An international randomised controlled trial to compare TARGeted Intraoperative radioTherapy (TARGIT) with conventional postoperative radiotherapy after breast-conserving surgery for women with early-stage breast cancer (the TARGIT-A trial)

Jayant S Vaidya, Frederik Wenz, Max Bulsara, Jeffrey S Tobias, David J Joseph, Christobel Saunders, Chris Brew-Graves, Ingrid Potyka, Stephen Morris, Hrisheekesh J Vaidya, Norman R Williams and Michael Baum
An international randomised controlled trial to compare TARGeted Intraoperative radioTherapy (TARGIT) with conventional postoperative radiotherapy after breast-conserving surgery for women with early-stage breast cancer (the TARGIT-A trial)

Jayant S Vaidya,1,2* Frederik Wenz,3 Max Bulsara,4 Jeffrey S Tobias,5 David J Joseph,6 Christobel Saunders,7 Chris Brew-Graves,1 Ingrid Potyka,1 Stephen Morris,8 Hrisheekesh J Vaidya,9 Norman R Williams1 and Michael Baum1

1Division of Surgery and Interventional Science, University College London, London, UK
2Department of Surgery, Whittington Hospital, Royal Free Hospital and University College London Hospital, London, UK
3Department of Radiation Oncology, University Medical Centre Mannheim, University of Heidelberg, Heidelberg, Germany
4Department of Biostatistics, University of Notre Dame, Fremantle, WA, Australia
5Department of Clinical Oncology, University College London Hospitals, London, UK
6Department of Radiation Oncology, Sir Charles Gairdner Hospital, Perth, WA, Australia
7Department of Surgery, University of Western Australia, Perth, WA, Australia
8Health Economics Group, Department of Biomedical Engineering, University College London, London, UK
9Keble College, Oxford University, Oxford, UK

*Corresponding author
Declared competing interests of authors: Jayant S Vaidya has received a research grant from Photoelectron Corp. (1996–9) and from Carl Zeiss for supporting data management at the University of Dundee (Dundee, UK) and has subsequently received honoraria. Jayant S Vaidya also has a patent for the use of the word TARGIT for TARGeted Intraoperative radioTherapy. Frederik Wenz has received a research grant from Carl Zeiss for supporting radiobiological research. Frederik Wenz also has patents for US 8,724,775B2, US 2013/058460 A, PCT/EP2011/057518, DE/18.12.09/DEA10200905877 and DE/17.12.09/DEA10200905058581, all issues to Wenz/Zeiss. Chris Brew-Graves, Ingrid Potyka and Norman R Williams report that the Clinical Trials Group was paid an unrestricted grant from 1 November 2001 to 31 October 2010. Michael Baum was on the scientific advisory board of Carl Zeiss and was paid monthly consultancy fees until 2010. In addition, Jayant S Vaidya, Frederik Wenz, Max Bulsara, Jeffrey S Tobias, David J Joseph, Christobel Saunders and Michael Baum report that Carl Zeiss sponsors most of the travel and accommodation for meetings of the International Steering Committee and Data Monitoring Committee and, when necessary, for conferences where a presentation about targeted intraoperative radiotherapy is being made for all authors.

Published September 2016
DOI: 10.3310/hta20730

This report should be referenced as follows:


*Health Technology Assessment* is indexed and abstracted in *Index Medicus/MEDLINE*, Excerpta Medica/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®/Clinical Medicine*. 
Criteria for inclusion in the Health Technology Assessment journal

Reports are published in Health Technology Assessment (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in Health Technology Assessment are termed ‘systematic’ when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 07/60/49. The contractual start date was in September 2009. The draft report began editorial review in October 2014 and was accepted for publication in June 2016. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors’ report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health.

© Queen’s Printer and Controller of HMSO 2016. This work was produced by Vaidya et al. under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).
**Health Technology Assessment Editor-in-Chief**

**Professor Hywel Williams**  Director, HTA Programme, UK and Foundation Professor and Co-Director of the Centre of Evidence-Based Dermatology, University of Nottingham, UK

**NIHR Journals Library Editor-in-Chief**

**Professor Tom Walley**  Director, NIHR Evaluation, Trials and Studies and Director of the EME Programme, UK

**NIHR Journals Library Editors**

**Professor Ken Stein**  Chair of HTA Editorial Board and Professor of Public Health, University of Exeter Medical School, UK

**Professor Andree Le May**  Chair of NIHR Journals Library Editorial Group (EME, HS&DR, PGfAR, PHR journals)

**Dr Martin Ashton-Key**  Consultant in Public Health Medicine/Consultant Advisor, NETSCC, UK

**Professor Matthias Beck**  Chair in Public Sector Management and Subject Leader (Management Group), Queen's University Management School, Queen's University Belfast, UK

**Professor Aileen Clarke**  Professor of Public Health and Health Services Research, Warwick Medical School, University of Warwick, UK

**Dr Tessa Crilly**  Director, Crystal Blue Consulting Ltd, UK

**Dr Eugenia Cronin**  Senior Scientific Advisor, Wessex Institute, UK

**Ms Tara Lamont**  Scientific Advisor, NETSCC, UK

**Professor Elaine McColl**  Director, Newcastle Clinical Trials Unit, Institute of Health and Society, Newcastle University, UK

**Professor William McGuire**  Professor of Child Health, Hull York Medical School, University of York, UK

**Professor Geoffrey Meads**  Professor of Health Sciences Research, Health and Wellbeing Research and Development Group, University of Winchester, UK

**Professor John Norrie**  Health Services Research Unit, University of Aberdeen, UK

**Professor John Powell**  Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK

**Professor James Raftery**  Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

**Dr Rob Riemsma**  Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

**Professor Helen Roberts**  Professor of Child Health Research, UCL Institute of Child Health, UK

**Professor Jonathan Ross**  Professor of Sexual Health and HIV, University Hospital Birmingham, UK

**Professor Helen Snooks**  Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

**Professor Jim Thornton**  Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK

**Professor Martin Underwood**  Director, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, UK

Please visit the website for a list of members of the NIHR Journals Library Board: www.journalslibrary.nihr.ac.uk/about/editors

**Editorial contact:** nihredit@southampton.ac.uk
Abstract

An international randomised controlled trial to compare TARGeted Intraoperative radioTherapy (TARGIT) with conventional postoperative radiotherapy after breast-conserving surgery for women with early-stage breast cancer (the TARGIT-A trial)

Jayant S Vaidya,1,2* Frederik Wenz,3 Max Bulsara,4 Jeffrey S Tobias,5 David J Joseph,6 Christobel Saunders,7 Chris Brew-Graves,1 Ingrid Potyka,1 Stephen Morris,8 Hrisheekesh J Vaidya,9 Norman R Williams1 and Michael Baum1

1Division of Surgery and Interventional Science, University College London, London, UK
2Department of Surgery, Whittington Hospital, Royal Free Hospital and University College London Hospital, London, UK
3Department of Radiation Oncology, University Medical Centre Mannheim, University of Heidelberg, Heidelberg, Germany
4Department of Biostatistics, University of Notre Dame, Fremantle, WA, Australia
5Department of Clinical Oncology, University College London Hospitals, London, UK
6Department of Radiation Oncology, Sir Charles Gairdner Hospital, Perth, WA, Australia
7Department of Surgery, University of Western Australia, Perth, WA, Australia
8Health Economics Group, Department of Biomedical Engineering, University College London, London, UK
9Keble College, Oxford University, Oxford, UK

*Corresponding author jayantvaidya@gmail.com

Background: Based on our laboratory work and clinical trials we hypothesised that radiotherapy after lumpectomy for breast cancer could be restricted to the tumour bed. In collaboration with the industry we developed a new radiotherapy device and a new surgical operation for delivering single-dose radiation to the tumour bed – the tissues at highest risk of local recurrence. We named it TARGeted Intraoperative radioTherapy (TARGIT). From 1998 we confirmed its feasibility and safety in pilot studies.

