriving these values or the rationale used. The source study[96] used a standard gamble approach to estimate utility values, which were not obtained from the general population. This is a limitation as it

was shown in the systematic review of HRQoL (Section 5.2) that there were several other more recent and relevant HRQoL studies that used the EQ-5D measure.

Estimation of costs

Treatment unit costs were obtained from the following sources: expert opinion, Reference Costs 2012-2013,[98] Payments by Results tariff 2013-14, and the study by Wolowacz and colleagues.[99] As with effectiveness and utilities, the methods of deriving the costs were not adequately described. The costs associated with travel/parking/accommodation were appropriately not included within the EBRT arm (it was stated that these expenses might range from £ 50-100 per patient per fraction delivered).

The validity of the costs estimates is questionable. The cost of INTRABEAM per patient was obtained from expert opinion, and whilst the manufacturer provided the cost compositions of INTRABEAM, it was not transparent in explaining the assumed cost per patient. In addition, cost of EBRT was obtained from an inappropriate HRG code: the code used in the model for EBRT was for "Other Radiotherapy treatment"; whereas the AG considers that the HRG code description required for the purpose of this analysis is "deliver a fraction of radiotherapy on a megavoltage machine", which includes external beam radiotherapy delivered by linear accelerator, as per the NICE scope. The AG considers that HRG codes SC22Z and SC23Z are required for treatment delivery, and SC45Z, SC46Z, SC47Z and SC48Z are required for EBRT (see Section 5.4). Costs were only varied by ±10% in PSA. There were also inconsistencies in the sources used to populate the reported costs; for instance, the costs of treating post INTRABEAM local recurrence (salvage lumpectomy) and that of treating post EBRT local recurrence (salvage mastectomy) were obtained from Payments by Results tariff 2013-14, whereas the cost of EBRT was obtained from the Reference Costs 2012-13.

Cost-effectiveness results

The base-case results from the submission are shown in Table 21 and indicate that INTRABEAM is associated with higher QALYs and lower costs. The submission states that the incremental analysis shows dominance of INTRABEAM over EBRT.

Table 21: Base-case results for the Carl Zeiss submission

	Mean QALYs	Mean cost £	ICER vs EBRT(Cost/QALY)
INTRABEAM	13.230	£14,461	Dominates
EBRT	13.223	£20,926	
Incremental	0.012	-£6,465	

One way sensitivity analyses and scenario analyses were not conducted. A PSA was undertaken using Monte Carlo simulation with 1,000 iterations. The cost parameters in the model were assigned to beta-pert distributions, and beta distributions were assigned to utilities. For the cost parameters, the AG considers that gamma distribution would have been a more standard choice; it is not usual practice to assign beta-pert distributions. For the PSA, at the £20,000 and £30,000 willingness to pay thresholds, INTRABEAM has the highest probability of being cost effective, at 100% for both thresholds.

Critique of the manufacturers' submission

- The MS provides very limited information on model structure; baseline characteristics of the patient population and setting.
- Limited information is provided with respect to input parameters such as costs and utilities. The MS is not transparent in providing the methodology adopted to inform the input parameters.
- The method to derive costs of INTRABEAM is not clear.
- No rationale is provided for using the specific distributions assigned to the parameters.
- The method of extrapolation of local recurrence and survival data is not justified.
- The number of fractions for the EBRT arm used in the model (23 fractions) is higher than UK practice; this will lead to an overestimation of EBRT costs.
- The manufacturer's model assesses health benefit in terms of QALYs which is a valid measure of health in the UK NHS setting. The source study[96] used standard gamble from a 1997 publication to estimate utilities. No details were provided whether a systematic search was conducted to identify utilities for the model.
- Model validation was not conducted; hence the generalisability of model results remains questionable.
- PSA was conducted for only 1000 simulations; no one-way or scenario analyses were conducted. Limited sensitivity analyses conducted around the base case model results raise questions on the robustness of the model predictions.
- In summary, results of the MS model should be viewed with caution due to the methodological and reporting limitations outlined above.

5.4 Independent economic evaluation

Overview

We developed a new model to estimate the costs, benefits and cost-effectiveness of the INTRABEAM Photon Radiotherapy System compared to EBRT for early operable breast cancer.

The effects of the intervention on the clinical course of the disease are obtained from the TARGIT-A trial included in the systematic review of clinical effectiveness (Section 4). The patient population included in the economic model reflects the patient population in the pre-pathology stratum of this trial. This is because the TARGIT-A study recommends INTRABEAM concurrent with lumpectomy as an alternative to postoperative EBRT[65] but does not recommend the use of postoperative INTRABEAM as an alternative to EBRT (as non-inferiority was not established in this stratum). Use of the pre-pathology stratum furthermore provides consistency with the manufacturer's economic model, which is also based on the results of the pre-pathology stratum.[97]

The analysis takes the perspective of the NHS and PSS in the UK. The model adopts a lifetime (40 year) horizon to estimate costs and benefits from each treatment. Future costs and benefits are discounted at 3.5% per annum as recommended by the UK Treasury.[100] The outcome of the economic evaluation is reported as the cost saved per QALY lost.

5.5 Methods for economic analysis

The model uses transition probabilities obtained from the clinical literature to simulate the progression of early operable breast cancer in a cohort of patients and to estimate the cost-effectiveness of the radiotherapy treatments under consideration. The model was constructed using the TreeAge Pro 2014 software.[101] The model structure was informed by a review of other published models of early breast cancer[78;102-106] and the evidence available to inform disease progression, which is drawn from the only existing RCT, the TARGIT-A trial[65] (Section 4).

The model structure follows the disease pathway for early-stage breast cancer. It is slightly modified from an economic model structure used in a previous HTA report to NICE[102] in order to reflect the clinical evidence available. The structure is also similar to the model structure adopted by Alvarado and colleagues[78] in their cost-effectiveness analysis of IORT. The SHTAC model uses six distinct health states: recurrence free; local recurrence; disease free after local recurrence; any other recurrence; death from breast cancer; and death from other causes (Figure 5). The local recurrence, disease free after local recurrence and any other recurrence health states were chosen pragmatically in order to match the definitions and data supplied by the TARGIT-A trial publication.[65]

Local recurrence is defined in the TARGIT-A trial as recurrence in the conserved breast whilst any other recurrence incorporates regional recurrence (axilla plus supraclavicular), contralateral breast recurrence, and distant recurrence.[65] The AG notes that regional recurrence, contralateral recurrence and distant recurrence have very different prognoses and costs but they are not modelled separately as no data were available to inform possible transitions to or from these health states.

Non-death health states are associated with a HRQoL utility and a cost estimate.

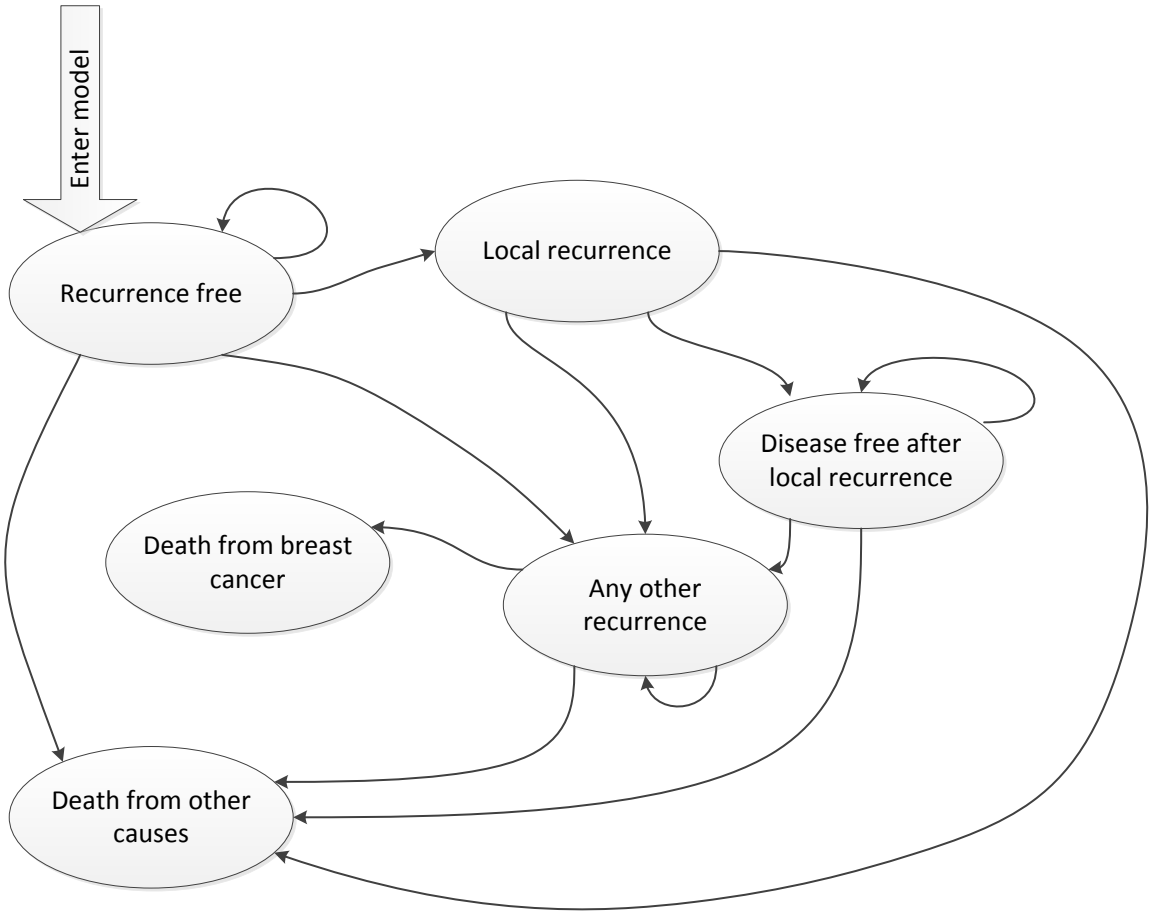


Figure 5: Influence diagram for the SHTAC breast cancer cost-effectiveness model.

All patients start the model in the recurrence free state and may then either: stay in the recurrence free state; have a local recurrence and move to the local recurrence state; have another type of recurrence and move to the any other recurrence state; or die from non-BC causes. From the local recurrence state a patient may move either to the disease free after local recurrence state; suffer any other recurrence; or die from other causes. A patient in the disease free after local recurrence state may remain either in this state, suffer any other recurrence, or die from other causes. From the any other recurrence state it is possible to die from breast cancer, die from other causes; or stay in the state. The local recurrence state is temporary and it is only possible to remain here for one cycle.

Model cycle length is 1 year and a lifetime horizon of 40 years was adopted in the base case which is sufficiently long to capture all clinically and economically important events. A half-cycle correction was applied.

The baseline disease progression parameters used in the model were obtained from the TARGIT-A trial (Section 4).[65] These inform the annual probabilities of local recurrence; any other recurrence while recurrence free; and death from breast cancer. Data from de Bock and colleagues[107] were used to inform the probability of any other recurrence given local recurrence. ONS data were used to inform the probability of all-cause mortality by age.[108] Parametric curves were fitted to Kaplan-Meier data in order to provide the probabilities of local recurrence in both treatment arms.

The costs included in the model are those for initial radiation treatment and repeat lumpectomy and mastectomy and reconstruction, with or without radiation treatment, at local recurrence. Full details of the costs used in the model are given in Section 5.5.1.

The model includes the following assumptions:

- All patients enter the model in the recurrence free state after initial BCS and radiation therapy
- It is not possible to die from breast cancer whilst in the local recurrence state or the disease free after local recurrence state. It is only possible to die from breast cancer whilst in the any other recurrence state.
- Only one local recurrence is allowed; repeat local recurrence is not modelled.
- Death rates for non-breast cancer causes are based on mortality statistics for England and are applied across all health states.
- The survival of patients with recurrence of any sort is assumed to be independent of the time of recurrence.

A further simplification is that due to data limitations the costs of post-progression therapies are not included in the base case.

In each cycle the total costs and QALYs are calculated by multiplying the individual costs and HRQoL of each model state by the proportion of the model cohort in that state, for each of the radiotherapy types. The total discounted lifetime costs and QALYs are calculated by aggregating the costs and QALYs for all cycles. The ICER is calculated as

$$ICER = \frac{Cost\ of\ therapy\ B - Cost\ of\ therapy\ A}{QALYs\ of\ therapy\ B - QALYs\ of\ therapy\ A} \qquad (1)$$

where by convention therapy A is the current standard of care and therapy B is a new therapy. The associated incremental net monetary benefit (NMB) of a specific treatment versus a comparator may be calculated as

*Incremental NMB = Incremental QALYs * WTP – Incremental costs* (2)

where the incremental QALYs and incremental costs are simply the denominator and numerator respectively of equation (1) and WTP stands for Willingness to Pay, the maximum amount a decision-maker is prepared to pay per QALY gained.[57] As long as the incremental NMB is more than zero then a treatment is cost-effective, and larger NMBs represent greater cost-effectiveness than smaller NMBs.

Model validation

The model was validated by checking the model structure, calculations and data inputs for correctness. The structure was reviewed by clinical experts to establish that it was appropriate for the disease and its treatment. Internal consistency was examined by varying input values and verification that any change to the input values produced changes in the model outputs of the expected direction and magnitude. A second modeller reproduced the model in Excel and checked that the outputs were the same as the TreeAge Pro implementation. To establish its external consistency the model results were compared with published outcomes of survival in early breast cancer.

Evaluation of uncertainty

The evaluation of the cost-effectiveness of radiotherapy treatment options for early operable breast cancer is based on uncertain information which includes uncertainty about the clinical effects of treatment, HRQoL whilst in the various health states, and resource use. Such uncertainty is examined using deterministic and probabilistic sensitivity analyses.

One-way deterministic sensitivity analyses were conducted to test the robustness of the cost-effectiveness results to variations in parameter input values when altered one at a time (Section 5.6).

Joint variation and potential correlation in multiple parameters was addressed using PSA (Section 5.6). In the PSA probability distributions were assigned to the parameter point estimates used in the base case analysis. The model was then run for 10,000 iterations with parameter values sampled at random from these distributions. The uncertainty surrounding the cost-effectiveness of the treatments is represented on a cost-effectiveness acceptability curve (CEAC) which plots the probability that an intervention will be cost-effective at a particular WTP threshold.

Scenario analysis was used to investigate the effect of uncertainty in model assumptions and structure.

5.5.1 Data sources

Recurrence free state: probability of local recurrence

The baseline risk of local recurrence in the economic model is taken from the pre-pathology subgroup of the TARGIT-A trial.[65] The TARGIT-A trial was the only trial included in the review of clinical effectiveness (Section 4) and as such is the main source of evidence of the clinical efficacy of INTRABEAM.

Local recurrence probabilities in the pre-pathology substratum for INTRABEAM and EBRT were extracted from a Kaplan-Meier plot in the trial publication[65] using the digitising software PlotDigitizer and the method of survival curve reconstruction described in Guyot and colleagues.[109] Parametric survival models were then fitted to the observed data using Stata software[110] in order to extrapolate local recurrence beyond the five years reported.[65] In line with the recommendation of Latimer[111] all of the 'standard' parametric models were considered (exponential, Weibull, Gompertz, loglogistic, lognormal).

Akaike information criterion (AIC) values obtained for each distribution are given in Table 22 which shows that the lognormal, loglogistic and Weibull distributions provide the best fit to the data based upon this criterion. The Gompertz and exponential distributions fit the data less well. The lognormal and Weibull fits are compared graphically with the five years of trial data in Figure 6. (The loglogistic fit is similar to the lognormal and is not considered further.) The figure demonstrates that the lognormal and Weibull fits are similar over this time period. Figure 7 shows the behaviour of the lognormal and Weibull fits over the model time horizon of 40 years. It can be seen from Figure 7 that local recurrences continue to occur throughout the time horizon with both models, but that the proportion with local recurrence after 40 years is much higher under the Weibull model than under the lognormal model. Previous economic evaluations to NICE have assumed that patients who have experienced an episode of early-stage breast cancer but are in remission after 15 years will have the same risk of progression as the general population.[102] However clinical advice to the AG is that the risk of local recurrence continues throughout life and is relatively linear over time. Data on local recurrence at nine years from the ELIOT trial,[112] and the study of Kreike and colleagues[113] which follows up BCS+radiotherapy patients for fifteen years, also suggest that risk of local recurrence does not decrease over time.

The model adopts the lognormal curve in the base case. It is both a better fit by the AIC criterion and its rate of local recurrence does not accelerate so steeply through time as that of the Weibull model (Figure 7). This behaviour means that median survival is longer under this model and as such it provides a better fit to other published data on survival after breast cancer (see section 5.5.1 on model validation below). Coefficients of the fitted lognormal regression model are given in Table 23.

Table 22: Values of AIC obtained for parametric survival models fitted to reconstructed local recurrence data from TARGIT-A trial.[65] Lower values of AIC indicate a better fit to the data.

Model	AIC
Lognormal	213.0
Loglogistic	214.2
Weibull	214.2
Gompertz	217.6
Exponential	219.2

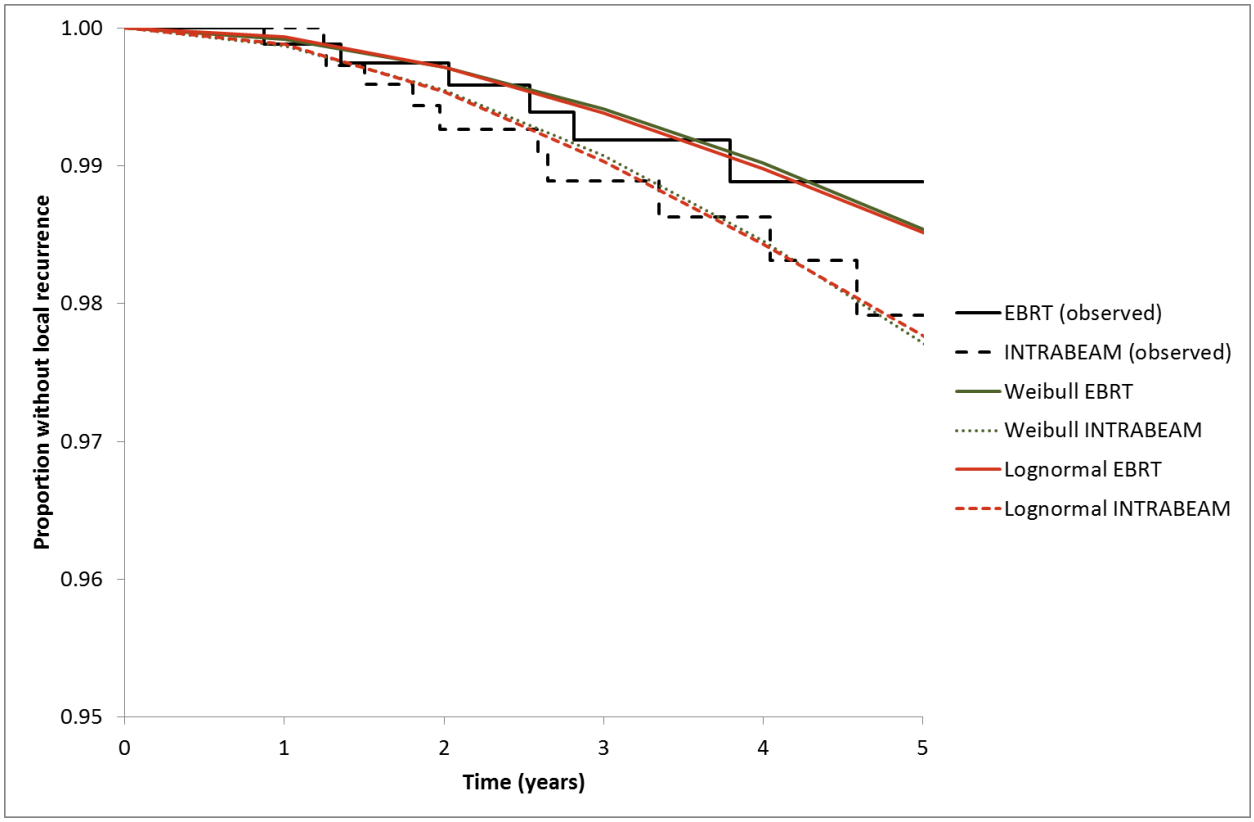


Figure 6: Kaplan-Meier plot of local recurrence in the pre-pathology subgroup of the TARGIT-A trial[65] compared with fitted lognormal and Weibull local recurrence curves

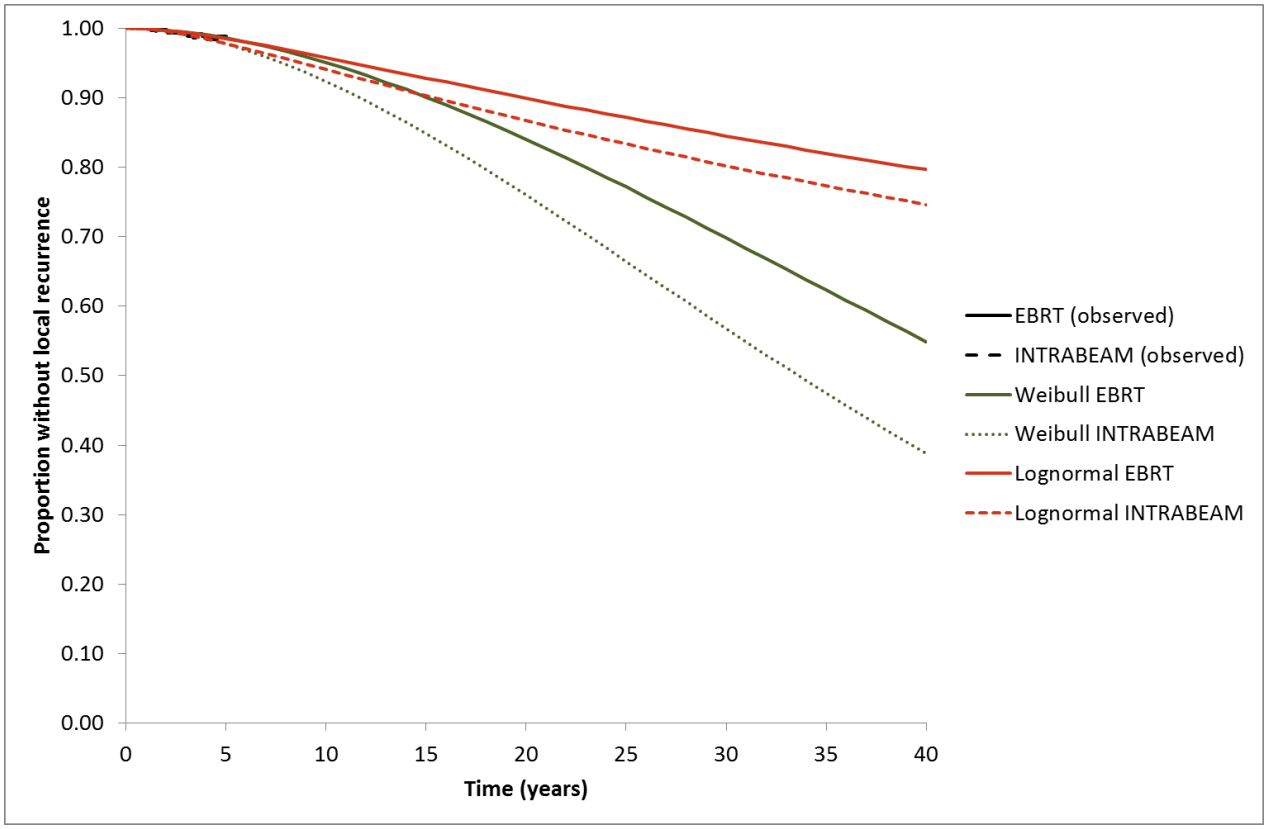


Figure 7: Kaplan-Meier plot of local recurrence in the pre-pathology subgroup of the TARGIT-A trial[65] compared with fitted lognormal and Weibull local recurrence curves over 40 year time horizon.

Recurrence free and local recurrence states: probability of any other recurrence

The baseline risk of any other recurrence whilst in the recurrence free state is taken from the pre-pathology subgroup of the TARGIT-A trial.[65] The five-year probability of any other recurrence in the EBRT pre-pathology subgroup is given in the trial publication as 4.7%. The corresponding five-year probability for INTRABEAM is 4.8%.[65] These probabilities are converted to one-year probabilities for use in the economic model to inform the transition from the recurrence free health state to the any other recurrence health state (Table 23).

The probability of any other recurrence is higher for those who have already experienced a local recurrence compared to those who have not but these more detailed data are not available from the TARGIT-A trial and would not be robust due to the low numbers in TARGIT-A with local recurrence.[65] A previous HTA submission to NICE[102] uses the study of Kamby and Sengelov[114] to inform a model transition from loco-regional relapse to metastatic disease. In this study the proportion with distant disease was 72% at 10 years after loco-regional relapse, giving a one-year probability of distant disease of 0.1195 (Table 23). In an analysis of 3,601 women enrolled in randomised trials and treated for early-stage breast cancer, de Bock and colleagues[107] report that of

310 women who experience loco-regional recurrence, 129 experienced distant metastases after loco-regional recurrence, at a median follow-up of 10.2 years. This broadly equates to a one-year probability of distant disease given local recurrence of 0.0514. This probability is based upon a much bigger sample and is more recent than the study of Kamby and Sengelov.[114] Consequently the probability of 0.0514 derived from de Bock and colleagues data[107] is adopted for use in the economic model to inform the transitions from the local recurrence and disease free after local recurrence health states to the any other recurrence health state (Table 23).

Probability of breast cancer death

In common with other economic models of early breast cancer the SHTAC model assumes that all breast cancer deaths occur from the 'any other recurrence' state, which includes metastatic cancer.[102;104;105] Thus in the model a breast cancer death is conditional upon having had any other recurrence beforehand (Figure 5). The TARGIT-A trial ascribed a death to breast cancer if breast cancer was present at the time of death.[65] Consequently it is possible that a small proportion of the breast cancer deaths observed in the TARGIT-A trial occurred whilst a patient was experiencing local recurrence, before repeat surgery. However given the small numbers of likely deaths from the local recurrence state, which patients only pass through for one model cycle, this is felt to be an acceptable modelling simplification.

The model requires the probability that a patient in the 'any other recurrence' state dies from breast cancer in a given cycle. The TARGIT-A trial publication reports both the probability of death from breast cancer and the probability of any other recurrence, by treatment arm.[65] Thus, with the model assumption that all breast cancer deaths occur after 'any other recurrence', the five-year probability of death from breast cancer, given any other recurrence, can be calculated. For the EBRT pre-pathology subgroup this probability is approximately given by 0.0055/0.0096 (=0.5698 with no input data rounding), whilst for the INTRABEAM pre-pathology subgroup the corresponding probability is approximately 0.0067/0.0098 (=0.6832 with no input data rounding) (Table 23). Assuming that time to death after any other recurrence is exponentially distributed these probabilities correspond to a mean survival after any other recurrence of around 21 months for EBRT, and 17.5 months for INTRABEAM.

Probability of non-breast cancer death

The general underlying risk of mortality was modelled using a cohort life table generated from the 2010-2012 female interim life tables for England.[108] The age-related mortality for each year in the model was determined from these data using the demographic characteristics of breast cancer patients in England. Specifically, in the base case, patients enter the model at an age of 62 years. This is the median age of breast cancer diagnosis in females in England.[115]

Table 23: Summary of baseline disease progression parameters

Variable	Values	Transition probability per one year model cycle	Source
Lognormal model of time to local recurrence EBRT	constant=4.97 sigma= 0.436	Varies through time	Model fitted to KM data in Vaidya 2014[65]
β coefficient for INTRABEAM in lognormal model of time to local recurrence	-0.256	NA	Model fitted to KM data in Vaidya 2014[65]
Probability of any other recurrence EBRT while recurrence free	0.047 (5 year)	0.0096	Vaidya 2014[65]
Probability of any other recurrence INTRABEAM while recurrence free	0.048 (5 year)	0.0098	Vaidya 2014[65]
Probability of any other recurrence given local recurrence	0.416 (10.2 year)	0.0514	de Bock et al[107]
Probability of breast cancer death EBRT	0.027 (5 year)	0.0055	Vaidya 2014[65]
Probability of breast cancer death INTRABEAM	0.033 (5 year)	0.0067	Vaidya 2014[65]
Probability of breast cancer death given other recurrence EBRT	-	0.5698	Calculation
Probability of breast cancer death given other recurrence INTRABEAM	-	0.6832	Calculation
Probability of non-breast cancer death	Age-dependent	Varies through time	ONS mortality tables[108]

NA: not applicable; KM: Kaplan-Meier

In the model base case the same probabilities of non-breast cancer death by age are used for both treatment arms. However the TARGIT-A trial publication notes a statistically significant difference in non-breast cancer deaths between treatment arms, with fewer deaths in the INTRABEAM arm.[65]

These data are based on a small number of events (12 non-breast cancer deaths on the INTRABEAM arm and 27 on the EBRT arm). The TARGIT-A trial publication shows that the higher number of deaths on the EBRT arm is due to cardiovascular causes and other cancers and states that it is improbable that there was a substantial imbalance in baseline comorbidities between the two randomised groups[65] The AG notes however that patients on the EBRT arm were slightly older at baseline.[64] A mean age is not supplied but the AG calculates a mean age of 62.5 for the EBRT arm and of 62 for the INTRABEAM arm, for all patients. (Ages at baseline for the pre-pathology stratum alone are not supplied.) The AG has also compared the annual probabilities of death on the EBRT arm with annual all-cause mortality probabilities obtained from ONS data[108] and found that they are similar. The AG does not therefore consider that there is an excess of deaths on the EBRT arm, but rather a shortfall of deaths on the INTRABEAM arm which is likely to have arisen due to chance and/or the slightly younger mean age of patients on this arm.

The model does not therefore adopt trial-observed non-breast cancer mortality data for use in the base case, but they are examined in scenario analysis reported in section 5.6.

Health-related quality of life

The systematic review of HRQoL identified nine studies which met the inclusion criteria (Table 18). Five of the included studies provide EQ-5D values for the 'recurrence free' state in the economic model (Table 19). Two of these studies are US-based,[88;89] one is Swedish,[91], one is German[93] and two are UK-based.[86] Breast cancer treatment in other countries can differ from the UK and so a UK-based study is preferable. However one of the UK-based studies[86] has a mean participant age of approximately 72 years. This is ten years older than the population under consideration here. Consequently the other UK study, the COMICE trial of Turnbull and colleagues,[87] was selected which provides EQ-5D for younger patients after wide local excision.[87] The COMICE trial was a reasonably large RCT (1623 participants in two arms) in women with biopsy proven primary breast cancer scheduled for WLE, and reports EQ-5D at four time points. Participants had a mean age at randomisation of 57 years. The time points of 'eight weeks post randomisation' and '12 months post initial surgery' were chosen from the no intervention arm of the trial for use in the recurrence-free state in the model. These reflect utility in the first year after WLE, and utility thereafter (Table 24).

The Swedish Lidgren study[91] identified in the systematic review of QoL provides EQ-5D estimates for four states of breast cancer and uses the UK EQ-5D index tariff (Table 19). 52% of participants in this study were aged 50-64 years and 22% were aged 65 or older and as such it conforms reasonably to the population age in the SHTAC model. The study indicates that utilities in the first year after local recurrence, and in the second and following years after both primary breast cancer and local

recurrence, are the same.[91] Accordingly the SHTAC model uses the same utility value from the COMICE trial of 0.8112 for these three health states, as shown in Table 24.

The similarity of EQ-5D values across breast cancer health states is also reflected in the recent study in the German population by Hildebrandt and colleagues which found the same median EQ-5D scores for primary disease, metastatic disease and recurrent disease (Table 19).[93] A previous HTA report to NICE uses utilities valued by either patients or clinical experts using time trade off (TTO).[102] This set of utilities is examined in scenario analysis described in section 5.6. It is not adopted in the base case as the utilities were not valued by the general population and were not obtained via the EQ-5D.

It is assumed that utility whilst in the 'any other recurrence' health state is equivalent to utility for metastatic disease. The Lidgren and colleagues study gives a utility of 0.685 for metastatic disease (Table 19).[91] This was adopted in the economic model as no utility for metastatic disease is given in the COMICE trial publication.[87] A utility for metastatic disease is given in Sherrill and colleagues[94] but this is based on an international multicentre study with a young participant age (median in pooled population approximately 52 years)[116] and so does not appear to be as relevant to the model. However the EQ-5D value of 0.66 is similar to the value of 0.685 given in Lidgren and colleagues for this state[91] (Table 24).

The systematic review of QoL identified two studies which give EQ-5D values for mastectomy and immediate reconstruction.[90;92] Conner-Spady and colleagues do not report the EQ-5D for mastectomy patients specifically.[92] Robertson and colleagues report an EQ-5D value of 0.83 for mastectomy and reconstruction at a median of four years' follow-up but an immediate post-operative value is not reported.[90] The value of 0.83 is higher than the utility given in the COMICE trial at the twelve month time point after WLE.[87] This may reflect the lower mean age of 50 years[90] but on the basis of this study mastectomy and reconstruction does not appear to be associated with disutility compared to WLE utility observed in the COMICE trial. Consequently a mastectomy disutility is not included in the base case but is examined in scenario analysis described in Section 5.6.

