Breast cancer (early) - intrabeam radiotherapy system [ID618]

Overview and resources

Breast cancer (early) - intrabeam radiotherapy system: appraisal consultation document

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using the Intrabeam Radiotherapy System in the NHS in England. The Appraisal Committee has considered the evidence submitted and the views of non-manufacturer consultees and commentators, and clinical specialists and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from the consultees and commentators for this appraisal (see section 10) and the public. This document should be read along with the evidence base (the evaluation report).

The Appraisal Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Note that this document is not NICE's final guidance on this technology. The

consultees.

- After considering these comments, the Committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using the Intrabeam Radiotherapy System in the NHS in England.

For further details, see the Guides to the technology appraisal process.

The key dates for this appraisal are:

Closing date for comments: **15 August 2014**

Second Appraisal Committee meeting: **27 August 2014**

Details of membership of the Appraisal Committee are given in section 9, and a list of the sources of evidence used in the preparation of this document is given in section 10.

1 Appraisal Committee's preliminary recommendations

1.1 The Intrabeam Radiotherapy System is recommended as an option for adjuvant treatment of early invasive breast cancer during breast conserving surgical removal of the tumour, only if clinicians:

- fully explain the treatment options available to patients, including their associated risks and benefits, so that patients can make an informed choice about their treatment. Clinicians should ensure that patients understand that less is known about the long-term outcomes of treatment with the Intrabeam Radiotherapy System than with conventional external beam radiotherapy and that the rate of local recurrence with Intrabeam could be higher than with external beam radiotherapy **and** enter details about all patients having treatment with the Intrabeam Radiotherapy System for adjuvant treatment of early invasive breast cancer onto a national register. They should audit, review and document clinical outcomes (see section 6) locally and consider the relationship between outcomes and patients' characteristics.

2 Clinical need and practice

2.1 Breast cancer is the most common cancer in the UK, accounting for about 1 in 3 of all cancers in women.

2.2 Early invasive breast cancer is cancer that is confined to the breast and ipsilateral axillary lymph nodes. This is usually classified as stage I and II (or operable breast cancer).

2011 over 9700 people died in England as a result of breast cancer. Breast cancer incidence rates generally increase with age; with over 80% of new diagnoses in women older than 50. It is estimated that 95% of women are expected to survive their disease for at least 1 year and 85% of women survive 5 years or more.

2.5 Primary treatment for early disease usually involves surgical removal of the tumour. Adjuvant treatment can include radiotherapy, hormone therapy, biological therapies, or chemotherapy after removal of the primary cancer by surgery.

2.6 Surgery is usually the first treatment option for early breast cancer. Preoperative assessment of the breast and axilla determines the size of the primary tumour in relation to breast volume and this information is used to decide whether breast-conserving surgery with wide local excision of the tumour (also known as lumpectomy) is possible, instead of mastectomy. Patients who have a mastectomy can be offered immediate breast reconstruction (carried out at the same time as the mastectomy) or delayed breast reconstruction. After surgical removal of the primary tumour, the breast cancer multidisciplinary team plans subsequent treatment using the information on prognostic and predictive factors obtained by histological examination, the outcome of tests for oestrogen receptor and human epidermal growth factor receptor 2 status, and other patient and tumour characteristics. Early and locally advanced breast cancer: Diagnosis and treatment (NICE clinical guideline 80) recommends adjuvant chemotherapy or radiotherapy for people with early breast cancer after successful breast-conserving surgery (that is, removal of tumour with clear margins) to prevent local or regional recurrence. Adjuvant radiotherapy is currently given in UK clinical practice by external beam radiotherapy (EBRT) using a linear accelerator and may be supplemented with an external beam tumour bed boost dose. EBRT is given either within 4 6 weeks of surgery or 4–6 months later after completion of chemotherapy. Standard practice in the UK is to give 40 grays in 15 fractions, typically over 3 weeks. Sometimes radiotherapy may be given over a longer period, such as 50 grays in 25 fractions over 5 weeks. This may be followed by a boost dose (12 grays in 4 fractions, 10 grays in 5 fractions, or 16 grays in 8 fractions) to the tumour bed over 1 or 2 weeks in patients considered to be at a higher risk of local recurrence.

2.7 Patient groups highlighted that although early breast cancer is treatable it might recur and spread to other parts of the body. They noted that the psychological burden of the disease is high for the patient and their family and that people want to ensure they have the best chance of a future free from cancer. Patient groups highlighted that current radiotherapy practice frequently involves hospital appointments, with potentially inconvenient and disruptive travelling times to

3 The technology

3.1 The Intrabeam Radiotherapy System (Carl Zeiss UK) is a mobile irradiation system designed to deliver a single dose of targeted low energy radiation (X-rays) directly to the tumour bed while limiting healthy tissue exposure to radiation. Because it delivers low energy radiation, it can be used in an ordinary operating theatre at the time of surgery. The Intrabeam Radiotherapy System provides a source of 50 kV energy from a spherical applicator of between 1.5 and 5.0 cm diameter. The applicator is sutured to the tumour bed so that breast tissue at risk of local recurrence receives the prescribed dose while skin and deeper structures are protected. Radiation is delivered over 20 to 30 minutes. The surface of the tumour bed typically receives a single fraction of 20 grays, which attenuates to 5 to 7 grays at 1 cm depth. The Intrabeam Radiotherapy Systemwas granted a CE (Conformité Européene) mark in 1999 for use in radiotherapy.

3.2 Intrabeam can be used as an intraoperative radiotherapy system given as the sole treatment or as a boost treatment followed by external beam radiotherapy (EBRT). When intraoperative radiotherapy is given as a boost treatment with Intrabeam and followed by EBRT, there is no need for further external boost treatment. Six NHS centres in the UK have usedIntrabeam for adjuvant treatment of early breast cancer.

3.3 Adverse reactions were mostly related to wound-related complications and radiotherapy-related complications. For full details of adverse reactions recorded in the clinical trial (TARGIT-A), see section 4.1.5.

3.4 The manufacturer has stated that the cost of the Intrabeam Radiotherapy System (including the spherical applicators) is £435,000 (excluding VAT, Carl Zeiss UK personal notification). The manufacturer estimated that device maintenance and servicing costs per year are approximately £35,000. Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (section 9) considered evidence from a number of sources (section 10).

4.1 Clinical effectiveness

4.1.1 The Assessment Group conducted a systematic review and identified 1 randomised trial. TARGIT-A is a prospective randomised, non-inferiority clinical trial conducted in 33 centres in 11 different countries including the UK. Patients were treated either with Intrabeam as a single treatment at the same time as surgery (known as the pre-pathology group) or with conventional external beam radiotherapy (EBRT; typically 40–56 grays with or without a boost dose of

the post-pathology group). For these patients, a second surgical procedure was needed to open the wound and give the Intrabeam treatment.