Objective: To compare TARGIT within a risk-adapted approach with whole-breast external beam radiotherapy (EBRT) over several weeks.

Design: The TARGeted Intraoperative radioTherapy Alone (TARGIT-A) trial was a pragmatic, prospective, international, multicentre, non-inferiority, non-blinded, randomised (1 : 1 ratio) clinical trial. Originally, randomisation occurred before initial lumpectomy (prepathology) and, if allocated TARGIT, the patient received it during the lumpectomy. Subsequently, the postpathology stratum was added in which randomisation occurred after initial lumpectomy, allowing potentially easier logistics and a more stringent case selection, but which needed a reoperation to reopen the wound to give TARGIT as a delayed procedure. The risk-adapted approach meant that, in the experimental arm, if pre-specified unsuspected adverse factors were found postoperatively after receiving TARGIT, EBRT was recommended. Pragmatically, this reflected how TARGIT would be practised in the real world.
Setting: Thirty-three centres in 11 countries.

Participants: Women who were aged ≥ 45 years with unifocal invasive ductal carcinoma preferably ≤ 3.5 cm in size.

Interventions: TARGIT within a risk-adapted approach and whole-breast EBRT.

Main outcome measures: The primary outcome measure was absolute difference in local recurrence, with a non-inferiority margin of 2.5%. Secondary outcome measures included toxicity and breast cancer-specific and non-breast-cancer mortality.

Results: In total, 3451 patients were recruited between March 2000 and June 2012. The following values are 5-year Kaplan–Meier rates for TARGIT compared with EBRT. There was no statistically significant difference in local recurrence between TARGIT and EBRT. TARGIT was non-inferior to EBRT overall [TARGIT 3.3%, 95% confidence interval (CI) 2.1% to 5.1% vs. EBRT 1.3%, 95% CI 0.7% to 2.5%; p = 0.04; Pnon-inferiority = 0.00000012] and in the prepathology stratum (n = 2298) when TARGIT was given concurrently with lumpectomy (TARGIT 2.1%, 95% CI 1.1% to 4.2% vs. EBRT 1.1%, 95% CI 0.5% to 2.5%; p = 0.31; Pnon-inferiority = 0.0000000013). With delayed TARGIT postpathology (n = 1153), the between-group difference was larger than 2.5% and non-inferiority was not established for this stratum (TARGIT 5.4%, 95% CI 3.0% to 9.7% vs. EBRT 1.7%, 95% CI 0.6% to 4.9%; p = 0.069; Pnon-inferiority = 0.06640). The local recurrence-free survival was 93.9% (95% CI 90.9% to 95.9%) when TARGIT was given with lumpectomy compared with 92.5% (95% CI 89.7% to 94.6%) for EBRT (p = 0.35). In a planned subgroup analysis, progesterone receptor (PgR) status was found to be the only predictor of outcome: hormone-responsive patients (PgR positive) had similar 5-year local recurrence with TARGIT during lumpectomy (1.4%, 95% CI 0.5% to 3.9%) as with EBRT (1.2%, 95% CI 0.5% to 2.9%; p = 0.77). Grade 3 or 4 radiotherapy toxicity was significantly reduced with TARGIT. Overall, breast cancer mortality was much the same between groups (TARGIT 2.6%, 95% CI 1.5% to 4.3% vs. EBRT 1.9%, 95% CI 1.1% to 3.2%; p = 0.56) but there were significantly fewer non-breast-cancer deaths with TARGIT (1.4%, 95% CI 0.8% to 2.5% vs. 3.5%, 95% CI 2.3% to 5.2%; p = 0.0086), attributable to fewer deaths from cardiovascular causes and other cancers, leading to a trend in reduced overall mortality in the TARGIT arm (3.9%, 95% CI 2.7% to 5.8% vs. 5.3%, 95% CI 3.9% to 7.3%; p = 0.099). Health economic analyses suggest that TARGIT was statistically significantly less costly than EBRT, produced similar quality-adjusted life-years, had a positive incremental net monetary benefit that was borderline statistically significantly different from zero and had a probability of >90% of being cost-effective. There appears to be little uncertainty in the point estimates, based on deterministic and probabilistic sensitivity analyses. If TARGIT were given instead of EBRT in suitable patients, it might potentially reduce costs to the health-care providers in the UK by £8–9.1 million each year. This does not include environmental, patient and societal costs.

Limitations: The number of local recurrences is small but the number of events for local recurrence-free survival is not as small (TARGIT 57 vs. EBRT 59); occurrence of so few events (<3.5%) also implies that both treatments are effective and any difference is unlikely to be large. Not all 3451 patients were followed up for 5 years; however, more than the number of patients required to answer the main trial question (n = 585) were followed up for >5 years.

Conclusions: For patients with breast cancer (women who are aged ≥ 45 years with hormone-sensitive invasive ductal carcinoma that is up to 3.5 cm in size), TARGIT concurrent with lumpectomy within a risk-adapted approach is as effective as, safer than and less expensive than postoperative EBRT.

Future work: The analyses will be repeated with longer follow-up. Although this may not change the primary result, the larger number of events may confirm the effect on overall mortality and allow more detailed subgroup analyses. The TARGeted Intraoperative radioTherapy Boost (TARGIT-B) trial is testing whether or not a tumour bed boost given intraoperatively (TARGIT) boost is superior to a tumour bed boost given as part of postoperative EBRT.

Trial registration: Current Controlled Trials ISRCTN34086741 and ClinicalTrials.gov NCT00983684.
Funding: University College London Hospitals (UCLH)/University College London (UCL) Comprehensive Biomedical Research Centre, UCLH Charities, Ninewells Cancer Campaign, National Health and Medical Research Council and German Federal Ministry of Education and Research (BMBF). From September 2009 this project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 20, No. 73. See the NIHR Journals Library website for further project information.
Chapter 6 Cost–utility analysis of external beam radiotherapy compared with targeted intraoperative radiotherapy in breast cancer

Background

There is limited evidence about the cost-effectiveness of TARGIT. Picot et al. recently undertook a systematic review of published economic evaluations and found two primary studies. Both were modelling studies using aggregate data from the TARGIT-A trial supplemented with data from other sources. Alvarado et al. found that TARGIT was less costly and produced more quality-adjusted life-years (QALYs) than EBRT and concluded that TARGIT was the dominant strategy. Based on the results of a cost-minimisation analysis, TARGIT was associated with substantial cost savings compared with whole-breast irradiation delivered using three-dimensional conformal radiotherapy or accelerated PBI delivered with intensity-modulated radiotherapy. Both studies were based in the USA and because of differences in treatment practices and patients the results are unlikely to be applicable to the UK.

Picot et al. undertook a UK-based cost–utility analysis of TARGIT using data from the TARGIT-A trial supplemented with data from other sources. They found that TARGIT was less costly than EBRT and also less effective, producing fewer QALYs. This is more relevant than the studies by Alvarado et al. and Shah et al. because it is a UK-based study, but it is a modelling study using aggregate data from the TARGIT-A trial. Hence, we undertook a cost–utility analysis of TARGIT compared with EBRT using patient-level data from the TARGIT-A trial.

Methods

Patients

The analysis was based on costs and outcomes for the 817 patients randomised in the ‘earliest cohort’ in the prepathology stratum of the TARGIT-A trial. Several issues were considered when deciding which cohort of patients to include in the cost–utility analysis:

1. We did not include the postpathology stratum from the earliest cohort because the results in this group were less favourable than those of the prepathology stratum. Hence, it is highly unlikely that TARGIT would be adopted in clinical practice for this group. As patients from this stratum were not included in the analysis, the results cannot be applied to this group.
2. The number of participants needed to prove non-inferiority was calculated to be 585 and therefore the earliest cohort of 817 patients had enough power to draw reliable conclusions.
3. The earliest cohort was randomised between 2000 and 2008 and the average follow-up was 5 years, permitting a reasonable follow-up period without a large number of missing data. The complete prepathology stratum from TARGIT-A consisted of 2298 patients, with an average follow-up of 2 years 4 months. Hence, by including the full cohort we would have substantially increased the proportion of missing data in the sample if we wanted to use a 5-year time horizon or we would have had to use a shorter time horizon.

