*TARG*eted *I*ntraoperative radio*T*herapy Boost

vs.

Standard external beam Radiotherapy Boost

Short title: TARGIT B

TARGIT-B: An international randomised controlled trial to compare targeted intra-operative radiotherapy boost with conventional external beam radiotherapy boost after lumpectomy for breast cancer in women with a high risk of local recurrence.

TARGIT B Protocol Version 6, Dated 10 September 18

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2. Signature page

Signatures of all healthcare professionals involved in the trial

I have read the trial protocol and will ensure that the trial is conducted according to the terms of that protocol and in accordance with agreed international standards for randomised clinical trials.

Signature:_____

Name (printed): _____

Date: _____

3. Contents page

4. List of abbreviations and definitions

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GAfREC	Governance Arrangement for NHS Research Ethics
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HES	Hospital Episode Statistics
HTA	Human Tissue Authority
IB	Investigator Brochure
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
MD	Medical Device
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
ONS	Office for National Statistics
PDS	Personal Demographics Service
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Clinical Study
REC	Research Ethics committee
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
SSI	Site Specific Information
SmPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction

TMG	Trial Management Group
TMF	Trial Master File
TSC	Trial Steering Committee

5. Summary

TARGIT-Boost is an international randomised clinical trial designed to test the hypothesis that the tumour bed boost delivered as a single dose of targeted intraoperative radiotherapy (TARGIT-B) is superior to the conventional course of external beam radiotherapy boost (EBRT-Boost), especially in women with high risk of local recurrence. It is a pragmatic trial in which each participating centre can use the local predefined inclusion/exclusion criteria for entry into the trial. Only centres with access to the Intrabeam® (Carl Zeiss) are eligible to enter patients into the trial.

Eligible patients are those with a higher risk of local recurrence after breast conserving surgery. After giving consent patients are randomised to either TARGIT Boost or EBRT Boost. All patients will receive whole breast EBRT. They may receive any other adjuvant treatments as deemed necessary. The protocol recommends that patients be followed at six monthly intervals for three years and then annually.

The primary endpoint is ipsilateral breast recurrence rate. Secondary endpoints are relapse-free survival, site of recurrence, overall survival (breast-cancer specific and non-breast cancer deaths) quality of life and cost-effectiveness. Cosmetic outcome, cardiopulmonary toxicity, patient satisfaction and patient preference will be discussed in separate subprotocols.

6. Background

Patients receiving breast conservation surgery benefit from radiotherapy to the whole breast [1] as well as a tumour bed boost. Although the absolute benefit is higher in absolute terms in younger women, they still have a high recurrence rate (e.g., 8.7% and 13.5% for those <50 years and <40years respectively in the EORTC study [2]). The reasons for this could be an inherent resistance to radiotherapy but the following issues need attention:

Geographical miss: Targeting the boost dose to the tumour bed can be difficult; the use of ultrasound or clips may help but it is not universal and with increasing use of oncoplastic surgery, the configuration of the tumour bed can become completely distorted. Thus in many cases the potential benefit of the boost may be reduced [3].

Temporal miss: Our translational work found that surgical wound fluid stimulates proliferation, migration and invasion. This stimulation of cancer cells by the normal response to wounding may contribute to local recurrence, especially in younger women who may evolutionarily mount a stronger response to wound healing. Interestingly, this effect is abrogated by targeted intraoperative radiotherapy (TARGIT) which utilises a window of opportunity that has always been missed by traditional radiotherapy, through the novel effect of radiotherapy on tumour microenvironment [4]. Addition of this effect to the tumouricidal effect of radiotherapy may significantly improve outcomes.

Models: Our mathematical models [5 6] as well as the recent START trials [7] support the concept that a shorter well-targeted higher dose of radiotherapy may have a higher than expected radiobiological effect without jeopardising normal tissues.

Phase 2 data: Since 1998, we have been treating patients undergoing breast conserving surgery with TARGIT [8 9]: a single fraction of radiotherapy (~20Gy) is delivered to the tumour bed, avoiding the risk of a geographical or a temporal miss. The phase II study started in 1998 found the technique to be feasible and safe and the early results were encouraging [8 10]. We recently reported [11] and published [12] the long term data at the median follow up of 5 years (maximum 10 years) and found a local recurrence rate (1.73% (SE 0.77) that was half of the expected from the cohort. Our results appear superior to those seen in the boosted patients in the EORTC study (4.3%) and the START-B study (2.8%) despite a higher node positivity (29%). Furthermore, in this study, women younger than 50 years had a 5-year Kaplan-Meier recurrence rate of 2.1% (standard error 1.5), compared with 6.9% in the EORTC study [2 13].