In common with the manufacturer's economic model and the IORT economic evaluation of Alvarado and colleagues[78] the SHTAC model does not reflect any utility benefit associated with initial INTRABEAM treatment. Given that the duration of EBRT in England is three weeks, any utility benefit associated with the one-off INTRABEAM delivery is likely to be very small when considered within the annual model cycle length. Any impact of treatment on HRQoL is assumed to occur because of its effect on disease progression, and this is already accounted for in the model.

A summary of the health state utility values used in the economic model base case is given in Table 24.

Table 24: EQ-5D utility values by model health state

Model health state	EQ-5D (SE)	Source
Recurrence free in 1st year	0.7728 (0.0079)	Turnbull et al[87] no MRI arm 8 weeks post-randomisation time point
Recurrence free after 1st year	0.8112 (0.0072)	Turnbull et al[87] no MRI arm 12 months post-initial surgery
Local recurrence	0.8112 (0.0072)	Turnbull et al[87] no MRI arm 12 months post-initial surgery
Disease-free after local recurrence	0.8112 (0.0072)	Turnbull et al[87] no MRI arm 12 months post-initial surgery
Any other recurrence	0.685 (0.0293)	Lidgren et al[91]

Resource Use and Costs

This section considers the resource use and costs associated with the clinical pathway of the modelled population.

The proportion of INTRABEAM patients who also receive EBRT is taken from the TARGIT-A trial where 15.2% of INTRABEAM patients also received EBRT (Table 25).[65] The model assumes that 15 EBRT deliveries are required to complete a course of treatment as recommended in NICE CG80.[11] Alternatives to this value are examined in deterministic sensitivity analysis described in Section 5.6.

In contrast to the manufacturer's model where it is assumed that all INTRABEAM patients will have repeat lumpectomy at local recurrence, the SHTAC model assumes that only a minority of INTRABEAM patients will have repeat lumpectomy at local recurrence. Clinical advice to the AG is that the most common and evidence-based approach in the UK is to offer mastectomy at local recurrence, and that approximately 70-80% of patients opt for mastectomy. The SHTAC model assumes 80% in the base case (Table 25). All EBRT patients are assumed to have mastectomy at local recurrence.

Clinical advice to the AG also indicates that well under 50% of patients who have mastectomy will opt for reconstruction. This is borne out by figures obtained from the National Mastectomy and

Breast Reconstruction Audit[117] which show that only around 31% of those undergoing mastectomy choose to have a reconstruction (Table 25).

Table 25: Model parameter values for clinical pathway

Parameter	Units	Value	Source
Proportion of INTRABEAM patients who also receive EBRT	proportion	0.152	Vaidya 2014[65]
Number of EBRT deliveries required to complete a course of treatment	deliveries	15	NICE CG80[11]
Proportion of INTRABEAM patients having mastectomy at local recurrence	proportion	0.8	Expert opinion
Proportion of mastectomy patients who have reconstruction	proportion	0.31	National Mastectomy and Breast Reconstruction Audit 2011[117]

The working lifetime of an INTRABEAM device is assumed to be 10 years in the base case (Table 26). This value is informed by the manufacturer and radiotherapy expert opinion; an alternative value of five years is examined in deterministic sensitivity analysis described in Section 5.6.

Use of INTRABEAM requires appropriate shielding from radiation. The manufacturer observes that radiation protection shields are not required in all hospitals in England.[118] However the proportion of hospitals which would not need shields is unclear. The SHTAC model base case therefore assumes that radiation shields are required in all cases (Table 26) and examines alternative values for this proportion in deterministic sensitivity analysis.

Table 26: INTRABEAM device lifetime and resource use assumptions in model base case

Parameter	Units	Value	Source
Lifetime of INTRABEAM device	years	10	Carl Zeiss
Proportion of INTRABEAM patients requiring radiation shield	proportion	1	Assumption

INTRABEAM requires additional staff time both in support of the device and during its use. Staff time is costed in the SHTAC economic model using the NHS staff pay bands of surgical consultant and 8b, 7 and 5. Hourly costs for each of these pay bands are taken from the PSSRU Unit Costs of Health and Social Care 2013[119] and are given in Table 27.

Table 27: Staff unit costs per hour assumed by economic model

Staff Band	Unit Cost Per Hour(£)	Source
Surgical consultant	100	PSSRU 2013 (Table 15.6)[119]
AfC Band 8b	73	Mean annual basic pay from PSSRU 2013 (Table 17.3); overheads added as per other staff unit cost derivations in PSSRU 2013[119]
AfC Band 7	50	PSSRU 2013 (Table 14.1)[119]
AfC Band 5	34	PSSRU 2013 (Table 14.3)[119]

AfC: Agenda for Change

The staff time required in support of INTRABEAM at each pay band is detailed in Table 28 by activity. Radiotherapy and clinical expert opinion was used to identify these activities and estimate the staff time required at each band. Two experts were consulted. The cost of each activity shown in Table 28 is derived using the unit costs given in Table 27. It is assumed that operating procedure development and initial INTRABEAM training are one-off costs which are incurred only once within the lifetime of each device, i.e. every ten years in the base case. Technical commissioning and radiation protection refresher training costs are assumed to be required on an annual basis. Expert advice to the AG is that technical commissioning is required annually after annual maintenance by the manufacturer. All other costs are incurred on a per treatment basis (Table 28). Variation to these costs is considered in deterministic sensitivity analysis described in Section 5.6.

Table 28: Additional staff resources required for use of INTRABEAM assumed by economic model

Frequency of Cost	Activity	Number of staff	Staff Band	Time required	Cost (£)	Source
One-off	INTRABEAM operating procedure development	1	7	2 days[a]	757	Expert opinion
One-off	Initial INTRABEAM training	4	7	2 days[a]	5,227	Expert opinion of time / assumption for no. of staff & band
		2	8b			
Annual	Technical commissioning	2	7	3 days[a]	2,271	Expert opinion
Annual	Technical commissioning sign off	1	8b	0.5 days[a]	275	Expert opinion
Annual	Refresher training on radiation protection	4	7	1 hour	920	Expert opinion of time / assumption for no. of staff & band
		2	8b			
		5	5			
		4	Surgical consultant [b]			
Per treatment	Pre-treatment QC check	1	7	30 minutes	25	Expert opinion
Per treatment	Planning INTRABEAM dose in operating theatre	2	Surgical consultant [b]	6 minutes	25	Expert opinion/ TARGIT-A trial
		1	7			
Per treatment	Delivering INTRABEAM dose in operating theatre	1	Surgical consultant [b]	33 minutes	83	Expert opinion/ TARGIT-A trial
		1	7			
Per treatment	Additional time required by medical physicist in support of INTRABEAM use	1	7	1.5 hours	76	Expert opinion

[a] Working day is 7.5 hours, [b] Includes anaesthetist

The costs of consumables required for INTRABEAM use, and the number of uses which each consumable supports, are given in Table 29. Other costs used in the model are shown in Table 30. These include the capital cost of each INTRABEAM device and its associated annual maintenance cost, provided by Carl Zeiss UK. Based on a capital cost of £435,000, a device lifetime of 10 years and a discount rate of 3.5% the equivalent annual cost (EAC) of INTRABEAM is £53,025 (Table 30).

INTRABEAM use requires extra time in the operating theatre for both treatment planning and delivery. A cost for 1 hour in theatre at Southampton General Hospital is £569 (Table 30). This cost includes nurse cost but does not include any medical staff or anaesthetist cost. Additional staff time in the operating theatre for INTRABEAM use is costed separately and given in Table 28.

Table 29: Cost of consumables required for use of INTRABEAM

Description	Cost per unit (£)	Number of treatments	Cost per treatment (£)	Source
Spherical applicator	3,170	100	31.70	Carl Zeiss UK.
Radiation protection shields pack of 10	1,041	5	208.20	
Sterile plastic drapes pack of 5	96	5	19.20	

Table 30: Other costs used in model

Description	Cost (£)	Source
INTRABEAM device capital cost	435,000	Carl Zeiss UK
Annual maintenance INTRABEAM device	35,000	
INTRABEAM device equivalent annual cost (EAC) of capital and initial costs	53,025	Calculation from capital cost and one-off costs (Table 28) using device lifetime of 10 years and discount rate of 3.5%
Cost of 1 hour in operating theatre[a]	569	University Hospitals Southampton Finance Department January 2014

[a] includes nurse cost but does not include any medical staff or anaesthetist cost

Costs for mastectomy with and without reconstruction, wide local excision, and planning and delivery of EBRT were obtained as weighted averages from NHS Reference Costs 2012-13[98] and are given in Table 31 with associated healthcare resource group (HRG) codes.

Table 31: Weighted average unit costs of medical procedures assumed by economic model

HRG codes	Description	Weighted Average Unit Cost (£)	Weighted Average Lower Quartile (£)	Weighted Average Upper Quartile (£)	Source
JA27Z JA28Z	Mastectomy with reconstruction	7,822	6,169	9,241	NHS Reference Costs 2012-13[98]
JA24D JA24E JA24F	Wide local excision	1,542	1,185	1,804	NHS Reference Costs 2012-13[98]
JA20D JA20E JA20F	Mastectomy	2,510	2,041	2,850	NHS Reference Costs 2012-13[98]
SC22Z SC23Z	Deliver a fraction of radiotherapy on a megavoltage machine	118.44	101.53	138.82	NHS Reference Costs 2012-13[98]
SC45Z SC46Z SC47Z SC48Z	Preparation for simple radiotherapy	323.65	198.08	413.75	NHS Reference Costs 2012-13[98]

HRG: healthcare resource group

Only serious adverse events of Common Terminology Criteria (CTC) grades 3 and 4 which occur in >5% of patients in any treatment arm are included in the economic model as these are considered to be those that incur additional NHS costs. Adverse events are moreover only included if the adverse event incidence differs significantly between treatment arms, in line with the modelling guidelines of Philips and colleagues.[58] The review of clinical effectiveness indicates that although there are two statistically significant differences in adverse event incidence between treatment arms (Table 12), these occur in less than 3% of patients. Therefore no costs for adverse events associated with INTRABEAM and EBRT are included in the economic model. This is consistent with the manufacturer's model and the model of Alvarado and colleagues.[78]

In order to avoid potentially confounding assumptions the costs of post-progression therapies are not included in the model base case. These costs are also not included in the manufacturer's model (which has no health state for any other recurrence) but are included in the IORT model of Alvarado and colleagues.[78] The AG notes that in order to accurately capture the costs of the 'any other recurrence' health state it would be necessary to know the proportions in this state with regional recurrence, contralateral breast recurrence, and distant recurrence as these types of recurrence are associated with very different costs. However these proportions are not given in the trial publication for the pre-pathology stratum.[65] The AG notes that INTRABEAM is associated with higher mortality from breast cancer than EBRT and that this may be because the proportions with each type of 'any other recurrence' differed between the treatment arms. Without information on the proportions with each type of recurrence the AG does not consider that it is appropriate to include post-progression costs in the base case. A scenario which does include post-progression costs is given in Section 5.6.

Demand for INTRABEAM

In the base case the SHTAC model assumes that the INTRABEAM device is deployed in a large district hospital with a catchment population of 1,000,000. With approximately 41,523 incident breast cancer cases in England in 2011[1] and an English population in 2011 of approximately 53.1 million (Table 32), the expected number of breast cancer cases per year in a hospital catchment of this size is 782. Opinion obtained from two clinical experts differed as to the proportion of these incident cases which might be suitable for treatment with INTRABEAM. One expert estimated 10-20% of cases whilst a second expert suggested up to 50%. A study by Leonardi and colleagues[120] retrospectively applies the ASTRO consensus statement guidelines for the application of accelerated partial breast irradiation[121] to participants in an intraoperative radiotherapy trial and finds that 16% of the patients would have been considered suitable using these guidelines. This figure corresponds with the lower estimate provided by the clinical experts and is adopted for use in the economic model base case. The alternative estimate of 50% is examined in deterministic sensitivity analysis described in Section 5.6.

With a hospital catchment of 1,000,000 and 16% of incident cases of breast cancer suitable for INTRABEAM, 126 INTRABEAM procedures might be carried out per year. This is shown in Table 33.

Table 33 also shows how variations to the base case assumptions of hospital catchment size and INTRABEAM device lifetime affect the cost per INTRABEAM procedure. With a device lifetime of 10 years and a hospital catchment population of one million, the cost per INTRABEAM procedure is £1,882. At 100 procedures per year, as assumed in the manufacturer's economic model, the cost per

procedure is £2,069 (Table 33). This is similar to the cost used in the manufacturer's economic model of £2,165 per procedure.

With a five year equipment lifetime the cost per INTRABEAM procedure rises to £2,236 with base case assumptions (Table 33). A five year device lifetime is examined in deterministic sensitivity analysis described in Section 5.6.

Table 32: Base case assumptions for INTRABEAM demand

Parameter	Units	Value	Source
Population served by 1 INTRABEAM device	people	1,000,000	Assumption
Incident breast cancer cases in England 2011	people	41,523	[1]
Population of England 2011	people	53,107,200	ONS[122]
Proportion of incident breast cancer cases which are early breast cancer and suitable for INTRABEAM	proportion	0.16	Leonardi et al [120]

Table 33: Cost of INTRABEAM use per patient by population served and assumed device lifetime (from SHTAC economic model)

Population served by 1 device	Calculated number of INTRABEAM procedures per year	Calculated cost of INTRABEAM procedure by lifetime of device (£)	
		10 year lifetime	5 year lifetime
795,000	100	2,069	2,514
1,000,000	126	1,882	2,236
5,000,000	631	1,302	1,373

Model Validation

The overall survival (OS) predictions from the model base case are compared with the trial-observed Kaplan-Meier data for the pre-pathology subgroup in Figure 8. The model OS predictions in Figure 8 were obtained using TARGIT-A trial data to model non breast cancer death for the first five model cycles and provide a good fit to the observed data. Data from the TARGIT-A trial show that OS in the INTRABEAM treatment arm is somewhat better than OS in the EBRT arm at five years and this is reflected in the model predictions (Figure 8). The model thus appears to be performing satisfactorily in this respect.

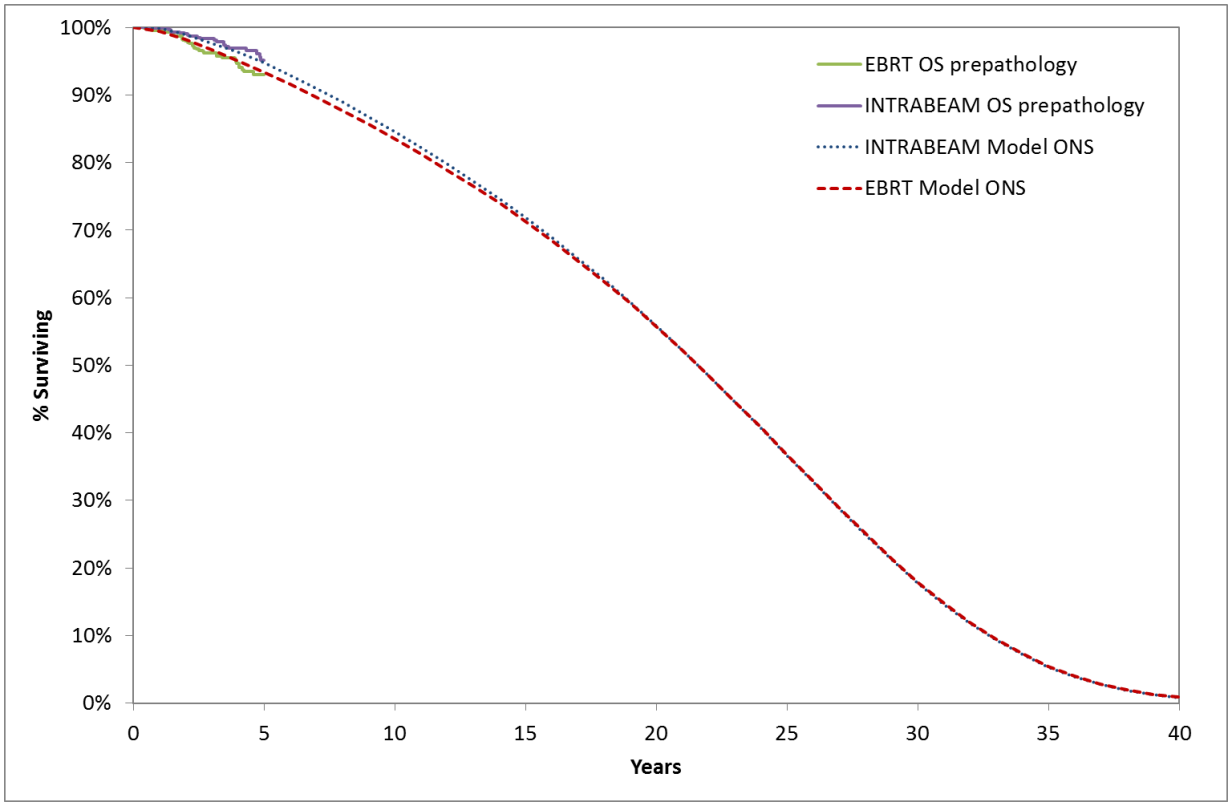


Figure 8: Kaplan-Meier plot of overall survival in the pre-pathology subgroup of the TARGIT-A trial[65] compared with overall survival predicted by the SHTAC economic model using TARGIT-A trial data to model non breast cancer death for first five cycles.

The model base case does not use trial-observed data for non-breast cancer death, for reasons given in Section 5.5.1. Figure 9 gives the model predictions for OS in each of the treatment arms in the pre-pathology subgroup when only ONS mortality data are used to model non-breast cancer death. Figure 9 shows that when using these data predicted OS in the INTRABEAM treatment arm is worse than observed in the trial, although the OS prediction for the EBRT arm is still a good fit. This is to be expected because ONS age-specific all-cause mortality rates are higher than the non-breast cancer mortality rates seen on the INTRABEAM arm in the TARGIT-A trial. The model predictions change in reflection of these differences (compare Figure 8 and Figure 9) and so again the model appears to be working satisfactorily.

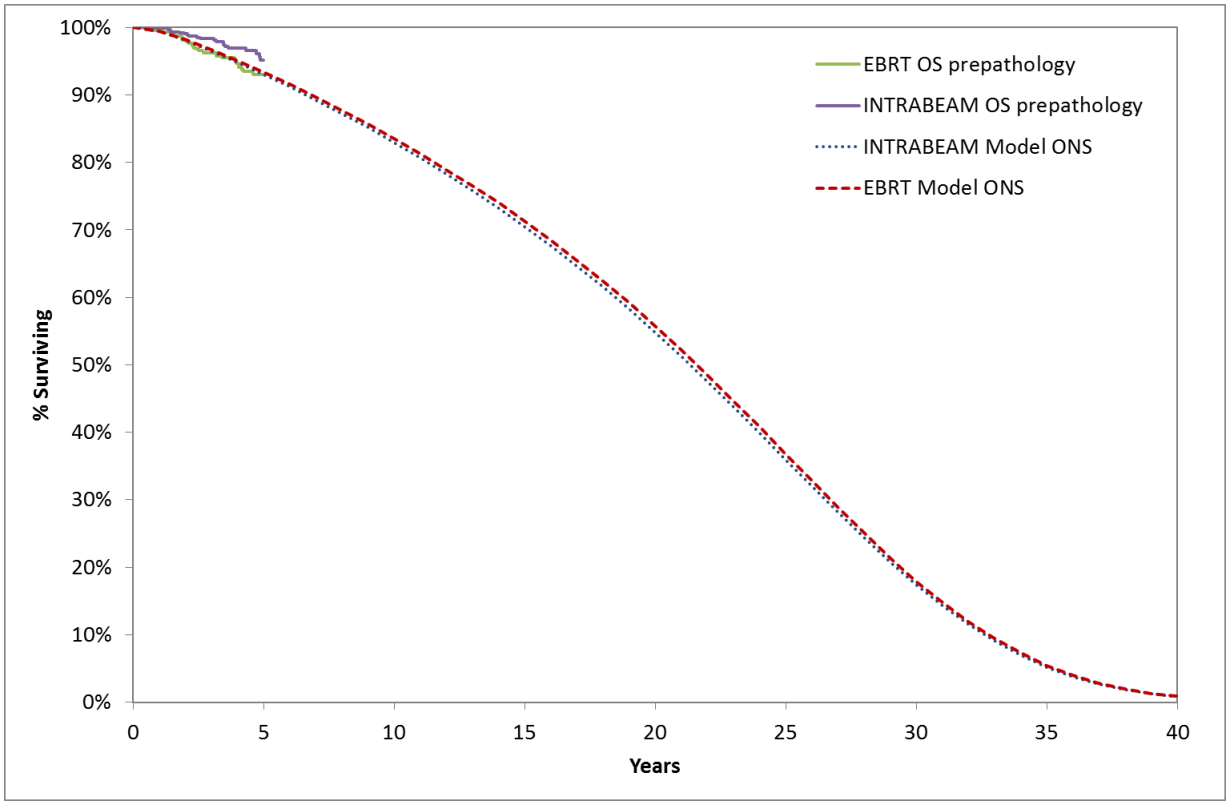


Figure 9: Kaplan-Meier plot of overall survival in the pre-pathology subgroup of the TARGIT-A trial[65] compared with overall survival predicted by the SHTAC economic model using ONS mortality data to model non breast cancer death in all cycles.

It may be seen from Figure 8 and Figure 9 that median overall survival predicted by the model base case for early operable breast cancer patients is approximately 21.5 years, and that overall survival is approximately 56% at 20 years . Relative survival at 20 years is 82% and at 25 years is 77%. Relative survival compares the survival of people with the cancer to that of people without cancer in order to help correct for deaths from things other than breast cancer. Exact comparison with other data sources is difficult, however the SEER database of the US National Cancer Institute has 20-year relative survival of 64.7% in breast cancer patients aged 50+ diagnosed between 1985 and 1989.[123] Figures from Cancer Research UK for England and Wales indicate that relative survival from breast cancer at twenty years is 64.5%.[124] Thus the relative survival of 82% at 20 years given by the model is somewhat higher than these estimates but this is to be expected as treatment has improved in the 25 or so years since the patients on whom these estimates are based were diagnosed.

Relative survival compares the survival of people with the cancer to that of people without cancer in order to help correct for deaths from things other than breast cancer. Thus it is reasonable that the overall survival of 56% in the model is lower than these published estimates of relative survival because it does reflect deaths from other causes.

5.6 Results of independent economic analysis

This section reports the cost effectiveness of INTRABEAM compared to EBRT in a cohort of early operable breast cancer patients. Base case discounted cost-effectiveness summary results are given in Table 34 and are broken down by health state in Table 36. Results with no discounting of costs and outcomes are given in Table 35. INTRABEAM is less expensive but also less effective than EBRT as it has lower total costs but also fewer total QALYs. The ICERs given in Table 34 and Table 35 therefore represent the money saved per QALY lost that is associated with replacing EBRT by INTRABEAM.

In situations where a new intervention (INTRABEAM) is both less costly and less effective than the current standard of care (EBRT), the ICER for INTRABEAM to replace EBRT must lie above the usual NICE cost-effectiveness thresholds of £20,000 and £30,000 per QALY if INTRABEAM is to be considered a cost-effective alternative to EBRT. However the ICER value of £1,596 saved per QALY lost shown in Table 34 indicates that EBRT is the cost-effective treatment option within the WTP threshold of £20,000 per QALY. Over the 40 year time horizon of the model it is associated with more QALYs at broadly similar overall cost. EBRT is also cost-effective in the undiscounted analysis where incremental QALYs are nearly twice those seen in the discounted results and the ICER (£ saved/QALY lost) is smaller (Table 35).

Table 34: Base-case discounted cost-effectiveness results.

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental Cost (£)	Incremental QALYs	ICER (£ saved / QALY lost)
EBRT	2,368	20.72	11.329	-	-	-
INTRABEAM	2,227	20.51	11.241	-140	-0.088	1,596*

* INTRABEAM is both cheaper and less effective than EBRT therefore the ICER represents the £ saved per QALY lost associated with replacing EBRT with INTRABEAM

Table 35: Base-case undiscounted cost-effectiveness results.

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental Cost (£)	Incremental QALYs	ICER (£ saved / QALY lost)
EBRT	2,522	20.72	16.743	-	-	-
INTRABEAM	2,346	20.51	16.576	-177	-0.167	1,062*

* INTRABEAM is both cheaper and less effective than EBRT therefore the ICER represents the £ saved per QALY lost associated with replacing EBRT with INTRABEAM

Table 36. Base case discounted total costs and QALYs by health state.

	EBRT		INTRABEAM	
Health state	**Total costs (£)**	**Total QALYs (£)**	**Total costs (£)**	**Total QALYs (£)**
Recurrence free	2,100	10.760	1,882	10.551
Local recurrence	268	0.052	345	0.069
Disease free after local recurrence	0	0.348	0	0.469
Any other recurrence	0	0.169	0	0.152
Dead background mortality	0	0	0	0
Dead breast cancer	0	0	0	0
Total	**2,368**	**11.329**	**2,227**	**11.241**

Sensitivity analysis

Deterministic and probabilistic sensitivity analyses were conducted in order to investigate the effect of uncertainty in model parameter values on the cost-effectiveness results. Deterministic sensitivity analysis was used to highlight the most influential parameters whilst the effect of uncertainty and interaction in multiple parameters was examined using PSA. Scenario analysis was used to investigate the effect of uncertainty in model assumptions and structure.

Each parameter was assumed to follow a probability distribution and these are given, with the distribution parameters, in Table 37. For beta distributions the distribution parameters were fitted using either the method of moments or information on the sample size and number of events when available. Distribution parameters were fitted to the gamma distributions using the method of moments. In cases where a standard error or standard deviation was not supplied in the source literature the standard error was calculated using an arbitrary ±20% from the base case value. Correlation between the parameters of the lognormal distribution used to inform time to local recurrence was incorporated by sampling from a multivariate normal distribution with covariance matrix as specified in Table 37.

The model parameters were varied in deterministic sensitivity analysis between the 2.5th and 97.5th percentiles of the assumed parameter distribution of the mean value and these are given in Table 37. Table 38 gives upper and lower bounds for parameters examined in deterministic sensitivity analysis where these are different from the upper and lower bounds examined in probabilistic sensitivity analysis..

Table 37: Parameters, distributions and associated upper and lower values used in probabilistic and deterministic sensitivity analysis

Parameter	Distribution	Distribution parameters	Mean / base-case	2.5th percentile for mean	97.5th percentile for mean
Costs					
INTRABEAM commissioning*	GAMMA	α = 96.04; β = 26.51	£2,546	£2,062	£3,080
One EBRT delivery	GAMMA	α = 18.36; β = 6.45	£118	£71	£178
EBRT planning	GAMMA	α = 4.10; β = 78.97	£324	£90	£704
INTRABEAM setup costs*	GAMMA	α = 96.04; β = 62.31	£5,984	£4,847	£7,239
Mastectomy and reconstruction	GAMMA	α = 99.63; β = 78.51	£7,822	£6,362	£9,431
Mastectomy	GAMMA	α = 147.71; β = 16.99	£2,510	£2,122	£2,931
One hour in operating theatre*	GAMMA	α = 96.04; β = 5.92	£569	£461	£688
Pre-treatment QC INTRABEAM*	GAMMA	α = 96.04; β = 0.26	£25	£20	£31
Staff time per hour in theatre during INTRABEAM delivery*	GAMMA	α = 96.04; β = 1.57	£150	£122	£182
Staff time per hour in theatre during INTRABEAM planning*	GAMMA	α = 96.04; β = 2.61	£250	£203	£303
Annual staff training in radiation protection*	GAMMA	α = 96.04; β = 9.58	£920	£745	£1,113
Staff time in support of INTRABEAM delivery*	GAMMA	α = 96.04; β = 0.79	£76	£61	£92
Repeat lumpectomy	GAMMA	α = 95.55; β = 16.13	£1,542	£1,248	£1,866
Survival curve parameters					
Time to local recurrence	MULTIVARIATE NORMAL[a]				
β (treatment arm)	Covariance matrix		-0.256	-0.815	0.307
constant	0.081 −0.077 0.531		4.97	3.553	6.383
sigma	−0.008 0.131 0.035		0.436	0.072	0.797

Probabilities					
Other recurrence INTRABEAM from recurrence free (5 year)	BETA	α = 19.1; β = 378	0.048	0.029	0.071
Other recurrence EBRT from recurrence free (5 year)	BETA	α = 16.7; β = 337.9	0.047	0.028	0.071
Other recurrence after local recurrence (10.2 year)	BETA	α = 129; β = 181	0.416	0.362	0.471
INTRABEAM patient receives EBRT	BETA	α = 239; β = 1332	0.152	0.135	0.170
Mastectomy patient has reconstruction	BETA	α = 5120; β = 11365	0.311	0.304	0.318
INTRABEAM patient has mastectomy at local recurrence*	BETA	α = 18.4; β = 4.6	0.800	0.618	0.933
INTRABEAM patient dies from breast cancer (5 year)	BETA	α = 10.6; β = 310.8	0.033	0.016	0.055
EBRT patient dies from breast cancer (5 year)	BETA	α = 11.3; β = 407.8	0.027	0.014	0.045
Incident breast cancer patients suitable for INTRABEAM*	BETA	α = 294; β = 1528	0.161	0.145	0.179
Resource Use					
INTRABEAM delivery time*	NORMAL	Mean = 33; SE = 3.37	33	26.40	39.60
INTRABEAM planning time*	NORMAL	Mean = 6; SE = 0.61	6	4.80	7.20
Utilities					
Recurrence free after the first year	BETA	α = 2400; β = 558.5	0.811	0.8	0.83
Recurrence free in the first year	BETA	α = 2161; β = 635.3	0.773	0.76	0.79
Other recurrence	BETA	α = 171; β = 78.7	0.685	0.63	0.74
Other					
Catchment population served by one INTRABEAM device*	NORMAL	Mean = 1,000,000; SE = 102,041	1,000,000	800,004	1,199,996

* Distribution calculated after arbitrary ±20% variation applied to mean to obtain standard error; [a] On log scale

Table 38: Lower and upper parameter values examined in deterministic sensitivity analysis (where different from 2.5th and 97.5th percentiles given in Table 37)

Parameter	Base case	Lower value	Upper value
Proportion of incident breast cancer patients suitable for INTRABEAM	0.16	0.1	0.5
Fractions of EBRT required to complete a course of treatment	15	5	23
Lifetime of INTRABEAM device	10	5	10
Proportion of INTRABEAM patients requiring radiation shield	1	0.25	1
Age of cohort entering model	62	55	72
Discount rate for costs	0.035	0	0.06
Discount rate for health	0.035	0	0.06

Deterministic sensitivity analysis

Table 39 shows the results of the deterministic sensitivity analyses for INTRABEAM compared to EBRT for the most influential parameters. A tornado diagram depicting the range in incremental NMB given in this table is given in Figure 10. A complete set of deterministic sensitivity analysis results is given in Appendix 11.

Incremental NMB rather than ICER is used in Table 39 and Figure 10 as the ICER for INTRABEAM compared to EBRT is sometimes negative (Figure 11) and incremental NMB has a more straightforward interpretation. A WTP of £20,000 and equation (2) were used to calculate the incremental NMB.

Table 39 and Figure 10 compare INTRABEAM incrementally to EBRT in order to be consistent with the base case (Table 34). Thus a negative incremental NMB indicates that INTRABEAM is not cost-effective compared to EBRT (or conversely that EBRT is cost-effective compared to INTRABEAM). A positive incremental NMB indicates that INTRABEAM is cost-effective compared to EBRT (or conversely that EBRT is not cost-effective compared to INTRABEAM).

The results show that the incremental NMB is, above all, very sensitive to the probability of any other recurrence which is assumed for both EBRT and INTRABEAM as there is a very wide difference in the incremental NMB between the low and high values of these parameters. The differences lead to a

switch in which treatment is considered cost-effective at a WTP threshold of £20,000 per QALY. At a low probability of any other recurrence on the INTRABEAM arm INTRABEAM is cost-effective compared to EBRT at a WTP of £20,000 (shown by positive incremental NMB in Table 39). At high probability of any other recurrence on the INTRABEAM arm EBRT is a cost-effective treatment option at the £20,000 per QALY WTP threshold (shown by negative incremental NMB in Table 39). With low probability of any other recurrence on the EBRT arm EBRT is a cost-effective treatment option compared to INTRABEAM at the £20,000 per QALY WTP threshold, but this is reversed with high probability of any other recurrence on the EBRT arm, i.e. INTRABEAM becomes cost-effective at the £20,000 per QALY WTP threshold (Table 39).