We therefore balanced the number of patients in the whole cohort compared with the number in the earliest cohort against the duration of follow-up in the two cohorts against the fact that the earliest cohort had enough statistical power to draw reliable conclusions and decided to base our analysis on the 817 patients randomised in the earliest cohort of the TARGIT-A trial in the prepathology stratum. In this cohort,
as in the mature cohort in the prepathology stratum and all patients in the prepathology stratum, TARGIT was non-inferior to EBRT with respect to local recurrence and the 5-year estimated risks of local recurrence were not statistically different between the treatment groups.

Overview of the cost–utility analysis

We undertook a cost–utility analysis to compare the costs and outcomes associated with TARGIT compared with EBRT in the prepathology stratum of the TARGIT-A trial. The outcome measure was QALYs, which combine length of life and quality of life, consistent with NICE guidelines.\(^7\) Cost-effectiveness was expressed as incremental net monetary benefits.\(^7\) The analysis took a UK NHS and personal social services (PSS) perspective.\(^7\) Resource use data were included from all participating centres and UK unit costs were applied. Costs are presented in 2013/14 UK pounds. The time horizon was 5 years, reflecting the average follow-up in the earliest cohort in the prepathology stratum of the TARGIT-A trial. Extrapolation beyond the end of the trial using decision-analytical modelling was not undertaken because the within-trial analysis found no evidence of significant differences in QALYs between the groups. This probably reflects the main finding from the TARGIT-A trial that TARGIT was non-inferior to EBRT with regard to local recurrence. Although there was some evidence of differences in costs, these differences were accrued during the first year, with no evidence of significant differences in costs beyond the first year. Hence, the 5-year time horizon was long enough to reflect all important differences in costs or outcomes between the two treatments. An annual discount rate of 3.5% was applied to costs and outcomes.\(^7\)

Resource use and costs

Cost components

We calculated the costs incurred by every patient during the 5-year time horizon using resource use and event data collected prospectively in the trial. The following costs were included: TARGIT, EBRT, index procedure, additional procedures, chemotherapy, mastectomy, complications, recurrence-free survival, local recurrence, distant recurrence, breast cancer deaths and non-breast-cancer deaths. Unit costs were obtained from published sources\(^72,76^–80\) (Table 12), inflated when appropriate\(^82\) and multiplied by resource use. Annual costs were calculated for every patient for each year of the 5-year time horizon. These were discounted and summed across all 5 years to calculate total costs per patient over the whole period.

<table>
<thead>
<tr>
<th>Table 12 Unit costs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost item</strong></td>
</tr>
<tr>
<td>TARGIT</td>
</tr>
<tr>
<td>EBRT</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>EBRT boost</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>NHS patient transport</td>
</tr>
<tr>
<td>Index procedure</td>
</tr>
<tr>
<td>Cost item</td>
</tr>
<tr>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>Overnight stay related to index procedure</td>
</tr>
<tr>
<td>Mastectomy with breast reconstruction</td>
</tr>
<tr>
<td>Additional procedures (excision of positive margins, axillary dissection or clearance)</td>
</tr>
<tr>
<td>Chemotherapy</td>
</tr>
</tbody>
</table>

**Complications**

| Surgical evacuation of haematoma                       | £362 per procedure                 | Department of Health\(^9\) – Currency Code JA12C. Day case |
| Aspiration for seroma                                  | £397 per complication               | Department of Health\(^9\) – treatment function 370, consultant led WF01B for first and WF01A for second and third aspirations. Only applied each time three aspirations of seroma noted. Outpatient |
| Wound infection requiring oral antibiotics             | £2.60 per course of treatment       | British National Formulary\(^79\) – treatment using flucloxacillin 500 mg, £2.60 for a 28-tablet pack (1 week) |
| Wound infection requiring intravenous antibiotics      | £362 per course of treatment        | Department of Health\(^76\) – Currency code JA12C. Day case |
| Skin breakdown/delayed wound healing                  | £29 per course of treatment         | British National Formulary\(^79\) – soft non-woven dressing impregnated with Intrasite\(^8\) (Smith & Nephew, London, UK) gel, 10 cm x 10 cm, £1.70 (2 weeks) = £23.80 plus flucloxacillin 500 mg, £2.60 for a 28-tablet pack (2 weeks) = £5.20 |
| RTOG toxicity grade 3                                  | £5 per course of treatment          | British National Formulary\(^79\) – aqueous cream 500 g |
| RTOG toxicity grade 4                                  | £23.80 per course of treatment      | British National Formulary\(^79\) – soft non-woven dressing impregnated with Intrasite\(^8\) gel, 10 cm x 10 cm, £1.70 (2 weeks) = £23.80 |
| Pain in the irradiated field                          | £3 per course of treatment          | British National Formulary\(^79\) – paracetamol 500 mg, 100-tablet pack |

**Events**

| Recurrence free                                       | £1057 per year                       | Hind et al.\(^81\) – one oncologist visit per year for 5 years, one mammogram per year for 5 years, 5 years of anastrozole/tamoxifen (70 : 30) hormonal therapy |
| Local recurrence                                       | Mean £4956 (SD £3953) per recurrence | Mean (SD) from patient-level costing |
| Distant recurrence                                     | £1040 per month                      | Hind et al.\(^81\) – monthly cost of supportive care for metastatic breast cancer |
| Breast cancer death                                    | £3659 per death                      | Hind et al.\(^81\) – cost of death from breast cancer |
| Non-breast-cancer death                                | £3659 per death                      | Hind et al.\(^81\) – assumed to be the same as cost of death from breast cancer |

\(\text{SD, standard deviation.}
\)
\(\text{a Costs are in 2013/14 UK pounds.}
\)
Targeted intraoperative radiotherapy
A fixed cost per patient was assumed for TARGIT, based on recently published calculations by Picot et al.\textsuperscript{72} This cost includes one-off capital costs and annual maintenance costs associated with the INTRABEAM device; one-off, annual and per-treatment costs requiring additional staff resources; the cost of consumables required for each use of the device; and the cost of additional operating theatre time for each use of the device. The capital and one-off costs were annualised using a device lifetime of 10 years. These costs and the annual costs were assigned to individual treatments assuming that each device was used to undertake 126 procedures per year. On this basis Picot et al.\textsuperscript{72} calculate the unit cost per patient to be £1882 (2013/14 prices), which is the value that we used in our analysis for the base case. This was varied in sensitivity analysis.

External beam radiotherapy
Patient-level data were collected in the TARGIT-A trial on the number of fractions of EBRT received by each patient. A proportion of patients randomised to TARGIT also received EBRT and these were also included in the analysis. The mean [standard deviation (SD)] number of fractions given to patients in the trial who received EBRT was 23 (5). This is higher than current recommendations stating that 15 fractions are required to complete a course of treatment for patients with early invasive breast cancer after breast-conserving surgery or mastectomy.\textsuperscript{78} In our base case we therefore assumed that all patients in the TARGIT-A trial who received EBRT received a fixed number of 15 fractions. We applied a unit cost per fraction plus a one-off cost for a planning meeting (see Table 12). In sensitivity analyses we estimated cost-effectiveness based on the actual number of fractions of EBRT received in the trial.