4.1.2 Women aged 45 years or older were randomised in a 1:1 ratio to receive either single-dose Intrabeam or EBRT as per a standard schedule over several weeks. In total, 3451 patients were recruited to TARGIT-A between 2000 and 2012, of which 1721 patients were randomised to receive treatment with Intrabeam and 1730 patients were randomised to receive EBRT. There were 2298 and 1153 patients randomised in the pre-pathology and post-pathology groups respectively. Among patients having treatment with Intrabeam (1571 patients after accounting for patient withdrawals), 15.2% (239 of 1571 patients) had treatment with Intrabeam and EBRT, 21.6% in the pre-pathology group (219 of 1012 patients) and 3.6% (20 of 559 patients) in the post-pathology group. The overall median follow-up in the trial was 2 years and 5 months and 35% of the patients (1222 of 3451) reached a median follow-up of 5 years. A total of 77% of the patients in the trial were between 51 and 70 years, approximately 35%, 50% and 15% of the patients had grade 1, 2 and 3 tumours respectively. Tumours of up to 2 cm were seen in 87% of patients and in approximately 84% of patients cancer was not present in their lymph nodes. Approximately 90% of the patients had oestrogen receptor positive status, approximately 66% of the patients were having hormonal therapy as adjuvant systemic therapy and approximately 12% of the patients were having chemotherapy. The primary outcome was the absolute difference in local recurrence in the conserved breast and secondary outcomes were toxicity and overall survival.

4.1.3 The trial was designed as a non-inferiority trial. The non-inferiority margin was specified as 2.5% based on an expected 5-year local recurrence rate in the EBRT group of 6%. Analysis of the primary outcome, including all patients in TARGIT-A, showed that the difference in local recurrence between Intrabeam and EBRT did not exceed the non-inferiority margin of 2.5%. Statistical significance levels were set at $p<0.01$ for this outcome. The 5-year risk of local recurrence in the conserved breast in the whole population was 3.3% and 1.3% in people having treatment with Intrabeam and EBRT respectively ($p=0.042$). Local recurrence in the pre-pathology group was 2.1% in people having Intrabeam and 1.1% in people having EBRT ($p=0.31$). Local recurrence in the post-pathology group was 5.4% and 1.7% in people having treatment with Intrabeam and EBRT respectively ($p=0.069$). The manufacturer stated that as a result of this analysis, the authors of TARGIT-A noted that caution should be taken and suggested that Intrabeam should be used only at the same time as wide local excision. Therefore, the post-pathology method of treatment was not recommended further. The manufacturer noted that the post-pathology group had the same or even fewer risk factors than

p<0.0001). The non-inferiority criterion was not met for the post-pathology group (absolute difference 1.39%; 90% CI 0 to 2.8, p=0.0664).

4.1.4 For the analysis of overall survival, statistical significance levels were set at p<0.05. There were 37 and 51 deaths in the Intrabeam and EBRT groups respectively. The results showed that the 5-year cumulative risk of mortality was 3.9% in the Intrabeam group compared with 5.3% in the EBRT group and that the difference in overall survival between groups was not statistically significant (p=0.099). Breast cancer mortality was higher in people who had Intrabeam (2.6%) than in people who had EBRT (1.9%) but the difference between treatment groups was not statistically significant (p=0.56).

4.1.5 There were statistically significantly fewer non-breast cancer deaths in the Intrabeam group (1.4%) than in the EBRT group (3.5%; p=0.0086) in the whole population and in the pre-pathology group (1.3% of non-breast cancer deaths in the Intrabeam group compared with 4.4% in the EBRT group; p=0.016). However the Assessment Group noted that these results were based on a small number of events (in the pre-pathology group, 12 non-breast cancer deaths in the Intrabeam group and 27 in the EBRT group). It commented that TARGIT-A showed that the higher number of non-breast cancer deaths in the EBRT group could be because of cardiovascular causes and other cancers and that it was improbable that there was a substantial imbalance in baseline comorbidities between the 2 treatment groups. The Assessment Group also commented that patients in the EBRT group were slightly older at baseline (the Assessment Group calculated a mean age of 62.5 years for the EBRT group and 62 years for the Intrabeam group). The Assessment Group also compared the annual probability of death in the EBRT group with the annual all-cause mortality probability obtained from the Office of National Statistics data and found that they were similar. The Assessment Group did not consider that there were excess deaths in the EBRT group, but a shortfall of deaths in the Intrabeam group because of chance or the slightly younger mean age of patients in this group. The professional groups noted that it is not possible to confirm whether there would be any difference between Intrabeam and EBRT in terms of non-breast cancer deaths and highlighted that, although the results from TARGIT-A showed statistically significant differences between treatment groups, the excess non-breast cancer deaths with EBRT compared with Intrabeam could not be explained by radiation or treatment exposure with EBRT. The professional groups noted that for example, based on the expected median radiation dose to the heart in TARGIT-A, EBRT could only be considered the cause of 1 of the 11 cardiovascular deaths and that any excess cardiovascular deaths could be explained by an imbalance between treatment groups in the relevant risk factors at presentation or under-reporting of cardiovascular deaths in the Intrabeam group. They also noted that

statistically significantly fewer grade 3 and 4 radiotherapy-related complications in the Intrabeam group compared with the EBRT group. The Assessment Group provided further details of the complications in the form of local toxicity and morbidity. It noted that the incidence of any early complication was similar between treatment groups. Wound seroma needing more than 3 aspirations occurred more frequently in people having Intrabeam (2.1%) than in people having EBRT (0.8%; p=0.012). Radiotherapy-related complications, Radiation Therapy Oncology Group (RTOG) toxicity score of grade 3 or 4, were less frequent in people having Intrabeam (0.5%) compared with people having EBRT (2.1%, p=0.002). The Assessment Group further noted that the incidence of complications arising 6 months after randomisation was lower than the incidence of early complications in both treatment groups, but highlighted that it was not clear whether these complications occurred in any of the same patients reporting early complications. The professional groups noted that the safety profile of Intrabeam was similar to EBRT and highlighted that radiotherapy-specific toxicity was lower with Intrabeam than with EBRT possibly because of the smaller volume of breast treated with a lower dose. A professional group highlighted that in TARGIT-A, quality control of EBRT in the group was minimal and that protocol variations commonly affect outcomes. This could have an effect on the differences between treatment groups (for example, increased toxicity in the EBRT group).

4.1.7 The manufacturer included data on quality of life and preferences from people who had treatment with Intrabeam as a boost followed by EBRT. Based on a study by Welzel et al. (2013) which analysed results from a subset of patients (2.5%) included in TARGIT-A and assessed quality of life using the EORTC–QLQ-C30 and the QLQ-BR-23 (breast cancer module) questionnaires, the manufacturer concluded that patients having Intrabeam showed the ability to carry out more professional and other daily activities, and had fewer general pain symptoms compared with patients having EBRT. The Assessment Group further noted that the study by Welzel et al. included results from an intention-to-treat analysis and an as-treated analysis (in which 4 of 5 patients from the Intrabeam group were moved to the EBRT group because it was the actual treatment they received and 1 patient was excluded from the analysis because they refused EBRT). The results from the intention-to-treat analysis did not show any statistically significant difference between treatment groups in any quality of life measure (statistical significance set at $p<0.01$). The as-treated analysis showed a statistically significant benefit for Intrabeam in daily activities, general pain, breast symptoms and arm symptoms compared with EBRT. The Assessment Group noted that these data should be interpreted with caution because of the small number of patients included in the analyses and because of the non-randomised nature of these data.

mastectomy/lumpectomy); non-breast cancer death and breast cancer death. The cost-effectiveness analysis was conducted from an NHS perspective, costs and outcomes were discounted at a rate of 3.5% per annum, the cycle duration was 1 year and the time horizon was 20 years.