The model is also somewhat sensitive to the probability of death from breast cancer on the INTRABEAM arm, and again this difference leads to a switch in which treatment is considered cost-effective at a WTP threshold of £20,000 per QALY. At low values for probability of death from breast cancer on the INTRABEAM arm INTRABEAM is cost-effective at a WTP of £20,000 per QALY, but it is not cost-effective compared to EBRT at high values for probability of death from breast cancer on the INTRABEAM arm (Table 39).

Change in which treatment is considered cost-effective at a WTP threshold of £20,000 per QALY also occurs between the low and high parameter values considered for the beta coefficient for the INTRABEAM arm in the lognormal model of time to local recurrence (Table 39). At low values of this coefficient EBRT is cost-effective compared to INTRABEAM, but at the highest values considered INTRABEAM becomes slightly more cost-effective than EBRT.

In summary the results of the DSA indicate that there is a degree of uncertainty surrounding the base case results. In the case of four parameters the difference between upper and lower values results in a switch in the treatment option which is considered cost-effective at a WTP of £20,000 per QALY.

Table 39: Key deterministic sensitivity analysis results for INTRABEAM vs EBRT. WTP set to £20,000 per QALY.

Variable description	Low value	High value	Low value incremental NMB (£)	High value incremental NMB (£)	Range (£)
Five-year probability of any other recurrence INTRABEAM	0.029	0.071	5,781	-9171	14,952
Five-year probability of any other recurrence EBRT	0.028	0.071	-8,760	5,977	14,737
Beta coefficient for INTRABEAM arm time to local recurrence	-0.815	0.307	-4,512	118	4,630
Five-year probability of death from breast cancer EBRT	0.014	0.045	-4,150	-346	3,804
Five-year probability of death from breast cancer INTRABEAM	0.016	0.055	1,051	-2,518	3,569
Constant - time to local recurrence	3.553	6.383	-3,367	-836	2,531
Discount rate for utilities	0	0.06	-3,192	-1,042	2,150
Number of EBRT deliveries required in course of treatment	5	23	-2,604	-832	1,772
Starting age of model cohort	55	72	-2,273	-757	1,516
Cost of delivering one fraction EBRT	71	178	-2,211	-877	1,334
Proportion of incident cases which are suitable for INTRABEAM	0.1	0.5	-2,064	-1,128	936
Sigma - time to local recurrence	0.072	0.797	-1,110	-2,018	908

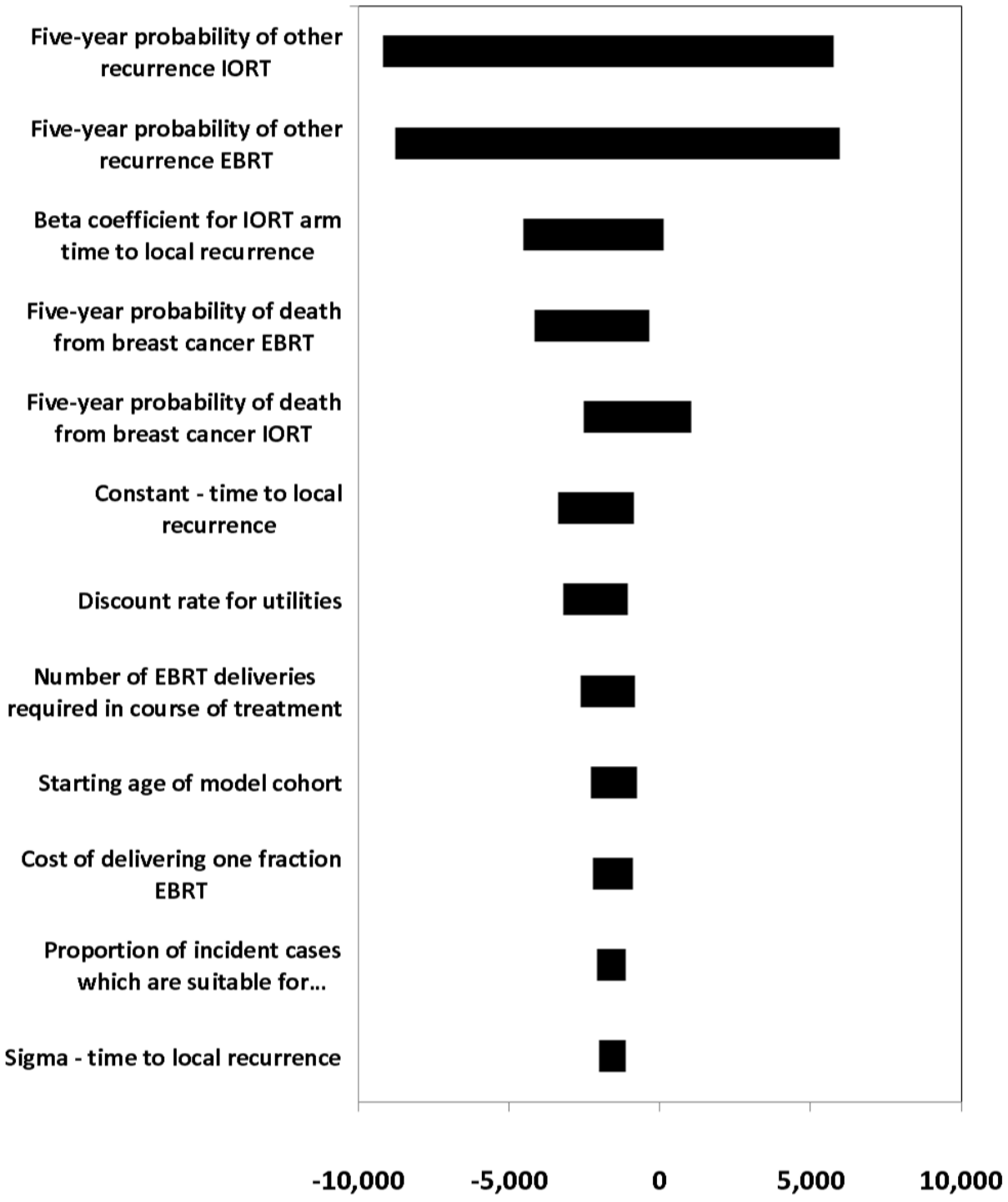


Figure 10: Tornado diagram showing key results of deterministic sensitivity analysis for INTRABEAM vs. EBRT. Bars indicate spread in incremental net monetary benefit between upper and lower parameter bounds (£s). WTP set to £20,000 per QALY.

Probabilistic sensitivity analysis

Ten thousand PSA simulations were run. The mean results for these simulations are presented in Table 40 and are similar to results for the base case given in Table 34. The scatter plot for cost and health outcomes is shown in Figure 11 and, similar to the DSA findings, indicates considerable

uncertainty in the results. There are many points in the north west quadrant of Figure 11 which demonstrate that in a large number of the PSA simulations INTRABEAM is less effective than EBRT, as well as being more costly. Conversely in many of the PSA simulations EBRT is more effective and cheaper than INTRABEAM, shown by the large number of points in the south east quadrant of Figure 11.

The cost-effectiveness acceptability curve (CEAC) calculated from the PSA simulations is given in Figure 12 and indicates that at the £20,000 WTP threshold EBRT has the highest probability (61.3%) of being cost-effective. EBRT also has the highest probability of being cost-effective (61.4%) at a WTP of £30,000 per QALY. INTRABEAM has a higher probability of being cost-effective than EBRT at WTP thresholds of around £5,000 per QALY or less (Figure 12).

Table 40: Baseline PSA cost-effectiveness results

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental Cost (£)	Incremental QALYs	ICER (£ saved / QALY lost)
EBRT	2,398	20.73	11.327	-	-	-
INTRABEAM	2,272	20.52	11.240	-126	-0.087	1,447*

* INTRABEAM is both cheaper and less effective than EBRT therefore the ICER represents the £ saved per QALY lost associated with replacing EBRT with INTRABEAM

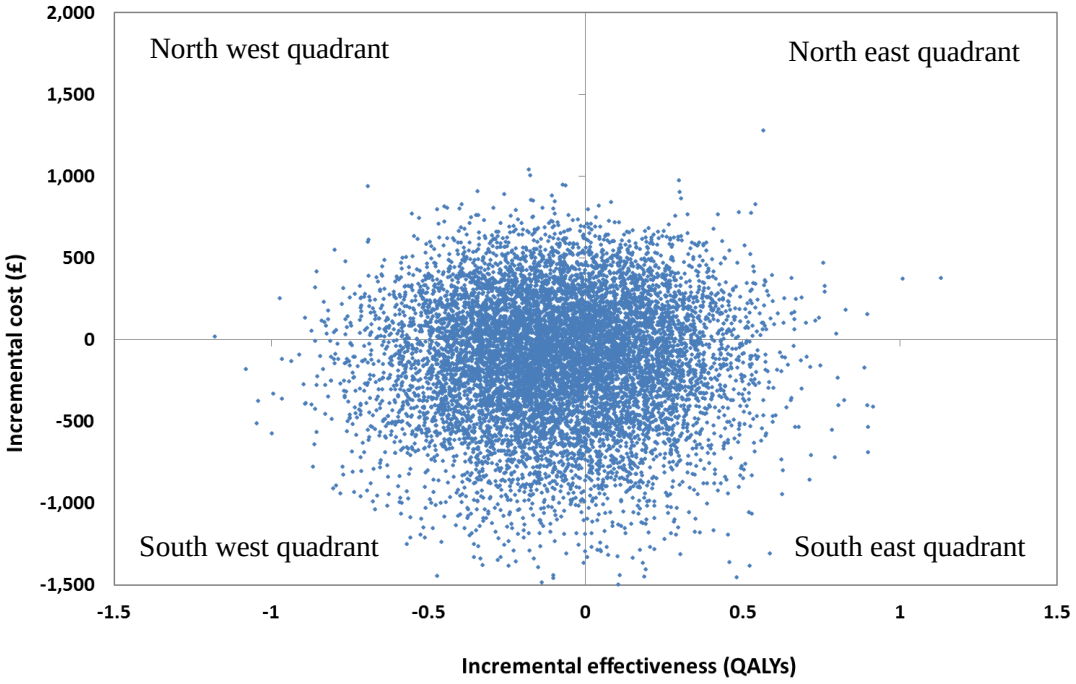


Figure 11: Scatter plot of the costs and health benefits from PSA, INTRABEAM vs EBRT

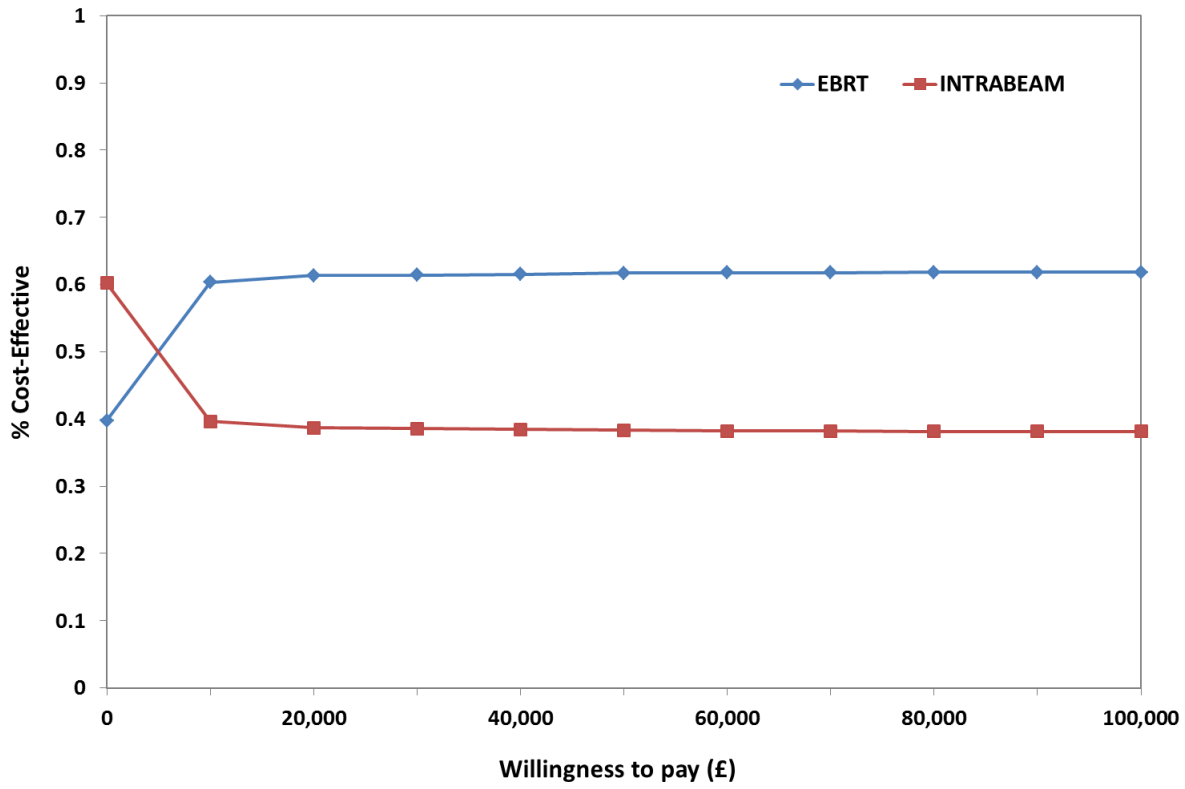


Figure 12: Cost effectiveness acceptability curve from the PSA

Scenario analysis

In addition to the sensitivity analyses five scenarios were examined to investigate the uncertainty surrounding the structural assumptions made by the model.

Trial-observed non-breast cancer mortality data

The model base case uses ONS all-cause mortality tables to give the probability of non-breast cancer death. As an alternative to using ONS data in all model cycles the use of non-breast cancer mortality data from the TARGIT-A trial was examined. A Weibull fit to TARGIT-A Kaplan-Meier data[65] was used to obtain trial-observed non-breast cancer mortality probabilities for the first five model cycles. ONS mortality data were used thereafter. INTRABEAM dominates EBRT in this scenario as it is associated with lower total costs and greater total QALYs (Table 41).

Table 41: Cost-effectiveness results using trial-observed non-breast cancer mortality data for first five model cycles

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental Cost (£)	Incremental QALYs	ICER (£/QALY)
EBRT	2,366	20.58	11.259	-	-	-
INTRABEAM	2,234	20.83	11.425	-132	0.166	Dominating

Population served by one device

The manufacturer's model assumes that 100 patients are treated with INTRABEAM each year in a district general hospital.[125] To replicate this assumption in the SHTAC model requires a corresponding assumption about the typical catchment population of a hospital offering INTRABEAM. In the base case the SHTAC model assumes that the catchment population is one million which implies 126 INTRABEAM procedures a year (Table 33). A catchment population of 795,000 is required to give 100 INTRABEAM procedures a year. Results using this catchment population are given in Table 42. The table shows that INTRABEAM is now dominated by EBRT as it is associated with slightly higher total cost, but fewer QALYs.

Table 42: Cost-effectiveness results using a population served by one INTRABEAM device of 795,000

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental Cost (£)	Incremental QALYs	ICER (£/QALY)
EBRT	2,368	20.72	11.329	-	-	-
INTRABEAM	2,414	20.51	11.241	47	-0.088	Dominated

Mastectomy disutility

The manufacturer's model uses a utility of 0.87 for lumpectomy at local recurrence, and a utility of 0.82 for mastectomy. These figures imply a disutility for mastectomy of 0.05. The AG considers that it is unclear from the literature if mastectomy is associated with significant disutility to HRQoL as measured with EQ-5D.[126;127] A scenario analysis was conducted to examine the effect of a mastectomy disutility of 0.05 on model outcomes. In the SHTAC model it is assumed that this disutility is a weighted average of the disutilities associated with mastectomy and mastectomy and reconstruction.

Results are given in Table 43 and Table 44. Table 43 shows results obtained when it is assumed that the mastectomy utility decrement applies to both the local recurrence and disease free after local recurrence health states; Table 44 shows results obtained when it is assumed that the mastectomy

utility decrement applies to the local recurrence health state only. Applying the utility decrement to both the local recurrence and disease free after local recurrence health states has more impact on final ICER than applying the decrement to the local recurrence state alone, but in neither case does the utility decrement make an appreciable difference to model outcome. The ICER decreases by less than £50 per QALY compared to the base case (Table 34).

The decrease in ICER compared to the base case indicates that EBRT becomes more cost-effective compared to INTRABEAM in this scenario. Although in the base case a smaller proportion of INTRABEAM patients have mastectomy at local recurrence (80% compared to 100% for EBRT), more INTRABEAM patients experience a local recurrence. The net effect is that the total mastectomy utility decrement is greater on the INTRABEAM arm, and consequently the incremental QALYs associated with EBRT are slightly higher than in the base case.

Table 43: Cost-effectiveness results using utility decrement of 0.05 for mastectomy (applied to local recurrence and disease free after local recurrence health states)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental Cost (£)	Incremental QALYs	ICER (£ saved / QALY lost)
EBRT	2,368	20.72	11.304	-	-	-
INTRABEAM	2,227	20.51	11.214	-140	-0.090	1,563*

* INTRABEAM is both cheaper and less effective than EBRT therefore the ICER represents the £ saved per QALY lost associated with replacing EBRT with INTRABEAM

Table 44: Cost-effectiveness results using utility decrement of 0.05 for mastectomy (applied to local recurrence health state only)

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental Cost (£)	Incremental QALYs	ICER (£ saved / QALY lost)
EBRT	2,368	20.72	11.326	-	-	-
INTRABEAM	2,227	20.51	11.238	-47	-0.088	1,592*

* INTRABEAM is both cheaper and less effective than EBRT therefore the ICER represents the £ saved per QALY lost associated with replacing EBRT with INTRABEAM

Alternative set of health state utilities

The health state utilities used in the model base case are the same in the local recurrence health state and the recurrence free health state after the first year (Table 24). Although these utilities are based on the studies of Lidgren and colleagues[91] and Turnbull and colleagues[87] it is arguably not appropriate that these two health states should have the same utility. Their identical values may arise because

EQ-5D is not a particularly sensitive instrument to use when examining QoL in early breast cancer patients, as found for example by Hildebrandt and colleagues.[93] An alternative set of health state utility values used in a previous HTA report to NICE was examined.[102] These were valued by either patients or clinical experts using the time trade off (TTO) and are given in Table 45.

Table 45: Alternative health state utility values examined in scenario analysis

Health state	Utility value	Source
Recurrence free	0.78	Hind and colleagues[102]
Local recurrence	0.61	
Disease free after local recurrence	0.71	
Any other recurrence	0.42	

Results for the scenario are given in Table 46. These show that although total QALYs decline in both treatment arms with use of the alternative utility set, the incremental QALYs do not change appreciably from the base case. Thus the overall ICER is very similar to the base case: £1,517 saved per QALY lost, compared to £1,596 in the base case (Table 34).

Table 46: Cost-effectiveness results using alternative set of health state utilities from Hind and colleagues[102]

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental Cost (£)	Incremental QALYs	ICER (£ saved / QALY lost)
EBRT	2,368	20.72	10.812	-	-	-
INTRABEAM	2,227	20.51	10.719	-140	-0.093	1,517*

* INTRABEAM is both cheaper and less effective than EBRT therefore the ICER represents the £ saved per QALY lost associated with replacing EBRT with INTRABEAM

Costs post-progression

The base case does not include costs of treatment post any other recurrence because of lack of information on the types of recurrence within this category. The trial publication reports the proportions with regional recurrence (1.1% INTRABEAM vs 0.9% EBRT) and distant recurrence (3.9% INTRABEAM vs 3.2% EBRT) for all patients, but does not give these data for the pre-pathology stratum.[65] However the costs for treating these types of recurrence are quite different.[102] Using costs given in the HTA report of Hind and colleagues,[102] inflated to 2013 using the Hospital and Community Health Services prices index,[119] the AG calculated the annual cost of metastatic disease (active treatment and supportive care) as £12,122, and the cost of end of life care for a breast cancer

patient as £3,669. In contrast the costs of contralateral disease are more similar to those incurred at local recurrence.[102]

For illustrative purposes the AG has considered a scenario in which 60% of recurrences in the 'any other recurrence' health state are assumed to be distant recurrences, and where mortality following any other recurrence is the same in both treatment arms [using the probability for EBRT in the base case (Table 23)]. This latter assumption is necessary because trial data show that mortality following any other recurrence is higher for INTRABEAM, and consequently including costs for this state without such adjustment would simply result in additional incremental cost for EBRT (as EBRT patients live longer in this state). A figure of 60% with distant recurrence was estimated based on data given in the TARGIT-A publication for all patients, and data in the literature.[102] The costs for distant recurrence are the major costs in the any other recurrence health state and as a simplification costs for the types of recurrence in this category were not considered. Using the costs given above for distant recurrence and end of life care the results shown in Table 47 were obtained. Health state costs for this scenario are given in Table 48.

Table 47. Illustrative cost-effectiveness results using post-progression costs

Intervention	Total costs (£)	Total LYG	Total QALYs	Incremental Cost (£)	Incremental QALYs	ICER (£ saved / QALY lost)
EBRT	4,652	20.72	11.329	-	-	-
INTRABEAM	4,662	20.51	11.268	-10	-0.061	157*

* INTRABEAM is both cheaper and less effective than EBRT therefore the ICER represents the £ saved per QALY lost associated with replacing EBRT with INTRABEAM

Table 48. Costs by health state including post-progression costs

Health state	EBRT total costs (£)	INTRABEAM total costs (£)
Recurrence free	2,100	1,882
Local recurrence	268	345
Disease free after local recurrence	0	0
Any other recurrence	1,795	1,897
Dead background mortality	0	0
Dead breast cancer	499	527

Table 47 shows that the base case conclusion does not change when post-progression costs for distant disease and end of life care are considered, i.e. INTRABEAM is not cost-effective compared to EBRT at a WTP threshold of £20,000 per QALY. However the cost saving associated with replacing EBRT with INTRABEAM is much smaller as the ICER is reduced from £1,596 saved per QALY lost in the base case, to £157 saved per QALY lost in the scenario. INTRABEAM is only £10 less expensive than EBRT per patient over the 40 year time horizon considered in the model.

5.7 Discussion

INTRABEAM is less expensive but also less effective than EBRT as it is associated with lower total costs but fewer total QALYs. The base case ICER for replacing EBRT with INTRABEAM is £1,596 saved per QALY lost. INTRABEAM is therefore not cost-effective compared to EBRT at the WTP threshold of £20,000 per QALY as the cost saved per QALY lost is less than £20,000.

The CEAC calculated from PSA indicates that at the £20,000 WTP threshold EBRT has a greater probability than INTRABEAM of being cost-effective, at 61.3%. EBRT also has the highest probability of being cost-effective (61.4%) at a WTP of £30,000 per QALY.

The base case result is subject to a degree of uncertainty as the disease progression parameters included in the model are largely drawn from the TARGIT-A trial[65] As discussed elsewhere this trial has relatively short follow-up. The numbers experiencing local recurrence in the pre-pathology stratum which is used to inform the economic model are also quite small. Results of DSA show that the base case finding that INTRABEAM is not cost-effective at a WTP of £20,000 per QALY compared to EBRT would be reversed if the probability of experiencing any other recurrence on the INTRABEAM arm was at the low end of its likely range; or if the probability of death from breast cancer on the INTRABEAM arm was at the low end of its likely range.

A strength of the economic model is that it is based upon data identified from systematic searches for clinical, cost-effectiveness and quality of life evidence. Other strengths are that quality of life/health state utility weights are taken from studies using the EQ-5D and valued using the UK general population tariff; and that a transparent approach was taken to costing the use of Intrabeam per procedure by considering all elements of the cost base.

Possible weaknesses of the model are that the systematic review of quality of life did not find EQ-5D values to populate all of the model health states, and that the clinical effectiveness data used to inform disease progression in the model are drawn largely from one study which has a relatively short follow up time. This study also has a small number of events for the primary outcome in the pre-pathology

stratum and the base case results are therefore subject to some uncertainty. Due to data limitations the model does not include costs for the any other recurrence health state in the base case.

5.7.1 Comparison of the economic models

A key structural difference between the Carl Zeiss economic model and the SHTAC model is that the Zeiss model has four health states while the SHTAC model has six health states. The SHTAC model includes an additional (temporary) health state at local recurrence, and also an 'any other recurrence' health state which includes metastatic disease. A further structural difference is that the Zeiss model uses an exponential assumption to extrapolate trial local recurrence data over the time horizon of the model, while the SHTAC model assumes a lognormal fit to these data. The Zeiss model is run over a ten year time horizon rather than the 40 year horizon used in the SHTAC model.

Different cost and utility data were also used. The Zeiss model uses expert opinion to inform the cost of each INTRABEAM procedure whilst the SHTAC model uses a micro-costing approach. The Zeiss model assumes that at local recurrence all INTRABEAM patients have salvage lumpectomy and that all EBRT patients have salvage mastectomy. The cost of salvage mastectomy in the Zeiss model appears to include the cost of breast reconstruction for all patients. In contrast the SHTAC model considers that most INTRABEAM patients will have mastectomy at local recurrence, and that of patients having mastectomy, not all of them will have reconstruction.

Utilities used in the Zeiss model were obtained via standard gamble and were not obtained from the general population. Utilities used in the SHTAC model were obtained using the EQ-5D and valued with the UK tariff.

6 ASSESSMENT OF FACTORS RELEVANT TO THE NHS AND OTHER PARTIES

The report "Radiotherapy Services in England 2012"[128] states that there are currently 265 linear accelerators operating in UK/England across 58 sites with new sites planned. Breast cancer accounted for 28% of radiotherapy services activity for the year 2011/2012. To meet projected increases in the need for radiotherapy (due to cancers in an aging population) it has been estimated that 412 linear accelerators will be required by 2016. In contrast, as noted in section 1.3 just eight INTRABEAM devices are known to have been purchased (four in London, and one each in Winchester, Dundee, Liverpool and Harlow) for use in the NHS with a further ten NHS Trusts expressing an interest in purchasing the device. Therefore there would be a need for significant investment in INTRABEAM equipment if this technology were to be available across the NHS. Furthermore in addition to the investment in equipment there would also need to be investment in staff training both for surgeons, physicists, oncologists and radiographers.

Advice from the Advisory Group for this assessment indicated that theatre capacity is also a consideration. The additional time needed in theatre to administer INTRABEAM therapy could add to pressure on breast clinics especially if they already find it difficult to meet waiting time targets. However, in centres where lymph node analysis is already undertaken intraoperatively using the RD-100i OSNA system (currently 22 in use in the UK, section 1.2) INTRABEAM therapy could be delivered and completed within this time and therefore would have less impact on theatre time.

As noted above breast cancer currently accounts for about 28% of activity across radiotherapy centres. How much radiotherapy resource could be freed up by increased use of INTRABEAM therapy depends in part on the proportion of patients who would be eligible for INTRABEAM treatment. In the AG's independent economic model (section 5.5.1 Demand for INTRABEAM) the proportion of incident cases of early breast cancer suitable for INTRABEAM therapy is estimated at 16%. If this were the case breast cancer would then account for about 24% of radiotherapy centre activity, a drop of 4%. However it should be remembered that the actual drop would be likely to be lower than this for two reasons. Firstly after INTRABEAM treatment some patients may be found to have tumours with unfavourable features that put them at high risk of recurrence, in which case they would receive EBRT in addition. Secondly, some patients will experience recurrence and, depending on their preference and extent of disease at recurrence, may opt for local excision and EBRT.

In the future radiotherapy resources may also be freed up if the current 3-week EBRT treatment schedule can be shortened. For example a clinical trial, the FAST-Forward non-inferiority RCT[129] is currently testing a one week (5-fraction) course of EBRT to see if it is as effective and as safe as the

current UK 15-fraction standard. The estimated publication date for this HTA funded trial is 2021. If this trial demonstrates that a one week course of EBRT is as effective and safe in this patient group then adoption of this shortened radiotherapy regimen would have a larger impact on radiotherapy resources than the introduction of INTRABEAM. The ability to identify a sub-set of women who could safely be treated without receiving EBRT might also free up radiotherapy resources in the future.

From the patient perspective INTRABEAM therapy may be viewed as an attractive option because the standard 15 fraction course of EBRT would be avoided for the majority of those eligible for INTRABEAM treatment. The benefits of this include a reduction in the disruption to work and family life both in terms of time (for travel as well as for treatment) and costs (e.g. travel, parking, loss of earnings) which may be significant particularly for those who live farthest from a radiotherapy centre and for those at the lower end of the income spectrum.

7 DISCUSSION

7.1 Statement of principal findings

- One international, multicentre, non-inferiority RCT[64;65] was included in the systematic review of clinical effectiveness. It examined IORT using the INTRABEAM device compared to conventional whole breast EBRT and was judged to be at a low risk of bias.
- Participants could be randomised to INTRABEAM or EBRT prior to surgery to remove the tumour (pre-pathology stratum) or could receive surgery to remove the tumour and be randomised into the trial after surgery providing initial histopathology showed no adverse criteria (post-pathology stratum). Participants in either stratum who were randomised to INTRABEAM and subsequently found to have unfavourable pathological features received EBRT in addition (i.e. INTRABEAM + EBRT).
- The primary outcome of the RCT was local recurrence in the conserved breast. The pre-stated non-inferiority margin was an absolute difference of 2.5% between groups. Non-inferiority of INTRABEAM compared with EBRT was demonstrated for the whole trial population and for the pre-pathology stratum. However non-inferiority was not established for the post-pathology stratum where the absolute difference in the 5-year local recurrence exceeded the pre-defined non-inferiority margin of 2.5%. In considering these results it should be remembered that the median follow-up of the total trial population was two years five months, 1222 (35%) had reached a median follow-up of five years.
- Overall survival was a secondary outcome of the RCT. Differences between the groups in overall mortality and for breast cancer mortality were not statistically significant for the whole trial population, the pre-pathology stratum or the post-pathology stratum. In contrast the analysis of non-breast cancer deaths showed that there were significantly fewer non-breast cancer deaths in the INTRABEAM group compared to the EBRT group in the whole trial population and when the pre-pathology stratum was analysed separately. In the post-pathology stratum there was no statistically significant difference in non-breast cancer mortality between the groups.
- For participants in the pre-pathology stratum treatment with INTRABEAM resulted in a 1% increase in local recurrence but this was counterbalanced with a potential 2.3% decrease in overall mortality.
- Clinically significant complications reported to differ statistically significantly between the groups were wound seroma requiring more than three aspirations which occurred more frequently in the INTRABEAM group and RTOG toxicity score of grade 3 or 4 which was less frequent in the INTRABEAM group. Early complications and complications arising six months after randomisation appeared similar between the groups.

- Limited information was available from one sub-study undertaken by one trial centre on quality of life.[63] Approximately 2.5% of the total trial population were involved in this study which did not identify any statistically significant differences in QoL measures (EORTC QLQ-C30 (version 3) and the QLQ-BR23) between the study arms.

Cost-effectiveness

- The systematic review identified two relevant economic evaluations,[78;80] both of which were based on the TARGIT-A trial. Both studies were associated with a number of limitations.
- Alvarado and colleagues[78] developed a Markov decision analytic model with six health states. Costs and benefits were discounted at 3%, costs were expressed in US$ and the price year was 2011. INTRABEAM was found to be associated with less cost and greater QALYs than EBRT.
- Shah and colleagues[80] analysed cost-effectiveness through reimbursement models and conducted a cost-minimisation analysis. Methods and assumptions were based on previously published articles. The authors concluded that although INTRABEAM represented a potential cost-saving alternative, EBRT represented a cost-effective modality compared to INTRABEAM based on cost per QALY analyses when additional medical costs and nonmedical costs associated with INTRABEAM were factored in.
- Both studies were based in the US and adopted a societal perspective, and are therefore not generalisable to the UK NHS.
- The horizon was ten years in one study[78] and not clearly stated in the other study[80] (but assumed to be ten years based on the estimation of mean utility), which is inappropriate as the risk of local recurrence continues over a lifetime.
- Alvarado and colleagues[78] used a standard 33 fractions of EBRT in their model; this is more than the current standard UK practice of 15 fractions and will lead to an overestimation of EBRT costs. The number of fractions of EBRT was not reported by Shah and colleagues.[80]
- The quality of utility data used in both the studies is questionable. The source study[81] was an old publication and more recent data would have been appropriate, such as those identified in section 5.2.

Quality of life

- The systematic review on HRQoL studies was conducted with an aim to identify utility data for the SHTAC independent model. Nine studies were identified; these were diverse with respect to their aims, interventions, comparators, study designs, and methodologies. When assessing the studies on the basis of their relevance to the NICE reference case, only three met all of the criteria (details in Appendix 9).[86;87;91]

- The studies provide a source of EQ-5D data for five of the seven health states identified *a priori* as being potentially relevant for the SHTAC independent model. EQ-5D data were not identified for the health states 'WLE+INTRABEAM' or 'WLE+INTABEAM+EBRT'.