Whether this technique is adequate as the only radiotherapy given is being tested in an international randomised controlled non-inferiority trial across 30 centres in patients at low risk of recurrence in

the TARGIT-A trial (HTA funded Ref: 07/60/49)). With the approval of the Trial Steering Committee (TSC) and the prompting of Data Monitoring Committee (DMC) the data from this trial (n=2232) was analysed and presented at the 2010 ASCO meeting and simultaneously fast-tracked and published online-first in *The Lancet* on 5 June and subsequently published in print [14]. Our results found that the TARGIT approach was non-inferior in terms of local recurrence at 4 years and the conclusion was that in selected patients a single dose of radiotherapy delivered at the time of surgery should be considered as an alternative to several weeks of whole breast external beam radiotherapy. We continued accrual in this trial and closed it in June 2012 with accrual of 3451, and updated analysis with first analysis of survival presented in December 2012.

Ultimately our vision is to develop a risk-adjusted strategy for radiotherapy, rather than a one-size-fits-all approach, so that women with lower risk can be treated with only a single dose of radiotherapy (TARGIT-Alone) at the time of lumpectomy while younger women and those at high risk of recurrence can be given their tumour bed boost at the time of operation, accurately targeted and timely, followed by additional whole breast radiotherapy (TARGIT-Boost).

The quality of local control in postmenopausal women is now excellent. This is attributable to earlier diagnosis of smaller tumours due to widespread use of screening mammography, meticulous attention to margins, well planned delivery of postoperative radiotherapy to most patients and finally, the use the more effective systemic therapy viz., aromatase inhibitors.

There is a significant subgroup of women undergoing breast conserving surgery in whom a high risk of local recurrence (8-13%) remains despite having the current gold-standard treatment [2 13]. These are mainly women younger than 45 and those with high risk features such as high grade and lymphovascular invasion. We believe that this could partly be attributed to events in the peri-operative period.

With better systemic treatment, the outcome of these younger women is better than ever and we believe that it should not be jeopardised by poorer local control. In the Oxford Overview, it was found that for every 4 local recurrences prevented at 5 years, 1 life would be saved at 15 years. This 4:1 ratio was in the era before the use of systemic therapy. It has been suggested (Jay Harris, St Gallen 2009) that with better systemic therapy there will be better local control, but the ratio may also be less than 4:1 such as 2:1 or 1:1. This means that there is an imperative that we keep local recurrence to the minimum as a 2.74% reduction in local recurrence may reduce mortality at least 0.7% - an absolute amount that may be worthwhile particularly when it also saves 5 days of external boost treatment.

We believe that we now in a position to test in a randomised controlled clinical trial whether giving a TARGIT–Boost achieves superior local control compared with EBRT. This is backed by a robust

conceptual framework (avoiding geographical and temporal miss), mathematical models, and long term pilot data.

We first proposed this study in 2005. Since then the (IMPORT- High) study is being planned in the UK to test whether a higher tumour bed dose reduces local recurrence in high risk patients. However, our study is unique in terms of the localisation and timing of delivery of tumour bed boost and may achieve a better tumour control because of the reasons explained above. The Milan group is now planning to test whether intraoperative boost using the ELIOT technique may yield superior outcome. The ELIOT technique could in theory suffer from the problem that the high dose of radiotherapy (20Gy) is delivered in a very short time (2-4 minutes) and the long term cosmetic or toxicity of such an approach is not yet known. The longer duration (25-30 min) of radiotherapy during the TARGIT intra-operative procedure, in theory, would allow for repair of DNA damage by normal tissues (but not tumour cells), thus reducing long term toxicity. This theoretical concept has been vindicated by our long term toxicity and local recurrence outcome data. Hence the TARGIT-B trial remains unique and will address a very important question and could potentially provide a better clinical outcome.

7. Trial objectives and purpose

This is a randomised controlled trial that compares two treatments in patients with early breast cancer who have undergone local excision of a breast cancer and face a relatively higher risk of local recurrence. The conventional policy for such a patient is to receive radiation boost to the tumour bed delivered by external beam radiotherapy (EBRT) in addition to whole breast EBRT according to local treatment guidelines. The experimental policy is to give targeted intra-operative radiotherapy (TARGIT-Boost) in a single dose to substitute for the usual boost dose.