4.2.2 The manufacturer did not provide details on how the parameters were implemented in the model. It used public sources for the cost of EBRT, the cost of wide local excision and the cost of mastectomy. The manufacturer assumed that the number of annual procedures with Intrabeam was 100 and that the average number of fractions with EBRT was 23. It also assumed that Intrabeam was given concurrently with wide local excision, and that patients would have wide local excision after local recurrence with Intrabeam and mastectomy after local recurrence with EBRT. The transition probabilities were derived from TARGIT-A, and the utilities in the model were taken from a study by Hayman et al. (1997). Mortality in the disease-free state was equal to mortality in the general population. The manufacturer did not provide further details on assumptions applied in the economic model.

4.2.3 The results of the manufacturer's base-case analysis showed that Intrabeam was a dominant strategy (that is, it had lower costs and better outcomes) compared with EBRT. Intrabeam provided an additional 0.007 quality-adjusted life years (QALYs) and cost £6465 less than EBRT. The manufacturer conducted probabilistic sensitivity analysis to assess uncertainty in the model parameters and concluded that the model results were robust to parameter uncertainty because they yielded similar results to the deterministic analysis. The manufacturer stated that Intrabeam was a cost-effective strategy compared with EBRT at various maximum acceptable incremental cost-effectiveness ratios (ICERs).

4.2.4 The Assessment Group noted that the manufacturer did not conduct a systematic review of economic evaluations and that the information provided about the manufacturer's model was limited. It also noted that some of the manufacturer's assumptions in the model were not in line with UK clinical practice. The Assessment Group noted that the manufacturer assumed that people receiving Intrabeam would have wide local excision after local recurrence, but in the UK most patients would have mastectomy after local recurrence. The Assessment Group also highlighted that in contrast with the manufacturer's assumption, not all patients who have mastectomy would also have breast reconstruction and that the cost of mastectomy after local recurrence with EBRT in the manufacturer's model includes the cost of breast reconstruction for all patients. It noted that in the UK, only approximately 31% of patients having mastectomy would have breast reconstruction. It also noted that in the UK, the average number of fractions with

TARGIT-A did not provide the best fit. The Assessment Group also noted that the cost of EBRT that the manufacturer used in its model was inappropriate because it was costed as 'other radiotherapy treatment'. It considered that it was more appropriate to cost it as 'deliver a fraction of radiotherapy on a megavoltage machine' which included 'external beam radiotherapy delivered by linear accelerator'. The Assessment Group concluded that overall, the results of the manufacturer's model should be considered with caution because of methodological and reporting limitations.

The Assessment Group's model

4.2.5 The Assessment Group developed an independent de novo economic model to estimate the cost effectiveness of Intrabeam compared with EBRT for adjuvant treatment of early operable breast cancer. The Assessment Group used a Markov model structure with 6 states: recurrence-free, local recurrence, disease-free after local recurrence, any other recurrence, death from breast cancer and death from other causes. Data from the pre-pathology group from TARGIT-A were used to guide the model inputs because the conclusions from the trial suggested that Intrabeam could be used during surgery as an alternative to postoperative EBRT but should not be used postoperatively as an alternative to EBRT. The cost-effectiveness analysis was conducted from an NHS and personal social services perspective, costs and outcomes were discounted at 3.5% per annum and a lifetime time horizon that equates to 40 years was used. The cycle length was 1 year and a half-cycle correction was applied. The Assessment Group assumed that all patients entered the model at 62 years, which is the median age of diagnosis of breast cancer in women in England.

4.2.6 All patients were assumed to enter the model in the recurrence-free state and moved to local recurrence, any other recurrence or death from other cancer. The Assessment Group assumed that only 1 local recurrence was possible and that it was only possible to die from breast cancer in the any other recurrence state.

4.2.7 Local recurrence probabilities were derived from the Kaplan-Meier data from TARGIT-A for both treatment groups and parametric curves were fitted to extrapolate the data beyond the 5-year duration of the trial. The Assessment Group noted that its clinical advisers suggested that the risk of local recurrence continues relatively linearly over the lifetime of the patient. Because using the log-normal distribution did not accelerate the rate of local recurrence as steeply as the Weibull distribution, it showed that median survival was longer, therefore the Assessment Group chose the log-normal distribution for the base-case analysis.

4.2.9 The probability of death from breast cancer depends on any other recurrence in the Assessment Group's model. The Assessment Group derived these probabilities for both treatment groups from TARGIT-A and it assumed that time to death after any other recurrence was exponentially distributed. For the analysis of overall mortality, the mortality risk was obtained from life tables in England and adjusted for the demographic characteristics of women with breast cancer. The Assessment Group confirmed that the annual probability of death in the EBRT group was similar to that stated in the life tables in England and therefore, it applied the same probability of non-breast cancer death by age to both groups in the model. The Assessment Group applied non-breast cancer mortality from TARGIT-A in sensitivity analyses.

4.2.10 The Assessment Group obtained health-related quality of life data from its systematic review. The Assessment Group applied the same utility value to the first year after local recurrence and to the second and following years after both primary breast cancer and local recurrence. The Assessment Group did not apply a disutility associated with mastectomy based on the study by Robertson et al. (2012), which reported a higher utility value for people who had mastectomy and breast reconstruction than the utility value from the COMICE trial for wide local excision.

4.2.11 The Assessment Group stated that its model reflected the UK clinical pathway and based on Early and locally advanced breast cancer: Diagnosis and treatment (NICE clinical guideline 80) it assumed that the number of fractions needed to complete a course of treatment with EBRT was 15. It also assumed that 80% of the patients had mastectomy at local recurrence based on advice from its clinical advisers and that 31% of patients who had mastectomy would also have breast reconstruction, based on advice from its clinical advisers and data from the National Mastectomy and Breast Reconstruction Audit (2011). The Assessment Group noted that varying the proportion of patients who have mastectomy after local recurrence and the proportion of patients who have breast reconstruction following mastectomy did not have a big impact on the ICER. The proportion of patients having Intrabeam who also had EBRT was assumed to be 15.2% based on the whole population of TARGIT-A. The Assessment Group assumed that the lifetime of the Intrabeam device was 10 years and conservatively, that all patients having treatment with Intrabeam would need a radiation protection shield. Based on a study by Leonardi et al. (2012) and advice from its clinical advisers, the Assessment Group assumed that 16% of people diagnosed with breast cancer would be eligible to receive treatment with Intrabeam. The Assessment Group applied an alternative proportion of 50% in a sensitivity analysis, based on clinical advice. With a hospital catchment of 1 million people, the number of annual procedures

theatre was obtained from the University Hospitals Southampton Finance Department (January 2014). Costs for mastectomy with and without breast reconstruction, wide local excision, and planning and delivery of EBRT were obtained as weighted averages from NHS reference costs (2012/13). With a hospital catchment of 1 million people and the number of annual procedures with Intrabeam estimated to be 126, the cost of Intrabeam per procedure was calculated to be £1882. The Assessment Group did not include costs associated with adverse events because the only adverse events that showed a statistically significant difference between treatment groups occurred in less than 3% of the population in TARGIT-A. It did not include any costs for post-progression therapies in the model to avoid potential confounding assumptions and because of lack of data on the type of any other recurrence in the pre-pathology group in TARGIT-A.

4.2.13 The results of the Assessment Group's cost-effectiveness analysis of Intrabeam compared with EBRT for adjuvant treatment of early breast cancer showed that Intrabeam cost £140 less and provided 0.088 less QALYs compared with EBRT resulting in an ICER of £1596 saved per QALY lost. The Assessment Group noted that in situations in which an ICER is derived from a technology that is less effective and less costly than its comparator, the commonly assumed rule of accepting ICERs below a given threshold is reversed, and so the higher the ICER, the more cost effective a treatment becomes.