Manufacturer's submission

- The MS evaluated the cost-effectiveness of INTRABEAM in early breast cancer patients when compared with radiotherapy usually given in the UK over 3-6 weeks as EBRT. The total costs, QALYs gained and cost-effectiveness associated with the intervention and comparator under consideration in the appraisal were reported. A multi-state Markov model consisting of four health states was constructed. The analysis was conducted for a time-period of 20 years with an annual cycle length. The perspective was that of the NHS. Benefits and costs were discounted at 3.5%.
- The base case results indicate that INTABEAM is associated with greater QALYs and lower costs than EBRT. One way sensitivity analyses and scenario analyses were not conducted. PSA found that at the £20,000 and £30,000 willingness to pay thresholds, INTRABEAM has the highest probability of being cost effective, at 100% for both thresholds.
- Limited information on the model structure and input parameters is provided in the MS and the AG has raised a number of concerns regarding the methods used; as a consequence the results of the MS model should be viewed with caution.

SHTAC Model

- INTRABEAM is less expensive but less effective than EBRT. The base case ICER for replacing EBRT with INTRABEAM is £1,596 saved per QALY lost. INTRABEAM is therefore not cost-effective compared to EBRT at the WTP threshold of £20,000 per QALY.
- At the £20,000 WTP threshold EBRT has a greater probability than INTRABEAM of being cost-effective, of 61.3%. EBRT also has the highest probability of being cost-effective (61.4%) at a WTP of £30,000 per QALY.
- The base case result is subject to a degree of uncertainty. For four model parameters the difference in their upper and lower values causes a switch in the treatment option which is considered cost-effective at a WTP of £20,000 per QALY. Model outcomes are particularly sensitive to the probability of any other recurrence.
- Alternative model health state utility values examined in scenario analysis do not substantively change the base case findings. Other scenario analyses show that: INTRABEAM is dominated by EBRT if it is assumed to serve a smaller catchment population than the base case; and that INTRABEAM dominates EBRT if trial-observed mortality data are used for the first five model cycles.

7.2 Strengths and limitations of the assessment

This assessment has the following strengths:

- The systematic reviews and economic evaluation have been carried out independent of any vested interest, and the results are presented in a consistent and transparent manner.
- The systematic reviews have been undertaken following established methodology and principles for conducting a systematic review. The methods used were set out in a research protocol (Appendix 1), which defined the research question in line with the NICE scope, and set out the inclusion and quality assessment criteria, data extraction process and the other methods to be employed during the evidence synthesis.
- An advisory group has informed the review from its initiation. The research protocol was informed by comments received from the advisory group and reviewed and the advisory group as commented on a draft of the final report.
- A de novo economic model has been developed following recognised guidelines. The model structure and data inputs are clearly presented in this report. The main results have been summarised and presented. This should facilitate replication and testing of our model assumptions.
- The economic model is based upon data identified from systematic searches for clinical, cost-effectiveness and quality of life evidence.
- The quality of life/health state utility weights used in the economic model are taken from studies using the EQ-5D and valued using the UK general population tariff.
- A transparent approach was taken to costing the use of Intrabeam per procedure by considering all elements of the cost base.
- The model is validated against external data.

In contrast, this assessment also has certain limitations:

- Only one RCT has been published that met the inclusion criteria for the review.
- The length of follow-up in the published reports of the included trial may be inadequate.
- The economic model is based upon estimates of efficacy from the included trial which may have inadequate follow-up.
- The systematic review of quality of life did not find EQ-5D values to populate all of the model health states.
- The economic model does not include any costs for the ‘any other recurrence’ health state in the base case due to limitations in the evidence base.

7.3 Uncertainties

- The TARGIT-A trial was a non-inferiority RCT with ITT results presented. An extension to the consort statement[72] for non-inferiority trials that there would be greater confidence in the results of a non-inferiority trial both ITT and non-ITT (per-protocol) results were presented and shown to be consistent with one another. As no per-protocol analysis was presented it is not known whether the results of such an analysis would confirm the findings of the ITT analysis.
- In the EBRT arm of the TARGIT-A trial centres were allowed to stipulate local policy for the delivery of EBRT and therefore there would have been some differences between EBRT delivered at different centres, for example in dose delivered or quality control. The impact of these differences is unknown however it seems unlikely that variations in EBRT as delivered in non-UK TARGIT-A trial centres and the standard UK radiotherapy schedule (40Gy in 15 fractions over 3 weeks[11]) would have an impact on results. Evidence from the UK based START-B trial[130] which was recruiting patients with operable early invasive breast cancer at a similar time to TARGIT-A compared a radiotherapy schedule of 50 Gy in 25 fractions over 5 weeks with 40 Gy in 15 fractions over 3 weeks. After a median follow-up of 6 years START-B showed that 5-year local-regional relapse from a 40 Gy in 15 fraction schedule (2·2%, 95% CI 1·3–3·1) were as least as favourable as the 50 Gy in 25 fraction schedule (3·3%, 95% CI 2·2 to 4·5). A potentially more important consideration is the possibility of variable quality control of EBRT between centres. The TARGIT-A trial protocol[66] voiced the expectation that all trial investigators would be working to local or national standards conforming to international guidelines for quality assurance and thus no trial specific quality control measures were put in place.
- Some key estimates of clinical efficacy used in the economic model have wide confidence intervals. Base case results are therefore subject to a degree of uncertainty which stems from uncertainty in the evidence base. For a few parameters the cost-effectiveness findings are reversed when values at the upper and lower bounds of the appropriate confidence interval are considered.

8 CONCLUSIONS

8.1 Implications for service provision

There would be a need for significant investment in INTRABEAM equipment, and in staff training for surgeons and physicists if this technology were to be available across the NHS. Theatre capacity is also a consideration.

8.2 Suggested research priorities

The evidence base for the use of INTRABEAM for the adjuvant treatment of early stage breast cancer is limited to one RCT, the TARGIT-A trial, which has reported on outcomes after a median follow-up of two years and five months. The population enrolled in the trial has a low risk of local recurrence and of mortality and therefore there is scope for uncertainty about whether the results observed to date will hold over the longer term. To increase confidence in the results longer term follow up data from the TARGIT-A trial are required. Future analyses should report the numbers experiencing each type of recurrence within the 'any other recurrence' category. 'Any other recurrence' included regional recurrence, contralateral breast recurrence, and distance recurrence which have very different prognoses and contribute to the slightly higher breast cancer mortality associated with INTRABEAM. The economic model is very sensitive to this.

To address the effectiveness of INTRABEAM in a wider range of patients analysis from other trials and analysis of registry data will be needed when sufficient data with an appropriate length of follow-up has been accrued [ongoing currently: one RCT (TARGIT-B), one prospective single arm study (TARGIT-E) and three registry database studies, Section 4.3].

Further HRQoL data are desirable. A very limited quantity has been published from the TARGIT-A trial and it is not clear whether HRQoL outcome data will be available for the whole trial population in the future.

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10 APPENDICES

Appendix 1 Protocol methods

Below is an extract showing the methods text from the original protocol for this review. The full protocol (including reference list and appendices) is available on the NICE website http://guidance.nice.org.uk/TAG/353/FinalProtocol/pdf/English and is registered on the International prospective register of systematic review (registration number CRD42013006720).

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.

Appendix 2 Search dates and example Medline search strategies for clinical effectiveness, cost-effectiveness and HRQoL

Databases searched for the systematic reviews of clinical effectiveness, cost-effectiveness and HRQoL are presented below. Searches were updated in March 2014.

Database searched (host)	**Clinical effectiveness searches**	**Cost effectiveness and QoL searches**
Cochrane Central, Cochrane CDSR, Cochrane DARE, Cochrane HTA, and Cochrane Methods (Cochrane Library)	All available years to 19/03/2014	
Cochrane Central, Cochrane DARE, Cochrane Economic Evaluations, and Cochrane Methods (Cochrane Library)		All available years to 18/03/2014 (QoL) and to 19/03/2014 (cost)
Centre for Reviews and Dissemination databases: DARE, HTA, and NHS EED (CRD)	All available years to 19/03/2014	All available years to 18/03/2014 (both)
Conference Proceedings Citation Index- Science (CPCI-S) (Web of Science)	All available years to 19/03/2014	All available years to 18/03/2014 (both)
Cost-effectiveness analysis (CEA) registry (Tufts Medical Center)		Searched to 19/03/2014 (cost)
EMBASE (Ovid)	All available years to 19/03/2014	All available years to 18/03/2014 (both)
MEDLINE(R) (Ovid)	All available years to 19/03/2014	All available years to 18/03/2014 (both)
MEDLINE(R) In-Process (MEIP) & Other Non-Indexed Citations (Ovid)	Searched to 19/03/2014	Searched to 18/03/2014 (both)
Science Citation Index Expanded (SCI-EXPANDED) (Web of Science)	1995 to 19/03/2014	1970 to 18/03/2014 (both)
ScienceDirect.com		Searched to19/03/2014 (cost)
Biosis Previews (Web of Science)	1995 to 19/03/2014	All available years to 18/03/2014 (both)
Zetoc (Mimas)		Searched to 19/03/2014 (cost)

Searched for ongoing trials (all searched on 25/03/2014)
National Institute for Health Research Clinical Research Network (NIHR CRN Portfolio, formally UKCRN website)
Controlled-trials.com
Clinical trials.gov
WHO International Clinical Trials Registry Platform (ICTRP)
American Society of Clinical Oncology (ASCO)

Example search strategies

Clinical Effectiveness

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

Cost-effectiveness

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 exp economics/

29 exp economics hospital/

30 exp economics pharmaceutical/

31 exp economics nursing/

32 exp economics medical/

33 exp "Costs and Cost Analysis"/

34 Cost Benefit Analysis/

35 exp models economic/

36 exp fees/ and charges/

37 exp budgets/

38 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*).tw.

39 (value adj1 money).tw.

40 budget$.tw.

41 or/28-40

42 ((energy or oxygen) adj cost).tw.

43 (metabolic adj cost).tw.

44 ((energy or oxygen) adj expenditure).tw.

45 or/42-44

46 41 not 45

47 (letter or editorial or comment or historical article).pt.

48 46 not 47

49 27 and 48

Lines 50-54 added to strategy on 25/09/2013. Nothing extra found as a consequence.

50 accelerated partial breast irradiation.mp. 430

51 APBI.tw. 266

52 50 or 51

53 48 and 52

54 53 not 49

HRQoL

1 exp Breast Neoplasms/

2 (breast* adj3 (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.

3 (mammar* adj3 (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.

4 or/1-3

5 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab.

6 (euroqol or euro qol or eq5d or eq 5d).ti,ab.

7 (hui or hui1 or hui2 or hui3).ti,ab.

8 (health adj3 utilit$ ind$).mp.

9 "EORTC QLQ-BR23".tw.

10 "FACT-B".tw.

11 "Functional Assessment of Cancer Therapy Breast".tw.

12 "BCQ".tw.

13 "breast cancer chemotherapy questionnaire".tw.

14 or/5-13

15 4 and 14

Appendix 3 Excluded clinical effectiveness studies with rationale

Excluded study	Primary reason for exclusion (comment)
Andersen KG, Gartner R, Kroman N, Flyger H, Kehlet H. Persistent pain after targeted intraoperative radiotherapy (TARGIT) or external breast radiotherapy for breast cancer: a randomized trial. The Breast 2012;21:46-9	Outcome (sub-study)
Andersen KG, Gartner R, Kroman N, Flyger H, Kehlet H. Persistent Pain After Targeted Intraoperative Radiotherapy (TARGIT) or External Breast Radiotherapy for Breast Cancer - a Randomized Trial. European Journal of Cancer 2011;47:S388.	Abstract [a]
Anon. HTA - 10/104/07: Targit B: An international randomised controlled trial to compare targeted intra-operative radiotherapy boost with conventional external beam radiotherapy boost after lumpectomy for breast cancer in women with a high risk of local recurrence. http://www.nets.nihr.ac.uk/projects/hta/1010407 (accessed 26\03\2014)	Ongoing (no data yet)
Baum M, Joseph DJ, Tobias JS, Wenz FK, Keshtgar MR, Alvarado M et al. Safety and efficacy of targeted intraoperative radiotherapy (TARGIT) for early breast cancer: first report of a randomized controlled trial at 10-years maximum follow-up. Journal of Clinical Oncology 2010;28.	Abstract [a]
Baum M, Vaidya JS, Tobias JS, Keshtgar M, Williams NR, Wenz F et al. Targit (targeted intra-operative radiotherapy for early stage breast cancer): Results from the targit a randomized controlled trial. European Journal of Cancer Supplement 2010;8:19.	Abstract [a]
Drago S, Ciabattoni A, Piccirillo R, Bellotti A, Cresti R, Ciccone V et al. Intraoperative radiation boost in early breast cancer: initial results of a randomized trial. Breast Cancer Research and Treatment 2004;88:S172.	Intervention (abstract)
Engel D, Schnitzer A, Brade J, Blank E, Wenz F, Suetterlin M et al. Are mammographic changes in the tumor bed more pronounced after intraoperative radiotherapy for breast cancer? Subgroup analysis from a randomized trial (TARGIT-A). Breast Journal 2013;19:92-5.	Outcomes [a]
HAYES,.Inc. Intraoperative Radiation Therapy (IORT) for breast cancer (CRD Database Structured abstract http://www.crd.york.ac.uk/crdweb/ShowRecord.asp?ID=32012000152). Health Technology Assessment 2011.	Design
Holmes DR, Baum M, Joseph D. The TARGIT trial: targeted intraoperative radiation	Abstract [a]

therapy versus conventional postoperative whole-breast radiotherapy after breast-conserving surgery for the management of early-stage invasive breast cancer (a trial update). American Journal of Surgery 2007;194:507-10.	
Joseph DJ. Targit. Radiotherapy and Oncology 2012;103:S4.	Abstract [a]
Keshtgar M, Vaidya J, Tobias J, Williams N, Baum M. TARGIT (Targeted intra-operative radiotherapy for early stage breast cancer): Early results from the multi-centre randomized controlled trial. European Journal of Surgical Oncology 2010;36:1098.	Abstract [a]
Keshtgar M, Williams N, Corica T, Saunders C, Joseph D, Bulsara M. Cosmetic outcome after targit compared with external beam radiotherapy for early breast cancer. Radiotherapy and Oncology 2011;99:S251.	Abstract [a]
Keshtgar M, Williams N, Corica T, Saunders C, Joseph D, Bulsara M. Cosmetic outcome one, two, three and four years after intra-operative radiotherapy compared with external beam radiotherapy for early breast cancer: an objective assessment of patients from a randomised controlled trial. Breast 2011;20:S63.	Abstract [a]
Keshtgar M, Williams N, Corica T, Saunders C, Joseph D. Better cosmetic outcome after intraoperative radiotherapy compared with external beam radiotherapy for early breast cancer: Objective assessment of patients from a randomized controlled trial. Annals of Surgical Oncology 2010;17:S178.	Abstract [a]
Keshtgar M, Williams N, Corica T, Saunders C, Joseph D. Cosmetic outcome one, two and three years after intra-operative radiotherapy compared with external beam radiotherapy for early breast cancer: An objective assessment of patients from a randomised controlled trial. European Journal of Surgical Oncology 2010;36:1105.	Abstract [a]
Keshtgar M, Williams N, Corica T, Saunders C, Joseph D. Significantly better cosmetic outcome after intraoperative radiotherapy compared with external beam radiotherapy for early breast cancer: Objective assessment of patients from a randomized controlled trial. Annals of Surgical Oncology 2011;18:S171.	Abstract [a]
Keshtgar M, Williams NR, Corica T, Bulsara M, Saunders C, Flyger H et al. An objective assessment of cosmetic outcome after intraoperative radiotherapy or external beam radiotherapy for early breast cancer in patients from a randomized controlled trial. European Journal of Cancer 2013;49:S450.	Abstract [a]
Keshtgar M, Williams NR, Corica T, Hedges R, Saunders C, Joseph D. Early evidence of better cosmetic outcome after intra-operative radiotherapy compared with external beam radiotherapy for early breast cancer: Objective assessment of patients from a randomised controlled trial. Annals of Surgical Oncology 2010;17:S13.	Abstract [a]
Keshtgar M, Williams NR, Corica T, Saunders C, Bulsara M, Joseph D. Improved	Abstract [a]

cosmetic outcome after TARGIT compared with external beam radiotherapy for early breast cancer. European Journal of Cancer 2012;48:S186-S187.	
Keshtgar MR, Williams NR, Bulsara M, Saunders C, Flyger H, Cardoso JS et al. Objective assessment of cosmetic outcome after targeted intraoperative radiotherapy in breast cancer: results from a randomised controlled trial. Breast Cancer Research & Treatment 2013;140:519-25.	Outcome (sub-study) [a]
Keshtgar MR, Williams NR, Corica T, Bulsara M, Saunders C, Flyger H et al. Cosmetic outcome after intraoperative radiotherapy or external beam radiotherapy for early breast cancer: An objective assessment of patients from a randomized controlled trial. Journal of Clinical Oncology 2013;31:var.pagings.	Abstract [a]
Keshtgar MR, Williams NR, Corica T, Bulsara M, Saunders C, Flyger H et al. Cosmetic outcome after intraoperative radiotherapy or external beam radiotherapy for early breast cancer: An objective assessment of patients from a randomized controlled trial. Journal of Clinical Oncology 2013;15:1110.	Abstract [a]
Keshtgar MR, Williams NR, Corica T, Saunders C, Bulsara M, Joseph D. Cosmetic outcome one, Two, Three, and four years after intra-operative radiotherapy compared with external beam radiotherapy for treatment of early breast cancer: An objective assessment of patients from a randomized controlled trial. International Journal of Radiation Oncology Biology Physics 2011;81:S225.	Abstract [a]
Keshtgar MR, Williams NR, Corica T, Saunders C, Joseph DJ, Bulsara M. Cosmetic outcome 1, 2, 3, and 4 years after intraoperative radiotherapy or external beam radiotherapy for early breast cancer: An objective assessment of patients from a randomized controlled trial. Journal of Clinical Oncology 2011;29:94.	Abstract [a]
Keshtgar MR, Williams NR, Corica T, Saunders C, Joseph DJ. Cosmetic outcome two and three years after intraoperative radiotherapy compared with external beam radiotherapy for early breast cancer: An objective assessment of patients from a randomized controlled trial. Journal of Clinical Oncology 2010;28:570.	Abstract [a]
Sperk E, Welzel G, Keller A, Kraus-Tiefenbacher U, Gerhardt A, Sutterlin M et al. Late radiation toxicity after intraoperative radiotherapy (IORT) for breast cancer: Results from the randomized phase III trial TARGIT A. Strahlentherapie und Onkologie 2012;188:62.	Abstract [a]
Sperk E, Welzel G, Keller A, Kraus-Tiefenbacher U, Gerhardt A, Sutterlin M et al. Late radiation toxicity after intraoperative radiotherapy (IORT) for breast cancer: results from the randomized phase III trial TARGIT A. Breast Cancer Research & Treatment 2012;135:253-60.	Outcome (sub-study) [a]
Sperk E, Welzel G, Keller A, Kraus-Tiefenbacher U, Gerhardt A, Sutterlin M et al.	Abstract [a]

Late Radiation Toxicity After Intraoperative Radiotherapy (IORT) for Breast Cancer: Results From the Randomized Phase III Trial TARGIT A. European Journal of Cancer 2012;48:S187-S188.	
Vaidya JS, Baum M, Tobias JS, Houghton J, Keshtgar M, Sainsbury R et al. Targeted intraoperative radiotherapy for breast cancer - a randomised trial. Breast Cancer Research and Treatment 2001;69:228.	Outcomes [a] (abstract)
Vaidya JS, Massarut S, Tobias JS, Wenz F, Bulsara M, Keshtgar M et al. Targeted intra-operative radiotherapy boost-TARGIT-B trial: A randomized trial for young and high risk patients including those after post-neoadjuvant systemic therapy lumpectomy. European Journal of Surgical Oncology 2010;36:820.	Outcomes (abstract)
Vaidya JS, Tobias JS, Baum M, Houghton J, Keshtgar M, Sainsbury R. Targeted intra-operative radiotherapy (TARGIT) for breast cancer: A randomised trial. Radiology 2001;221:278.	Outcomes [a] (abstract)
Vaidya JS. An international randomised controlled trial to compare targeted intra-operative radiotherapy (TARGIT) with conventional post-operative radiotherapy for women with early breast cancer (Project record). Health Technology Assessment 2010;In Progress (Estimated publication date mid-2015).	Outcomes [a] (trial protocol)
Valachis A, Mauri D, Polyzos NP, Mavroudis D, Georgoulias V, Casazza G. Partial Breast Irradiation or Whole Breast Radiotherapy for Early Breast Cancer: A Meta-Analysis of Randomized Controlled Trials. Breast Journal 2010;16:245-51.	Intervention
Welzel G, Boch A, Blank E, Kraus-Tiefenbacher U, Keller A, Hermann B et al. Radiation-related Quality of Life Parameters after Targeted Intraoperative Radiotherapy vs. Whole Breast Radiotherapy in Patients with Breast Cancer: Results from the Randomized Phase III Trial TARGIT-A. International Journal of Radiation Oncology Biology Physics 2011;81:S206-S207.	Abstract [a]
Williams N, Keshtgar M, Corica T, Saunders C, Bulsara M, Joseph DJ. Cosmetic outcome after intra-operative radiotherapy for early breast cancer in women over 50 years. Radiotherapy and Oncology 2012;103:S128-S129.	Abstract [a]
Williams NR, Keshtgar M, Corica T, Saunders C, Joseph D, Bulsara MK. Early Breast Cancer and Cosmetic Outcome One, Two, Three and Four Years After Intra-operative Radiotherapy Compared With External Beam Radiotherapy: an Objective Assessment of Patients From a Randomised Controlled Trial (on Behalf of the TARGIT Trialists' Group). European Journal of Cancer 2011;47:S365.	Abstract [a]
Williams NR, Keshtgar M, Corica T, Saunders C, Joseph D. Significantly better cosmetic outcome after intra-operative radiotherapy compared with external beam radiotherapy for early breast cancer: Objective assessment of patients from a	Abstract [a]

randomised controlled trial. European Journal of Cancer Supplements 2010;8:129.	
Zhou SF, Shi WF, Meng D, Sun CL, Jin JR, Zhao YT. Interoperative radiotherapy of seventy-two cases of early breast cancer patients during breast-conserving surgery. Asian Pacific Journal of Cancer Prevention: Apjcp 2012;13:1131-5.	Intervention

[a] Linked to the TARGIT-A trial

Appendix 4 Clinical effectiveness data extraction tables

Reviewer 1: JP **Date:** 13/11/13	**Reviewer 2:** DH **Date:** 19/11/13	**Version:** 2	
Reference and design	**Intervention and Comparator**	**Participants**	**Outcome measures**
Vaidya *et al.*,2014,[65] 2010[64] Linked sub-studies[63;73-75] (separate data extractions) TARGIT-A trial (TARGeted Intraoperative radioTherapy Alone) *Study design*: International, multicentre, non-inferiority RCT *Countries:* UK, Europe, Australia, USA, Canada *Number of centres*: 33 centres in 11 countries[65] UK (6), Germany (7), Italy (3), Switzerland (2), Denmark (1), Poland (1), Norway (1), USA (7), Canada (1), Australia (2), France (2) (for the mature cohort reported in 2010[64] 28 centres in 10 countries UK [5], Germany [6], Italy [2], Switzerland [2], Denmark [1], Poland [1], Norway [1], USA [7], Canada [1], Australia [2])	*Intervention*: Targeted intraoperative radiotherapy – Targit* (Intrabeam device) *Dose*: typically 20Gy to surface of tumour bed attenuating to 5-7Gy at 1cm depth. *Comparator*: Whole breast external beam radiotherapy – EBRT *Dose*: typically 40-56Gy +/- boost of 10-16Gy. *Other interventions used*: Adjuvant systemic treatment as appropriate - hormone therapy, chemotherapy or other (not specified). A risk-adapted approach in the Targit arm was prespecified. Any participants in the	*Number of randomised participants*: 2014 paper[65] n= 3451 Targit, n= 1721 EBRT, n= 1730 (n=2298 in prepathology stratum, n=1153 in postpathology)[65] 2010 paper[64] n = 2232 Targit, n= 1113 EBRT, n= 1119 (n=1482 in prepathology stratum, n=672 in postpathology stratum, n=78 in contralateral stratum)[64] *Inclusion criteria*: Women with early breast cancer, aged ≥ 45 years, suitable for wide local	*Primary outcomes:* Local recurrence (in the conserved breast) *Secondary outcomes:* Local toxicity or morbidity (complications pre-specified).[64] Overall survival (breast cancer and non-breast cancer deaths)[65] Specimen weight, margin status and re-operation for margins (analysed to compare the extent of local surgery).[64] *Method of assessing outcomes:* Described in the paper reporting initial results:[64] Assessments at entry, 3 & 6 months, then every 6 months for up to 5 years and every year for up to 10 years. Local recurrence was pathologically

Recruitment dates: 24th Mar 2000 to 25th June 2012 *Funding*: University College London (UCL) Hospitals, UCL Comprehensive Biomedical Research Centre, UCLH Charities, NIHR HTA Programme (primary funder), Ninewells Cancer Campaign, National Health and Medical Research Council, German Federal Ministry of Education and Research. This was an academically driven trial and the funding bodies had no role in trial design, data analysis or interpretation, or writing the report.	Targit group with prespecified unfavourable pathological features found subsequently received EBRT in addition after Targit. Three adverse features were defined in the core protocol (tumour-free margin < 1mm; extensive in-situ component; unexpected invasive lobular carcinoma) & centres could prespecify additional features before starting recruitment. *Some patients received Intrabeam during initial surgery following tumour removal but protocol allowed for post-pathology entry of patients whereby patients underwent initial surgery and were then randomised to receive EBRT or Targit as a 2nd procedure.	excision for invasive ductal carcinoma that was unifocal on conventional examination and imaging. *Exclusion criteria*: Pre-operative diagnosis of lobular carcinoma. (More detailed exclusion criteria are given in the protocol www.hta.ac.uk/project/1981.asp)	confirmed (no further details). Toxicity or morbidity assessed from data recorded on a complications form containing a pre-specified checklist (haematoma, seroma, wound infection, skin breakdown, delayed wound healing, Radiation Therapy Oncology Group (RTOG) toxicity grade 3 or 4 for dermatitis, telangiectasia, pain in irradiated field, or other). Skin breakdown or delayed wound healing or RTOG toxicity grade >2 classified as major toxicity. Described in the 2014 paper:[65] If breast cancer was present at the time of death, the death was presumed to be from breast cancer. *Length of follow-up:* Overall median 2 years & 5 months (IRQ 12–52 months). A median follow up of 4 years was reached by 2020

			participants and of 5 years by 1222 participants. The mature cohort of 2232 participants (first reported on in 2010[64]) had a median follow up of 3 years and 7 months (IRQ 30–61 months) in the 2014 paper.[65] For the earlier 2010 paper follow-up was up to 10 years (data lock 2nd May 2010)[64]
Baseline characteristics[65]	**Targit n=1721**	**EBRT n= 1730**	**p-value**
Age (years), n/N (%):			0.274
≤50	150/1721 (9)	122/1730 (7)	
51-60	527/1721 (31)	548/1730 (32)	
61-70	781/1721 (45)	807/1730 (47)	
>70	263/1721 (15)	253/1730 (15)	
Pathological tumour size (cm), n/N (%):			0.273
≤1	611/1552 (39)	597/1530 (39)	
1.1-2	751/1552 (48)	726/1530 (48)	
>2	190/1552 (12)	207/1530 (14)	
Unknown	169/1721 (10)	200/1730 (12)	
Grade[a], n/N (%):			0.394
1	528/1517 (35)	558/1505 (37)	
2	757/1517 (50)	720/1505 (48)	
3	232/1517 (15)	227/1505 (15)	
Unknown	194/1721 (11)	225/1730 (13)	
Lymphovascular invasion, n/N (%):			0.224
Absent	1348/1542(87)	1343/1521 (88)	
Present	194/1542 (13)	178/1521 (12)	

Unknown	179/1721 (10)	209/1730 (12)	
Nodes involved, n/N (%):			0.091
0	1307/1569 (83)	1303/1543 (85)	
1-3	219/1569 (14)	211/1543 (14)	
>3	43/1569 (3)	29/1543 (2)	
Unknown	152/1721 (9)	187/1721 (11)	
ER status, n/N (%):			0.090
ER +ve	1441/1561 (92)	1433/1532 (94)	
ER -ve	120/1561 (8)	99/1532 (7)	
ER unknown	160/1721 (9)	198/1730 (12)	
PgR status, n/N (%):			0.179
PgR +ve	1232/1521 (81)	1230/1495 (82)	
PgR -ve	289/1521 (19)	265/1495 (18)	
PgR unknown	200/1721 (12)	235/1730 (14)	
HER 2, n/N (%):			0.585
Positive	170/1499 (11)	178/1487 (12)	
Negative	1329/1499 (89)	1309/1487 (88)	
Unknown	222/1721 (13)	243/1730 (14)	
Additional baseline characteristics present only in the 2010 paper[64]	**Targit n=1113**	**EBRT n= 1119**	**Comments**
Height (cm)	164 (159-168)	163 (159-168)	
Weight (kg)	70 (62-80)	70 (62-80)	
Tumour type: Invasive ductal carcinoma Invasive lobular carcinoma Mixed Unknown	 1012/1070 (95%) 47/1070 (4%) 32/1070 (3%) 43/1113 (4%)	 1018/1079 (94%) 45/1079 (4%) 35/1079 (3%) 40/1119 (4%)	
Ductal carcinoma in situ: Present Absent Unknown	 529/1063 (50%) 534/1063 (50%) 50/1113 (4%)	 547/1069 (51%) 522/1069 (49%) 50/1119 (4%)	
Adjuvant therapy: Hormone therapy Chemotherapy Other	 727/1113 (65%) 116/1113 (10%) 48/1113 (4%)	 753/1119 (67%) 141/1119 (13%) 41/1119 (4%)	

Unknown	100/1113 (9%)	89/1119 (8%)	

Comments: ER - estrogen receptor; PgR - progesterone receptor; HER 2 - human epidermal growth factor receptor 2. Data are n/N (%) or median (IQR). The denominator for 'unknown' percentages is the number of randomised patients; the denominator for each category is the number of known cases. Percentages are rounded so may not add up to 100%. [a]Grading system not stated. Most of the unknown data in the 2014 paper[65] is from the 342 patients randomised in the last 6 months before data lock. States that most cancers were small and with good prognosis (87% [2685/3082] up to 2 cm, 85% [2573/3032] grades 1 or 2, 84% [2610/3112] node negative, 93% [2874/3093] oestrogen-receptor positive and 82% [2462/3016] progesterone-receptor positive). The majority were detected by screening (69% [2102 of 3063]). Reviewers note there may be an error in the reported data for n/N with grades 1 or 2 because data in the baseline table sum to 2563/3022 (still 85%).

Results

Primary Outcome	**Targit n=1721**	**EBRT n=1730**	**Absolute difference; p-value**
Events/N; 5-year cumulative risk % (95% CI)[65]			
Local recurrence, all patients[b]	23/1679 3.3% (2.1-5.1)	11/1696 1.3 (0.7-2.5)	12 (2.0%); p=0.042
Local recurrence, prepathology stratum	10/1107 2.1% (1.1 to 4.2)	6/1127 1·1% (0.5 to 2.5)	4 (1.0%); p=0.31
Local recurrence, postpathology stratum	13/572 5.4% (3.0 to 9.7)	5/569 1.7%(0.6 to 4.9)	8 (3.7%), p=0.069

Comments: [b] Patients who had undergone a mastectomy were not included in the analysis of local recurrence.

An analysis of cumulative incidence for local recurrence in the presence of competing risks (death and withdrawal from trial) when compared to Kaplan-Meier estimates were no different indicating that the competing risks did not bias the main results. Limiting analysis to the mature cohort (first reported in 2010[64]) was undertaken but not reported in the 2014[65] paper which states that it yielded much the same results as most events had occurred (32/34 local recurrences, 85/88 deaths).

Local recurrence: Calculation of $p_{non\text{-}inferiority}$[65]	**Median follow-up**	**Events, n/N**	**Absolute difference (90% CI) in the binomial proportions[c] of ipsilateral local recurrence (Targit minus EBRT)**	**Z score**	**$p_{non\text{-}inferiority}$**
Whole trial:	2 yr 5 months	34/3451	0.72% (0.2 to 1.3)	-5.168	<0.0001

all patients					
Whole trial: Mature cohort	3 yr 7 months	32/2232	1.13% (0.3 to 2.0)	-2.652	0.0040
Whole trial: Earliest cohort	5 years	23/1222	1.14% (-0.1 to 2.4)	-1.750	0.0400
Prepathology: all patients	2 yr 4 months	16/2298	0.37% (-0.2 to 1.0)	-5.954	<0.0001
Prepathology: Mature cohort	3 yr 8 months	14/1450	0.6% (-0.3 to 1.5)	-3.552	0.0002
Prepathology: Earliest cohort	5 years	9/817	0.76% (-0.4 to 2.0)	-2.360	0.0091
Postpathology: all patients	2 yr 4 months	18/1153	1.39% (0.2 to 2.6)	-1.503	0.0664
Postpathology: Mature cohort	3 yr 7 months	18/782	2.04% (0.3 to 3.8)	-0.429	0.3339
Postpathology: Earliest cohort	5 years	14/405	1.8% (-1.2 to 4.8)	-0.382	0.3511

Comments: [c] Binomial proportion = number of recurrences/number of patients.
The prespecified non-inferiority margin was 2.5%. Mature cohort = participants previously reported on in 2010;[64] earliest cohort excludes participants enrolled in the last 4 years of the study. Non inferiority is established for the whole cohort and for pre-pathology patients but not for post-pathology patients.