Standard treatment of breast cancer includes an EBRT boost as part of the course of whole-breast radiotherapy; however, it is sometimes omitted in patients at a lower risk of local recurrence.\textsuperscript{83–85} In the TARGIT-A trial, patient-level data were also recorded on whether or not patients received an EBRT boost and if so the number of fractions received. These were included in our base case. We applied a unit cost per fraction plus a one-off cost for an additional planning meeting (see Table 12). In sensitivity analysis we estimated cost-effectiveness assuming no EBRT boost.

External beam radiotherapy requires several trips to hospital for treatment, incurring time and travel costs for patients and their families. Our analysis was undertaken from a NHS and PSS perspective and so we did not include these costs. However, some patients use NHS patient transport to travel to hospital for EBRT, which is a cost incurred by the NHS. We were unable to find any pre-existing evidence on the proportion of EBRT patients who use NHS patient transport and so we undertook a short survey at two sites. The first site was Great Western Hospital in Swindon, where patients receiving EBRT typically travel to radiotherapy centres at the John Radcliffe Hospital, Oxford, the Royal United Hospital, Bath, or Cheltenham General Hospital for treatment. The second was Princess Alexandra Hospital, Harlow, where patients typically travel to North Middlesex Hospital, Enfield, for treatment. Patients were asked to indicate their method of transport to the radiotherapy centre, with possible responses being by car, by hospital transport or by public transport. We received 37 responses (17 from patients at Great Western Hospital and 20 from patients at Princess Alexandra Hospital), with five (13.5\%) patients reporting using hospital transport. In our base case we therefore assumed that 13.5\% of patients receiving EBRT use NHS patient transport over the course of their treatment and applied a unit cost per return journey (see Table 12). We varied the proportion of patients using NHS patient transport to travel to hospital for EBRT in sensitivity analysis.

Other cost components
The cost of the index procedure included the cost of the lumpectomy procedure itself plus the cost of any associated hospital stay, which was recorded in the trial. Any additional procedures related to excision of margins or axillary dissection and/or clearance were recorded, as well as whether or not the patient received chemotherapy and had a mastectomy. For the index procedure, additional procedures and mastectomies, unit costs based on NHS reference costs\textsuperscript{76} were applied. Costs for a course of chemotherapy were based on current treatment recommendations.\textsuperscript{78}
Data were recorded in the trial on the number of the following complications: haematoma requiring surgical evacuation; seroma requiring three or more aspirations; infection requiring oral or intravenous antibiotics or surgical intervention; skin breakdown or delayed wound healing; and RTOG toxicity of grade 3 or 4. Details were recorded on how each individual complication was treated and these were costed separately and included in the analysis (see Table 12).

We included the costs of remaining recurrence free, local recurrence, distant recurrence, breast cancer death and non-breast-cancer death. Unit costs were taken from a published source and applied to patient-level data from the trial. Treatments for local recurrence were recorded in the trial and were costed on an individual patient basis. Treatments for local recurrence included mastectomy, TARGIT, EBRT, hormone therapy and chemotherapy. The mean (SD) cost per patient of local recurrence was £4956 (£3953; see Table 12).

**Utilities and quality-adjusted life-years**

The outcome measure in our cost–utility analysis was QALYs, which combine length of life and quality of life, the latter being measured by utility scores. A utility score of 1 represents full health and a score of 0 denotes death; negative values represent states worse than death.

Utility data were not collected in the TARGIT-A trial. Patient-level data on the timing of events were collected and for every patient we created a data set describing the health state that they were in during every day of the 5-year time horizon. Utility values from published sources were then applied to each health state. These were used to construct five 1-year utility profiles for every patient covering the 5-year time horizon. QALYs for every patient for each year were calculated as the area under the utility profile for that year. These were discounted and summed across all 5 years to calculate QALYs per patient over the whole period.

The health states included in the cost–utility analysis were recurrence free, local recurrence, distant recurrence, breast cancer death and non-breast-cancer death. A review of the Cost-Effectiveness Analysis Registry was undertaken using the search term ‘breast cancer’ to identify studies reporting relevant utility scores and 1291 results (utility scores) were identified. Picot et al. recently undertook an extensive literature search of studies providing utility values for such patients and identified nine suitable studies. The criteria for the values that they selected in their analysis were that they would ideally be based on EQ-5D scores, would ideally have been derived from UK patients and these patients would ideally reflect the younger age range of patients in the TARGIT-A trial. The values that they selected, from studies by Turnbull et al. and Lidgren et al., were as follows:

- recurrence free in first year: 0.7728
- recurrence free after first year: 0.8112
- local recurrence: 0.8112
- recurrence free after local recurrence: 0.8112
- distant recurrence: 0.658.

We used these values in our base case. The values imply that the utility associated with local recurrence is the same as the utility associated with being recurrence free after the first year and the utility associated with being recurrence free after local recurrence. We undertook a sensitivity analysis using values from an alternative study by Hayman et al., which have been used in previous studies, as follows:

- recurrence free: 0.92
- local recurrence: 0.87
- recurrence free after local recurrence: 0.92
- distant recurrence: 0.70.
Patients who died in the TARGIT-A trial (either from breast cancer or from other causes) were assigned a utility value of 0 at their date of death until the end of the 5-year time horizon.

In the cost–utility analysis we did not incorporate utility losses associated with additional procedures, chemotherapy, mastectomy or complications. Given the low incidence of these events, that they were evenly distributed between treatment groups and that the time period affected is likely to be short, this is unlikely to affect the QALYs associated with each treatment group. We also did not include any utility losses associated with EBRT. Therefore, this would make our estimates more conservative because such an omission would work against TARGIT.

**Missing data**

There were some missing data on patient follow-up, meaning that for some patients we did not know whether or not they had experienced events. This affected both the total costs incurred by each patient and the total QALYs. Multiple imputation was used to impute missing data separately for costs in years 1–5, total costs, QALYs in years 1–5 and total QALYs. The following variables were included in the imputation models as additional explanatory variables: cost of EBRT, cost of the index procedure, cost of additional procedures, cost of chemotherapy, cost of mastectomy, whether or not the patient had each type of complication, age at randomisation, tumour size in millimetres at randomisation, ER status at randomisation, PgR status at randomisation, contralateral cancer or not, whether the cancer was screen detected or not, study centre, year of randomisation and treatment allocation. We used multivariate normal regression to impute missing values and generated 20 imputed data sets. We repeated the multiple imputation several times using different random number seeds to investigate whether or not the conclusions of the analysis changed.

**Statistical methods**

Mean costs, outcomes and net monetary benefits were compared between all patients randomly assigned to EBRT and TARGIT, irrespective of which treatment was administered and whether or not patients received additional therapies of either type. We calculated differences in mean costs and QALYs and incremental net monetary benefits between groups. Net monetary benefits for EBRT and TARGIT were calculated as the mean QALYs per patient multiplied by the maximum willingness to pay for a QALY minus the mean cost per patient. Incremental net monetary benefits were calculated as the difference in mean QALYs per patient with TARGIT compared with EBRT multiplied by the maximum willingness to pay for a QALY minus the difference in mean costs per patient. We used the cost-effectiveness threshold range recommended by NICE of £20,000–30,000 as the lower and upper limits of the maximum willingness to pay for a QALY. If the incremental net monetary benefit is positive (negative) then TARGIT (EBRT) is preferred on cost-effectiveness grounds. The QALYs gained and incremental costs were adjusted for age at randomisation, tumour size in millimetres at randomisation, ER status at randomisation, PgR status at randomisation, contralateral cancer or not, whether the cancer was screen detected or not, study centre and year of randomisation. For each of the 20 imputed data sets we ran 1000 bootstrap replications and combined the results using equations described by Briggs et al. to calculate standard errors (SEs) around mean values accounting for uncertainty in the imputed values, the skewed nature of the cost data and utility values and sampling variation. SEs were used to calculate 95% CIs around point estimates. A similar analytical approach has been used previously.