4.2.14 The Assessment Group conducted sensitivity analyses to explore the effect of changes to the parameters in the ICER. The results of the deterministic sensitivity analyses showed that the cost-effectiveness results were most sensitive to the probability of any other recurrence for both treatment groups. The cost-effectiveness results were also sensitive to the probability of death from breast cancer in the Intrabeam group and to changes in parameter values considered for the beta coefficient for the Intrabeam group in the log-normal model of time to local recurrence. Changes in these parameters affected which treatment was the most cost-effective alternative at a maximum acceptable ICER of £20,000 per QALY gained. The results of the probabilistic sensitivity analysis also showed that the degree of uncertainty around the cost-effectiveness results was high. The cost-effectiveness plane showed that simulations of the ICER of Intrabeam compared with EBRT fell in the 4 quadrants.

4.2.15 The Assessment Group also conducted 5 scenario analyses, applying the following assumptions to the model:

- Scenario 1: Fitting and applying a Weibull distribution to the 5-year Kaplan-Meier data from TARGIT-A for the probability of non-breast cancer death, and applying mortality from the general population based on life tables from England thereafter. The results showed that

- Scenario 3: Applying a disutility because of mastectomy to the local recurrence and the disease free after local recurrence states. The results showed that Intrabeam cost £140 less and provided 0.090 fewer QALYs compared with EBRT, resulting in an ICER of £1563 saved per QALY lost.
- Scenario 4: Applying a disutility because of mastectomy to the local recurrence state only. The Assessment Group noted that although fewer patients had a mastectomy in the Intrabeam group compared with the EBRT group at local recurrence, the rate of local recurrence was higher in the Intrabeam group than in the EBRT group. Therefore, the net effect was that the utility decrement because of mastectomy was greater in the Intrabeam group than in the EBRT group. The results showed that Intrabeam cost £47 less and provided 0.088 fewer QALYs compared with EBRT, resulting in an ICER of £1592 saved per QALY lost.
- Scenario 5: Using alternative utility values from Hind et al. (2007), the results showed that Intrabeam cost £140 less and provided 0.093 fewer QALYs compared with EBRT, resulting in an ICER of £1517 saved per QALY lost.

4.2.16 The Assessment Group also conducted an illustrative scenario analysis including post-progression therapies. The Assessment Group assumed that 60% of recurrences in the any other recurrence state were distant recurrences based on TARGIT-A data for the whole population and data from the literature, and that mortality after any other recurrence was the same in both treatment groups. The Assessment Group noted that it assumed the same mortality after any other recurrence (applying the probability of death for EBRT in the base case) because the data from the trial showed that it was higher in the Intrabeam group and including costs for this state without adjustment would result in additional incremental costs for EBRT. The costs of post-progression therapies used were £12,122 for the annual cost of metastatic disease (active treatment and supportive care) and £3669 for the cost of end-of-life care for a patient with breast cancer. The results showed that Intrabeam cost £10 less and provided 0.061 fewer QALYs compared with EBRT, resulting in an ICER of £157 saved per QALY lost.

4.3 Factors relevant to the NHS and other parties

4.3.1 The Assessment Group also included an assessment of factors relevant to the NHS and other parties. It noted that for the year 2011/12, breast cancer accounted for 28% of radiotherapy services delivered by 265 linear accelerators in the UK, and that it is expected that the need for radiotherapy would increase during the next few years, estimating an increase up to 412 linear accelerators by 2016. Because there are only 6 Intrabeam devices currently available in the

the RD-100i OSNA system (Intraoperative tests [RD-100i OSNA system and Metasin test] for detecting sentinel lymph node metastases in breast cancer NICE diagnostics guidance 8) because treatment with Intrabeam could be completed at the same time. The Assessment Group also commented on the potential for Intrabeam to free up radiotherapy resources. It assumed that the proportion of people with a diagnosis of breast cancer who would be eligible to receive treatment with Intrabeam was 16%, and therefore the proportion of radiotherapy services needed for treating breast cancer would decrease to 24%. The Assessment Group highlighted that this drop would be expected to be less than 24% because some patients having Intrabeam may be at high risk of recurrence and receive additional treatment with EBRT. Others could have recurrence and choose wide local excision and further treatment with EBRT. The Assessment Group and the professional groups also noted the ongoing FAST-Forward trial, which is investigating the potential to provide a shorter course of treatment with EBRT (5 fractions compared with the 15 fractions given as established practice in the UK), and that the potential effect this could have in freeing up radiotherapy resources would be greater than the introduction of Intrabeam. It also noted that identifying a subset of patients who would not need to have EBRT treatment might also free up radiotherapy resources in the future.

4.4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of the Intrabeam Radiotherapy System, having considered evidence on the nature of early breast cancer and the value placed on the benefits of the Intrabeam Radiotherapy System by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources.

4.4.1 The Committee discussed the current management of early breast cancer. It heard from the clinical specialists that usual clinical practice in the NHS is to give adjuvant radiotherapy to people with early breast cancer after successful breast-conserving surgery (that is, removal of the tumour with clear margins). This is given by external beam radiotherapy (EBRT) using a linear accelerator delivering 40 grays in 15 fractions over 3 weeks in line with NICE clinical guideline 80. The Committee heard from the clinical specialists that there was some variation in clinical practice, with some oncologists recommending EBRT over a period of 5 weeks but that in general, most oncologists would recommend EBRT in line with NICE clinical guideline 80. An additional external radiotherapy boost dose to the site of the excised tumour lasting a further 1 to 2 weeks could be offered to people with a higher risk of local recurrence. The Committee also heard from the clinical specialists that in some radiotherapy centres in the NHS intensity

use of external radiotherapy may change in the future. The Committee noted that Intrabeam could be used at the time of surgery as an alternative to postoperative treatment with EBRT. If there were adverse histological features identified in the cancer cells at final pathology after treatment with Intrabeam and subsequent EBRT was recommended, a further external boost dose would not be needed.

4.4.2 The Committee discussed the potential advantages of Intrabeam compared with EBRT as an adjuvant treatment for early breast cancer. It noted that Intrabeam delivers a single dose of targeted low energy (X-ray) radiation to the tumour bed and it can be used in an operating theatre as a single treatment at the same time as surgery, whereas for patients receiving EBRT, treatment can only begin once the surgical wound has healed. The Committee heard from the clinical specialists that there were techniques allowing clinical oncologists to more accurately target the dose with EBRT such as using clips during surgery to mark the site of the tumour. Although there was a risk of clips moving within the cavity, treatment with EBRT has evolved and is considered accurate for targeting the tumour site. The Committee also noted comments from professional groups highlighting that the main aim of giving radiotherapy after surgical removal of the tumour is to prevent local recurrence. The Committee heard from the clinical specialists that if there is local recurrence after breast-conserving surgery and EBRT, this is usually treated by mastectomy. The clinical specialists also added that for some patients, brachytherapy may be a suitable breast-conserving treatment option for treating local recurrence after EBRT, instead of mastectomy. However, if there is recurrence after treatment with Intrabeam, further breast-conserving surgery and EBRT still remained a theoretical treatment option. The Committee also heard from the patient expert that Intrabeam could be used when EBRT was unsuitable or not possible, for example for those patients who were unable to raise their arm. The Committee understood from the clinical specialists that people for whom EBRT was not a suitable treatment would be offered mastectomy and that Intrabeam might be an appropriate option for these patients. The Committee concluded that Intrabeam, given at the same time as surgery, provided a potential advantage in delivering radiotherapy in direct contact with the tumour bed, and represented an alternative treatment option for people for whom EBRT is not suitable.