Primary Objective: To evaluate whether a tumour bed boost in the form of a single fraction of radiotherapy given intra-operatively and targeted to the tissues at the highest risk of local recurrence is superior (in terms of local tumour control) to standard post-operative external beam radiotherapy boost, after breast conserving surgery in women undergoing breast conserving therapy who have a higher risk of local recurrence.

Secondary Objectives: To compare the treatment arms with respect to site of relapse within the breast; relapse-free survival and overall survival (breast cancer and non-breast cancer deaths –such as cardiac and other cancers), local toxicity/morbidity, cost-effectiveness and quality of life.

Separate sub-protocols, not included in this protocol, will address other endpoints, including cosmetic outcome, cardiopulmonary toxicity, patient satisfaction and patient preference. These sub-protocols will be subject to their own sponsorship and regulatory reviews.

8. Study design

Core Protocol: This pragmatic, parallel group, superiority randomised trial is designed to directly compare the outcome, primarily in terms of local control, of two approaches of adjuvant radiotherapy.

Patients selected for breast-conserving surgery who are considered to have a high risk of local recurrence are eligible to participate in the trial once they have received information and given their consent.

Individual centres may choose to recruit only a subset of patients eligible as per the entry and management criteria given in the protocol; for example some centres may decide not to enter patients who require a second procedure solely to give the TARGIT-boost. These policies are to be documented in advance and all trial patients treated according to this pre-declared policy. The study will be analysed under an 'intention to treat policy' (ITT) with stratified analyses performed.

This trial allows entry of patients who are suitable, (or have been rendered suitable by neoadjuvant systemic therapy) to be treated by breast conserving therapy and who are expected to have a high risk of local recurrence, (young age, grade III histology, lymphovascular invasion, grossly involved axillary nodes, etc.), or risk of recurrence in other quadrants of the breast such as extensive intraduct component (EIC) or lobular carcinoma. Preferably, tumours should not be more than 4 cm in size, as the largest applicator size is 5cm. Patient consent is sought and randomisation is carried out prior to the surgical removal of the tumour. After wide local excision of the tumour, a tumour bed boost is delivered using the Intrabeam system as described previously in the patients who are randomised to TARGIT Boost. Those randomised to EBRT boost will have this boost delivered by conventional External Beam Radiation Therapy (EBRT).

Most patients who require treatment for a metachronous breast cancer are excluded from entry to trials of local treatment. Although there are good reasons for this, later development of recurrence cannot be ascribed to the first or second breast tumour for instance, they do need to be treated and intraoperative treatment may be particularly suitable. The trial will only assess these patients for ipsilateral local control and their data will be censored for other endpoint assessments.

Changes to protocol

Protocol v2.0 included entry into the trial after the initial surgery was performed. However, at the first trial steering committee meeting it was decided that this mode of entry was not desirable and should be removed from the protocol based on the findings of the TARGIT-A trial – which found that when given as a delayed procedure, TARGIT does not appear to be as effective as when it is given concurrently with lumpectomy [15]. It has also been found that progesterone receptor status predicts the response to radiation. Therefore, there will be no stratification as per timing of

randomisation with respect to lumpectomy [15]. Instead, we shall stratify as per hormone receptor status (see Table) [16]. This is based on the finding in the TARGIT-A trial that progesterone receptor status appears to be the only factor that predicts the efficacy of TARGIT. The eligibility criteria will also be simplified as it will not include positive margin at first excision as an entry criterion. Therefore, randomisation will be stratified according to participating site as well as by the hormone receptor status. These changes have been incorporated into Protocol v3.0.

Protocol v4.0 included that a 'minimum' of Five "pilot" cases (non-randomised patients suitable to receive TARGIT) will be performed followed by an audit by a member of the Steering Committee (or an appointed delegate). Also, patients will be issued with a participant card so that patients can provide this card whenever they are asked about what type or how much radiation treatment they have received.

Stratification by hormone receptor status

		Tumour ER status		
		ER positive	ER negative	ER unknown*
Tumour PgR status	PgR positive	Stratum 1	Stratum 4	Stratum 0
	PgR negative	Stratum 2	Stratum 4	Stratum 0
	PgR unknown	Stratum 3	Stratum 4	Stratum 0