Local recurrence in conserved breast for pre-pathology stratum	**Absolute difference in 5-year Kaplan-Meier estimate (SE)**
Whole cohort, n=2298, median follow-up 2yr 4 months	1.1 (0.2 to 1.9)
Mature cohort, n=1450, median follow-up 3yr 8 months	1.1 (0.2 to 1.9)
Earliest cohort, n=817, median follow-up 5yr	1.0 (0.1 to 1.9)

Comments: Data estimated from graph (Fig 4) by reviewer using Engauge digitizing software.
Unplanned post-hoc exploratory analyses are reported in the appendix (e-table 2) for primary and secondary outcomes in the following 3 groups: prepathology receiving Targit alone; prepathology receiving Targit + EBRT; postpathology receiving Targit alone. These post-hoc, non-randomised data have not been extracted.

Secondary Outcome: Mortality, Events n/N	**Targit**	**EBRT**	**Absolute difference; p-value**

5yr cumulative risk (95% CI)			
Death, all patients	37/1721 3.9% (2.7 to 5.8)	51/1730 5.3% (3.9 to 7.3)	-14 (-1.4%); p=0.099
Death, prepathology stratum	29/1140 4.6% (1.8 to 6.0)	42/1158 6.9% (4.3 to 9.6)	-13 (-2.3%)
Death, postpathology stratum	8/581 2.8% (1.3 to 5.9)	9/572 2.3% (1.0 to 5.2)	-1 (0.5%)
Breast cancer mortality, all patients	20/1721 2.6% (1.5 to 4.3)	16/1730 1.9% (1.1 to 3.2)	p=0.56
Breast cancer mortality, prepathology stratum	17/1140 3.3% (1.9 to 5.8)	15/1158 2.7% (1.5 to 4.6)	p=0.72
Breast cancer mortality, postpathology stratum	3/581 1.2% (0.4 to 4.2)	1/572 0.5% (0.1 to 3.5)	p=0.35
Non-breast cancer mortality, all patients	17/1721 1.4% (0.8 to 2.5)	35/1730 3.5% (2.3 to 5.2)	p=0.0086
Non-breast cancer mortality, prepathology stratum	12/1140 1.3% (0.7 to 2.8)	27/1158 4.4% (2.8 to 6.9)	p=0.016
Non-breast cancer mortality, postpathology stratum	5/581 1.58% (0.62 to 3.97)	8/572 1.76 (0.7 to 4.4)	p=0.32
Comments: In absolute terms in the Targit group compared to the EBRT group there were: In the Targit group overall 12 additional local recurrences and 14 fewer deaths In the Targit group, pre-pathology stratum 4 additional local recurrences and 13 fewer deaths In the Targit group, post-pathology stratum 8 additional local recurrences and one less death			
Non-breast cancer mortality, causes of death	**Targit n=1721**	**EBRT n=1730**	
Other cancers	8	16	
Cardiovascular causes			
Cardiac[d]	2	8	
Stroke	0	2	
Ischemic bowel	0	1	
Other[e]	7	8	
Total	17	35	
Comments: [d] Included one "sudden death at home" in the EBRT group. [e] Targit: 2 diabetes, 1 renal failure, 1 liver failure, 1 sepsis, 1 Alzheimer's disease, 1 unknown; EBRT: 1 myelopathy, 1 perforated bowel, 1 pneumonia, 1 old age, 4 unknown.			

Overall mortality for pre-pathology stratum	**Absolute difference in 5-year Kaplan-Meier estimate (SE)**
Whole cohort, n=2298, median follow-up 2yr 4 months	-2.3 (-0.7 to -3.9)
Mature cohort, n=1450, median follow-up 3yr 8 months	-2.6 (-1.0 to -4.2)
Earliest cohort, n=817, median follow-up 5yr	-2.2 (-0.3 to -4.1)
Comment: Data estimated from graph (Figure 4) in trial paper[65] by reviewer using Engauge digitizing software.	

Secondary Outcome: Early[f] complications	**Targit n=1113**	**EBRT n= 1119**	
No. of complications per patient:[64]			
0	917/1113 (82.4%)	946/1119 (84.5%)	NR
1	151/1113 (13.6%)	139/1119 (12.4%)	NR
2	29/1113 (2.6%)	27/1119 (2.4%)	NR
3	11/1113 (1.0%)	5/1119 (0.4%)	NR
4	3/1113 (0.3%)	0/1119	NR
5	2/1113 (0.2%)	0/1119	NR
6	0/1113	3/1119 (0.3%)	NR
Any complication[g]	196/1113 (17.6%)	174/1119 (15.5%)	$\chi 2$ 1.74, p=0.19[c]
Comments: [f] The 2010 paper[64] does not indicate the time period over which these complications arose but the 2014[65] paper describes them as 'early complications'. [g] Targit vs EBRT for no complications vs any number of complications, degree of freedom = 1. Data are number of patients (%).			
Clinically significant complications[h]:[64]			
Haematoma needing surgical evacuation	11/1113 (1.0%)	7/1119 (0.6%)	0.338
Seroma needing more than 3 aspirations	23/1113 (2.1%)	9/1119 (0.8%)	0.012
Infection needing i.v. antibiotics or surgical intervention	20/1113 (1.8%)	14/1119 (1.3%)	0.292
Skin breakdown or delayed wound healing[i]	31/1113 (2.8%)	21/1119 (1.9%)	0.155
RTOG toxicity grade 3 or 4[j]	6/1113 (0.5%)	23/1119 (2.1%)	0.002

Major toxicity[k]	37/1113 (3.3%)	44/1119 (3.9%)	0.443
Comments: RTOG, Radiation Therapy Oncology Group. Data are number of patients (%).[h] The 2010 paper[64] does not indicate the time period over which these complications arose but the 2014[65] paper describes them as 'early complications'. [i]Some patients in 1st 3 rows could be included in 4th row. [j]No patient had grade 4 toxicity. [k]Defined as skin breakdown or delayed wound healing and RTOG toxicity grade of 3 or 4.			
Complications arising 6 months after randomisation[65]	**Targit n=1721**	**EBRT n=1730**	p-value
Wound related:			
Haematoma/seroma needing >3 aspirations	4/1721 (0.2%)[l]	2/1730 (0.1%)[l]	
Infection needing i.v. antibiotics or surgery	12/1721 (0.7%)[l]	9/1730 (0.5%)[l]	
Skin breakdown or delayed wound healing	3/1721 (0.2%)[l]	5/1730 (0.3%)[l]	
Total	19/1721 (1.1%)	16/1730 (0.9%)	0.599
Radiotherapy-related: RTOG Grade 3 or 4 toxicity	4/1721 (0.2%)	13/1730 (0.8%)	0.029
Comment: It is not clear whether the complications arising 6 months after randomisation occurred in any of the same patients who are reported in the 2010 paper[64] as having clinically significant complications. [l]Percentages calculated by reviewer.			
Secondary outcome: extent of local surgery[64]	**Targit n=1113**	**Targit n=1119**	
Specimen weight (g)[l]	46 (28-72)	47 (29-76)	
Margins at 1st excision:			
Free	970/1072 (90.5%)	968/1073 (90.2%)	NR
DCIS only	46/1072 (4.3%)	43/1073 (4.0%)	NR
Invasive	56/1072 (5.2%)	62/1073 (5.8%)	NR
Unknown	41/1113 (3.7%)	46/1119 (4.1%)	NR
Re-excision for margins:			
Pre-pathology stratum	52/766 (6.8%)	67/768 (8.72%)	NR
Post-pathology stratum	27/347 (7.8%)	36/351 (10.3%)	NR
Total	79/1113 (7.1%)	103/1119 (9.2%)	p=0.07
Comments: DCIS, ductal carcinoma in situ. Data are median (IQR) or n/N (%). [l]Specimen weights			

available for n=614 (Targit) and n=605 (EBRT). The denominator for 'unknown' percentages is the number of randomised patients; the denominator for each category is the number of known cases. Percentages are rounded so may not add up to 100%. Total pre-pathology 119 (7.8%) vs total post-pathology 63 (9.0%), p=0.31.

Exploratory Outcomes			
Any other recurrence, all patients	46/1679 4.9% (3.5 to 6.9)	37/1696 4.4% (3.0 to 6.4)	9 (0.5%)
Any other recurrence, prepathology stratum	29/1107 4.8% (3.1 to 7.3)	25/1127 4.7% (3.0 to 7.4)	4 (0.1%)
Any other recurrence, postpathology stratum	17/572 5.2% (3.0 to 8.8)	12/569 3.7% (1.9 to 7.0)	5 (1.5%)
Regional recurrence (axillary and supraclavicular)	8/1679	6/1696	Log-rank p = 0.609

Comments: Three of the 14 regional recurrences had breast recurrence as well (1 Targit; 2 EBRT). Although not explicitly stated it is presumed that these analyses were conducted post-hoc. Other post-hoc exploratory analyses indicated that there was no significant difference in the 5-year risk of regional recurrence, distant recurrence, any other recurrence or all recurrence (data not extracted). Post hoc exploratory analyses comparing all recurrence in pre- and post- pathology strata and loco-regional recurrence in these two strata have also not been data extracted.

Methodological comments

- *Allocation to treatment groups*: Described in detail in the paper reporting initial results.[64] Randomisation schedules were generated centrally by computer and kept securely in two centres (Perth for Australian centres, London for all other centres). Requests for randomisation were made (before lumpectomy[65]) via phone or fax to one of the two centres where patient eligibility was checked. Treatment was allocated from a pre-printed randomisation schedule available to authorised staff only. Patients were randomly assigned in a 1:1 ratio with blocks stratified by centre and by timing of delivery of Targit therapy. The 2010 paper reporting initial results[64] states that the latter (timing of delivery of Targit therapy) had three strata: pre-pathology entry, post-pathology entry/Targit as a second procedure, and history of previous contralateral breast cancer. The 2014 paper[65] describes and reports results for only two strata: prepathology and post-pathology and states that the post-pathology stratum was added via a protocol amendment in 2004. This was because the option to provide IORT as a second procedure (by reopening the wound) was requested by some centres planning to join the trial. The postpathology stratum had a completely separate randomisation table. Post pathology patients had to be randomised within 30 days of lumpectomy.[65]

- *Blinding*: No. The paper reporting initial results[64] states that neither patients, investigators nor teams were masked to treatment (though given the nature of the treatments, this would not have been possible). Individual centres were not blinded to their own patients. States that confidential unblinded reports for the Data Monitoring Committee (DMC) and blinded reports for the International Steering Committee (ISC) were produced by the trial statistician, but also states that unblinded analyses were performed according to a pre-specified statistical analysis plan. Hence, it is unclear whether the ISC reports were also unblinded. For ascertainment of cause of death available data were reviewed by an independent senior clinician who was masked to randomisation.[65]
- *Comparability of treatment groups*: p values are presented[65] indicating no statistically significant differences in baseline characteristics between the groups. States that there was no significant difference between prepathology and postpathology strata in the timing of delivery of EBRT (p=0.58).[65]
- *Method of data analysis*: All randomised patients were included in an ITT analysis. Patients who had undergone a mastectomy were not included in the analysis of local recurrence.[65] The separate analysis of the prepathology and post-pathology strata was planned.[65] A formal analysis for deaths from cardiovascular causes and deaths from other cancers was prespecified.[65] Exploratory analyses (presumably not prespecified) were conducted for regional recurrence, loco-regional recurrence, distant recurrence, any other recurrence, and all recurrence.[65]
  - In the 2010 paper reporting initial results:[64] For the analysis of local recurrence, patients who underwent mastectomy as their definitive surgery and those who died or withdrew consent for further follow-up were censored on that date. All other recurrences in the conserved breast, but not axilla, were analysed and Kaplan-Meier curves were plotted to account for time to event and censoring of the data and included all patients. Analysis of the annual hazards of local recurrence was restricted to 4 years as <20% patients had follow-up beyond this point. SAS System version 9.2 for Windows XP and STATA version 11.0 were used for data compilation and analysis. Pearson χ^2 test and log-rank test were used to obtain p-values. Analysis done in accordance with consort guidelines.
  - In the 2014 paper:[65] The non-inferiority statistic was analysed by calculating the difference in binomial proportions of local recurrences in the conserved breast between the two randomised groups (Targit vs EBRT). To assess stability over time this statistic was also calculated for the mature cohort (n=2232) reported in 2010,[64] and for the earliest cohort (excluding the last 4 years of enrolment; n=1222) who had a median follow-up of 5 years. Established methods were used to calculated the Z score and $p_{\text{non-inferiority}}$ for the whole cohort and the two prespecified strata (prepathology and postpathology). Overall mortality was also reported for the whole cohort, the mature cohort and the earliest cohort. If a patient had at least 5 years of

follow-up, or if they were seen within the year before database lock they were deemed to have adequate follow-up. Patients were censored when last seen or withdrawn from the trial. SAS System version 9.3, Excel 2011, STATA version 12.0 and SPSS version 20.0 were used for data compilation, validation and analysis. A log-rank test was used to compare the difference between survival function and to obtain p-values (significance levels set at $p<0.01$ for local recurrence and $p<0.05$ for survival).

- *Sample size/power calculation*: Described in detail in the paper reporting initial results.[64] The pre-defined non-inferiority margin was an absolute difference of 2.5% in the primary endpoint between groups. To test for non-inferiority with a background recurrence rate of 6% and an absolute non-inferiority margin of 2.5%, a total sample size of 2232 patients was calculated for 80% power at a 5% significance level. Randomisation continued after the initial analysis in 2010 to allow accrual in sub-protocols and the trial was closed after the planned 1200 additional patients (1219 accrued) had been accrued.[65]
- *Attrition/drop-out*:
  - 2010 paper[64] Targit 17/1113 (1.5%) (4 withdrawn, 13 unknown); EBRT 28/1119 (2.5%) (11withdrawn, 17 unknown). Received allocated treatment:[64] Targit 996/1113, EBRT 1025/1119.
  - 2014 paper:[65] Targit 9/1721 withdrawn; 141 did not receive allocated treatment (78 received EBRT, 42 had mastectomy, 21 received neither Targit nor EBRT), 1571/1721 (91%) received allocated treatment (239/1571 [15.2%] received Targit+EBRT; 1332/1571 [84.8%] received Targit alone). EBRT 27/1730 withdrawn, 113 did not receive allocated treatment (12 received Targit, 14 received Targit+EBRT, 34 had mastectomy, 53 received neither Targit nor EBRT), 1590/1730 (92%) received allocated treatment .

  States that 93.7% (3234/3451) of patients were seen in year before datalock or had at least 5 years of follow-up.

General comments

- *Generalisability*: Women with early breast cancer (though definition of 'early' is vague); international study with 6 of 33 centres in the UK. Unsure whether population is typical of those with early breast cancer. Also unclear how similar the EBRT treatment is to standard EBRT in the UK.
- *Outcome measures*: Outcomes reported are appropriate. Outcomes reported in linked publications though are from only one or two participating centres, not for the whole trial population.
- *Inter-centre variability*: Teams at each centre were trained and audited by a member of the trial ISC.[64] Observation of the baseline stratification data[64] show differences between centres in the number of patients entering the trial according to the three timings of delivery strata, particularly pre-pathology and post-pathology. 7 centres had patients in all 3 strata, 10 centres had patients in

2 strata (pre- & post-pathology n=3, pre-pathology & contralateral n=6, post-pathology & contralateral n=1), 11 centres had patients in 1 stratum only (pre-pathology n=8, post-pathology n=3).[64] Centres were allowed to restrict the inclusion criteria beyond the core protocol (e.g. age, tumour size, grade, node) and to stipulate local policy for the delivery of EBRT. Results are not presented by treatment centre nor any comment made in the text so inter-centre variability in outcomes is unknown.

- *Conflict of interests*: Appear the same for both the 2010[64] and 2014[65] papers. Lead author received a research grant from Photoelectron Corp and Carl Zeiss and also honoraria; one author receives monthly consultancy fees from Carl Zeiss; one author has received a research grant and two authors have received honoraria from Carl Zeiss; Carl Zeiss sponsors most of the travel and accommodation costs for meetings/conferences relating to Targit. Only 3 authors' travel/accommodation had not been sponsored by Carl Zeiss.
- *Other*: Pivotal trial for Targit (Intrabeam). Registered with ClinicalTrials.gov number NCT00983684.

Cochrane criteria for assessment of risk of bias in RCTs[56]	**Judgement[a]**	**Support for Judgement**
Selection bias		
Random sequence generation	Low risk	Computer-generated randomisation schedules
Allocation concealment	Low risk	Central allocation
Performance bias		
Blinding of participants and personnel	Low risk	Patients nor investigators were blinded. However, outcomes were unlikely to be influenced by lack of blinding.
Detection bias		
Blinding of outcome assessment	Low risk	Some investigators and teams were not blinded and it is not clear whether all the analyses were performed unblinded. However, most outcomes were objective measures and hence unlikely to be influenced by lack of blinding.
Attrition bias		
Incomplete outcome data addressed	Low risk	Low proportion of withdrawals and participants not receiving allocated treatment (reasons similar between groups). Analyses by ITT.

Reporting bias		
Selective reporting	Low risk	The protocol is available online (www.hta.ac.uk/project/1981.asp) and specifies all outcomes including relapse-free survival and overall survival (as a secondary outcome).
Other bias		
Other sources of bias	Low risk	None evident.

[a] 'Low risk', 'high risk' or 'unclear risk' of bias

Reviewer 1: DH **Date: 5/11/13**	**Reviewer 2: JP** **Date: 19/11/13**	**Version: 3** **(Reviewer JC replaces DH 08/04/14)**
Linked study reference	**Participants**	**Outcome measures**
Sub-study of Targit A trial:[64;65] Welzel *et al.*, 2013[63] *Aim of sub-study*: To assess radiation-related QoL parameters in a sample of patients within the Targit RCT. *Number of centres contributing data*: 1 *Location of centres contributing data*: Mannheim, Germany N=152[64] *Other:* Cross-sectional analysis using retrospective QoL questionnaires *Recruitment dates*: June 2002 to Feb 2009 (consented during	*Number of randomised participants*: n = 123 eligible (aim was to assess the first 123 women accrued to Targit trial at this centre), n=88 received questionnaires (ITT), n=87 included in As Treated analysis Targeted intraoperative radiotherapy (Targit), n= 46* ITT, (n=41 As Treated) Whole breast external beam radiotherapy (EBRT), n= 42 ITT, (n=46 As Treated). (*Further split into IORT (n=30) and IORT with EBRT boost (n=16) original allocation). *Doses*:	*Outcomes:* Radiation-related quality of life measures *Method of assessing outcomes:* 2 validated questionnaires of the European Organisation for Research and Treatment of Cancer (EORTC): QoL questionnaire C30 (QLQ-C30, version 3) for global health status, role functioning and general pain; Breast Cancer Module (QLQ-BR23) for breast symptoms and arm symptoms. The time frame for these questions was the situation in the last week. *Length of follow-up:* Mean 32.1 months (median 25 months, range 9 to 94)

Targit trial). Questionnaires sent out 8 to 94 months following treatment.	IORT: 20Gy at applicator surface during surgery; IORT-EBRT: additional boost of 46Gy in 23 fractions or 50Gy in 25 fractions; EBRT: 56Gy in 28 fractions (no additional boost). *Additional inclusion criteria (beyond those of Targit)*: Patients had to be randomised in the Targit trial between 2002 and 2009 to qualify. *Additional exclusion criteria (beyond those of Targit):* None reported.	

Results

QoL outcome, ITT analysis	**Targit n=46 (IORT n=30, IORT+EBRT n=16)**		**EBRT n=42**		
	N[a]	**Mean (SD)**	**N[a]**	**Mean (SD)**	**p-value**
Global health status[b]	46	61.6 (21.7)	40	54.8 (19.9)	0.183
Restrictions in daily activities[b]	46	72.8 (32.3)	41	61.8 (29.2)	0.055
General pain[c]	46	29.3 (32.8)	42	42.5 (33.0)	0.048
Breast symptoms[c]	45	17.0 (20.8)	42	18.1 (20.2)	0.629
Arm symptoms[c]	45	24.4 (26.7)	40	31.1 (27.9)	0.279

QoL outcome, As-treated analysis, mean (SD)	**IORT n=25**	**IORT-EBRT n=16**	**EBRT n=46**	**p-value**
Global health status[b]	63.6 (24.2)	60.9 (19.9)	52.4 (22.1)	>0.01
Restrictions in daily activities[b]	78.7 (35.2)	NR	60.5 (29.5)	0.007[e]
General pain[c,d]	21.3 (95% CI NR[h] to 54.4)	43.7 (95% CI 11.6 to 75.9)	40.9 (95% CI 8.6 to 73.2)	0.007[e] 0.018[f]
Breast symptoms[c,d]	7.2 (95% CI NR[h] to 20.9)	29.7 (95% CI 6.8 to 52.5)	19.0 (95% CI NR[h] to 39.2)	0.001[e] <0.001[f] 0.021[g]

Arm symptoms[c,d]	15.2 (95% CI NR[h] to 37.2)	32.6 (95% CI 6.8 to 58.4)	32.8 (95% CI 4.2 to 61.5)	0.009[e] 0.011[f]
Frequency of moderate and severe breast/arm symptoms,[i] As-treated analysis, % moderate / % severe	**IORT n=25**	**IORT-EBRT n=16**	**EBRT n=46**	**p-value**
Pain in area of affected breast	4% / 0	25% / 13%	11% / 4%	>0.01
Swelling in area of affected breast	0 / 0	7% / 7%	4% / 2%	
Oversensitivity in area of affected breast	4% / 0	20% / 7%	9% / 7%	
Skin problems on or in area of affected breast	4% / 4%	13% / 6%	9% / 4%	
Pain in arm or shoulder	8% / 8%	33% / 20%	18% / 23%	>0.01
Swelling in arm or hand	8% / 4%	6% / 6%	9% / 7%	
Difficulty in raising or moving arm sideways	20% / 0	13% / 7%	24% / 12%	>0.01

Comments: NR, not reported. [a]Number of valid assessments. [b]higher scores are equal to good functioning/good quality of life; [c]higher scores are equal to severe symptoms/worse quality of life. [d]Figures estimated from graph (4C) by reviewer using Engauge digitizing software. [e]IORT vs EBRT; [f]IORT vs IORT-EBRT; [g]EBRT vs IORT-EBRT. [h]Lower CI not specified on bar chart. [i]Reported by patients. Most commonly reported symptoms were moderate or severe pain in the arm or shoulder, difficulty in raising/moving arm sideways and pain in area of affected breast. States there were no significant differences between treatment groups (p>0.01) but unclear whether this relates to the 3 most common symptoms or all the symptoms.

All scores were linearly transformed to a 0-100 point scale. Univariate regression analysis revealed no influence of follow-up duration on self-reported pain, breast and arm symptoms. Between-group differences in the HADS, FACT-F, RSES and BIS scores were not observed (p>0.01) (no data reported).

Paper also reported the percentage of variance explained by multiple linear regression modelling in a bar chart. Having 2 or more medical co-morbidities was associated with worse global health status, more restrictions in other daily activities, i.e. worse role functioning and more general pain symptoms (p=0.004 to 0.043) (data not extracted). Breast and arm symptoms were independently predicted by tumour size >2cm (p=0.003 and 0.002) (data not extracted).

Methodological comments

- *Comparability of substudy population to main Targit-A trial population*: Narratively reports that compared to patients in the whole Targit-A trial, patients in this substudy had largely similar demographic and clinical characteristics. On observation of the data, reviewer would agree on the whole (though not all characteristics are presented in the substudy), although a lower proportion of the subsample had tumour size 0-1cm and a greater proportion had tumour size 1-2cm compared to the whole Targit-A population for both treatment arms.
- *Comparability of substudy treatment groups*: Demographic and clinical characteristics were similar between groups. P values were reported and there were no statistical differences although presume this was for comparison of the 3 groups (i.e. IORT arm was split into IORT alone and IORT-EBRT boost) and not IORT as a whole vs EBRT.
- *Method of data analysis*: Reports all analyses were performed on an ITT and as-treated basis. The level of statistical significance was 0.01 (0.05/5) to reduce type-1 error in multiple comparisons. Chi-squared tests (or Fisher's exact tests), Kruskal-Wallis one-way ANOVA, and post-hoc Mann-Whitney U-tests (or univariate ANOVA and post-hoc Scheffe tests) were used to compare treatment groups. Independent effects of demographic and clinical factors on QoL were tested using univariate linear regression analysis. Variables with a p-value <0.05 were further analysed with multiple linear regression analysis (stepwise forward method). The results from Targit-A patients were presented throughout as 3 groups with the IORT group split into IORT and IORT with EBRT boost.
- *Attrition/drop-out*: The main trial publication[64] indicates that there were 152 participants at the Mannheim centre (for recruitment 24th Mar 2000 to June 2012). This linked sub-study aimed to assess the first 123 patients recruited from this centre (recruited June 2002- Feb 2009), with 88 patients consenting (88/152=58%). Data are reported for the ITT (n=88) and As Treated (n=87) populations. 5 patients did not receive IORT (4 received EBRT instead and 1 patient refused EBRT). It is not possible to assess whether there are any other missing data as no 'n' is reported for tables or figures. However, none are apparent to the reviewer.
- *Other*: The paper includes an additional 2 non-randomised control groups of EBRT patients (from the same centre) treated with (1) IORT as a tumour bed boost + EBRT (outside of Targit-A trial) or (2) EBRT + EBRT boost. These groups served as control groups for some analyses but are not reported on here.

General comments

- *Generalisability*: This substudy reports on only 46 IORT and 42 EBRT group participants from the Targit-A trial representing only about 2.5% of the total trial population of 3451 randomised participants (1721 Targit, 1730 EBRT).[65] It is not clear how generalisable the results are to the remainder of the Targit-A trial population or to UK breast cancer patients.
- *Outcome measures*: Questionnaire response rate was 96-99%. The five functioning and symptom

scales of the QLQ-C30 and QLQ-BR23 questionnaires were preselected during the design of the study based on a pilot study and relevance for radiation-related QoL in breast cancer. Other subscales and items of the questionnaires were not presented. Also states that 4 other QoL scales were used - the Hospital Anxiety and Depression Scale (HADS), the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) subscale, the Rosenberg Self-Esteem Scale (RSES) and the Body Image Scale (BIS) to control for differences that may inherently exist between treatment groups. Scores for each questionnaire were summed for each scale. However, the paper only narratively comments on differences between groups for these scales (no data).

On observation of the data, ITT and As Treated QoL outcomes seem similar for the EBRT group but difficult to judge for the IORT group because of the way data is presented – for ITT results, IORT and IORT+EBRT are presented as a single group whereas for As Treated results, IORT alone and IORT+EBRT are reported separately.

Partial quality assessment

A complete risk of bias assessment has been conducted for the main Targit A trial.[64] Only the criteria which could potentially differ in the sub-study are reported here.

Cochrane criteria for assessment of risk of bias in RCTs[56]	**Judgement[a]**	**Support for Judgement**
Performance bias		
Blinding of participants and personnel in the HRQoL substudy	High risk	As part of the Targit-A trial neither patients nor investigators were blinded and the outcome could potentially be influenced by the lack of blinding.
Detection bias		
Blinding of outcome assessment	Unclear risk	No information provided regarding blinding (or lack of) for the assessment of QoL measures.
Attrition bias		
Incomplete outcome data addressed	Low risk	Reason for loss of one patient given.
Other bias		
Other sources of bias	Unclear risk	Retrospective questionnaire with no baseline QoL measurement.

[a]'Low risk', 'high risk' or 'unclear risk' of bias

Appendix 5 SHTAC critique of Manufacturer's submission

SHTAC peer review of clinical effectiveness data presented in Carl Zeiss UK's submission for the INTRABEAM Photon Radiotherapy system for early breast cancer MTA

Comprehensiveness of ascertainment of published studies

Clinical effectiveness:

The MS contains a narrative summary of the key RCT and other studies (non-randomised) with the results of each study presented separately. One table is presented in the executive summary detailing nine studies reporting on cosmesis and toxicity. Tables of patient and tumour characteristics are presented separately for each included study in Appendix 1. There is no formal systematic review of clinical effectiveness evidence although a systematic literature search is described.

- Were databases and dates of searches specified?

  Yes, pages 6 & 7 report that 3 databases were searched up to December 2013 with literature included only from 2007 onwards.
- Were search strategies supplied?

  Yes
- Was enough detail provided to be reproducible?

  Yes
- Did they search/report on ongoing studies?

  No searches for ongoing studies are reported
- Did they search for conference proceedings?

  Unclear - conference proceedings may have been included in the 3 databases searched but this is not specifically stated. Information is included from some conference posters.
- How much of the data is CIC/AIC?

  No data are CIC/AIC

Searches identified:

- Note the number of studies

  The MS does not state how many citations were identified by the search. The MS does not describe the processes or criteria (other than 'related to the subject to be evaluated') for selecting included studies. The MS does not state how many studies overall have been included in the submission. The reviewer has identified 26 studies, of which 6 are described as poster abstracts.
- Note what study types

  The MS does not consistently identify the study types for the studies included in the review. Only one RCT is included, the majority of the remaining 25 citations appear to be cohort studies.
- Did these meet our inclusion criteria

The included RCT meets our inclusion criteria as do the studies reporting on subgroups of Targit-A participants. The remaining studies included in the MS did not meet our inclusion criteria, chiefly on the grounds of study design.

- Were any studies identified that we have not included?

  No

- Any key details/issues

  No

Clinical Analysis:

- Any major differences in evidence reported?

  The MS discusses evidence from 4 articles which are all based on the key Targit-A trial and which are also included in the SHTAC systematic review. The MS has not included evidence from the initial Targit-A trial publication from 2010[64] stating that this is because more recent data are available and the 2010 results are expected to be included in the most recent (2014) publication.[65] The SHTAC systematic review does include evidence on early complications from the 2010 Targit-A trial publication since these are not reported by the more recent 2014 trial paper. The MS also does not include a study published by Sperk et al.[74] reporting on Long-term toxicity following treatment either with the INTRABEAM (n=54) device or EBRT (55) at one trial centre in Mannheim, Germany. The MS however does include a cohort study (Tuschy et al. 2013[77] that reports on post-operative complications within the first week following surgery among 208 patients treated with INTRABEAM at a centre in Mannheim Germany who were participating in the Targit-A trial. Tuschy et al.[77] is excluded from the SHTAC systematic review because it is likely that the data reported are either partially or wholly contained within the early complications reported by the initial Targit-A trial publication[64] and in addition Tuschy et al.[77] report no comparable data for the EBRT group.

  The MS also discusses evidence from n=22 studies (6 only reported as conference abstracts) that did not meet the inclusion criteria of the SHTAC review.

  The MS provides a narrative summary for each individual study that has been included. Individual tables of baseline patient characteristics for 13 of the included studies are provided in an appendix. Aside from one table for 8 of the 9 studies listed in section 1.2 "Literature related to side effects and cosmetic outcome after IORT as a single treatment" the MS does not provide summary tables for the included studies. There is no quality assessment of the included studies.

- Are their conclusions similar to ours?

  In the MS section 'Interpretation of clinical evidence' subsections a, b, and c the focus is on the Targit-A trial data, and consequently, with only 1 included trial there is no evidence to draw together and interpret. Therefore for the outcomes of recurrence and overall survival the MS and the SHTAC systematic review report on the same data as published in the 2014 Targit-A trial publication.[65]

  In some of the remaining subsections of the MS 'Interpretation of clinical evidence' the MS discusses evidence for outcomes which are also included in the SHTAC systematic review (e.g. subsection d: cosmetic outcome and toxicities, subsection f: quality of life) drawing not only on evidence from the Targit-A trial but also on evidence from included cohort studies which support the data from the Targit-A trial. Where the SHTAC review reports a small amount of additional information on early complications reported by the initial Targit-A trial publication[64] this does not impact on the overall conclusions. Other subsections of the MS 'Interpretation of clinical evidence' draw on cohort or other non-RCT studies to provide information to support other hypotheses which are not included within the SHTAC systematic review (e.g. subsection e: Side effects and impacts on critical organs are less in IORT than EBRT, subsection g: IORT can be administered to patients where EBRT is not advised, subsection i: Low risk of inducing secondary cancer).

- Any indirect comparisons, if so was this appropriate, and what were key results?

  There is no indirect comparison.

- Any extra adverse event info?

  None that meets the inclusion criteria for the SHTAC systematic review.

Interpretation:

- Does their interpretation of the clinical data match their analyses?