**Sensitivity analyses**

We undertook deterministic sensitivity analyses to evaluate the impact of uncertainty in the following components. In each case the changes made were applied one at a time to the base case.

- No adjustment for age at randomisation, tumour size in millimetres at randomisation, ER status at randomisation, PgR status at randomisation, contralateral cancer or not, whether the cancer was screen detected or not, study centre and year of randomisation.
Complete case analysis without imputing missing values.

Complete case analysis without imputing missing values plus with no adjustment for age at randomisation, tumour size in millimetres at randomisation, ER status at randomisation, PgR status at randomisation, contralateral cancer or not, whether the cancer was screen detected or not, study centre and year of randomisation.

EBRT costs based on number of fractions received in the trial [mean (SD) number of fractions administered per patient who received EBRT in the trial was 23 (5)].

No EBRT boost.

Costs of EBRT per fraction of £101 and £154, based on the lower and upper values of the IQR of the NHS reference costs. 

Costs of TARGIT of £1300, £1500, £1700, £1900, £2100, £2300, £2500 and £2700. The value of £1300 corresponds to the minimum value in Picot et al., in which the capital and one-off costs were annualised using a device lifetime of 10 years and these costs and the annual costs were assigned to individual treatments assuming that each device was used to undertake 631 procedures per year. The value of £2500 corresponds to the maximum value in Picot et al., with a device lifetime of 5 years and 100 procedures per year.

Percentage of patients using NHS transport for EBRT of 0% (no patients use NHS transport) and 30%.

Health states valued using utilities from Hayman et al.,

A cost-effectiveness acceptability curve showing the probability that TARGIT was cost-effective compared with EBRT at a range of values for the maximum willingness to pay for a QALY was generated based on the proportion of the bootstrap replications across all 20 imputed data sets with positive incremental net monetary benefits. The probability that TARGIT was cost-effective at a maximum willingness to pay for a QALY of £20,000 and £30,000 was reported, based on the proportion of bootstrap replications with positive incremental net monetary benefits at these values.

Results

Resource use and costs

In total, 15.2% of patients randomised to TARGIT also received EBRT (Table 13). We assumed that every patient receiving EBRT received 15 fractions. In total, 38% of patients randomised to EBRT also received an EBRT boost [mean (SD) 5 (2) fractions]. We assumed that 13.5% of all EBRT patients used NHS transport to travel to hospital for their radiotherapy treatment. The mean (median) number of nights in hospital for the initial procedure was 4 (3) for both TARGIT and EBRT patients. A total of 19% of EBRT patients received additional procedures, compared with 12% of TARGIT patients. In total, 20% of EBRT patients received chemotherapy and 4% had a mastectomy; for TARGIT the figures were 23% and 3%, respectively. The incidence of complications was low in both treatment groups. The number of events for TARGIT and EBRT were local recurrences (6 vs. 3), distant recurrences (21 vs. 18), breast cancer deaths (13 vs. 11) and non-breast-cancer deaths (7 vs. 18).

Accounting for missing data using multiple imputation, mean total costs per patient (95% CI) were £11,840 (£11,422 to £12,259) in the EBRT group (n = 416) and £11,404 (£10,800 to £12,008) in the TARGIT group (n = 401; Table 14). The mean radiotherapy cost per patient (summing the cost of TARGIT plus EBRT plus EBRT boost plus NHS transport for EBRT) was £3373 in the EBRT group and £2307 in the TARGIT group. Other costs were similar for EBRT and TARGIT. Values were similar for complete cases (Table 15).

Quality-adjusted life-years

Accounting for missing data using multiple imputation, mean QALYs per year were similar for the two groups and there was a decline over time. Mean QALYs per patient (95% CI) fell from 0.811 (0.808 to 0.812) in the EBRT group in year 1 to 0.657 (0.640 to 0.674) in year 5. In the TARGIT group the values were 0.811 (0.810 to 0.811) and 0.674 (0.660 to 0.689), respectively. Mean total QALYs per patient over
the 5-year period were 3.663 (3.614 to 3.713) in the EBRT group and 3.704 (3.664 to 3.744) in the TARGIT group (see Table 14). QALYs were similar for complete cases (see Table 15).

**Cost–utility analysis**
Accounting for missing data using multiple imputation, the mean net monetary benefits for EBRT and TARGIT were £61,426 (95% CI £60,299 to £62,544) and £62,678 (95% CI £61,542 to £63,762) at a maximum willingness to pay for a QALY of £20,000 and £98,059 (95% CI £96,470 to £99,644) and £99,720 (95% CI £98,228 to £101,147) at a maximum willingness to pay for a QALY of £30,000 (see Table 14).
**TABLE 14** Mean QALYs, costs and net monetary benefits: multiple imputation

<table>
<thead>
<tr>
<th>Variable</th>
<th>EBRT (n = 416)</th>
<th>TARGIT (n = 401)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Costs (£)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TARGIT</td>
<td>0</td>
<td>b</td>
</tr>
<tr>
<td>EBRt</td>
<td>2659</td>
<td>b</td>
</tr>
<tr>
<td>EBRt boost</td>
<td>557</td>
<td>487 to 628</td>
</tr>
<tr>
<td>NHS transport for EBRt</td>
<td>157</td>
<td>154 to 160</td>
</tr>
<tr>
<td>Total EBRt</td>
<td>3373</td>
<td>3300 to 3447</td>
</tr>
<tr>
<td>Total EBRt plus TARGIT</td>
<td>3373</td>
<td>3300 to 3447</td>
</tr>
<tr>
<td>Index operation</td>
<td>2069</td>
<td>1986 to 2153</td>
</tr>
<tr>
<td>Additional procedures</td>
<td>230</td>
<td>182 to 279</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>421</td>
<td>341 to 502</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>266</td>
<td>142 to 390</td>
</tr>
<tr>
<td><strong>Costs associated with health status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>1099</td>
<td>1063 to 1135</td>
</tr>
<tr>
<td>Year 2</td>
<td>1176</td>
<td>1073 to 1278</td>
</tr>
<tr>
<td>Year 3</td>
<td>1126</td>
<td>1014 to 1237</td>
</tr>
<tr>
<td>Year 4</td>
<td>1059</td>
<td>945 to 1173</td>
</tr>
<tr>
<td>Year 5</td>
<td>1020</td>
<td>879 to 1161</td>
</tr>
<tr>
<td>Total costs</td>
<td>11,840</td>
<td>11,422 to 12,259</td>
</tr>
<tr>
<td><strong>QALYs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>0.810</td>
<td>0.808 to 0.8120</td>
</tr>
<tr>
<td>Year 2</td>
<td>0.774</td>
<td>0.766 to 0.781</td>
</tr>
<tr>
<td>Year 3</td>
<td>0.728</td>
<td>0.714 to 0.742</td>
</tr>
<tr>
<td>Year 4</td>
<td>0.695</td>
<td>0.679 to 0.710</td>
</tr>
<tr>
<td>Year 5</td>
<td>0.657</td>
<td>0.640 to 0.674</td>
</tr>
<tr>
<td>Total QALYs</td>
<td>3.663</td>
<td>3.614 to 3.713</td>
</tr>
<tr>
<td><strong>Net monetary benefits (£)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>£20,000</td>
<td>61,426</td>
<td>60,299 to 62,544</td>
</tr>
<tr>
<td>£30,000</td>
<td>98,059</td>
<td>96,470 to 99,644</td>
</tr>
</tbody>
</table>

a Costs are in 2013/14 UK pounds.
b Values do not vary by patient.
c Costs associated with being disease free, local recurrence, distant recurrence, breast cancer death, non-breast-cancer death and complications.