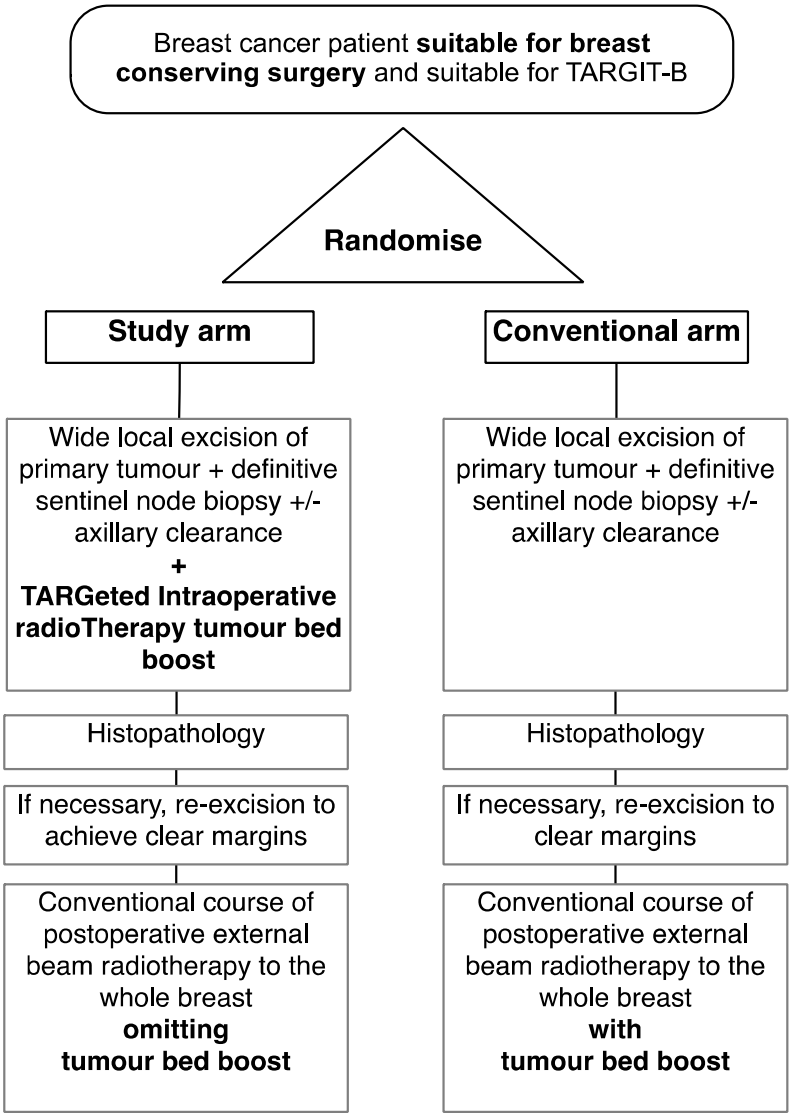
Stratum 0: ER unknown
Stratum 1: ER positive, PgR positive
Stratum 2: ER positive, PgR negative
Stratum 3: ER positive, PgR unknown
Stratum 4: ER negative, (any PgR status)

* ER should be preferably known before randomisation.

Protocol v5.0 allows the inclusion of 'no ink on margin' as a definition of 'free margin', as this is the new standard increasingly accepted around the world, and for fine needle aspiration cytology (FNAC) as part of triple assessment, in those sites where it is a long standing local practice that is not practically possible to change. Tumour grade and ER status from the cytology specimen will be used for assessing eligibility and for stratification; correlation with the final pathology will be performed at the time of analysis. Voluntary Breath Holding (VBH) or a similar technique can be used to protect the heart during whole breast external beam radiotherapy.

Each of these: the definition of free margin, use of FNAC and policy about VBH are to be recorded on the TPD of the individual site and the case record forms.

Trial Schema



Outcome measures:

Local tumour control (defined as no recurrent tumour in the ipsilateral breast). Confirmation of recurrence will follow clinical examination and core biopsy. If initial diagnosis of a local recurrence is by using fine needle aspiration, it is necessary to confirm this diagnosis by histology of either a therapeutic excision or a core biopsy.

Site of relapse within the breast will be recorded in order to assess whether the recurrence is at the site of the initial tumour or at a new site and whether it has occurred within the treated field (TARGIT or EBRT boost).

Relapse-free survival will be recorded as the time interval between randomisation and the date of confirmation of recurrence. The actual date to be used is the clinic day on which the investigations that led to a confirmed diagnosis of the recurrence were requested. Relapse-free survival will include any recurrence of breast cancer or death without a prior report of relapse.

Overall survival will be the time interval between randomisation and death. We shall ascertain the cause of death via a 'an independent cause of death committee'. Breast cancer deaths and non-breast cancer deaths (with particular attention to deaths from cardiovascular causes and other cancers) will be analysed in detail.

Local toxicity and morbidity will be recorded as adverse events related to the primary treatment of the breast cancer. Quality of life will be assessed though validated patient-completed questionnaires.