  As already noted above with only 1 included trial there is no evidence to draw together and interpret.

Questions:

Any areas of uncertainty/discrepancy compared with the SHTAC review?

None related to the key Targit-A trial. Other evidence presented by the MS does not meet the inclusion criteria for the SHTAC systematic review.

SHTAC critique of economic evaluation presented in Carl Zeiss UK's submission for the INTRABEAM Photon Radiotherapy system for early breast cancer MTA

Study Characteristics

1 Reference

Carl Zeiss UK, 2014[97]

1.1 Health technology

INTRABEAM Photon Radiotherapy System

1.2 Interventions and comparators

What interventions/ strategies were included?

INTRABEAM versus Whole Breast External Beam Radiotherapy (WB-EBRT)

Was a no treatment/ supportive care strategy included?

No

Describe interventions/ strategies

New Innovative TARGeted Intra Operative Radio Therapy (IORT) using the INTRABEAM radiotherapy system. Conventional therapy consisting of WB-EBRT.

1.3 Research question

What are the stated objectives of the evaluation?

To determine the cost-effectiveness of INTRABEAM in early breast cancer patients when compared with radiotherapy usually given in the UK over 3-6 weeks as WB-EBRT.

1.4 Study type Cost-effectiveness/ cost-utility/ cost-benefit analysis?

Cost-utility analysis

1.5 Study population

What definition was used for [condition]? What are the characteristics of the baseline cohort for the evaluation?

The baseline cohort included patients aged 55 years who were disease free after wide local excision. The economic model was based on the results of the pre-pathology stratum of the trial with 2298 patients (this was because the outcome in patients in whom IORT was given only after the final pathology showed much less favourable results than in the patients who received IORT during lumpectomy).

1.6 Institutional setting Where is/are the intervention(s) being evaluated usually provided?

Not reported

1.7 Country/ currency

Has a country setting been provided for the evaluation? What currency are costs expressed in and does the publication give the base year to which those costs relate?

UK; £

Price year for cost of INTRABEAM was unknown as based on expert opinion; price year of EBRT was 2012-13; the price year of post IORT local recurrence and post EBRT local recurrence was of 2013-14; and that of annual disease free follow up care was 2013*.

*****The cost was calculated to 2013 price using CCEMG - EPPI-Centre Cost Converter.

1.8 Funding source

Carl Zeiss UK.

1.9 Analytical perspective

What is the perspective adopted for the evaluation (health service, health and personal social services, third party payer, societal (i.e. including costs borne by individuals and lost productivity)?

NHS healthcare payer's perspective.

The manufacturer submission notes that travel/parking/accommodation expenses for EBRT patients were not included in the EBRT costs (it was stated that these expenses might range from £50-100 per patient per fraction delivered).

2 Effectiveness

Were the effectiveness data derived from: a single study, a review/ synthesis of previous studies or expert opinion? Give the definition of treatment effect used in the evaluation. Give the size of the treatment effect used in the evaluation

Data for effectiveness were derived from a single study by Vaidya and colleagues.[65] The source study reported 5-year cumulative risk which were converted to annual probabilities to populate the model by the manufacturer.

Parameters	**Probabilities**
Local recurrence after IORT	0.004
Local recurrence after EBRT	0.002
Breast cancer death after IORT	0.007
Non breast cancer death after IORT	0.003

Breast cancer Death after EBRT	0.005	
Non breast cancer death after EBRT	0.009	

3 Intervention Costs

Were the cost data derived from: a single (observational) study, a review/ synthesis of previous studies expert opinion? Were the methods for deriving these data adequately described (give sources if using data from other published studies)? List the direct intervention costs and other direct costs used in the evaluation – include resource estimates (and sources for these estimates, if appropriate) as well as sources for unit costs used.

Cost data were obtained from the following sources: expert opinion, Reference cost 2012-13, tariff information 2013-14, and the study by Wolowacz and colleagues.[99] The methods of deriving costs were not adequately described.

The following costs were used in the model:

Costs	**Prices**	**Source**
Costs of INTRABEAM	£ 2165	Expert opinion
Costs of EBRT	£ 7521	HRG code SC29Z (Reference Cost 2012-13)
Cost of treating post IORT LR (salvage lumpectomy)	£ 1558	HRG code JA09H (Tariff Information 2013-14)
Cost of treating post EBRT LR (salvage mastectomy)	£ 6504	HRG code JA16Z (Tariff Information 2013-14)
Annual disease free follow up care	£ 892	Wolowacz 2008

3.1 Indirect Costs (costs due to lost productivity, unpaid inputs to patient care)

Were indirect costs included?

Not included

4 Health state valuations/ utilities (if study uses quality of life adjustments to outcomes)

Were the utility data derived from: a single (observational) study, a review/ synthesis of previous studies expert opinion. Were the methods for deriving these data adequately described (give sources if using data from other published studies)?

The utility data were derived from a single study by Hayman and colleagues.[96] The method of deriving these values was not reported.

4.1 List the utility values used in the evaluation?

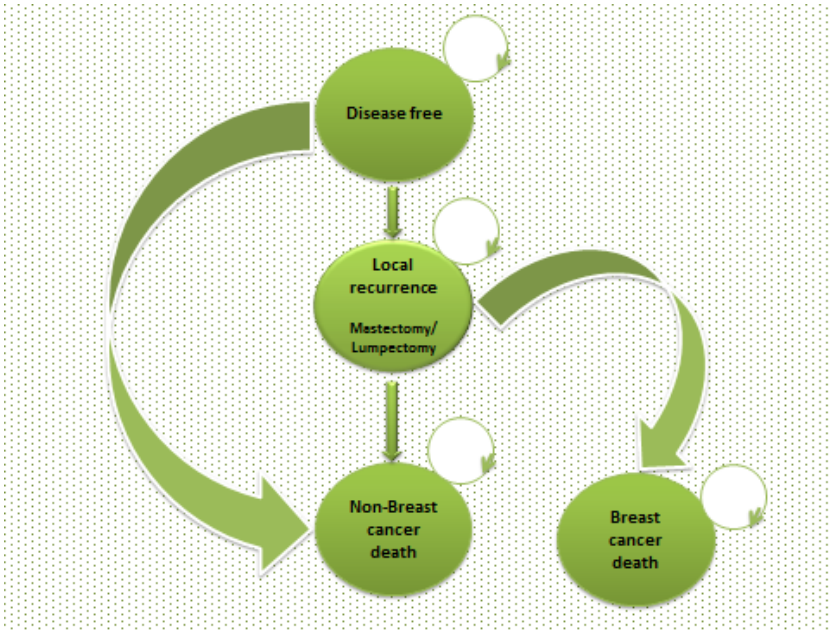
Health state	Utilities
Utility value in disease free patients	0.92
Utility value in salvage lumpectomy patients	0.87
Utility value in salvage mastectomy patients	0.82

5 Modelling

If a model was used, describe the type of model used (e.g. Markov state transition model, discrete event simulation). Was this a newly developed model or was it adapted from a previously reported model? If an adaptation, give the source of the original. What was the purpose of the model (i.e. why was a model required in this evaluation)? What are the main components of the model (e.g. health states within a Markov model)? Are sources for assumptions over model structure (e.g. allowable transitions) reported – list them if reported.

A multi- state Markov model was developed, over a time-horizon of 20 years. It was not reported if the model was newly developed or adapted from a previously reported model.

The purpose of the model was to assess the cost-effectiveness of INTRABEAM compared to WB-EBRT. The model consisted of 4 health states as shown in the figure:



No description was provided on patient progression through the health states. The model

assumptions were:

- After local recurrence IORT patients would have salvage lumpectomy
- After local recurrence EBRT patients would have salvage mastectomy
- Death rate in disease free patients was equal to general population
- Average 23 fractions of EBRT per patient delivered based on 15-30 fractions in the clinical practice
- All patients were given IORT concurrent with initial lumpectomy (pre-pathology stratum of TARGIT-A trial)

5.1 Extract transition probabilities for [natural history/disease progression] model and show sources (or refer to table in text).

Data for transitional probabilities were extracted from Vaidya and colleagues.[65]

Transitions	**Annual prob.**	**95% CI***
Local recurrence after IORT	0.0042	0.0022-0.0085
Local recurrence after EBRT	0.0022	0.0010-0.0051
Breast cancer death after IORT	0.0067	0.0038-0.0119
Non breast cancer death after IORT	0.0026	0.0014-0.0057
Breast cancer Death after EBRT	0.0055	0.0030-0.0094
Non breast cancer death after EBRT	0.0090	0.0057-0.0142

*: Rounded to 4 decimal places

5.2 What is the model time horizon?

20 years

5.3 What, if any, discount rates have been applied in the model? Same rate for costs and outcomes?

Costs and outcomes were discounted at 3.5%

6 Results/ Analysis

What measure(s) of benefit were reported in the evaluation?

Cost per QALY

6.1 Provide a summary of the clinical outcome/ benefits estimated for each intervention/ strategy assessed in the evaluation

Strategies	**Total QALYs (discounted)**
IORT	13.230
WB-EBRT	13.223

6.2 Provide a summary of the costs estimated for each intervention/ strategy assessed in the evaluation

Strategies	**Total Costs (discounted)**
IORT	£14,461
WB-EBRT	£20,926

6.3 Synthesis of costs and benefits – are the costs and outcomes reported together (e.g. as cost-effectiveness ratios)? If so, provide a summary of the results.

	vs WB-EBRT		
	Incremental Costs (discounted)	**Incremental QALYs (discounted)**	**ICER**
IORT	-£6,465	0.007	Dominates

6.4 Give results of any statistical analysis of the results of the evaluation.

None

6.5 Was any sensitivity analysis performed – if yes, what type(s) (i.e. deterministic (one-way, two-way etc) or probabilistic).

Probabilistic sensitivity analyses (ran for 1000 simulations)

6.6 What scenarios were tested in the sensitivity analysis? How do these relate to structural uncertainty (testing assumptions over model structure such as relationships between health states),

methodological uncertainty (such as choices of discount rate or inclusion of indirect costs) or parameter uncertainty (assumptions over values of parameters in the model, such as costs, quality of life or disease progression rates)?

No scenario analysis was conducted

6.7 Give a summary of the results of the sensitivity analysis – did they differ substantially from the base case analysis. If so, what were the suggested causes?

None; it was only reported that probabilistic results were similar to the base case results however no one-way sensitivity analysis was conducted.

7 Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

The authors concluded that INTRABEAM was a cost-effective strategy to treat early stage breast cancer patients in the UK.

7.1 What are the implications of the evaluation for practice?

The manufacturer submission stated that INTRABEAM could save valuable NHS resources in comparison to the current practice of EBRT.

8 SHTAC Commentary

Selection of comparators:

Number of fractions (23) for the EBRT arm was not relevant to UK practice

Validity of estimate of measure of benefit:

The manufacturer's model assessed health benefit in terms of QALYs which was a valid measure of health in the UK NHS setting. Standard gamble was used to estimate utilities in the source study which was a 1997 publication;[96] the reported values were not obtained from general population. In addition, no details were provided regarding whether a systematic search was conducted to identify utilities for the model.

Validity of estimate of costs:

The validity of the costs estimates remained questionable. The cost of INTRABEAM per patient was obtained from expert opinion. The manufacturer provided the cost compositions of INTRABEAM, however it was not transparent in explaining the assumed cost per patient. In addition, cost of WB-EBRT was obtained from inappropriate HRG code: the code used in the model for EBRT was for "Other Radiotherapy treatment". On the contrary, the HRG code required for the purpose of this analysis was "external beam radiotherapy delivered by linear accelerator" which required the weighted average of SC22Z & SC23Z (for delivery) and a weighed average SC45Z, SC46Z, SC47Z and SC48Z (for planning). Costs were only varied by ±10% in PSA. There were also inconsistencies in the price years of the reported costs: cost of

WB-EBRT was expressed in 2012-13; costs of treating post IORT local recurrence and post EBRT local recurrence were in 2013-14; and cost of annual disease follow-up was in 2013.

Table 3: Critical appraisal checklist of economic evaluation (Questions in this checklist based on Philips et al[58])

	Item	MS 1
1	Is there a clear statement of the decision problem?	Yes
2	Is the comparator routinely used in UK NHS?	?[a]
3	Is the patient group in the study similar to those of interest in UK NHS?	?[b]
4	Is the health care system comparable to UK?	Yes
5	Is the setting comparable to the UK?	Yes
6	Is the perspective of the model clearly stated?	Yes
7	Is the study type appropriate?	Yes
8	Is the modelling methodology appropriate?	?[c]
9	Is the model structure described and does it reflect the disease process?	Yes[d]
10	Are assumptions about model structure listed and justified?	No
11	Are the data inputs for the model described and justified?	No
12	Is the effectiveness of the intervention established based on a systematic review?	No[e]
13	Are health benefits measured in QALYs?	Yes
14	Are health benefits measured using a standardised and validated generic instrument?	Yes[f]
15	Are the resource costs described and justified?	No
16	Have the costs and outcomes been	Yes

	discounted?	
17	Has uncertainty been assessed?	?[g]
18	Has the model been validated?	No

Yes / No / ? (unclear)

[a:] Different number of fractions used in the model (23) than in the UK practice which is to include 15 fractions. However in the TARGIT trial, centres were allowed to use the number of fractions which were normal for them, but it is not clear from the publication what this number was in all cases. This might be an average of the fractions delivered in the study; but no details were provided

[b]: Although the manufacturer's submission reported that the analysis was based on UK population; no baseline characteristics of the included patient population were provided.

[c]: Very limited details were provided around the modelling methodology

[d]: A simplified model structure of 4 health states was included; an additional health state for "any other recurrence" would have been more appropriate.

[e]: However only 1 RCT was identified by the AG systematic review

[f:] The source study by Hayman and colleagues[96] used standard gamble technique to estimate utilities.

[g]: Only PSA was conducted; not deterministic sensitivity analysis or scenario analyses

Appendix 6 Excluded cost-effectiveness studies with rationale

Excluded study	Reasons for exclusion
Xoft Axxent eBx electronic brachytherapy system (iCAD Inc.) for early-stage breast cancer. 2012.	Not full economic evaluation; inappropriate intervention and comparator
Alvarado M, Ozanne E, Mohan A, Esserman L. Cost-effectiveness of intraoperative radiation therapy for breast conservation. Journal of Clinical Oncology Conference: ASCO Annual Meeting 2011 Chicago, IL United States Conference Start: 20110603 Conference End: 20110607 Conference Publication: (var pagings) 2011; 29(15 SUPPL.#1)	Abstract
BlueCross BlueShield Association. Accelerated partial breast irradiation as sole radiotherapy after breast-conserving surgery for early stage breast cancer. 2007.	Not full economic evaluation; Inappropriate population of interest, intervention and comparator.
BlueCross BlueShield Association. Accelerated radiotherapy after breast-conserving surgery for early stage breast cancer (2012). 2012	Not full economic evaluation
Santos M, Guerra JLL, Gordillo MJO, Fondevilla A, Calvo F, Samblas J et al. Cost-Effectiveness Analysis of Four Validated Techniques of Accelerated Partial Breast Irradiation for the Treatment of Early-Stage Breast Cancer: Spanish Public Health System Standard Estimations. Value in Health 2012; 15(7):A354	Abstract; inappropriate intervention
Sher DJ, Wittenberg E, Suh WW, Taghian AG, Punglia RS. Partial-Breast Irradiation Versus Whole-Breast Irradiation for Early-Stage Breast Cancer: A Cost-Effectiveness Analysis. International Journal of Radiation Oncology Biology Physics 2009; 74(2):440-446.	Inappropriate intervention
Xie X, Dendukuri N, McGregor M. Single-dose intraoperative radiotherapy using Intrabeam® for early-stage breast cancer: a health technology assessment. 2012.	Not full economic evaluation

Appendix 7 Cost-effectiveness data extraction tables

1	**Study**	Alvarado, 2013;[78] Esserman, 2014[79]
2	**Research question**	The study analysed, from a societal perspective, the cost-effectiveness of two radiation strategies for early-stage invasive breast cancer: single-dose intraoperative radiation therapy (IORT) and the standard 6-week course of whole breast external beam radiotherapy (WB-EBRT)
3	**Country/setting**	The model was based on the protocol of the international TARGIT-A trial; the economic evaluation is US based
4	**Funding source**	Not stated
5	**Analysis type**	CUA
6	**Study type**	A Markov decision-analytic model based on the TARGIT-A trial was developed consisting of 6 health states: ○ Disease-free status post breast conserving surgery ○ Recurrence in women initially with WB-EBRT had salvage mastectomy followed by immediate reconstruction ○ Recurrence in women who received IORT had the option of salvage lumpectomy followed by WB-EBRT ○ Metastases ○ Death due to other causes ○ Death due to metastatic breast cancer
7	**Perspective**	Societal
8	**Time horizon**	10 year period with annual cycle length
9	**Model assumptions**	○ All women were assumed to have had BCS followed by either IORT or 6-week WB-EBRT ○ 14.1% of women with IORT received an additional 5 weeks (28 fractions) of WB-EBRT ○ Recurrence in women who initially had WB-EBRT could only be treated with salvage mastectomy followed by immediate reconstruction ○ Recurrence in patients who received IORT had the option of salvage lumpectomy followed by WB-EBRT ○ Death resulting from breast cancer was only possible for women with metastatic breast cancer ○ The utilities of IORT and IORT followed by 5 week WB-EBRT were equal to that of 6-week WB-EBRT ○ Local recurrence rates were assumed to progress linearly over 10

<table>
<tr><td></td><td></td><td>years
○ For women treated with IORT followed by WB-EBRT, it was assumed that they incurred the same LRR as those who had IORT alone</td></tr>
<tr><td>10</td><td>Discounting (rate)</td><td>Yes at 3% for both costs and effectiveness</td></tr>
<tr><td>11</td><td>Costing year, currency</td><td>2011, US$</td></tr>
<tr><td>12</td><td>Population</td><td>Trial name: TARGIT-A.
Definition of condition: Women with early breast cancer who were ≥55 years old
Characteristics of baseline cohort/risk factors: Early-stage was defined as stage I-IIA estrogen-receptor positive (ER+), breast cancer</td></tr>
<tr><td>13</td><td>Intervention(s), comparator(s)</td><td>Intervention: Single dose intra-operative radiation therapy (IORT)-INTRABEAM
Comparator: 6-week course of whole-breast external beam radiation therapy (WB-EBRT) with a standard 33 fractions</td></tr>
<tr><td>14</td><td>Intervention effect</td><td>4-year local recurrence rates obtained from the TARGIT trial were converted to annual transitional probabilities and projected over 10 years. Kaplan Meier estimate of local recurrence in the conserved breast at 4 years was 1.2% (95% CI: 0.53 to 2.71) for the IORT arm and 0.95% (95% CI: 0.39 to 2.31) in the EBRT arm</td></tr>
<tr><td>15</td><td>Health state utilities</td><td>Where possible, health state utilities were obtained via standard-gamble preferences. Published literature was used to populate the remaining values (reference provided).
<table>
<tr><th>Health state utilities</th><th>Base case value</th><th>Range values</th></tr>
<tr><td>IORT</td><td>0.92</td><td>0.87-0.97</td></tr>
<tr><td>3 week WB-EBRT</td><td>0.92</td><td>0.87-0.97</td></tr>
<tr><td>6 week WB-EBRT</td><td>0.92</td><td>0.87-0.97</td></tr>
<tr><td>IORT followed by 5-week WB-EBRT</td><td>0.92</td><td>0.87-0.97</td></tr>
<tr><td>Salvage mastectomy</td><td>0.82</td><td>0.77-0.87</td></tr>
<tr><td>Salvage mastectomy and WB-EBRT</td><td>0.87</td><td>0.82-0.92</td></tr>
<tr><td>Metastatic BC</td><td>0.70</td><td>0.60-0.80</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><td></td><td></td><td>
<table>
<tr><td>Death</td><td>0</td><td>-</td></tr>
</table>

Details on the measurement technique and valuation approach were not provided</td></tr>
<tr><td>16</td><td>Intervention cost</td><td>

IORT: $5547
6 week WB-EBRT:$10,464
IORT followed by 5-week WB-EBRT: $13,640
3 week WB-EBRT:$6,640

Sources:

Medicare Physician Fee Schedule (MFS). U.S. Department of Health and Human Services; 2010. http://www.cms.gov/apps/physician-fee-schedule/overview.aspx.
Outpatient Prospective Payment System (OPPS). U.S. Department of Health and Human Services; 2010.

</td></tr>
<tr><td>17</td><td>Indirect costs</td><td>

Indirect costs (6-week WB-EBRT): $1467
Indirect costs (IORT followed by 5-week WB-EBRT): $1244
Indirect costs (3-week WB-EBRT): $667

The above figures were derived from the same sources:

Highlights of Women’s Earnings in 2010. In: Labor USDo, ed, U.S. Bureau of Labor Statistics; 2011.
CPI Inflation Calculator. U.S. Bureau of Labor Statistics; 2011. http://data.bls.gov/cgi-bin/cpicalc.pl.
IRS announces 2011 standard mileage rates: internal revenue service; 2010.
Gasoline and Diesel Fuel Update. U.S. Energy Information Administration;2011. http://www.eia.gov/oog/info/gdu/gasdiesel.asp.

</td></tr>
<tr><td>18</td><td colspan="2">Results
<table>
<tr><td>Discounted/ undiscounted</td><td>IORT</td><td>3-week WB-EBRT</td><td>6-week WB-EBRT</td></tr>
<tr><td>Costs</td><td>$28,879</td><td>$29,789</td><td>$34,070</td></tr>
<tr><td>LY</td><td>8.38240</td><td>8.38152</td><td>8.38257</td></tr>
<tr><td>QALY</td><td>7.66020</td><td>7.64618</td><td>7.65994</td></tr>
<tr><td>ICER</td><td></td><td>Dominated</td><td>Dominated</td></tr>
</table>
</td></tr>
</table>

19	**Sensitivity analysis** The model conducted a series of one-way and two-way sensitivity analyses. A scenario analysis of 3-week accelerated WB-EBRT schedule of 16 fractions was also conducted.	
20	**Author's conclusions**	Alvarado and colleagues concluded "with less cost and greater QALYs than WB-EBRT, IORT is the more valuable strategy" Esserman and colleagues concluded that the result of TARGIT-A trial was not likely to change.
21	**Reviewer's comments**	Overall, the analysis was well conducted. The results of the analysis were in line with the study conclusions. However, the model did not incorporate any probabilistic sensitivity analysis. Further, only two sets of 2-way sensitivity analyses were conducted. Hence the robustness of the cost-effectiveness results remains questionable.

Parameter / Scenario	**Value**	**ICER**
Utility of IORT	0.97	Dominated
	0.87	12,820
Utility of 6-week WB-EBRT	0.97	14,965
	0.87	Dominated
Utility of IORT followed by 5-week WB-EBRT	0.97	Dominated
	0.87	91,517
Utility of salvage lumpectomy after IORT	0.92	Dominated
	0.82	2,284,464
Local recurrence rate (LRR) of IORT (10 year)	6.0%	746,158
	1.5%	Dominated
LRR of 6 week WB-EBRT (10 year)	3.6%	Dominated
	1.2%	2.7 million
Proportion of women who receive IORT followed by 5 week WB-EBRT	28.2%	267 million
	7.1%	Dominated
Rate of MBC after salvage lumpectomy or mastectomy (10 year rates)	40.0%	21 million
	10%	Dominated

Quality assessment checklist for economic evaluations

Item	**Y/N/?**
1. Is the decision problem (including interventions compared and patient group) relevant to the UK?	Y[a]

2. Is the setting comparable to the UK?	N
3. Is the analytical and modelling methodology appropriate?	Y
4. Are all the relevant costs and consequences for each alternative identified?	Y
5. Are the data inputs for the model described and justified?	Y
6. Are health outcomes measured in QALYs?	Y
7. Is the time horizon considered appropriate?	N[b]
8. Are costs and outcomes discounted?	Y
9. Is an incremental analysis performed?	Y
10. Is uncertainty assessed?	Y[c]
Y – yes, N – no, ? – unclear	
Comments [a] The number of fractions of EBRT (comparator) was not relevant to UK practice as the study used the assumption of using EBRT with a standard 33 fractions whereas the current standard UK practice is 15 fractions. [b] A lifetime horizon would have been appropriate as the risk of local recurrence continues over a lifetime [c] PSA was not conducted	

Critical appraisal checklist for economic evaluations (based on Drummond and colleagues[57])

1	**Study**	Shah, 2014[80]
2	**Research question**	The study analysed the cost-efficacy of intraoperative radiation therapy (IORT) compared with whole breast irradiation (referred to as EBRT henceforth) and accelerated partial-breast irradiation (APBI) for early-stage breast cancer.
3	**Country/setting**	The analysis was based on data from two phase III trials: TARGIT-A trial and the ELIOT trial; the economic evaluation was US based.
4	**Funding source**	Not stated
5	**Analysis type**	CUA; CMA
6	**Study type**	The study used local recurrence data from two trials: TARGIT-A and ELIOT. For the cost effectiveness analyses, reimbursement models were calculated in 4 ways: o Reimbursement only (professional and facility) o Reimbursement incorporating additional medical costs (eg. Increased operative time with IORT, fraction of IORT patients requiring additional radiation)

		○ Reimbursement requiring non-medical costs ○ Reimbursement incorporating costs associated with recurrences The ICER analysis provided the increased reimbursement required to use EBRT or APBI compared with IORT per percentage point of improvement in local recurrence.
7	**Perspective**	Societal
8	**Time horizon**	Not clearly stated; it is assumed that the time horizon was for 10 years based on the estimation of mean utility by technique.
9	**Model assumptions**	○ Average round-trip travel was 40 miles to the radiation centre (6 cents per mile) ○ The time involved was 2 hours per treatment, including travel of which 30 minutes were spent receiving treatment ($14.78 per hour) ○ Patients receiving twice-daily treatment returned to work during the inter-fraction interval The study reported that all assumptions and methodology adopted were based on and consistent with previously published articles, discussed elsewhere.
10	**Discounting (rate)**	Not stated
11	**Costing year, currency**	Not stated
12	**Population**	TARGIT-A trial: Women with early-stage ductal breast cancer who were ≥45 years old ELIOT trial: Women with unicentric cancer less than 2.5 cm who were >45 years old
13	**Intervention(s), comparator(s)**	• Intervention: IORT (INTRABEAM in TARGIT-A trial) or Electron Intraoperative Radiotherapy (in ELIOT trial). The latter is not eligible for inclusion in this review. • Comparator(s): EBRT 3D-CRT; APBI 3D-CRT; APBI IMRT; APBI SL; APBI ML; APBI Interstitial
14	**Intervention effect**	Local recurrence rates for both the INTRABEAM and EBRT arms (3.3% for IORT vs. 1.3% for EBRT) were obtained from the TARGIT trial. Data from the ELIOT trial was not extracted as the intervention is not

<table>
<tr><td></td><td></td><td>eligible.</td></tr>
<tr><td>15</td><td>Health state utilities</td><td>The utility values for the outcome states (shown below) were based on the study by Hayman and colleagues.

<table><tr><th>Health state utilities</th><th>Base case value</th></tr><tr><td>No recurrence</td><td>0.92</td></tr><tr><td>Local recurrence</td><td>0.779</td></tr><tr><td>Other recurrence</td><td>0.685</td></tr></table></td></tr>
<tr><td>16</td><td>Intervention cost</td><td>Reimbursement costs were reported.

<table><tr><th></th><th>IORT</th><th>EBRT</th></tr><tr><td>Total reimbursement</td><td>$3094</td><td>$11,726</td></tr><tr><td>Reimbursement including additional medical costs[a]</td><td>$8003 - $8706</td><td>$11,726</td></tr><tr><td>Reimbursement including medical and nonmedical costs[a]</td><td>$8192 - $8971</td><td>$12,985</td></tr><tr><td>Reimbursement including medical, nonmedical, and recurrence costs (TARGIT)[a]</td><td>$9399 - $10,179</td><td>$13,122</td></tr></table>[a] Range based on differences in EBRT rates (15% - 21%)
Data for APBI not extracted as it is not relevant for the purpose of this review</td></tr>
<tr><td>17</td><td>Indirect costs</td><td>Nonmedical costs including travel costs were estimated to be $44.96 and $89.92 per day respectively for once-daily and twice-daily schedules of treatment</td></tr>
<tr><td>18</td><td colspan="2">Results
The results for ICER and costs per QALY are extracted based on the TARGIT-A trial as ELIOT trial was not relevant for the purpose of this review. These are:
When all associated costs are incorporated, using the local recurrence rates (3.3% for INTRABEAM vs 1.3% for EBRT), the ICERs for local recurrence ranges from $1782-$2172 for EBRT based on difference in whole breast irradiation rates (15% - 21%).
The costs per QALY for EBRT compared with IORT range from $89,234/QALY - $108,735/QALY depending on the difference in whole breast irradiation rates.</td></tr>
<tr><td>19</td><td colspan="2">Sensitivity analysis
Not reported</td></tr>
</table>

20	**Author's conclusions**	"IORT represents a potentially cost-effective treatment option for women with early stage breast cancer; however despite reduced reimbursement rates with IORT, WBI and APBI represent cost-effective modalities to deliver radiation therapy based on cost per QALY analyses."
21	**Reviewer's comments**	Limited information surrounding the model structure was presented in the study. Time-horizon for the model was not clearly stated. Although the techniques adopted to estimate costs associated with non-medical, follow-up, local recurrence or other recurrence (including salvage mastectomy) were mentioned, the costs were not reported, except for non-medical costs. Sensitivity analysis was not conducted.

3D-CRT: 3-dimensional conformal radiotherapy; APBI: accelerated partial-breast irradiation; ELIOT: Electron Intraoperative Radiotherapy; IMRT: Intensity-modulated radiation therapy; IORT: Intraoperative radiation therapy; ML: Multilumen; SL: Single-lumen; TARGIT: Targeted Intraoperative Radiotherapy trial; WBI: Whole Breast Irradiation

Quality assessment checklist for economic evaluations

Item	**Y/N/?**
1. Is the decision problem (including interventions compared and patient group) relevant to the UK?	Y[a]
2. Is the setting comparable to the UK?	N
3. Is the analytical and modelling methodology appropriate?	Y[b]
4. Are all the relevant costs and consequences for each alternative identified?	Y[c]
5. Are the data inputs for the model described and justified?	Y
6. Are health outcomes measured in QALYs?	Y
7. Is the time horizon considered appropriate?	?[d]
8. Are costs and outcomes discounted?	N
9. Is an incremental analysis performed?	N
10. Is uncertainty assessed?	N
Y – yes, N – no, ? – unclear	
Comments [a] Details on the number of fractions used in the EBRT (comparator) arm was not presented. [b] Details surrounding the modelling methodology not presented but references provided and checked. [c] Details not presented but references provided and checked [d] It is assumed that the time horizon was for 10 years based on the estimation of mean utility by	

technique; a lifetime horizon would have been appropriate as the risk of recurrence continues over a lifetime.