4.4.3 The Committee was aware that although people with early breast cancer have a treatable disease, it might recur in the breast, and there is a risk of the cancer spreading to other parts of the body. It heard from the patient expert that the psychological burden of the disease is high for patients and their families. The patient expert explained that when a patient is diagnosed with breast cancer, the thought of many radiotherapy sessions over a number of weeks can cause emotional stress and anxiety and is highly disruptive to daily living. The patient may need to stop

compared with EBRT because the patient receives the treatment at the same time as surgery and for most people no further treatment will be needed. The Committee also heard from the patient expert that Intrabeam was associated with better cosmetic outcomes and that adverse events associated with EBRT such as local tenderness, breast pain, swelling, reduced range of movement or change in breast appearance and texture were avoided or reduced with Intrabeam. The patient expert highlighted that cosmetic outcomes have a big effect on patients' quality of life. The Committee heard slightly differing opinions from the clinical specialists as to whether the cosmetic outcome from Intrabeam was superior to modern EBRT because EBRT outcomes have improved substantially in recent years. The Committee also heard that in general the adverse events of EBRT were mainly fatigue and that only a few patients have radiosensitivity, which can cause swelling and weeping of the breast. The Committee noted comments from the manufacturer and patient groups stating that treatment with EBRT was associated with potential long-term damage to other organs including the heart, and that treatment with Intrabeam would reduce the radiation dose to adjacent tissues. However, a clinical specialist stated that the radiation dose to the heart with modern EBRT was not clinically significant. The Committee concluded that patients generally tolerated EBRT well, with good outcomes, but avoiding repeated radiotherapy sessions with EBRT by receiving a single treatment with Intrabeam at the same time as surgery would be considered a major advantage by some patients.

4.4.4 The Committee discussed the clinical evidence presented for Intrabeam, which came from the TARGIT-A study. The Committee had a number of concerns with the trial and noted several comments received from professional groups and comments made by the Assessment Group highlighting concerns about the robustness and generalisability of the trial to NHS clinical practice. The Committee noted that in TARGIT-A, in which only 6 of the 33 centres were in the UK, EBRT was delivered in an average of 23 fractions, longer than the 15 fractions delivered in established clinical practice in the NHS. The radiation doses administered with EBRT also ranged from 40 to 56 grays in TARGIT-A, whereas established clinical practice in the NHS is a dose of 40 grays. The Committee also noted comments from professional groups highlighting that quality control of EBRT was not reported in some centres, and may have shown considerable variation internationally. The clinical specialists stated that it was not possible to predict what effect the variation in dose may have had on the results of the trial. The Committee concluded that some doubt remained about the generalisability of the trial data to NHS clinical practice.

4.4.5 The Committee noted comments received from professional groups that the length of follow-up in the trial was too short to reliably demonstrate the clinical effectiveness of Intrabeam

4.4.6 The Committee noted that TARGIT-A was defined as a non-inferiority trial and that the primary end point was local recurrence in the conserved breast. The Committee noted that some patients receiving Intrabeam also had further treatment with EBRT depending on their final pathology report, but that the results were not presented for this group separately. The Committee heard from the manufacturer that there were no differences in the rate of local recurrence in this group compared with the rest of the trial population. The Committee noted that the pre-specified non-inferiority margin at 5 years for the absolute difference of local recurrence between treatment groups was 2.5%. The Committee heard from the clinical specialists that this was based on an estimated rate of 5-year local recurrence of 6% in the EBRT group. The Committee noted that the non-inferiority margin was normally estimated based on the expected hazard ratio rather than on an estimated rate in the control group and an absolute difference in rates between groups. It considered that the estimated 5-year rate of 6% for local recurrence on which the non-inferiority margin was based was higher than the current expected rate of local recurrence in people receiving treatment with EBRT. The Committee was also aware that patients in the trial had a relatively good prognosis and low risk of local recurrence and heard from the clinical specialists that since 2000, when patients were first recruited into the trial, the 5-year local recurrence rate had fallen to much lower than 6% with EBRT. The Committee noted that the 5-year rate of local recurrence was higher in the Intrabeam group than in the EBRT group in TARGIT-A, but the absolute difference in the 5-year rate of local recurrence between treatment groups met the pre-defined non-inferiority criterion. The Committee acknowledged that the 5-year rate of local recurrence in TARGIT-A was low in both treatment arms and that longer follow-up of patients in TARGIT-A would be helpful to provide more long-term data. However, it considered that the criterion for non-inferiority was not appropriately defined and the trial was therefore underpowered and the results could not be considered robust enough to determine whether Intrabeam was non-inferior to EBRT in terms of local recurrence. The Committee therefore concluded that the non-inferiority of Intrabeam compared with EBRT in terms of local recurrence was unproven. However, it also acknowledged that the recurrence rates reported in the Intrabeam group could be considered low in absolute terms, and based on the evidence available so far, not out of line with current recurrence rates with EBRT in the NHS.

4.4.7 The Committee noted that TARGIT-A included a pre-pathology group (that is, treatment with Intrabeam was delivered at the same time as surgical removal of the tumour) and a post-pathology group (that is, treatment with Intrabeam was delayed and provided after a second surgical procedure to re-open the wound) and that this stratification was included as a protocol amendment. A clinical specialist commented that this stratification was included because of centre preferences. Some trial centres gave Intrabeam only at a second operation after the

develop its economic model. The Committee heard from a clinical specialist that there were plausible reasons for worse results with Intrabeam when the treatment was delivered post-pathology, which involved re-opening the wound and placing the device into the cavity. At a second operation there could be scar tissue or seroma present, and targeting the exact tumour bed would be more difficult. The Committee concluded that it was reasonable to consider treatment with Intrabeam only at the time of primary surgical removal of the tumour.

4.4.8 The Committee discussed the overall survival results from TARGIT-A. It noted that the number of breast cancer deaths was higher in the Intrabeam group compared with the EBRT group although the difference was not statistically significant. The Committee also noted that there were fewer non-breast cancer deaths in the Intrabeam group compared with the EBRT group and that this difference was statistically significant. The Committee noted the Assessment Group's considerations and the comments received on the Assessment Group's report from professional groups and the manufacturer on the difference in overall survival between the 2 treatment groups in TARGIT-A. It understood that the Assessment Group had reported that the difference in overall survival was based on a small number of events and that it did not consider that there was an excess of deaths in the EBRT group, but rather a shortfall of deaths in the Intrabeam group occurring by chance. The Committee noted that the Assessment Group had compared the non-breast cancer mortality data from the EBRT group with the annual all-cause mortality probabilities obtained from the Office of National Statistics data and found that they were similar. The Committee acknowledged that caution is needed when comparing international trial data (such as data from TARGIT-A) and country-specific data (such as data from the Office of National Statistics in the UK). The Committee also noted comments received from professional groups and the manufacturer on the Assessment Group's report suggesting that the Assessment Group's conclusion on the difference in non-breast cancer death between treatment groups occurring by chance was erroneous, and that whole breast radiation was associated with cardiac toxicity, which can increase the subsequent rate of ischaemic cardiac events. The Committee heard from a clinical specialist that the mean radiation dose to the heart was not provided in the TARGIT-A publication and that the mean dose to the heart delivered with EBRT in clinical practice in the NHS is minimal. Therefore it was highly unlikely that the difference in non-breast cancer deaths between treatment groups in TARGIT-A could be explained by an increased risk of cardiovascular death related to EBRT. The clinical specialists suggested that it was not possible to draw any conclusions from TARGIT-A in terms of an overall survival benefit with Intrabeam compared with EBRT. The Committee agreed with the clinical specialists and, given that the patient baseline characteristics did not include cardiovascular risk factors, it concluded that it was not possible to confirm that there was an overall survival benefit with Intrabeam