**Notes**

Data include values imputed using multiple imputation (see Missing data and Statistical methods). The 95% CIs were derived from 1000 bootstrap replications of each of the 20 imputed data sets (see Missing data and Statistical methods). The net monetary benefit is calculated at a maximum willingness to pay for a QALY of £20,000 and £30,000.
In the base-case analysis TARGIT was less costly than EBRT (mean incremental cost £685) and produced slightly more QALYs than EBRT (mean QALYs gained 0.034; Table 16). The difference in costs between the two groups was statistically significant (mean incremental cost for TARGIT vs. EBRT £685, 95% CI £1131 to £63) but the difference in QALYs was not (mean QALYs gained 0.034, 95% CI 0.026 to 0.095). The incremental net monetary benefit for TARGIT compared with EBRT was positive indicating that TARGIT was cost-effective: at a maximum willingness to pay for a QALY of £20,000 or £30,000 the mean incremental net monetary benefit was £1363 and £1730 (see Table 16). The incremental net monetary benefit was not significantly different from zero at a maximum willingness to pay for a QALY of £20,000 (mean £1363, 95% CI £66 to £2838) or £30,000 (mean £1730, 95% CI £284 to £3740). However, the incremental net monetary benefit for TARGIT compared with EBRT was borderline significantly different from zero: at a maximum willingness to pay for a QALY of £20,000 the 90% CI was £175 to £2818 and at £30,000 it was

<table>
<thead>
<tr>
<th>Variable</th>
<th>EBRT</th>
<th>TARGIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs (£)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TARGIT</td>
<td>0</td>
<td>1882</td>
</tr>
<tr>
<td>EBRT</td>
<td>2659</td>
<td>405</td>
</tr>
<tr>
<td>EBRT boost</td>
<td>557</td>
<td>0</td>
</tr>
<tr>
<td>NHS transport for EBRT</td>
<td>157</td>
<td>21</td>
</tr>
<tr>
<td>Total EBRT</td>
<td>3373</td>
<td>2307</td>
</tr>
<tr>
<td>Total EBRT plus TARGIT</td>
<td>3373</td>
<td>2307</td>
</tr>
<tr>
<td>Index operation</td>
<td>2069</td>
<td>2101</td>
</tr>
<tr>
<td>Additional procedures</td>
<td>230</td>
<td>143</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>421</td>
<td>484</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>266</td>
<td>211</td>
</tr>
<tr>
<td>Costs associated with health statusb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>1099</td>
<td>1125</td>
</tr>
<tr>
<td>Year 2</td>
<td>1184</td>
<td>1261</td>
</tr>
<tr>
<td>Year 3</td>
<td>1129</td>
<td>1264</td>
</tr>
<tr>
<td>Year 4</td>
<td>1052</td>
<td>1279</td>
</tr>
<tr>
<td>Year 5</td>
<td>1057</td>
<td>1260</td>
</tr>
<tr>
<td>Total costs</td>
<td>11,956</td>
<td>11,789</td>
</tr>
<tr>
<td>QALYs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>0.810</td>
<td>0.811</td>
</tr>
<tr>
<td>Year 2</td>
<td>0.773</td>
<td>0.777</td>
</tr>
<tr>
<td>Year 3</td>
<td>0.726</td>
<td>0.737</td>
</tr>
<tr>
<td>Year 4</td>
<td>0.689</td>
<td>0.700</td>
</tr>
<tr>
<td>Year 5</td>
<td>0.631</td>
<td>0.651</td>
</tr>
<tr>
<td>Total QALYs</td>
<td>3.593</td>
<td>3.642</td>
</tr>
</tbody>
</table>

a Costs are in 2013/14 UK pounds.
b Costs associated with being disease free, local recurrence, distant recurrence, breast cancer death, non-breast-cancer death and complications.
In a hypothesis test, this would indicate that against a null hypothesis the incremental net monetary benefit equals zero; the \( p \) -value for rejecting the null hypothesis would be between 0.05 and 0.1.

We repeated the analysis several times using alternative versions of the multiple imputation process using different random number seeds to investigate whether or not the conclusions of the analysis changed; in every case the results were qualitatively the same.

Sensitivity analyses

In all but one of the scenarios tested in the deterministic sensitivity analysis TARGIT was less costly than EBRT (Table 17). The exception was when the cost of TARGIT was £2700 per patient, which is higher than the maximum value in Picot et al.\(^72\) (£2500). The costs were statistically significantly lower for TARGIT compared with EBRT (the 95% CI did not cross zero) when EBRT costs were based on the number of fractions received in the trial, the unit cost per fraction of EBRT was £154 (the upper quartile unit cost in the NHS reference costs\(^76\)), the cost of TARGIT was \( \leq \) £1900 per patient and the alternative utility values were used.

In every case the QALYs gained were small, positive and non-significant. Note that these were unlikely to change given that the parameters varied in the deterministic sensitivity analysis were mainly cost parameters.

In all cases tested the incremental net monetary benefits for TARGIT compared with EBRT were positive at a maximum willingness to pay for a QALY of £20,000 and £30,000. The incremental net monetary benefits were significantly greater than zero (the 95% CI did not cross zero) when EBRT costs were based on the number of fractions received in the trial, the unit cost per fraction of EBRT was £154 and the cost of TARGIT was \( \leq \) £1700 per patient at a maximum willingness to pay for a QALY of £20,000 or \( \leq \) £1300 per patient at a maximum willingness to pay for a QALY of £30,000.

The probability that EBRT is cost-effective is equal to 1 minus the probability that TARGIT is cost-effective at each value of the maximum willingness to pay for a QALY. The cost-effectiveness acceptability curve shows that, at a maximum willingness to pay for a QALY of £20,000 (£30,000), the probability that TARGIT was cost-effective was 0.965 (0.950) in the base case (Figure 30 and see Table 17). In the deterministic sensitivity analyses the probability that TARGIT was cost-effective at a maximum willingness...
### Table 17: Incremental cost-effectiveness of TARGIT compared with EBRT: deterministic sensitivity analysis