Critical appraisal checklist for economic evaluations (based on Drummond and colleagues[57])

Appendix 8 Excluded QoL studies with rationale

Excluded study	Primary reason for exclusion
Bao T, Cai L, Snyder C, Betts K, Tarpinian K, Gould J et al. Patient-reported outcomes in women with breast cancer enrolled in a dual-center, double-blind, randomized controlled trial assessing the effect of acupuncture in reducing aromatase inhibitor-induced musculoskeletal symptoms. Cancer 2014; 120(3):381-389.	Not EQ-5D
Bonnetain F, Conroy T, Velten M, Jolly D, Mercier M, Causeret S et al. Impact of response shift in longitudinal postoperative quality of life (QoL) analysis among breast cancer (BC) patients: A randomized multicenter cohort study. *Journal of Clinical Oncology* 2010; Conference(var.pagings):15.	Abstract
Brown DS, Trogdon J, Ekwueme DU, Chamiec-Case L, Tangka FK, Guy GP et al. Preference-based estimates of the health utility impacts of breast cancer in women ages 18-44 in the United States. *Value in Health* 2012; Conference(var.pagings):4.	Abstract
Chandwani KD, Thornton B, Perkins GH, Arun B, Raghuram NV, Nagendra HR et al. Yoga improves quality of life and benefit finding in women undergoing radiotherapy for breast cancer. *Journal of the Society for Integrative Oncology* 2010; 8(2):43-55.	Not EQ-5D
Chang J, Couture FA, Young SD, Lau CY, Lee MK. Weekly administration of epoetin alfa improves cognition and quality of life in patients with breast cancer receiving chemotherapy. *Supportive Cancer Therapy* 2004; 2(1):52-58.	No relevant information on health states
Cheung YB, Lee CF, Luo N, Ng R, Wong NS, Yap YS et al. Comparison of the measurement properties between the 5-level euroqol group's 5-dimension (EQ-5D-5l) questionnaire and the functional assessment of cancer therapy-breast (FACT-B) in Asian breast cancer patients. *Value in Health* 2012; Conference(Republic of China):var.	Abstract
Cheville AL, Almoza M, Courmier JN, Basford JR. A prospective cohort study defining utilities using time trade-offs and the euroqol-5D to assess the impact of cancer-related lymphedema. *Cancer* 2010; 116(15):3722-3731.	Inappropriate participants
Conner-Spady B, Cumming C, Nabholtz JM, Jacobs P, Stewart D. Responsiveness of the EuroQol in breast cancer patients undergoing high	No relevant information on health

dose chemotherapy. *Quality of Life Research* 2001; 10(6):479-486.	states
Coyle D, Grunfeld E, Coyle K, Julian JA, Pond GR, Folkes A et al. Cost-effectiveness of a survivorship care plan for breast cancer survivors. *Journal of Clinical Oncology* 2011; Conference(var.pagings):15.	Abstract
Crott R, Briggs A. Mapping the QLQ-C30 quality of life cancer questionnaire to EQ-5D patient preferences. *European Journal of Health Economics* 2010; 11(4):427-434.	Not primary research
Dabakuyo TS, Guillemin F, Conroy T, Velten M, Jolly D, Mercier M et al. Response shift effects on measuring post-operative quality of life among breast cancer patients: a multicenter cohort study. *Quality of Life Research* 2013; 22(1):1-11.	Not EQ-5D
de KM, Dirksen CD, Kessels AG, van der Weijden T, van de Velde CJ, Roukema JA et al. Cost-effectiveness of a short stay admission programme for breast cancer surgery. *Acta Oncologica* 2010; 49(3):338-346.	No relevant information on health states
Dolbeault S, Cayrou S, Bredart A, Viala AL, Desclaux B, Saltel P et al. The effectiveness of a psycho-educational group after early-stage breast cancer treatment: results of a randomized French study. *Psycho-Oncology* 2009; 18(6):647-656.	Not EQ-5D
Domeyer PJ, Sergentanis TN, Zagouri F, Zografos GC. Health-related quality of life in vacuum-assisted breast biopsy: short-term effects, long-term effects and predictors. *Health & Quality of Life Outcomes* 2010; 8:11.	Inappropriate participants
Fang P, Tan KS, Troxel AB, Rengan R, Freedman G, Lin LL. High body mass index is associated with worse quality of life in breast cancer patients receiving radiotherapy. *Breast Cancer Research & Treatment* 2013; 141(1):125-133.	Not EQ-5D
Fang P, Tan K, Troxel A, Rengan R, Freedman G, Lin L. High BMI associated with worse quality of life in breast cancer patients receiving radiation therapy. *International Journal of Radiation Oncology Biology Physics* 2013; 87(2 suppl 1):S607	No relevant information on health states
Farkkila N, Roine R, Jahkola T, Sintonen H, Hanninen J, Taari K et al. Health state utilities in breast cancer. *Value in Health* 2011; Conference(var.pagings):7.	Abstract
Haines TP, Sinnamon P, Wetzig NG, Lehman M, Walpole E, Pratt T et al. Multimodal exercise improves quality of life of women being treated for breast cancer, but at what cost? Randomized trial with economic evaluation. *Breast Cancer Research & Treatment* 2010; 124(1):163-175.	No relevant information on health states

Hayran M, Cakir B, Cilingiroglu N, Erman M, Kilickap S, Ozisik YY et al. Validation and clinical evaluation of different quality of life (QoL) scales in patients (pts) with breast cancer (BC) in Turkey. *Journal of Clinical Oncology* 2011; Conference(var.pagings):15.	Abstract
Jansen SJ, Otten W, van de Velde CJ, Nortier JW, Stiggelbout AM. The impact of the perception of treatment choice on satisfaction with treatment, experienced chemotherapy burden and current quality of life. *British Journal of Cancer* 2004; 91(1):56-61.	No relevant information on health states
Jeruss JS, Hunt KK, Xing Y, Krishnamurthy S, Meric-Bernstam F, Cantor SB et al. Is intraoperative touch imprint cytology of sentinel lymph nodes in patients with breast cancer cost effective? *Cancer* 2006; 107(10):2328-2336.	Not primary research
Katharina WA, Schumacher A. Social connotations of breast cancer-work in progress. Psycho-Oncology 2013; 22(Nov):222.	Abstract
Kimman ML, Dirksen CD, Falger P, Voogd A, Kessels A, Gijsen B et al. Results of an RCT investigating the cost-effectiveness of four follow-up strategies after breast cancer. *European Journal of Cancer, Supplement* 2009; Conference(var.pagings):2-3.	Abstract
Kimman ML, Dirksen CD, Lambin P, Boersma LJ. Responsiveness of the EQ-5D in primary breast cancer survivors. *Ejc Supplements* 2008; 6(7):73-74.	Abstract
Kimman ML, Dirksen CD, Voogd AC, Falger P, Gijsen BC, Thuring M et al. Economic evaluation of four follow-up strategies after curative treatment for breast cancer: results of an RCT. *European Journal of Cancer* 2011; 47(8):1175-1185.	Inappropriate participants
Lee CF, Luo N, Ng R, Wong NS, Yap YS, Lo SK et al. Comparison of the measurement properties between a short and generic instrument, the 5-level EuroQoL Group's 5-dimension (EQ-5D-5L) questionnaire, and a longer and disease-specific instrument, the Functional Assessment of Cancer Therapy-Breast (FACT-B), in Asian breast cancer patients. *Quality of Life Research* 2013; 22(7):1745-1751.	Inappropriate participants
Lee CF, Ng R, Luo N, Wong NS, Yap YS, Lo SK et al. The English and Chinese versions of the five-level EuroQoL Group's five-dimension questionnaire (EQ-5D) were valid and reliable and provided comparable scores in Asian breast cancer patients. *Supportive Care in Cancer* 2013; 21(1):201-209.	Inappropriate participants

Lee J-A, Kim S-Y, Kim Y, Oh J, Kim H-J, Jo D-Y et al. Comparison of health-related quality of life between cancer survivors treated in designated cancer centers and the general public in Korea. Japanese Journal of Clinical Oncology 2014; 44(2):141-152.	No relevant information on health states
Lovrics PJ, Cornacchi SD, Barnabi F, Whelan T, Goldsmith CH. The feasibility and responsiveness of the health utilities index in patients with early-stage breast cancer: a prospective longitudinal study. *Quality of Life Research* 2008; 17(2):333-345.	Not EQ-5D
Matalqah LM, Radaideh KM, Yusoff ZM, Awaisu A. Health-related quality of life using EQ-5D among breast cancer survivors in comparison with age-matched peers from the general population in the state of Penang, Malaysia. *Journal of Public Health* 2011; 19(5):475-480.	Inappropriate participants
Milne RJ, Heaton-Brown KH, Hansen P, Thomas D, Harvey V, Cubitt A. Quality-of-life valuations of advanced breast cancer by New Zealand women. *Pharmacoeconomics* 2006; 24(3):281-292.	Inappropriate participants
Moro-Valdezate D, Peiro S, Buch-Villa E, Caballero-Garate A, Morales-Monsalve MD, Martinez-Agullo A et al. Evolution of Health-Related Quality of Life in Breast Cancer Patients during the First Year of Follow-Up. *Journal of Breast Cancer* 2013; 16(1):104-111.	No relevant information on health states
Ng R, Lee CF, Wong NS, Yap YS, Lo SK, Wong C et al. Measurement properties and equivalence of the english and chinese versions of the new 5-level EQ-5D in Asian breast cancer patients. *European Journal of Cancer* 2011; Conference(var.pagings):S235.	Abstract
Oh S, Heflin L, Meyerowitz BE, Desmond KA, Rowland JH, Ganz PA. Quality of life of breast cancer survivors after a recurrence: a follow-up study. *Breast Cancer Research and Treatment* 2004; 87(1):45-57.	Not EQ-5D
Peasgood T, Ward SE, Brazier J. Health state utility values in breast cancer: A review and metaanalysis. *Value in Health* 2010; Conference(var.pagings):7.	Not primary research
Polsky D, Keating NL, Weeks JC, Schulman KA. Patient choice of breast cancer treatment: impact on health state preferences. *Medical Care* 2002; 40(11):1068-1079.	Not EQ-5D
Polsky D, Mandelblatt JS, Weeks JC, Venditti L, Hwang YT, Glick HA et al. Economic evaluation of breast cancer treatment: considering the value of patient choice. *Journal of Clinical Oncology* 2003; 21(6):1139-1146.	Not EQ-5D
Postma EL, Koffijberg H, Verkooijen HM, Witkamp AJ, van den Bosch	No relevant

MA, van HR. Cost-effectiveness of radioguided occult lesion localization (ROLL) versus wire-guided localization (WGL) in breast conserving surgery for nonpalpable breast cancer: results from a randomized controlled multicenter trial. *Annals of Surgical Oncology* 2013; 20(7):2219-2226.	information on health states
Rand KL, Otte JL, Flockhart D, Hayes D, Storniolo AM, Stearns V et al. Modeling hot flushes and quality of life in breast cancer survivors. *Climacteric* 2011; 14(1):171-180.	No relevant information on health states
Shimozuma K, Shiroiwa T, Fukuda T, Mori M, Ohashi Y, Watanabe T. Comparison of Eq-5D Score Between Treatment with 4 Cycles of Anthracycline Followed by 4 Cycles of Taxane and 8 Cycles of Taxane for Node Positive Breast Cancer Patients After Surgery: N-Sas Bc 02 Trial. *Value in Health* 2010; 13(7):A274	Abstract
Shiroiwa T, Fukuda T, Shimozuma K, Kuranami M, Suemasu K, Ohashi Y et al. Comparison of EQ-5D scores among anthracycline-containing regimens followed by taxane and taxane-only regimens for node-positive breast cancer patients after surgery: the N-SAS BC 02 trial. *Value in Health* 2011; 14(5):746-751	No relevant information on health states
Slovacek L, Slovackova B, Slanska I, Petera J, Priester P, Filip S et al. Depression symptoms and health-related quality of life among patients with metastatic breast cancer in programme of palliative cancer care. *Neoplasma* 2009; 56(6):467-472.	No relevant information on health states
Slovacek L, Slovackova B, Slanska I, Petera J, Priester P. Quality of life and depression among metastatic breast cancer patients. *Medical Oncology* 2010; 27(3):958-959.	Abstract
Sun Y, Kang E, Heo C, Kim D, Hwang Y, Yom C et al. Comparison of Quality of Life According to the Surgical Techniques Among Breast Cancer Survivors. *Breast* 2013; 22(Suppl. 1):S117-S118.	Abstract
Sura K, Tan K, Freedman GM, Troxel AB, Lin LL. Factors affecting breast cancer patient quality of life in association with radiation. International Journal of Radiation Oncology Biology Physics 2013; 87(2 suppl 1):S115-S116.	Abstract
Takei H, Ohsumi S, Shimozuma K, Ohashi Y, Fujiki Y, Suemasu K et al. Health-related quality-of-life and psychological distress of breast cancer patients after surgery during phase III randomized trial comparing tamoxifen, exemestane, and anastrozole: N-SAS BC 04. *Breast Cancer Research and Treatment* 2006; 100(Suppl. 1):S189-S190.	Not EQ-5D

Teckle P, Peacock S, McTaggart-Cowan H, van der Hoek K, Chia S, Melosky B et al. The ability of cancer-specific and generic preference-based instruments to discriminate across clinical and self-reported measures of cancer severities. *Health & Quality of Life Outcomes* 2011; 9:106	Inappropriate participants
Velthuis MJ, May AM, Koppejan-Rensenbrink RA, Gijsen BC, van BE, de Wit GA et al. Physical Activity during Cancer Treatment (PACT) Study: design of a randomised clinical trial. *BMC Cancer* 2010; 10:272.	Not EQ-5D
Verkooijen HM, Buskens E, Peeters PH, Borel Rinkes IH, de Koning HJ, van Vroonhoven TJ et al. Diagnosing non-palpable breast disease: short-term impact on quality of life of large-core needle biopsy versus open breast biopsy. *Surgical Oncology* 2002; 10(4):177-181.	Inappropriate participants
von Meyenfeldt MF, de KM, Kessels AGH, van der Weijden T, Bell AVRJ, Roukema JA et al. Economic evaluation of a short stay admission programme for breast cancer surgery in four hospitals in the Netherlands. *European Journal of Cancer, Supplement* 2010; Conference(var.pagings):3.	Abstract
Wilking N, Bernow M, Kossler I, Wilking U, Jonsson B. Health Related Quality of Life (HRQoL) in Swedish Relapse Free Breast Cancer Patients. A Study of EQ5D and TTO in a Patient Advocacy Population. *Cancer Research* 2009; 69(24):780S-781S.	Abstract
Wu Y, Segreti A, Cella D, DiLeo A, Amonkar M, Koehler M et al. Lapatinib plus paclitaxel versus paclitaxel alone for first line metastatic breast cancer (MBC) in ErbB(2+) patients - Quality of Life (QOL) results. *Ejc Supplements* 2008; 6(7):171.	Abstract
Yaqata H, Iwase T, Ohtsu H, Komoike Y, Saji S, Takei H et al. Baseline assessment of patient-reported outcomes (PROs) for breast cancer patients after 5-years of endocrine treatment in a randomized clinical trial: NSAS-BC 05. *Breast* 2011; 20(Suppl. 1):S68.	Abstract
Zhou X, Cella D, Cameron D, Amonkar MM, Segreti A, Stein S et al. Lapatinib plus capecitabine versus capecitabine alone for HER2+ (ErbB2+) metastatic breast cancer: quality-of-life assessment. *Breast Cancer Research & Treatment* 2009; 117(3):577-589.	No relevant information on health states
Zhou X, Segreti A, Cella D, Cameron D, Geyer C, Amonkar M et al. Lapatinib plus capecitabine versus capecitabine alone for ErbB2-positive metastatic breast cancer (MBC) - Quality of Life (QOL) assessment. *Ejc Supplements* 2008; 6(7):216-217.	Abstract

Appendix 9 Data extraction forms for HRQoL studies (presented in order of health states)

Reference

Turnbull, 2010[87]

Study Characteristics

Research question

What are the stated objectives of the study?

To determine the potential benefits to the patient and to the NHS of the addition of MRI to the routine techniques employed for loco-regional staging of primary breast cancer.

Describe the type of study and study design.

Randomised controlled trial.

Was the sample from i) the general population, ii) patients with the disease of interest, iii) individuals with knowledge of the disease, iv) other?

Are inclusion/exclusion criteria clearly described? Do these exclude any individuals that may be relevant (eg >80 years)?

Women with biopsy-proven primary breast cancer, who were scheduled for wide local excision following triple assessment (clinical, radiological and pathological). Yes, the inclusion and exclusion criteria were clearly described; the study included patients aged 18 years or above.

What are the characteristics of the baseline cohort for the evaluation?

Age

	MRI scan	***No MRI scan***
Mean (yrs) (SD)	56.38 (9.67)	56.59 (10.09)
Median (yrs) (range)	57 (27 to 86)	57 (58 to 85)

*Clinical details based on ITT population

Age (as randomised)	***MRI scan***	***No MRI scan***
<50 years (n, %)	187 (22.9)	187 (23.2)
≥50 years (n, %)	629 (77.1)	620 (76.8)

*Clinical details based on ITT population

<table>
<tr><td></td><td></td></tr>
<tr><td>Sex</td><td>Female 100%</td></tr>
<tr><td>Race (if appropriate)</td><td>Not reported</td></tr>
<tr><td>Indication / disease</td><td>Primary breast cancer</td></tr>
<tr><td>Other characteristics (sample size)</td><td>n = 1625 (MRI scan: n=817; no MRI scan: 808)

<table>
<tr><th>Variables</th><th>Category</th><th>MRI scan</th><th>No MRI scan</th></tr>
<tr><td rowspan="4">Menopausal status</td><td></td><td></td><td></td></tr>
<tr><td>Pre-menopausal</td><td>232 (28.4)</td><td>234 (29.0)</td></tr>
<tr><td>Post-menopausal</td><td>574 (70.3)</td><td>565 (70.0)</td></tr>
<tr><td>Missing</td><td>10 (1.2)</td><td>8 (1.0)</td></tr>
<tr><td rowspan="5">HRT use (n, %)</td><td></td><td></td><td></td></tr>
<tr><td>Currently</td><td>63 (7.7)</td><td>46 (5.7)</td></tr>
<tr><td>Previously</td><td>232 (28.4)</td><td>231 (28.6)</td></tr>
<tr><td>Never</td><td>514 (63.0)</td><td>528 (65.4)</td></tr>
<tr><td>Missing</td><td>7 (0.9)</td><td>2 (0.2)</td></tr>
<tr><td rowspan="4">Preoperative neoadjuvant therapy (n, %)</td><td></td><td></td><td></td></tr>
<tr><td>Yes</td><td>6 (0.7)</td><td>11 (1.4)</td></tr>
<tr><td>No</td><td>808 (99.0)</td><td>792 (98.1)</td></tr>
<tr><td>Missing data</td><td>2 (0.2)</td><td>4 (0.5)</td></tr>
<tr><td rowspan="4">In situ disease Carcinoma in Situ present (n, %)</td><td></td><td></td><td></td></tr>
<tr><td>Yes</td><td>586 (71.8)</td><td>568 (70.4)</td></tr>
<tr><td>No</td><td>191 (23.4)</td><td>193 (23.9)</td></tr>
<tr><td>Missing data</td><td>39 (4.8)</td><td>46 (5.7)</td></tr>
<tr><td rowspan="5">Grade (n, %)</td><td></td><td></td><td></td></tr>
<tr><td>I</td><td>177 (23.8)</td><td>179 (24.8)</td></tr>
<tr><td>II</td><td>358 (48.2)</td><td>331 (45.8)</td></tr>
<tr><td>III</td><td>200 (26.9)</td><td>205 (28.4)</td></tr>
<tr><td>Missing</td><td>8 (1.1)</td><td>8 (1.1)</td></tr>
</table>
*Note: Other characteristics were reported but not data extracted</td></tr>
<tr><td>QoL instrument</td><td>EQ 5D</td></tr>
<tr><td>Utility values, (Y/N)</td><td>Yes</td></tr>
<tr><td>Treatment effect, if reported</td><td>Yes-Reoperation rates</td></tr>
</table>

Country/ setting

What is the country and setting for the evaluation?

UK, RCT

Data Sources

Effectiveness

Were the QoL data derived from: a single (observational) study, a review / synthesis or combination of previous studies, expert opinion?

QoL data were collected as part of the RCT

Results

Summarise the results

EQ-5D scores	***MRI scan,*** *Mean (SE), 95% CI*	***No MRI scan,*** *Mean (SE), 95% CI*
Baseline	0.8567 (0.0065), 95% CI: 0.8435 to 0.8699	0.8601 (0.0063), 95% CI:0.8475 to 0.8728
8 weeks post randomisation	0.7791 (0.0078), 95% CI: 0.7634 to 0.7948	0.7728 (0.0079), 95% CI: 0.7569 to 0.7887
6 months post initial surgery	0.8040 (0.0094), 95% CI: 0.7844 to 0.8237	0.7935 (0.0078), 95% CI: 0.7781 to 0.8089
12 months post initial surgery	0.8101 (0.0069), 95% CI:0.7965 to 0.8236	0.8112 (0.0072), 95% CI: 0.7970 to 0.8253

*Rounded to 4 decimal places; CI: Confidence Interval; SE: Standard error

Were the methods for deriving these data adequately described (give sources if using data from other published studies)? (Was a valid preference based instrument used to describe health states, such as EQ-5D? Was the valuation of health states from the UK general population?)

Yes- EQ 5D was used to assess health states; the valuation of health states were from the UK population.

Mapping

If a model was used, describe the type of model (eg. regression) or other conversion algorithm

Not applicable

Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

- Overall, QoL scores were similar between the two arms of the trial, with QoL decreasing minimally between baseline and 8 weeks post randomisation, then recovering at between 6 and 12 months post initial surgery.
- The authors reported that 12 months after initial surgery, there was no statistically significant difference in HRQoL as measured by EQ-5D between the two arms of the trial once baseline HRQoL and other covariates were controlled for. The nominal values of the point estimates of the mean changes between baseline and 12 months were also very similar.

What are the implications of the study for the model

The utility values were derived from EQ-5D estimates based on UK population, therefore the EQ-5D estimates reported for the no MRI arm could be used to inform the SHTAC model as this arm of the trial represented current UK treatment option for primary breast cancer. Specifically, the EQ-5D estimates in the baseline and 12 months post initial surgery for the cohort in no MRI arm could be used in the SHTAC model.

Criteria for assessment of study relevance to NICE reference case (adapted from[12])

Relevance questions	**Requirement for NICE (Y/N)**
Do the population characteristics (eg age, sex, co-morbidities, diagnosis, severity of disease) in the study match those described in the decision problem of the review and those modelled?	**Y**
Was a generic preference-based instrument (preferably EQ-5D) used to describe the health states?	**Y**
Was the change in HRQoL taken directly from the patient population?	**Y**
Was the valuation of changes in patients' HRQL undertaken from the general (UK) population?	**Y**
Was the technique used to value the health states a choice-based method (such as TTO)?	**Y**

Reference

Freedman, 2010[88]

Study Characteristics

Research question

What are the stated objectives of the study?

To use the EQ-5D instrument to evaluate the long term health states of women with early stage breast cancer treated by breast conserving surgery and radiation.

Describe the type of study and study design.

Single cohort study

Was the sample from i) the general population, ii) patients with the disease of interest, iii) individuals with knowledge of the disease, iv) other?

Are inclusion/exclusion criteria clearly described? Do these exclude any individuals that may be relevant (eg >80 years)?

Women with early breast cancer treated with breast conserving surgery and radiation with or without systemic therapy.

Yes, the inclusion and exclusion criteria were clearly described and do not exclude any individuals that may be relevant (the study excluded male breast cancer, T3-T4 disease, stage IV disease, mastectomy, or patients treated without radiation).

What are the characteristics of the baseline cohort for the evaluation?

Age	18-44: 13% 45-64: 57% >64: 30%
Sex	Female 100%
Race (if appropriate)	Not reported
Indication / disease	Early stage breast cancer, American Joint Committee on Cancer stages 0, I, or II breast cancer
Other characteristics (sample size)	n = 1050 **Tumor stage** • Tis: 192 (18%) • T1: 714 (68%) • T2: 141 (13%) **Nodal stage**

	• N0	644 (61%)
	• N1-3 positive	174 (17%)
	• N4+ positive	38 (4%)
	• NX	194 (18%)
QoL instrument	EQ-5D	
Utility values, (Y/N)	Yes- presented in a figure over time and in text	
Treatment effect, if reported	Not reported	

Country/ setting

What is the country and setting for the evaluation?

USA, Hospital outpatient clinic

Data Sources

Effectiveness

Were the QoL data derived from: a single (observational) study, a review / synthesis or combination of previous studies, expert opinion?

Single study.

Results

Summarise the results

- Mean descriptive index:

Time points	**EQ-5D scores**
5 years	0.89 (95% CI: 0.87 to 0.91)
10 years	0.9 (95% CI: 0.86 to 0.94)
15 years	0.9 (95% CI: 0.83 to 1.0)

- Mean scores by age:

Time points	**Age groups**		
	18-44 years	**45-64 years**	**>64 years**
5 years	0.95	0.9	0.88
10 years	0.96	0.93	0.76

- No significant differences in health states between patients by age

- States no significant differences in mean index score by the use of adjuvant systemic therapy when compared to those treated by chemotherapy only, tamoxifen only, both or neither (P>0.05); no data were reported
- States no apparent difference in mean score by use of IMRT versus conventional radiation although very few patients treated with IMRT had follow-up greater than 3 years. No data were reported.
- States no significant differences between patients with and without a recurrence, although the number of questionnaires from patients with recurrence was small (n=94) compared to those without recurrence (n=2,386). No data were reported.

Were the methods for deriving these data adequately described (give sources if using data from other published studies)? (Was a valid preference based instrument used to describe health states, such as EQ-5D? Was the valuation of health states from the UK general population?)

Yes- EQ-5D was used to assess health states. However the valuation of health states were not from the UK general population- the study was US based.

Mapping

If a model was used, describe the type of model (eg. regression) or other conversion algorithm

Not applicable

Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

"Patient self-reported quality of life by the EQ-5D was high and remained stable for up to 15 years after treatment with breast conserving surgery and radiation. There was good statistical correlation between patient-reported outcomes by either the VAS or descriptive system."

What are the implications of the study for the model

The study is not UK based; therefore the reported EQ-5D values could be used to inform the model for testing uncertainty or model validity. However, if no UK based study is found, the mean EQ-5D score reported for WLE+EBRT health state could be fed into the model. Data on mean index scores are reported for the entire cohort of patients (i.e. women treated with breast conserving surgery and radiation) but reports no significant difference between sub-groups (such as use of adjuvant systemic therapy, use of IMRT, recurrence- although the number of questionnaires from patients with recurrences was very small compared to those without recurrence)

Criteria for assessment of study relevance to NICE reference case (adapted from[62])

Relevance questions	**Requirement for NICE (Y/N)**
Do the population characteristics (eg age, sex, co-morbidities, diagnosis, severity of disease) in the study match those described in the decision problem of the review and those modelled?	**Y**
Was a generic preference-based instrument (preferably EQ-5D) used to describe the health states?	**Y**
Was the change in HRQoL taken directly from the patient population?	**Y**
Was the valuation of changes in patients' HRQL undertaken from the general (UK) population?	**N**
Was the technique used to value the health states a choice-based method (such as TTO)?	**Y**

Reference

Prescott, 2007[86]

Study Characteristics

Research question

What are the stated objectives of the study?

To assess whether omission of postoperative radiotherapy in women with "low-risk" axillary node negative breast cancer (T0-2) treated by breast conserving surgery and endocrine therapy improves quality of life and is more cost-effective

Describe the type of study and study design.

Randomised Controlled Trial (RCT). A non-randomised cohort was also recruited in order to complete a comprehensive cohort study

Was the sample from i) the general population, ii) patients with the disease of interest, iii) individuals with knowledge of the disease, iv) other?

Are inclusion/exclusion criteria clearly described? Do these exclude any individuals that may be relevant (eg >80 years)?

Breast cancer patients undergoing breast-conserving surgery and endocrine therapy with complete excision on histological assessment The inclusion and exclusion criteria were reported. The study did not include patients aged below 65 years

What are the characteristics of the baseline cohort for the evaluation?

Age	<table><tr><td></td><td colspan="2">Randomised (n= 255)</td></tr><tr><td></td><td>Radiotherapy (n=127)</td><td>No radiotherapy (n=128)</td></tr><tr><td>Mean Age at surgery (SD)</td><td>72.3 (5.0)</td><td>72.8 (5.2)</td></tr></table>
Sex	Female 100%
Race (if appropriate)	Not reported
Indication / disease	Breast cancer patients with "low risk", axillary node-negative

Other characteristics (sample size)	N = 255 (randomised patients); 253 patients were evaluable; EQ-5D data were available for 203 patients
QoL instrument	EQ-5D
Utility values, (Y/N)	Yes
Treatment effect, if reported	Not reported

Country/ setting

What is the country and setting for the evaluation?

UK; RCT

Data Sources

Effectiveness

Were the QoL data derived from: a single (observational) study, a review / synthesis or combination of previous studies, expert opinion?

Yes- an RCT and a cohort study

Results

Summarise the results

EQ-5D	***Radiotherapy (n=102)*** ***Mean (95% CI)***	***No-radiotherapy (n = 101)*** ***Mean (95% CI)***
Baseline	0.77 (0.73 to 0.80)	0.74 (0.70 to 0.77)
3.5 months	0.78 (0.74 to 0.81)	0.76 (0.73 to 0.79)
9 months	0.76 (0.71 to 0.81)	0.72 (0.68 to 0.76)
15 months	0.74 (0.70 to 0.78)	0.73 (0.69 to 0.77)
Unadjusted QALYs	**0.95 (0.90 to 0.99)**	**0.92 (0.88 to 0.95)**

Were the methods for deriving these data adequately described (give sources if using data from other published studies)? (Was a valid preference based instrument used to describe health states, such as EQ-5D? Was the valuation of health states from the UK general population?)

Yes- EQ-5D was used to assess health status; the study was UK based.

Mapping

If a model was used, describe the type of model (eg. regression) or other conversion algorithm

Not applicable

Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

"The utility scores were higher at baseline for the radiotherapy arm than the no radiotherapy arm. The estimated difference in QALYs between the two arms of the trial is adjusted for this baseline difference. The difference in adjusted QALYs was extremely small (-0.0075) and the 95% CI of the difference indicates that this difference was not statistically significant at the 5% level."

What are the implications of the study for the model

As this is a UK based study, the model inputs on utilities could be used to inform SHTAC CE model in development. In particular, this study could be used to populate the health state "Wide local excision followed by EBRT" with the value of 0.74 (95% CI: 0.70 to 0.78).

Criteria for assessment of study relevance to NICE reference case (adapted from[62])

Relevance questions	**Requirement for NICE (Y/N)**
Do the population characteristics (eg age, sex, co-morbidities, diagnosis, severity of disease) in the study match those described in the decision problem of the review and those modelled?	**Y**
Was a generic preference-based instrument (preferably EQ-5D) used to describe the health states?	**Y**
Was the change in HRQoL taken directly from the patient population?	**Y**
Was the valuation of changes in patients' HRQL undertaken from the general (UK) population?	**Y**
Was the technique used to value the health states a choice-based method (such as TTO)?	**Y**

Reference (Lead author, year, refid)

Serra, 2012[89]

Study Characteristics

Research question

What are the stated objectives of the study?

To evaluate the impact of guided imagery (a stress reduction technique) on patients undergoing radiation therapy for breast cancer.

Describe the type of study and study design.

Single cohort study

Was the sample from i) the general population, ii) patients with the disease of interest, iii) individuals with knowledge of the disease, iv) other?

Are inclusion/exclusion criteria clearly described? Do these exclude any individuals that may be relevant (eg >80 years)?

Women receiving radiation therapy for breast cancer Yes- inclusion/exclusion criteria were reported.

What are the characteristics of the baseline cohort for the evaluation?

<table>
<tr><td>Age</td><td>Mean age (range): 57 years (28-77)</td></tr>
<tr><td>Sex</td><td>Female 100%</td></tr>
<tr><td>Race (if appropriate)</td><td>Not reported</td></tr>
<tr><td>Indication / disease</td><td>Women undergoing radiation therapy for breast cancer</td></tr>
<tr><td>Other characteristics (sample size)</td><td>n=66

<table>
<tr><th>Characteristics</th><th>n</th></tr>
<tr><td colspan="2">Stage</td></tr>
<tr><td>0</td><td>18</td></tr>
<tr><td>I</td><td>24</td></tr>
<tr><td>II</td><td>11</td></tr>
<tr><td>III</td><td>9</td></tr>
<tr><td>Local recurrences</td><td>4</td></tr>
<tr><td colspan="2">Adjuvant therapy</td></tr>
<tr><td>Chemotherapy and hormones</td><td>13</td></tr>
</table>
</td></tr>
</table>

	Chemotherapy only: 9 Hormones only: 28 None: 16
QoL instrument	EQ-5D
Utility values, (Y/N)	Yes
Treatment effect, if reported	Not reported

Country/ setting

What is the country and setting for the evaluation?

USA

Data Sources

Effectiveness

Were the QoL data derived from: a single (observational) study, a review / synthesis or combination of previous studies, expert opinion?

Single study

Results

Summarise the results

- Health status was evaluated at two time points: prior to start of guided therapy (time 1) and at the end of radiation therapy (time 2)
- EQ-5D index at time 1: 0.88 (n=64), time 2 = 0.86 (n=54)

Were the methods for deriving these data adequately described (give sources if using data from other published studies)? (Was a valid preference based instrument used to describe health states, such as EQ-5D? Was the valuation of health states from the UK general population?)

Yes- EQ-5D questionnaire was used; the study was US based

Mapping

If a model was used, describe the type of model (eg. regression) or other conversion algorithm

Not applicable

Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

The authors stated that the results from the EQ-5D showed elevation in pain ratings attributed to the radiation-induced skin reactions in pain ratings attributed to the radiation-induced skin reactions and , not surprisingly, accompanied by a reduction in anxiety and depression, further supporting the use of Guided Imagery.

What are the implications of the study for the model?

Since the study was US based, the value of 0.86 (after radiation therapy) could be used to inform the health state of "wide local excision +EBRT" within the CE model, should there be no available UK based data. However, patients also received guided imagery and there was no control arm in the study. It is therefore unclear what impact guided imagery had. In other case, this value could be used in conducting sensitivity analysis.

Criteria for assessment of study relevance to NICE reference case (adapted from[62])

Relevance questions	**Requirement for NICE (Y/N)**
Do the population characteristics (eg age, sex, co-morbidities, diagnosis, severity of disease) in the study match those described in the decision problem of the review and those modelled?	**Y**
Was a generic preference-based instrument (preferably EQ-5D) used to describe the health states?	**Y**
Was the change in HRQoL taken directly from the patient population?	**Y**
Was the valuation of changes in patients' HRQL undertaken from the general (UK) population?	**?**
Was the technique used to value the health states a choice-based method (such as TTO)?	**Y**

Reference

Conner-Spady, 2005[92]

Study Characteristics

Research question

What are the stated objectives of the study?