to EBRT and could have a higher risk of local recurrence, and that a higher risk of local recurrence was seen when treatment with Intrabeam was delayed and provided after a second surgical procedure to re-open the wound. The Committee understood that some patients were willing to accept a slightly higher risk of local recurrence as long as the absolute risk remained low and the treatment had other benefits which they considered important (see sections 4.4.2 and 4.4.3). The Committee heard from the patient expert that patient choice should be based on an informed discussion between the patient and clinician and that it was really important that patients understood all the benefits and risks associated with the technology. The clinical specialists agreed that patient choice was important and the patient should be fully and clearly informed when making their decision. The Committee concluded there were benefits of Intrabeam to patients, particularly associated with length of treatment and quality of life.

4.4.10 The Committee considered the cost-effectiveness evidence presented for Intrabeam compared with EBRT. It noted that both the manufacturer and the Assessment Group focused on the pre-pathology group of TARGIT-A to develop their economic models. The Committee noted that the results from both the manufacturer's and the Assessment Group's models estimated that the QALY difference between Intrabeam and EBRT was very small, although in the manufacturer's model Intrabeam was associated with slightly more QALYs than EBRT, whereas in the Assessment Group's model Intrabeam was associated with fewer QALYs than EBRT. The Committee also noted that the results from both the manufacturer's and the Assessment Group's models indicated that Intrabeam provided some cost savings compared with EBRT, however these savings were higher in the manufacturer's model than in the Assessment Group's model. The Committee also noted that the assumptions used by the manufacturer and the Assessment Group to develop their models were different, particularly for the costs associated with both technologies. When existing capital equipment is decommissioned or freed up for other use the best way to incorporate this into the economic modelling is not clear. The Committee noted that section 5.5.8 of the NICE guide to the methods of technology appraisal 2013 states that if introduction of the technology needs changes in infrastructure, costs and savings should be included in the analysis. Section 5.12.6 of the guide states that if savings are anticipated, the extent to which these finances can actually be realised should be specified. The Committee debated whether the costs for Intrabeam and linear accelerator equipment should be included in the same way in the economic model that is, including the capital costs of equipment for both technologies, or using only the tariff cost associated with each technology. The Committee considered that if the capital cost of EBRT were included in the economic model, the cost savings associated with Intrabeam compared with EBRT would be greater. The Committee

and 4.4.8). The Committee noted the results from the Assessment Group's probabilistic sensitivity analysis, which also showed extreme uncertainty in the model results and that the point estimate of the ICER for Intrabeam compared with EBRT was associated with lower costs and fewer QALYs compared with EBRT. The Committee considered that, based on the high degree of uncertainty in the cost-effectiveness analysis, it was not possible to state a most plausible ICER for Intrabeam compared with EBRT, but concluded that Intrabeam was associated with slightly lower costs and fewer QALYs than EBRT.

4.4.12 The Committee discussed whether, based on the evidence available, it was reasonable to recommend Intrabeam as a clinical and cost-effective use of NHS resources. The Committee considered that the clinical and cost-effectiveness evidence for Intrabeam remained uncertain. The Committee also noted its previous conclusions that even if the length of follow-up of patients in TARGIT-A were longer, the quality of the trial and particularly its generalisability to NHS clinical practice would still not provide conclusive evidence to establish the relative clinical and cost-effectiveness of Intrabeam compared with EBRT as delivered in the NHS. The Committee also noted that the rate of local recurrence with Intrabeam might be higher than with EBRT. However, it did take into account that Intrabeam provides benefits that some patients would consider substantial and that there were some patients who could particularly benefit from Intrabeam, such as those people for whom EBRT is not suitable. The Committee recognised its role of not recommending treatments if the benefits to patients are unproven, or if the treatments are not cost effective, in line with section 6.1.2 of the guide to the methods of technology appraisal 2013. Nevertheless, it understood that some patients were willing to accept a treatment that might have a slightly higher risk of local recurrence in order to benefit from treatment with Intrabeam and noted that there were several benefits highlighted by the patient expert and clinical specialists in terms of improving patients' quality of life, which could not be captured in the QALY calculation. It also noted that although non-inferiority for Intrabeam compared with EBRT was unproven for local recurrence, the rates of recurrence in the Intrabeam group in the pre-pathology group were low. The Committee concluded that individual patient preference was important and agreed with the clinical specialists and the patient expert that patients should be fully informed of the evidence and treatment options available, the lack of information about long-term outcomes with Intrabeam and the risks and benefits associated with this technology.

4.4.13 The Committee also understood that treatment with Intrabeam needed considerable investment from the NHS and was associated with some irrecoverable costs. However, the additional option of localised single treatment with Intrabeam was welcomed by patients, and if ultimately its clinical and cost effectiveness could be confirmed, this could be beneficial for both

breast cancer during breast conserving surgical removal of the tumour, only if clinicians:

- fully explain the treatment options available to patients, including their associated risks and benefits, so that patients can make an informed choice about their treatment. Clinicians should ensure that patients understand that less is known about the long-term outcomes of treatment with the Intrabeam Radiotherapy System than with conventional external beam radiotherapy and that the rate of local recurrence with Intrabeam could be higher than with external beam radiotherapy **and**
- enter details about all patients having treatment with the Intrabeam Radiotherapy System for adjuvant treatment of early invasive breast cancer onto a national register. They should audit, review and document clinical outcomes (see section 6) locally and consider the relationship between outcomes and patients' characteristics.

4.4.14 The Committee considered whether NICE's duties under the equalities legislation required it to alter or to add to its recommendations. Subsequent to the Committee meeting a Committee member raised the question whether there was the potential for some patients to be disadvantaged by the preliminary recommendations as there may be some patients who lack the capacity to understand the information provided by the clinician and to make an informed choice such as people with learning disabilities or communication difficulties. The Committee considered that providing clinicians act in the interest of their patients, in line with their usual responsibilities, and tailor their explanation in accordance with each patient's level of understanding and discuss the risks and benefits with the patient's carers where applicable, patients would not be disadvantaged by the preliminary recommendations. The Committee concluded that there was no need to alter or add to its preliminary recommendations.