<table>
<thead>
<tr>
<th>Analysis</th>
<th>QALYs gained Mean</th>
<th>QALYs gained 95% CI</th>
<th>Incremental costs (£) Mean</th>
<th>Incremental costs 95% CI</th>
<th>Incremental net monetary benefits (£) £20,000 Mean</th>
<th>Incremental net monetary benefits 95% CI</th>
<th>Incremental net monetary benefits £30,000 Mean</th>
<th>Incremental net monetary benefits 95% CI</th>
<th>Probability TARGIT cost-effective £20,000</th>
<th>Probability TARGIT cost-effective £30,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>0.034</td>
<td>-0.026 to 0.095</td>
<td>-685</td>
<td>-1341 to -63</td>
<td>1363</td>
<td>-66 to 2838</td>
<td>1703</td>
<td>-284 to 3740</td>
<td>0.965</td>
<td>0.950</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.041</td>
<td>-0.022 to 0.102</td>
<td>-436</td>
<td>-1185 to 323</td>
<td>1253</td>
<td>-335 to 2796</td>
<td>1661</td>
<td>-502 to 3762</td>
<td>0.941</td>
<td>0.937</td>
</tr>
<tr>
<td>Complete case analysis adjusted</td>
<td>0.029</td>
<td>-0.072 to 0.125</td>
<td>-583</td>
<td>-1549 to 315</td>
<td>1159</td>
<td>-1199 to 3498</td>
<td>1446</td>
<td>-1860 to 4691</td>
<td>0.834</td>
<td>0.803</td>
</tr>
<tr>
<td>Complete case analysis unadjusted</td>
<td>0.049</td>
<td>-0.052 to 0.149</td>
<td>-167</td>
<td>-1272 to 926</td>
<td>1138</td>
<td>-1367 to 3650</td>
<td>1623</td>
<td>-1818 to 5069</td>
<td>0.817</td>
<td>0.824</td>
</tr>
<tr>
<td>EBRT costs based on number of fractions</td>
<td>0.034</td>
<td>-0.029 to 0.095</td>
<td>-1377</td>
<td>-2026 to -771</td>
<td>2055</td>
<td>562 to 3569</td>
<td>2394</td>
<td>313 to 4485</td>
<td>0.998</td>
<td>0.987</td>
</tr>
<tr>
<td>EBRT costs based on number of fractions</td>
<td>0.034</td>
<td>-0.028 to 0.095</td>
<td>-90</td>
<td>-733 to 519</td>
<td>766</td>
<td>-676 to 2226</td>
<td>1104</td>
<td>-913 to 3132</td>
<td>0.787</td>
<td>0.829</td>
</tr>
<tr>
<td>EBRT costs based on number of fractions</td>
<td>0.034</td>
<td>-0.026 to 0.095</td>
<td>-366</td>
<td>-1009 to 271</td>
<td>1041</td>
<td>-387 to 2504</td>
<td>1379</td>
<td>-607 to 3413</td>
<td>0.926</td>
<td>0.917</td>
</tr>
<tr>
<td>EBRT costs based on number of fractions</td>
<td>0.034</td>
<td>-0.028 to 0.093</td>
<td>-1042</td>
<td>-1664 to -443</td>
<td>1715</td>
<td>267 to 3149</td>
<td>2052</td>
<td>28 to 4043</td>
<td>0.989</td>
<td>0.978</td>
</tr>
<tr>
<td>Costs of EBRT per fraction (£)</td>
<td>0.034</td>
<td>-0.032 to 0.096</td>
<td>-1267</td>
<td>-1896 to -680</td>
<td>1940</td>
<td>420 to 3452</td>
<td>2276</td>
<td>141 to 4378</td>
<td>0.996</td>
<td>0.986</td>
</tr>
<tr>
<td>Costs of TARGIT (£)</td>
<td>0.034</td>
<td>-0.029 to 0.097</td>
<td>-1064</td>
<td>-1705 to -444</td>
<td>1738</td>
<td>247 to 3261</td>
<td>2075</td>
<td>-7 to 4194</td>
<td>0.994</td>
<td>0.980</td>
</tr>
<tr>
<td>Costs of TARGIT (£)</td>
<td>0.034</td>
<td>-0.026 to 0.095</td>
<td>-869</td>
<td>-1516 to -281</td>
<td>1544</td>
<td>150 to 3018</td>
<td>1881</td>
<td>-72 to 3924</td>
<td>0.979</td>
<td>0.963</td>
</tr>
<tr>
<td>Costs of TARGIT (£)</td>
<td>0.034</td>
<td>-0.025 to 0.092</td>
<td>-667</td>
<td>-1304 to -73</td>
<td>1342</td>
<td>-59 to 2765</td>
<td>1679</td>
<td>-271 to 3642</td>
<td>0.968</td>
<td>0.954</td>
</tr>
<tr>
<td>Costs of TARGIT (£)</td>
<td>0.034</td>
<td>-0.029 to 0.094</td>
<td>-471</td>
<td>-1130 to 146</td>
<td>1147</td>
<td>-336 to 2623</td>
<td>1486</td>
<td>-584 to 3524</td>
<td>0.936</td>
<td>0.920</td>
</tr>
<tr>
<td>Costs of TARGIT (£)</td>
<td>0.034</td>
<td>-0.025 to 0.094</td>
<td>-264</td>
<td>-910 to 329</td>
<td>944</td>
<td>-433 to 2395</td>
<td>1284</td>
<td>-638 to 2924</td>
<td>0.909</td>
<td>0.904</td>
</tr>
<tr>
<td>Costs of TARGIT (£)</td>
<td>0.034</td>
<td>-0.027 to 0.096</td>
<td>-65</td>
<td>-702 to 515</td>
<td>740</td>
<td>-695 to 2264</td>
<td>1078</td>
<td>-927 to 3186</td>
<td>0.855</td>
<td>0.863</td>
</tr>
<tr>
<td>Costs of TARGIT (£)</td>
<td>0.034</td>
<td>-0.023 to 0.092</td>
<td>135</td>
<td>-496 to 748</td>
<td>540</td>
<td>-840 to 1966</td>
<td>877</td>
<td>-1032 to 2847</td>
<td>0.785</td>
<td>0.818</td>
</tr>
</tbody>
</table>
### Analysis

<table>
<thead>
<tr>
<th>Analysis</th>
<th>QALYs gained Mean</th>
<th>95% CI</th>
<th>Incremental costs (£)* Mean</th>
<th>95% CI</th>
<th>Incremental net monetary benefits (£) Mean</th>
<th>95% CI</th>
<th>£20,000 Mean</th>
<th>95% CI</th>
<th>£30,000 Mean</th>
<th>95% CI</th>
<th>Probability TARGIT cost-effective</th>
<th>£20,000</th>
<th>£30,000</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients using NHS transport for EBRT (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.034</td>
<td>-0.028 to 0.096</td>
<td>-546</td>
<td>-1205 to 52</td>
<td>1220</td>
<td>-202 to 2728</td>
<td>1557</td>
<td>-437 to 3649</td>
<td>0.951</td>
<td>0.935</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>0.034</td>
<td>-0.025 to 0.097</td>
<td>-852</td>
<td>-1484 to -262</td>
<td>1530</td>
<td>176 to 3000</td>
<td>1868</td>
<td>-34 to 3924</td>
<td>0.990</td>
<td>0.981</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Health statuses valued using utilities from Hayman et al.</strong></td>
<td>0.033</td>
<td>-0.040 to 0.104</td>
<td>-686</td>
<td>-1338 to -67</td>
<td>1347</td>
<td>-367 to 3051</td>
<td>1678</td>
<td>-737 to 4061</td>
<td>0.912</td>
<td>0.903</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Costs are in 2013/14 UK pounds.

b Data include values imputed using multiple imputation (see Missing data and Statistical methods). The QALYs gained, incremental costs and incremental net monetary benefits are for TARGIT minus EBRT. The 95% CIs were derived from 1000 bootstrap replications of each of the 20 imputed data sets (see Missing data and Statistical methods). The QALYs gained and incremental costs are adjusted for age, tumour size, ER status and PgR status at baseline, whether the cancer was detected by screening or not, contralateral breast cancer or not, year of randomisation and centre. The incremental net monetary benefits and the probability that TARGIT is cost-effective are based on the adjusted QALYs gained and incremental costs and calculated at a maximum willingness to pay for a QALY of £20,000 and £30,000.

c As for the base-case analysis except that the QALYs gained and the incremental costs are unadjusted.

d As for the base-case analysis except that there is no multiple imputation of missing values and the 95% CIs were derived from 20,000 bootstrap replications of a single data set containing the 233 TARGIT patients and 266 EBRT patients with no missing values.

e As for the complete case analysis adjusted except that the QALYs gained and the incremental costs are unadjusted.

f The mean (SD) number of fractions administered per patient who received EBRT was 23 (5).
to pay for a QALY of £20,000 was > 0.75 in every case. At a maximum willingness to pay for a QALY of £30,000 the probability that TARGIT was cost-effective was > 0.80 in every case.

**Potential budget impact**

The cost savings per patient found in our base case could translate into cost savings per year for the NHS if TARGIT was carried our routinely instead of EBRT in eligible patients. The latest available evidence suggests that in 2011 there were 49,936 new cases of breast cancer in the UK.\textsuperscript{95} Figures from Germany\textsuperscript{96} based on 1108 new cases of breast cancer treated at a single centre between 2003 and 2009 suggest that 258 patients (23.3\% cases) would have met the eligibility criteria for participation in the TARGIT-C trial (ClinicalTrials.gov NCT02290782),\textsuperscript{97} which has similar but more restrictive inclusion and exclusion criteria than the TARGIT-A trial (e.g. age $\geq 50$ years rather than $\geq 45$ years, tumour size $\leq 2$ cm rather than $\leq 3.5$ cm). This conservatively suggests that around $49,936 \times 23.3\% = 11,600$ patients may be eligible for TARGIT in the UK each year. Applying the cost saving per patient in our base case to this estimate suggests that the NHS might save around $11,600 \times -£685 = £8$ million a year.