To examine changes in health related quality of life in breast cancer patients with poor prognosis (Stage II/III) receiving high dose chemotherapy (HDC) treatment with autologous blood stem cell transplantation (ASCT) during long term follow-up.

Describe the type of study and study design.

Prospective 2 year longitudinal study

Was the sample from i) the general population, ii) patients with the disease of interest, iii) individuals with knowledge of the disease, iv) other?

Are inclusion/exclusion criteria clearly described? Do these exclude any individuals that may be relevant (eg >80 years)?

Patients with breast cancer with poor prognosis (stage II/III) Yes- inclusion/exclusion criteria were described clearly; consecutive patients aged between 18 – 65 years

What are the characteristics of the baseline cohort for the evaluation?

<table>
<tr><td>Age</td><td>Mean age (range; s.d.): 44.7 (21 – 62; 8.5)

<table><tr><th>Age distribution</th><th>n</th><th>%</th></tr><tr><td>21-35</td><td>6</td><td>11.5</td></tr><tr><td>36-50</td><td>32</td><td>61.5</td></tr><tr><td>51-62</td><td>14</td><td>26.9</td></tr></table></td></tr>
<tr><td>Sex</td><td>Not reported specifically</td></tr>
<tr><td>Race (if appropriate)</td><td>Not reported</td></tr>
<tr><td>Indication / disease</td><td>Breast cancer patients with poor prognosis (stage II/III) who are at high risk of relapse</td></tr>
<tr><td>Other characteristics (sample size)</td><td>n= 52</td></tr>
</table>

	Variables	Category	n	Percent
	Marital status			
		Single	8	15.4
		Married/Partner	40	76.9
		Divorced	2	3.8
		Widowed	2	3.8
	Years of education	Grade 12 or less	18	35.3
		More than Grade 12	33	64.7
	Stage of cancer	II	18	34.6
		III	34	65.4
	Type of surgery	Modified radical mastectomy	22	42.3
		Total mastectomy	19	36.5
		Segmental	11	21.2
	Nodal status	10 or more	39	75.0
	Tamoxifen	Yes	5	10.0
	Menopausal status	Pre	37	71.2
		Post	15	28.8
QoL instrument	EQ-5D			
Utility values, (Y/N)	Yes			
Treatment effect, if reported	Not reported			

Country/ setting

What is the country and setting for the evaluation?

Canada; Phase II trial

Data Sources

Effectiveness

Were the QoL data derived from: a single (observational) study, a review / synthesis or combination of previous studies, expert opinion?

A prospective longitudinal study

Results

Summarise the results

- Mean QoL scores across different time-points

Time points	***EQ-5D scores (s.d.)***
T1: Pre-induction	0.78 (0.18)
T2: Day 1third cycle of FAC[a]	0.75 (0.18)
T3: 3 weeks post HDC[b]	0.61 (0.29)
T4: 6 months or 8 weeks post HDC	0.79 (0.19)
T5: 12 months	0.84 (0.19)
T6: 18 months	0.84 (0.13)
T7: 24 months	0.89 (0.13)

[a] Fluorouracil, Adriamycin, and cyclophosphamide; [b] High-dose chemotherapy

- There was a significant decrease in HRQoL from T1 to T3 and return to baseline levels at T4 i.e., 8 weeks post HDC. In the short term, HRQoL was impacted negatively by treatment but quickly rebounded

Were the methods for deriving these data adequately described (give sources if using data from other published studies)? (Was a valid preference based instrument used to describe health states, such as EQ-5D? Was the valuation of health states from the UK general population?)

Yes, EQ-5D questionnaire was used.
The valuation of health states was from a set of Canadian breast cancer patients group

Mapping

If a model was used, describe the type of model (eg. regression) or other conversion algorithm

Not applicable

Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

EQ-5D data showed a pattern of change with HRQL decreasing following the administration of HDC,

and returning to baseline levels post-HDC.

What are the implications of the study for the model

The study did not report utility values for the health states which are relevant for the SHTAC CE model in development. However, since the patients included in the study had all undergone mastectomy/surgery, the utility value reported by EQ-5D at the end of 2 years (i.e. at time-point T7) valued at 0.89 could be used to represent the utility value for "mastectomy & reconstruction" health state in the SHTAC CE model.

Criteria for assessment of study relevance to NICE reference case (adapted from[62])

Relevance questions	**Requirement for NICE (Y/N)**
Do the population characteristics (eg age, sex, co-morbidities, diagnosis, severity of disease) in the study match those described in the decision problem of the review and those modelled?	**N**
Was a generic preference-based instrument (preferably EQ-5D) used to describe the health states?	**Y**
Was the change in HRQoL taken directly from the patient population?	**Y**
Was the valuation of changes in patients' HRQL undertaken from the general (UK) population?	**Y***
Was the technique used to value the health states a choice-based method (such as TTO)?	**Y**

*Health states were converted to EQ-5D index using standardised weights derived from time-trade off measurements based on UK population.

Reference

Robertson, 2012[90]

Study Characteristics

Research question

What are the stated objectives of the study?

To present an audit of all Immediate Breast Reconstruction (IBRs) during the period 2005-2008 performed by breast surgeons, including post-operative HRQoL.

Describe the type of study and study design.

Retrospective descriptive study

Was the sample from i) the general population, ii) patients with the disease of interest, iii) individuals with knowledge of the disease, iv) other?

Are inclusion/exclusion criteria clearly described? Do these exclude any individuals that may be relevant (eg >80 years)?

Consecutive patients recruited between 2005 – 2008 who had undergone IBRs Inclusion and exclusion criteria were reported

What are the characteristics of the baseline cohort for the evaluation?

<table>
<tr><td>Age</td><td>Mean age at IBR: 50 years</td></tr>
<tr><td>Sex</td><td>Female 100%</td></tr>
<tr><td>Race (if appropriate)</td><td>Not reported</td></tr>
<tr><td>Indication / disease</td><td>IBR patients with implants</td></tr>
<tr><td>Other characteristics (sample size)</td><td>Sample size: 223 patients

<table>
<tr><th>Indication for IBR</th><th>Mastectomy as 1st treatment</th><th>Completion mastectomy</th><th>IBTR</th><th>Total</th></tr>
<tr><td></td><td>% (n)</td><td>% (n)</td><td>% (n)</td><td>% (n)</td></tr>
<tr><td>Patients</td><td>62.8 (140)</td><td>27.3 (61)</td><td>9.9 (22)</td><td>100 (223)</td></tr>
</table>
IBRT: Ipsilateral Breast Tumor Recurrence</td></tr>
<tr><td>QoL instrument</td><td>EQ-5D</td></tr>
<tr><td>Utility values, (Y/N)</td><td>Yes</td></tr>
</table>

Treatment effect, if reported	Not reported

Country/ setting

What is the country and setting for the evaluation?

Sweden

Data Sources

Effectiveness

Were the QoL data derived from: a single (observational) study, a review / synthesis or combination of previous studies, expert opinion?

Single study

Results

Summarise the results

- The calculated EQ-5D index for the patient population was 0.83
- EQ-5D questionnaire for patients' current state of health at median of 4 yrs postoperatively

Dimension	**Severity level of problem**			
	No problem	**Moderate**	**Severe**	**Missing**
	% (n)	**% (n)**	**% (n)**	**n**
Mobility	86.6 (142)	6.7 (11)	0 (0)	11
Self-care	92.7 (152)	0.6 (1)	0 (0)	11
Usual activities	78 (128)	13.4 (22)	1.8 (3)	11
Pain/discomfort	52.4 (86)	37.8 (62)	1.8 (3)	13
Anxiety/depression	53.7 (88)	37.8 (62)	1.8 (3)	11

Were the methods for deriving these data adequately described (give sources if using data from other published studies)? (Was a valid preference based instrument used to describe health states, such as EQ-5D? Was the valuation of health states from the UK general population?)

Yes- EQ-5D was used to assess health status of the patients. The valuation of health states was not from the UK general population; the study was based on Swedish population.

Mapping

If a model was used, describe the type of model (eg. regression) or other conversion algorithm

Not applicable

Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

"..overall satisfactory patient-reported outcomes concerning aesthetics of the breast reconstruction and items in everyday life, despite the high rate of irradiated patients. However we identified a high frequency of moderate problems with pain/discomfort and anxiety/depression at a median of 4 years after surgery, compared to norm data, although the general state of health was rated high."

What are the implications of the study for the model

The estimated EQ-5D score of 0.83 could be populated for the "mastectomy and reconstruction" health state within the SHTAC CE model in development

Criteria for assessment of study relevance to NICE reference case (adapted from[62])

Relevance questions	**Requirement for NICE (Y/N)**
Do the population characteristics (eg age, sex, co-morbidities, diagnosis, severity of disease) in the study match those described in the decision problem of the review and those modelled?	**Y**
Was a generic preference-based instrument (preferably EQ-5D) used to describe the health states?	**Y**
Was the change in HRQoL taken directly from the patient population?	**Y**
Was the valuation of changes in patients' HRQL undertaken from the general (UK) population?	**N**
Was the technique used to value the health states a choice-based method (such as TTO)?	**Y**

Y: Yes; N: No; ?: Unclear

Reference

Lidgren, 2007[91]

Study Characteristics

Research question

What are the stated objectives of the study?

To describe the health related quality of life (HRQoL) in different breast cancer disease states using preference-based measures

Describe the type of study and study design.

Cross sectional observational study.

Was the sample from i) the general population, ii) patients with the disease of interest, iii) individuals with knowledge of the disease, iv) other?

Are inclusion/exclusion criteria clearly described? Do these exclude any individuals that may be relevant (eg >80 years)?

Women with a previous diagnosis of breast cancer. The inclusion criteria are reported but exclusion criteria are not.

What are the characteristics of the baseline cohort for the evaluation?

<table>
<tr><td>Age</td><td>Mean age (range): 57 years (28 – 93)

<table><tr><th>Age distribution</th><th>Frequency</th><th>Percentage</th></tr><tr><td>< 50 years</td><td>91</td><td>26%</td></tr><tr><td>50-64</td><td>178</td><td>52%</td></tr><tr><td>65 and older</td><td>76</td><td>22%</td></tr><tr><td>Total</td><td>345</td><td>100%</td></tr></table></td></tr>
<tr><td>Sex</td><td>Female 100%</td></tr>
<tr><td>Race (if appropriate)</td><td>Not reported</td></tr>
<tr><td>Indication / disease</td><td>Women with a previous diagnosis of breast cancer</td></tr>
<tr><td>Other characteristics (sample size)</td><td>n =361; n=345 after exclusions</td></tr>
<tr><td>QoL instrument</td><td>EQ-5D</td></tr>
<tr><td>Utility values, (Y/N)</td><td>Yes</td></tr>
<tr><td>Treatment effect, if reported</td><td>Not reported</td></tr>
</table>

Country/ setting

What is the country and setting for the evaluation?

Sweden, breast cancer outpatient clinic

Data Sources

Effectiveness

Were the QoL data derived from: a single (observational) study, a review / synthesis or combination of previous studies, expert opinion?

A cross sectional observational study.

Results

Summarise the results

State	***N***	***%***	***Mean EQ-5D score***	***95% CI***
State P (Patients in their first year after a primary breast cancer)	72	21	0.696 [a]	0.634 to 0.747
State R (Patients in their first year after a recurrence)	21	6	0.779	0.700 to 0.849
State S (Patients who had not had a primary breast cancer diagnosis or a recurrence during the previous year)	177	53	0.779	0.745 to 0.811
State M (Patients with metastatic disease)	65	19	0.685 [a]	0.620 to 0.735

[a]: significant difference compared to second and following years after primary breast cancer/recurrence ($P<0.005$)

The main driver behind the reduction in HRQoL was pain and discomfort as well as anxiety and depression.

EQ-5D dimensions (no problems, moderate problems and severe problems) were reported but no data were extracted.

State	***N***	***Mean EQ-5D score***	***95% CI***
Patients in State P receiving adjuvant chemotherapy	23	0.620	0.509 to 0.697
Patients in State P receiving hormone therapy	17	0.744	0.573 to 0.841

Patients in State R receiving adjuvant chemotherapy	7	0.767	0.573 to 0.841
Patients in State R receiving adjuvant hormone therapy	4	0.816	0.729 to 0.963
Patients in State S receiving adjuvant hormone therapy	79	0.824	0.785 to 0.857
Patients in State M receiving hormone therapy	16	0.648	0.513 to 0.765
Patients in State M receiving chemotherapy	38	0.692	0.611 to 0.746
Metastatic patients who had at least 1 new distant recurrences more than 1 month after their first distant recurrence	10	0.661	0.454 to 0.812
Metastatic patients who did not have a new distant recurrences more than 1 month after their first distant recurrence	55	0.690	0.630 to 0.753

Were the methods for deriving these data adequately described (give sources if using data from other published studies)? (Was a valid preference based instrument used to describe health states, such as EQ-5D? Was the valuation of health states from the UK general population?)

Yes- EQ-5D data were presented clearly. The valuation was based on Swedish patients.

Mapping

If a model was used, describe the type of model (eg. regression) or other conversion algorithm

Not applicable

Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

"The study shows that breast cancer is associated with a reduction in HRQoL. This effect is most pronounced for patients with metastatic disease"

What are the implications of the study for the model

- <u>If UK based data are not available:</u>
  The utility value of 0.685 as derived for the patients with metastases could be used to inform the SHTAC CE model for the health state of distant recurrence, although the data are derived from Swedish patients. Also the value of 0.779 could be used to populate the utility value for health state "disease free after local recurrence"

- <u>If UK based data are available:</u>

  The above values could be used for conducting sensitivity analysis.

Criteria for assessment of study relevance to NICE reference case (adapted from[62])

Relevance questions	**Requirement for NICE (Y/N)**
Do the population characteristics (eg age, sex, co-morbidities, diagnosis, severity of disease) in the study match those described in the decision problem of the review and those modelled?	**Y**
Was a generic preference-based instrument (preferably EQ-5D) used to describe the health states?	**Y**
Was the change in HRQoL taken directly from the patient population?	**Y**
Was the valuation of changes in patients' HRQL undertaken from the general (UK) population?	**Y; the study used UK EQ-5D index tariff**
Was the technique used to value the health states a choice-based method (such as TTO)?	**Y**

Reference

Sherrill, 2008[94]

Study Characteristics

Research question

What are the stated objectives of the study?

To examine whether patients receiving combination therapy of lapatinib+capecitabine would experience, on average, more time in a better health state compared with patients on capecitabine alone.

Describe the type of study and study design.

RCT; Quality-adjusted time without symptoms of disease or toxicity of treatment (Q-TWiST) analysis

Was the sample from i) the general population, ii) patients with the disease of interest, iii) individuals with knowledge of the disease, iv) other?

Are inclusion/exclusion criteria clearly described? Do these exclude any individuals that may be relevant (eg >80 years)?

Advanced or metastatic HER2 + breast cancer patients who had progressive disease following prior therapy which included an anthracycline, a taxane and trastuzumab Inclusion and exclusion criteria were reported elsewhere (references provided)

What are the characteristics of the baseline cohort for the evaluation?

<table>
<tr><td>Age</td><td>Not reported</td></tr>
<tr><td>Sex</td><td>Female 100%</td></tr>
<tr><td>Race (if appropriate)</td><td>Not reported</td></tr>
<tr><td>Indication / disease</td><td>Advanced or metastatic HER2 + breast cancer who had progressive disease following prior therapy</td></tr>
<tr><td>Other characteristics (sample size)</td><td>n=399
<table>
<tr><th></th><th>Lapatinib + capecitabine arm</th><th>Capecitabine arm</th></tr>
<tr><td>n</td><td>198</td><td>201</td></tr>
</table>
Patients characteristics:
<table>
<tr><td rowspan="3">Prior therapy</td><td>Anthracycline</td><td>97%</td></tr>
<tr><td>Taxane</td><td>97%</td></tr>
<tr><td>Trastuzumab</td><td>97%</td></tr>
</table>
</td></tr>
</table>

	Patients with metastatic disease: 96% Patients with visceral lesions: 78% Patients with visceral at three or more sites: 49%
QoL instrument	EQ-5D
Utility values, (Y/N)	Yes
Treatment effect, if reported	Not reported

Country/ setting

What is the country and setting for the evaluation?

UK and USA; Phase 3 RCT

Data Sources

Effectiveness

Were the QoL data derived from: a single (observational) study, a review / synthesis or combination of previous studies, expert opinion?

Single study; patient reported utility weights were derived from the EQ-5D using published algorithms

Results

Summarise the results

Average utility values by health state, based on EQ-5D scores

Health-state ITT population	**Lapatinib plus capecitabine**	**Capecitabine monotherapy**
Toxicity[1]: Grade 3/4	0.60 (n=27)	0.59 (n=17)
TWiST	0.66 (n=168)	0.66 (n=157)
Relapse[2]	0.41 (n=50)	0.44 (n=67)

[1]Toxicity included all days spent with Grade 3 / 4 AEs after randomisation and prior to disease progression;

TWiST: Time period without symptoms of toxicity or disease progression

[2]Relapse includes period till death or end of follow-up

Were the methods for deriving these data adequately described (give sources if using data from other published studies)? (Was a valid preference based instrument used to describe health states, such as EQ-5D? Was the valuation of health states from the UK general population?)

Yes- EQ-5D questionnaire was used

Mapping

If a model was used, describe the type of model (eg. regression) or other conversion algorithm

Not applicable

Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

"the lapatinib plus capecitabine combination provided significantly greater Q-TWiST than did capecitabine alone. The full impact of the combination cannot be determined, because of the early closure to accrual and subsequent cross over, but it is likely that the average 7 weeks improvement is an underestimate of the overall benefits"

What are the implications of the study for the model

The utility value for the "relapse" health state could be used to inform the "distant recurrence" health state in the CE model.

Criteria for assessment of study relevance to NICE reference case (adapted from{843)

Relevance questions	**Requirement for NICE (Y/N)**
Do the population characteristics (eg age, sex, co-morbidities, diagnosis, severity of disease) in the study match those described in the decision problem of the review and those modelled?	**Y (for one of the health states of the model)**
Was a generic preference-based instrument (preferably EQ-5D) used to describe the health states?	**Y**
Was the change in HRQoL taken directly from the patient population?	**Y**
Was the valuation of changes in patients' HRQL undertaken from the general (UK) population?	**?**
Was the technique used to value the health states a choice-based method (such as TTO)?	**N**

?: unclear

Reference (Lead author, year, refid)

Hildebrandt, 2014[93]

Study Characteristics

Research question

What are the stated objectives of the study?

To investigate health utilities as cardinal values of the individual's preferences for specific health-related outcomes in women treated in Germany in the fields of gynaecological oncology and mastology in order to provide local data from Germany.

Describe the type of study and study design.

Cross-sectional survey from May 2009 to December 2009

Was the sample from i) the general population, ii) patients with the disease of interest, iii) individuals with knowledge of the disease, iv) other?

Are inclusion/exclusion criteria clearly described? Do these exclude any individuals that may be relevant (eg >80 years)?

The sample included patients (both men and women) who were affected by breast, cervical, endometrium, ovarian and other gynaecological cancer as well as healthy individuals. Limited information was provided; relevant individuals do not appear to be excluded

What are the characteristics of the baseline cohort for the evaluation?

Age	<table><tr><th></th><th>**All patients with disease**</th></tr><tr><td>Median age, years</td><td>59.07</td></tr><tr><td>Range, years</td><td>20.12 – 83.33</td></tr></table>
Sex	Female: 99.4%; Male: 0.6%
Race (if appropriate)	Not reported
Indication / disease	Patients with breast, ovarian, endometrial, cervical, and other gynaecological cancer.
Other characteristics (sample size)	Number taking part in the survey: n=655 (including 63 healthy controls)

	Number with disease: n=592 Number of patients with breast cancer: n= 497 (including 3 men)
QoL instrument	EQ-5D
Utility values, (Y/N)	Yes
Treatment effect, if reported	Not reported

Country/ setting

What is the country and setting for the evaluation?

Germany; Surgical and conservative oncological wards, specialist Outpatient Department for Breast diseases and Outpatient gynaecological oncology department.

Data Sources

Effectiveness

Were the QoL data derived from: a single (observational) study, a review / synthesis or combination of previous studies, expert opinion?

Single study

Results

Summarise the results

Breast cancer	**n**	**Min**	**Max**	**Median**
Overall	442	0.063	1.000	0.8870
Primary disease	312	0.262	1.000	0.8870
Metastatic disease	80	0.063	1.000	0.8870
Recurrent disease	21	0.175	1.000	0.8870
Both	29	0.788	1.000	0.8870

Were the methods for deriving these data adequately described (give sources if using data from other published studies)? (Was a valid preference based instrument used to describe health states, such as EQ-5D? Was the valuation of health states from the UK general population?)

EQ-5D valuation from German population

Mapping

If a model was used, describe the type of model (eg. regression) or other conversion algorithm

Not applicable

Conclusions/ Implications

Give a brief summary of the author's conclusions from their analysis

In patients with breast cancer, those with primary disease had the highest values of QoL as measured by EQ-5D VAS (not data extracted).QoL declined if the disease was already advanced. However, this difference was not evident from the EQ-5D health index, which had a consistent value at 0.8870.

What are the implications of the study for the model?

The study could be used as a reference point for assuming similar utility values for "recurrence" and "metastatic" possible health states within the independent model.

Criteria for assessment of study relevance to NICE reference case (adapted from[12])

Relevance questions	**Requirement for NICE (Y/N)**
Do the population characteristics (eg age, sex, co-morbidities, diagnosis, severity of disease) in the study match those described in the decision problem of the review and those modelled?	**Y**
Was a generic preference-based instrument (preferably EQ-5D) used to describe the health states?	**Y**
Was the change in HRQoL taken directly from the patient population?	**Y**
Was the valuation of changes in patients' HRQL undertaken from the general (UK) population?	**N**
Was the technique used to value the health states a choice-based method (such as TTO)?	**Y**

Y: Yes; N: No; ?: Unclear

Appendix 10 Critical appraisal checklist for HRQoL studies

Criteria Adapted from[59-62]	**Issues to consider**		**Studies**							
		Turnbull et al.[87]	**Freedman et al[88]**	**Prescott et al.[86]**	**Serra et al.[89]**	**Conner-Spady et al.[92]**	**Robertson et al.[90]**	**Lidgren et al.[91]**	**Sherill et al.[94]**	**Hildebrandt et al.[93]**
Conceptual										
Study objectives	**Were the objectives of the study clearly stated? HRQoL primary or secondary outcome?**	Yes- secondary outcome	Yes- primary outcome	Yes- primary outcome	Yes- primary outcome	Yes- primary outcome	Yes- primary outcome	Yes- primary outcome	Yes- secondary outcome	Yes- primary outcome
HRQoL instrument	**Was a reason provided to justify the HRQoL instrument selected? Was a validated tool used to assess QoL?**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Methodology										
Study design	**Was the design of the study clearly described? (eg cohort, cross**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes- RCT was described elsewhere	Yes

Criteria Adapted from[59-62]	**Issues to consider**		**Studies**							
		Turnbull et al.[87]	**Freedman et al[88]**	**Prescott et al.[86]**	**Serra et al.[89]**	**Conner-Spady et al.[92]**	**Robertson et al.[90]**	**Lidgren et al.[91]**	**Sherill et al.[94]**	**Hildebrandt et al.[93]**
	sectional, survey)									
Respondent selection and recruitment	**Was the sampling method for recruitment of participants adequately described?**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Inclusion/exclusion criteria	**Are inclusion/exclusion criteria clearly described?** **Do these exclude any individuals that might be relevant? (eg very elderly >80 years old)**	Yes- eligibility criteria were described; No- relevant patient population was included	Yes- eligibility criteria were described; No- relevant patient population was included	Yes; The study did not include patients <65 yrs	No- limited details were provided; ?-It is unclear if the study excluded any individuals that might be relevant	Yes; The study did not include those aged >65 yrs	No; ?- It is unclear if the study excluded any relevant individuals	Yes; No- relevant patient population was included	Yes- reference provided; No- relevant patient population was included	No Limited information was provided but it could be assumed that no relevant groups were excluded.

Criteria Adapted from[59-62]	**Issues to consider**		**Studies**							
		Turnbull et al.[87]	**Freedman et al[88]**	**Prescott et al.[86]**	**Serra et al.[89]**	**Conner-Spady et al.[92]**	**Robertson et al.[90]**	**Lidgren et al.[91]**	**Sherill et al.[94]**	**Hildebrandt et al.[93]**
Participant characteristics	**Were characteristics of participants clearly described? (demographics and clinical variables)**	Yes	Yes	Yes	Yes	Yes	?	Yes	Yes- reference provided	No
Sample size	**Was the sample size used appropriately justified?**	Yes	No- but the sample size was adequately large	? The sample size for the randomisation and that for the CE model were different	Yes	No	No	No	No- trial was stopped early before sample size reached	No
Instrument administration	**Is it reported who and/or in which clinical setting the instrument was administered?**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Timing of	**Is the timing of**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No

Criteria Adapted from[59-62]	**Issues to consider**		**Studies**							
		Turnbull et al.[87]	**Freedman et al[88]**	**Prescott et al.[86]**	**Serra et al.[89]**	**Conner-Spady et al.[92]**	**Robertson et al.[90]**	**Lidgren et al.[91]**	**Sherill et al.[94]**	**Hildebrandt et al.[93]**
assessments	**assessments reported? (eg baseline and/or at follow-up or after treatment)**									
Results										
Response rates to instrument used	**Are response rates reported and if so, are the rates likely to be a threat to validity?**	Yes- response rates were reported; No- the rates are not likely to threaten the validity of results	Yes- response rates were reported; There was low response rates from women with recurrence compared to those	Yes- response rates were reported; No- the rates are not likely to threaten the validity of results	Yes- the response rates were reported; No- the rates are not likely to threaten the validity of results	Yes- response rates were reported; No- the rates are not likely to threaten the validity of results	Yes- response rates were reported; No- the rates are not likely to threaten the validity of results	Yes- response rates were reported; No- the rates are not likely to threaten the validity of results	No- the response rates were not reported; ?-Possibly the rates could threaten the validity of the results	No- the response rates were not reported; N/A

Criteria Adapted from[59-62]	**Issues to consider**		**Studies**							
		Turnbull et al.[87]	**Freedman et al[88]**	**Prescott et al.[86]**	**Serra et al.[89]**	**Conner-Spady et al.[92]**	**Robertson et al.[90]**	**Lidgren et al.[91]**	**Sherill et al.[94]**	**Hildebrandt et al.[93]**
			without recurrence.							
Loss to follow-up	**Is the loss to follow-up reported and are reasons given?**	Yes- loss to follow-up was reported;	No- loss to follow-up was not reported;	Yes- loss to follow-up was reported;	No- loss to follow-up was not reported;	Yes- loss to follow-up was reported;	No- loss to follow-up was not reported;	Not applicable;	Yes- loss to follow-up was reported;	No-loss to follow up was not reported
	Are these likely to threaten the validity of results? (eg characteristics of non-responders different to responders)	No-they are not likely to threaten validity of results	It is not clear if these were likely to threaten the validity of the results	No-they are not likely to threaten validity of results	It is not clear if these were likely to threaten the validity of the results	No-they are not likely to threaten validity of results	It is not clear if these were likely to threaten the validity of the results	?-It is not clear	No-they are not likely to threaten validity of results	?-It is not clear
Missing data	**Are the levels of missing data reported?**	Yes- missing data were reported;	No- missing data were not	Yes- missing data were reported;	Mixed model regression and	Yes- missing data were reported;	Yes- missing data were reported;	Yes- missing data were reported;	Yes- missing data were reported;	No- missing data were not reported;

Criteria Adapted from[59-62]	**Issues to consider**		**Studies**							
		Turnbull et al.[87]	**Freedman et al[88]**	**Prescott et al.[86]**	**Serra et al.[89]**	**Conner-Spady et al.[92]**	**Robertson et al.[90]**	**Lidgren et al.[91]**	**Sherill et al.[94]**	**Hildebrandt et al.[93]**
	How are they dealt with? Could this threaten the validity of results?	No- they are not likely to threaten the validity of the results	reported; It is not clear if these were likely to threaten the validity of the results	No- they are not likely to threaten the validity of the results	generalised linear modelling allowed for the inclusion of patients with missing data over time on the assumption that the data were missing at random.	? Not clear; however subset of 27 patients with complete data showed similar results.	It is not clear if these were likely to threaten the validity of the results	It is not clear if these were likely to threaten the validity of the results	It is not clear if these were likely to threaten the validity of the results	It is not clear if these were likely to threaten the validity of the results
Statistical analysis	**Were appropriate statistical methods used?**	Yes	Yes	Yes	Yes	Yes	?	Yes	Yes	Only descriptive statistics was presented.
Interpretation										

Criteria Adapted from[59-62]	**Issues to consider**		**Studies**							
		Turnbull et al.[87]	**Freedman et al[88]**	**Prescott et al.[86]**	**Serra et al.[89]**	**Conner-Spady et al.[92]**	**Robertson et al.[90]**	**Lidgren et al.[91]**	**Sherill et al.[94]**	**Hildebrandt et al.[93]**
Study findings	**Were the key findings of the study clearly stated?**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Study limitations	**Were limitations of the study clearly described?**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Other	**Eg Relevance of location (eg patients not recruited in UK)**	Yes	This study is not UK based	Yes	? The study iss based on US population	? The study is based on Canadian population	? This study is not UK based	? The study is based on Swedish population	? It is assumed centres were in the USA and the UK	? The study is based on German population

Appendix 11. Complete set of results from deterministic sensitivity analysis, IORT vs EBRT. WTP set to £20,000 per QALY.

Variable description	Low value	High value	Low value incremental NMB (£)	High value incremental NMB (£)	Range (£)
Five-year probability of any other recurrence INTRABEAM	0.029	0.071	5,781	-9,171	14,952
Five-year probability of any other recurrence EBRT	0.028	0.071	-8,760	5,977	14,737
Beta coefficient for INTRABEAM arm time to local recurrence (lognormal)	-0.815	0.307	-4,512	118	4,630
Five-year probability of death from breast cancer EBRT	0.014	0.045	-4,150	-346	3,804
Five-year probability of death from breast cancer INTRABEAM	0.016	0.055	1,051	-2,518	3,569
Constant - time to local recurrence (lognormal)	3.553	6.383	-3,367	-836	2,531
Discount rate for utilities	0	0.06	-3,192	-1,042	2,150
Number of EBRT deliveries required to complete a course of treatment	5	23	-2,604	-832	1,772
Starting age of model cohort	55	72	-2,273	-757	1,516
Cost of delivering one fraction EBRT	71	178	-2,211	-877	1,334
Proportion of incident cases which are early BC and suitable for INTRABEAM	0.1	0.5	-2,064	-1,128	936
Sigma - time to local recurrence (lognormal)	0.072	0.797	-1,110	-2,018	908
EBRT planning cost	90	704	-1,813	-1,303	510
Lifetime of INTRABEAM equipment (years)	5	10	-1,973	-1,619	354
Population served by 1 INTRABEAM device	800,004	1,200,000	-1,800	-1,498	302
Probability of any other recurrence	0.362	0.471	-1,474	-1,764	290

given local recurrence					
Proportion of patients requiring radiation shield	0.25	1	-1,463	-1,619	156
Cost of one hour in operating room	461	688	-1,549	-1,696	147
Utility recurrence free subsequent years	0.8	0.83	-1,658	-1,555	103
Additional time required in theatre while delivering INTRABEAM	26.4	33	-1,540	-1,619	79
Discount rate for costs	0	0.06	-1,583	-1,658	75
Prop of INTRABEAM who also received EBRT	0.135	0.17	-1,583	-1,657	74
Utility associated with other recurrence state	0.63	0.74	-1,592	-1,647	55
Cost of staff time in theatre per hour of delivery time	122	182	-1,603	-1,636	33
Additional time required in theatre while planning INTRABEAM	4.8	7.2	-1,603	-1,635	32
Staff time required in supporting delivery of each INTRABEAM dose	61	92	-1,604	-1,635	31
Prop of INTRABEAM patients having mastectomy at local recurrence	0.618	0.933	-1,611	-1,625	14
Cost of staff time in theatre per hour of planning time	203	303	-1,614	-1,624	10
Cost of wide local excision	1248	1866	-1,614	-1,624	10
Cost of independent technical commissioning and calibration per year	2062	3080	-1,615	-1,623	8
Cost of mastectomy and reconstruction	6362	9431	-1,617	-1,621	4
Initial set up costs of INTRABEAM	4847	7239	-1,618	-1,620	2
Cost of mastectomy alone	2122	2931	-1,619	-1,621	2
Cost of annual radiation protection refresher training for theatre staff	745	1113	-1,618	-1,620	2
Cost of pre-treatment QC checks	20	31	-1,619	-1,619	0
Proportion having reconstruction	0.304	0.318	-1,620	-1,620	0

after mastectomy					
Utility recurrence free first year after WLE+RT	0.76	0.79	-1,619	-1,619	0