4.4.15 The Committee heard from the clinical specialists that although there were 6 Intrabeam devices in the UK, which had been used as part of TARGIT-A, not all of them were being used at the moment. The Committee considered that given these existing resources, which included staff trained in the use of Intrabeam, it would be reasonable to use these resources first. The Committee also understood that there is considerable pressure on the existing NHS infrastructure for providing radiotherapy and as demand rises, the NHS will have to make further investment in new radiotherapy resources taking into account emerging evidence on optimum pathways of care. Further information on the clinical effectiveness of Intrabeam obtained from its use in the NHS, added to that derived from longer follow-up of TARGIT-A, would be valuable for decision-making. The Committee also discussed the technical requirements for Intrabeam and noted comments received from professional groups and heard from the clinical specialists that,

TAXXX	Appraisal title: The Intrabeam Radiotherapy System for adjuvant treatment of early breast cancer	Section
Key conclusion		
The Intrabeam Radiotherapy System is recommended as an option for adjuvant treatment of early invasive breast cancer during breast conserving surgical removal of the tumour, only if clinicians: • fully explain the treatment options available to patients including their associated risks and benefits, so that patients can make an informed choice about their treatment. Clinicians should ensure that patients understand that less is known about the long-term outcomes of treatment with the Intrabeam Radiotherapy System than with conventional external beam radiotherapy and that the rate of local recurrence with Intrabeam could be higher than with external beam radiotherapy **and** • enter details about all patients having treatment with the Intrabeam Radiotherapy System for adjuvant treatment of early invasive breast cancer onto a national register. They should audit, review and document clinical outcomes (see section 6) locally consider the relationship between outcomes and patients' characteristics.		1.1
The Committee concluded that the non-inferiority of Intrabeam compared with EBRT in terms of local recurrence was unproven. However, it also acknowledged that the recurrence rates reported in the Intrabeam group could be considered low in absolute terms, and based on the evidence available so far, not out of line with current recurrence rates with EBRT in the NHS.		4.4.6 4.4.11 4.4.9, 4.4.12
The Committee considered that, based on the high degree of uncertainty in the cost-effectiveness analysis, it was not possible to state a most plausible ICER for Intrabeam compared with EBRT, but concluded that Intrabeam was associated with slightly lower costs and fewer QALYs than EBRT.		
The Committee noted that there were several benefits highlighted by the patient expert and clinical specialists in terms of length of treatment and improving patients' quality of life, which could not be captured in the		

Current practice		
Clinical need of patients, including the availability of alternative treatments	The Committee noted that Intrabeam could be used at the time of surgery as an alternative to postoperative treatment with EBRT. The Committee understood from the clinical specialists that people for whom EBRT was not a suitable treatment would be offered mastectomy and that Intrabeam might be an appropriate option for these patients. The Committee concluded that Intrabeam, given at the same time as surgery, provided a potential advantage in delivering radiotherapy in direct contact with the tumour bed, and represented an alternative treatment option for people for whom EBRT is not suitable.	4.4.1, 4.4.2
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee noted that there were several benefits highlighted by the patient expert and clinical specialists in terms of length of treatment and improving patients' quality of life, which could not be captured in the QALY calculation. The Committee concluded that individual patient preference was important and agreed with the clinical specialists and the patient expert that patients should be fully informed of the evidence and treatment options available, the lack of information about long-term outcomes with Intrabeam and the risks and benefits associated with this technology.	4.4.9, 4.4.12
What is the position of the treatment	The Committee noted that Intrabeam could be used at	

reactions	complications and radiotherapy-related complications.	
Evidence for clinical effectiveness		
Availability, nature and quality of evidence	The Committee discussed the clinical evidence presented for Intrabeam, which came from the TARGIT-A study. The Committee noted that TARGIT-A included a pre-pathology group (that is, treatment with Intrabeam was delivered at the same time as surgical removal of the tumour) and a post-pathology group (that is, treatment with Intrabeam was delayed and provided after a second surgical procedure to re-open the wound). The Committee concluded that it was reasonable to consider treatment with Intrabeam only at the time of primary surgical removal of the tumour.	4.4.4, 4.4.7
Relevance to general clinical practice in the NHS	The Committee had a number of concerns with the trial and noted several comments received from professional groups and comments made by the Assessment Group highlighting concerns about the robustness and generalisability of the trial to NHS clinical practice. The Committee concluded that some doubt remained about the generalisability of the trial data to NHS clinical practice.	4.4.4
Uncertainties generated by the evidence	The Committee concluded that the results of TARGIT-A should be interpreted with caution because the length of follow-up was less than 5 years for the full trial population. The Committee considered that the criterion for non-inferiority was not appropriately defined and the trial was therefore underpowered and the results could not be considered robust enough to determine whether Intrabeam was non-inferior to EBRT in terms of local recurrence. The Committee agreed with the clinical specialists who suggested that it was not possible to derive any conclusions from TARGIT-A in terms of an overall	4.4.5 4.4.6 4.4.8

Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee noted that TARGIT-A included a pre-pathology group (that is, treatment with Intrabeam was delivered at the same time as surgical removal of the tumour) and a post-pathology group (that is, treatment with Intrabeam was delayed and provided after a second surgical procedure to re-open the wound). The Committee noted that the rate of local recurrence in the post-pathology group was higher than in the pre-pathology group and that the manufacturer stated that non-inferiority for local recurrence had not been established in the post-pathology group. The Committee concluded that it was reasonable to consider treatment with Intrabeam only at the time of primary surgical removal of the tumour. The Committee also heard from the patient expert that Intrabeam could be used when EBRT was unsuitable or not possible, for example for those patients who were unable to raise their arm. The Committee understood from the clinical specialists that people for whom EBRT was not a suitable treatment would be offered mastectomy and that Intrabeam might be an appropriate option for these patients. The Committee concluded that Intrabeam, given at the same time as surgery, provided a potential advantage in delivering radiotherapy in direct contact with the tumour bed, and represented an alternative treatment option for people for whom EBRT is not suitable.	4.4.7 4.4.2
Estimate of the size of the clinical effectiveness including strength of	The Committee concluded that the non-inferiority of Intrabeam compared with EBRT in terms of local recurrence was unproven. However, it also acknowledged that the recurrence rates reported in the Intrabeam group could be considered low in absolute terms, and based on the evidence available so far, not	4.4.6

evidence	Group focused on the pre-pathology group of TARGIT-A to develop their economic models.	
Uncertainties around and plausibility of assumptions and inputs in the economic model	The Committee noted that the assumptions used by the manufacturer and the Assessment Group to develop their models were different, particularly for the costs associated with both technologies. When existing capital equipment is decommissioned or freed up for other use the best way to incorporate this into the economic modelling is not clear. The Committee debated whether the costs for Intrabeam and linear accelerator equipment should be included in the same way in the economic model that is, including the capital costs of equipment for both technologies, or using only the tariff cost associated with each technology. The Committee considered that if the capital cost of EBRT were included in the economic model, the cost savings associated with Intrabeam compared with EBRT would be greater.	4.4.10
Incorporation of health-related quality-of-life benefits and utility values Have any potential significant and substantial health-related benefits been identified that were not included in the economic	The Committee noted that the results from both the manufacturer's and the Assessment Group's models estimated that the QALY difference between Intrabeam and EBRT was very small, although in the manufacturer's model Intrabeam was associated with slightly more QALYs than EBRT, whereas in the Assessment Group's model Intrabeam was associated with fewer QALYs than EBRT. The Committee understood that some patients were willing to accept a treatment that might have a slightly higher risk of local recurrence in order to benefit from treatment with Intrabeam and noted that there were several benefits highlighted by the patient expert and clinical specialists in terms of improving patients' quality	4.4.10 4.4.12