Figures from France\textsuperscript{98} based on two cohorts of patients between 1980 and 2008 indicate that, across a combined total of 12,025 patients receiving breast-conserving surgery, 5545 patients (46\%) would have been eligible for TARGIT according to the eligibility criteria of the TARGIT-A trial. Approximately 58\% of newly diagnosed patients with breast cancer in the UK undergo lumpectomy.\textsuperscript{99} Therefore, according to these figures, around $49,936 \times 58\% \times 46\% = 13,300$ patients may be eligible for TARGIT in the UK each year. Applying the cost saving per patient in our base case to this estimate suggests that the NHS might save around $13,300 \times £685 = £9.1$ million a year.

Combined, these calculations suggest that if TARGIT was carried our routinely instead of EBRT in eligible patients the potential cost savings to the NHS would be around £8–9.1 million each year.
Discussion

Summary
We undertook a cost–utility analysis comparing TARGIT versus EBRT in the prepathology stratum of the earliest cohort of the TARGIT-A trial. In our base case TARGIT was statistically significantly less costly than EBRT, produced similar QALYs, had a positive incremental net monetary benefit that was borderline statistically significantly different from zero and had a probability of > 90% of being cost-effective. Although there appears to be some uncertainty about the statistical significance of the differences in costs and whether or not the incremental net monetary benefit is different from zero, the appears to be little uncertainty in the point estimates, based on deterministic and probabilistic sensitivity analyses.

Comparison with other studies
Alvarado et al.\textsuperscript{73} found that TARGIT dominated EBRT (was less costly and more effective) in that it resulted in a QALY gain of 0.00026 compared with EBRT and cost US$5191 less. Based on their analysis using TARGIT-A trial data, Shah et al.\textsuperscript{74} reported that use of TARGIT was associated with cost savings of US$3.6–4.3 million per 1000 patients compared with EBRT. Neither study reported CIs around the point estimates and so it is unclear if the QALYs gained or cost savings were significantly different from zero. Our results are qualitatively similar to those of Alvarado et al.\textsuperscript{73} in that based on the point estimates in our base case we also found a cost saving for TARGIT and a small QALY gain compared with EBRT. Our findings are also qualitatively similar to those of Shah et al.\textsuperscript{74} in that we also found a cost saving with TARGIT compared with EBRT. However, given that both studies were US based it is difficult to draw close comparisons.

Picot et al.\textsuperscript{72} found that TARGIT produced a small cost saving compared with EBRT and a small QALY loss; the authors’ conclusion was that EBRT was associated with more QALYs than TARGIT at a broadly similar overall cost. The point estimates of the costs saved per QALY lost were < £20,000, indicating that TARGIT was not cost-effective (in cases in which an intervention is less costly and less effective than the comparator then for it to be cost-effective the incremental cost-effectiveness ratio must lie above the threshold value). CIs around the cost and outcome differences and the incremental cost-effectiveness measures were not reported and so it is difficult to make a full comparison of the findings. Other than the use of patient-level data, the main differences between the study by Picot et al.\textsuperscript{72} and the present study were the time horizon and the range of costs included. Picot et al.\textsuperscript{72} modelled costs and outcomes using a time horizon of 40 years, whereas the time horizon in the present study was 5 years based on the average length of follow-up in the trial. We did not extrapolate beyond the end of the trial because the within-trial analysis found no evidence of significant differences in QALYs between the groups and, although there was some evidence of differences in costs, these differences were all accrued during the first year. In terms of costs included, there were several differences between the present study and that by Picot et al.\textsuperscript{72}. During the radiotherapy treatment period the present study included the cost of EBRT boost and NHS transport costs for EBRT, which were not included in the study by Picot et al.\textsuperscript{72}. More generally, the total cost per patient in the study by Picot et al.\textsuperscript{72} over the 40-year period, based on the costs included in the analysis, was around £2300 in both groups. In our study the total cost per patient over the 5-year period, based on the costs included in the analysis, was around £11,600 in both groups, suggesting large differences in the range of cost components included.

Strengths and limitations
The main strength of our analysis is that it is based on a large international multicentre randomised trial with detailed information on resource use and events for a median follow-up period of 5 years.

There are several limitations. First, the time horizon was 5 years. Extrapolation beyond the end of the trial using decision-analytical modelling was not undertaken because the within-trial analysis found no evidence of significant differences in QALYs between groups during the 5-year period. This probably reflects the main finding from the TARGIT-A trial that TARGIT was non-inferior to EBRT with regard to local recurrence. Although there was some evidence of differences in costs these differences were all accrued during the first year; there was no evidence of significant differences in costs beyond the first year. Hence, the 5-year time horizon was long enough to reflect all important differences in costs or outcomes between
the two treatments. Although local recurrence (and other events) are likely to continue to occur over a
patient’s lifetime, the evidence from the TARGIT-A trial is that TARGIT is non-inferior to EBRT. Hence,
taking a longer time horizon is unlikely to have affected the results of the incremental analyses.

Second, utility data were not collected in the TARGIT-A trial. We therefore applied utility values from
published sources to the health states experienced by patients in the trial. The utility values that we applied
may not reflect the values of patients in the study. Given the relatively small number of events, and that
the numbers of events were largely not different between the two groups, the QALY differences between
the two groups may not be expected to change much with alternative utility values. This is borne out by
our sensitivity analysis, which showed that the results did not change appreciably when we used
alternative values. We did not incorporate utility losses associated with additional procedures,
chemotherapy, mastectomy or complications in our analysis. Given the low incidence of these events, that
they were evenly distributed between treatment groups and that the time period affected is likely to be
short this is unlikely to affect the QALYs associated with each treatment group. We also did not include
any utility losses associated with EBRT. Therefore, this would make our estimates more conservative
because such an omission would work against TARGIT.

Third, the dose of EBRT administered to patients in the TARGIT-A trial does not reflect current UK
treatment guidelines. This reflects the multinational nature of the trial, plus that it began recruiting patients
in 2000 when treatment recommendations were different. We accounted for this in our base case by
assuming that all patients in the TARGIT-A trial who received EBRT received a fixed number of 15 fractions.

Fourth, the analysis took a NHS/PSS perspective on costs. A wider perspective (e.g. societal) could have
been taken to measure costs, including impacts on the rest of society, patients, families and businesses.
If a wider perspective was taken this should include the additional costs borne by patients and families in
terms of time and travel costs associated with additional radiotherapy visits for EBRT compared with
TARGIT. If these costs were included it is likely that the cost savings attributable to TARGIT would be
greater than demonstrated. Taking the example of the transport costs, we used the figure of 13.5% for
the proportion of patients for whom the NHS paid for transport for radiotherapy visits for EBRT. Assuming
that the same cost is paid out of pocket by the remaining patients, the difference in costs between TARGIT
and EBRT would be increased by £877 to £1562 per patient, taking the total saving to the UK national
economy to between $11,600 \times £1562 = £18.1 million and $13,400 \times £1562 = £20.9 million each year.
These are crude estimates and further research to evaluate the wider impacts of TARGIT, including on
other costs to the rest of society, would be useful.
References


REFERENCES


78. NICE. Early and Locally Advanced Breast Cancer: Diagnosis and Treatment. NICE clinical guideline 80. URL: www.nice.org.uk/guidance/cg80/chapter/1-recommendations (accessed 18 July 2015).


REFERENCES


This report presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.