specific groups of people for whom the technology is particularly cost effective?	None.	
What are the key drivers of cost effectiveness?	The results of the deterministic sensitivity analyses showed that the cost-effectiveness results were most sensitive to the probability of any other recurrence for both treatment groups, to the probability of death from breast cancer in the Intrabeam group and to changes in parameter values considered for the beta coefficient for the Intrabeam group in the log-normal model of time to local recurrence.	4.2.14
Most likely cost-effectiveness estimate (given as an ICER)	The Committee considered that, based on the high degree of uncertainty in the cost-effectiveness analysis, it was not possible to state a most plausible ICER for Intrabeam compared with EBRT, but concluded that Intrabeam was associated with slightly lower costs and fewer QALYs than EBRT.	4.4.11
Additional factors taken into account		
Patient access schemes (PPRS)	Not applicable.	
End-of-life considerations	Not applicable.	
	There were no equality issues identified during the scoping process or raised in the submissions. Subsequent to the Committee meeting a Committee member raised the question whether there was the potential for some patients to be disadvantaged by the preliminary recommendations as there may be some	

	patients, in line with their usual responsibilities, and tailor their explanation in accordance with each patient's level of understanding and discuss the risks and benefits with the patient's carers where applicable, patients would not be disadvantaged by the preliminary recommendations. The Committee concluded that there was no need to alter or add to its preliminary recommendations.	

5 Implementation

Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal. The normal period of compliance is 3 months, but may be extendedunder Section 7(5) of the Regulations.

5.1 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has breast cancer and the doctor responsible for their care thinks that the Intrabeam Radiotherapy System is the right treatment, it should be available for use, in line with NICE's recommendations.

5.2 NICE has developed tools [link to www.nice.org.uk/guidance/TAXXX] to help organisations put this guidance into practice (listed below). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing template and report to estimate the national and local savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Proposed recommendations for further research

6.1 For all patients who choose to have treatment with the Intrabeam Radiotherapy System for adjuvant treatment of early invasive breast cancer during breast conserving surgical removal of the tumour, clinicians should:

- histology of the cancer and patients' characteristics (including type, size, side of tumour, grade, lymph node status, oestrogen receptor status, progesterone receptor status, human epidermal growth factor receptor 2 status and age of the patient)
- local recurrence
- treatment received after local recurrence
- development of metastatic disease
- disease-free survival
- overall survival
- adverse effects of treatment
- health-related quality of life (including EQ-5D).

7 Related NICE guidance

Details are correct at the time of consultation and will be removed when the final guidance is published. Further information is available on the NICE website.

- Early and locally advanced breast cancer: diagnosis and treatment. NICE clinical guideline 80 (2009).
- Hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer. NICE technology appraisal guidance112 (2006).
- Breast reconstruction using lipomodelling after breast cancer treatment. NICE interventional procedure guidance 417 (2012).
- Image-guided radiofrequency excision biopsy of breast lesions. NICE interventional procedure guidance 308 (2009).
- Endoscopic mastectomy and endoscopic wide local excision for breast cancer. NICE interventional procedure guidance 296 (2009).
- Brachytherapy as the sole method of adjuvant radiotherapy for breast cancer after local excision. NICE interventional procedure guidance 268 (2008).
- Laparoscopic mobilisation of the greater omentum for breast reconstruction. NICE interventional procedure guidance 253 (2008).
- Endoscopic axillary lymph node retrieval for breast cancer. NICE interventional procedure guidance 147 (2005).
- Interstitial laser therapy for breast cancer. NICE interventional procedure guidance 89 (2004).
- Gene expression profiling and expanded immunohistochemistry tests for guiding adjuvant chemotherapy decisions in early breast cancer management: MammaPrint, Oncotype DX, IHC4 and Mammostrat. NICE diagnostics guidance 10 (2013).

proposed date. The Guidance Executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators

Jane Adam
Chair, Appraisal Committee
July 2014

9 Appraisal Committee members and NICE project team

9.1 Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr Jane Adam (Chair)
Department of Diagnostic Radiology, St George's Hospital, London

Professor Iain Squire (Vice-Chair)
Consultant Physician, University Hospitals of Leicester

Professor Thanos Athanasiou
Professor of Cardiovascular Sciences and Cardiac Surgery, Imperial College London; Consultant Cardiothoracic Surgeon, Imperial College Healthcare NHS Trust

Dr Graham Ash
Consultant in General Adult Psychiatry, Lancashire Care NHS Foundation Trust

Dr Jeremy Braybrooke

Professor Aileen Clarke
Professor of Public Health and Health Services Research, University of Warwick

Mr Adrian Griffin
Vice President, HTA and International Policy, Johnson & Johnson

Dr Brian Hawkins
Chief Pharmacist, Cwm Taf Health Board, South Wales

Dr Peter Heywood
Consultant Neurologist, Frenchay Hospital, Bristol

Dr Sharon Saint Lamont
Head of Clinical Quality, NHS England (North)

Dr Ian Lewin
Honorary Consultant Physician and Endocrinologist, North Devon District Hospital

Dr Louise Longworth
Reader in Health Economics, HERG, Brunel University

Dr Anne McCune
Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust

Dr Alec Miners
Senior lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Ms Sarah Parry
CNS Paediatric Pain Management, Bristol Royal Hospital for Children

Dr Ann Richardson
Lay Member

Ms Ellen Rule
Programme Director, NHS Bristol

Dr Brian Shine
Consultant Chemical Pathologist, John Radcliffe Hospital

Dr Peter Sims
GP, Devon

Health Service Wales

Professor Olivia Wu
Professor of Health Technology Assessment, University of Glasgow

9.2 NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Pilar Pinilla-Dominguez
Technical Lead

Joanna Richardson
Technical Adviser

Bijal Joshi
Project Manager

10 Sources of evidence considered by the Committee

A. The assessment report for this appraisal was prepared by Southampton Health Technology Assessments Centre (SHTAC):

- Picot J, et al. The clinical and cost effectiveness of the INTRABEAM Photon Radiotherapy System for the adjuvant treatment of early breast cancer, April 2014

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I, II and III were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I. Manufacturers/sponsors:

- Carl Zeiss UK (Intrabeam Radiotherapy System)

II. Professional/specialist and patient/carer groups:

- Institute of Physics and Engineering Medicine (IPEM)
- Royal College of Nursing
- Royal College of Physicians (NCRI/RCP/ACP/JCCO)
- Society and College of Radiographers
- United Kingdom Clinical Pharmacy Association

III. Other consultees:

- Department of Health
- HS England
- Welsh Government

IV. Commentator organisations (without the right of appeal):

- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- National Institute for Health Research Health Technology Assessment Programme
- Southampton Health Technology Assessment Centre (SHTAC), University of Southampton
- National Collaborating Centre for Cancer

C. The following individuals were selected from clinical specialist and patient expert nominations from the consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on the Intrabeam Radiotherapy System by attending the initial Committee discussion and/or providing written evidence to the Committee. They are invited to comment on the ACD.

- Dr Charlotte Coles, Consultant Clinical Oncologist, nominated by organisation representing Royal College of Physicians (NCRI/RCP/ACP/JCCO) – clinical specialist
- Mr David Eaton, Lead Clinical Scientist, nominated by organisation representing Institute of Physics and Engineering in Medicine – clinical specialist
- Dr Michael Douek, Reader in Surgery and Consultant Surgeon, nominated by organisation representing Association of Breast Surgery – clinical specialist
- Ms Marcelle Clark, Author and journalist, nominated by organisation representing Breakthrough Breast Cancer – patient expert

E. Representatives from the following manufacturers/sponsors attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment

Get involved