Quality of life: The primary PRO endpoint for QOL will be the FACT-B+4 trial outcome index (TOI) score. The TOI score (0-180) is a sum of the scores of the 27 items included in the physical well-being, functional well-being and breast cancer subscales of the FACT-B+4. A change of at least 5 points in TOI is considered to be clinically relevant or a minimally important difference (Eton et al. 2004).Secondary endpoints will be: 1) the five item arm functioning subscale score (0-20) 2) The 40 item FACT B+4 score (0-160), which reflects global quality of life including social and emotional well-being.

Health economics: resource use, HR QOL and cost-effectiveness.

Sub-protocols

The following sub-protocols are planned for the TARGIT B Trial. Each will have their own protocol, patient information leaflet and consent form; they have been included for completeness.

A concurrent sub-protocol will assess cosmesis in a sub-set of patients. Patient's own assessment of cosmesis will be used along with objective assessment from a frontal digital photograph. The assessments will be made annually and assessed, blind to treatment, using specialist, validated software (BCCT.core 2.0, INESC Porto, Portugal) which produces a composite score (Excellent, Good, Fair, Poor) based on symmetry, colour and scar. We have used this tool already within the TARGIT–A trial and recently presented some results [17]

A patient preference subprotocol will be an interview-based determination asking patients whether they would choose EBRT or TARGIT given hypothetical recurrence risks. This approach has been used in the TARGIT A Trial.

A cardio-pulmonary subprotocol will assess the degree of radiotherapy-induced heart and lung damage. The less penetrating X-rays from Intrabeam are expected to cause less damage, but this should be formally tested.

These sub-protocols will be subject to their own sponsorship and regulatory reviews.

Assessment and follow up

The schedule for assessment and follow-up will be as follows:

Baseline (soon after surgery), pre-EBRT (around 6 months), 12, 18, 24, 30, 36, 48, 60, 72, 84, 96, 108, 120 months.

Assessment of efficacy/effectiveness:

Follow-up will be balanced between the two arms and be at least every 6 months for the first 3 years, then annually to 10 years. Each follow up will include clinical history and examination and mammograms as per local guidelines, but at least annually for the first 5 years and/or then until the patient is eligible for national screening programme.

Assessment of safety:

Local toxicity and morbidity will be recorded as adverse events related to the primary treatment of breast cancer. The expected toxicities of acute skin reaction, wound infection, wound breakdown, late skin reactions (i.e. after 90 days) and pain due to radiation will be graded according to RTOG and LENT SOMA criteria. Any other toxicity will be recorded and graded according to standard clinical criteria.

Data on safety will be gathered from the following forms: Serious Adverse Event, Protocol Violation/Deviation, and Complication Form. These forms will collect treatment related adverse events, including postoperative complications such as haematoma, seroma, wound infection, skin breakdown, and delayed wound healing.

Upon receipt of a completed form the TARGIT Trials Office will ascertain that the event meets the definition of a SAE, and if required, actively ensure full completion of other related forms such as the complications form. It is the responsibility of TARGIT Trials Office personnel to provide summary information to the TSC or DMC. Any local requirements of reporting SAEs to IRB or local EC are the responsibilities of the investigator.

Functional Assessment of Cancer Therapy-Breast +4

Quality of life will be assessed using the Functional Assessment of Cancer Therapy-Breast +4 questionnaire (FACT-B+4). The FACT-B is a validated instrument comprised of several subscales:- physical well-being (7 items), social well-being (7 items), emotional well-being (6 items), functional well-being (7 items), and concerns specific to patients with breast cancer (13 items). It provides a comprehensive measure of overall health related quality of life and has been used in many large clinical trials of breast cancer treatment. However the FACT-B has only a single item about arm morbidity so 4 additional items were added creating a validated arm morbidity sub-scale to use with the FACT B evaluating swelling/tenderness, numbness, painful movement, range of movement and stiffness, (FACT-B+4).

Patients indicate, using a five-point scale ranging from 0 (not at all), 1 (a little bit), 2 (somewhat), 3 (quite a bit), to 4 (very much), to what degree each item has applied over the past 7 days. The scores of negatively framed statements are reversed for analysis. High FACT scores equate with a good quality of life and lower scores with a poorer one.

Data will be analysed according to ITT. Any missing data and / or imputation will follow standardised rules as defined by the PRO measurement manuals. Mean change scores for FACT B+4, TOI and subscales will be compared between groups using unpaired t tests. Differences in proportions will be analysed using Chi2.

Procedure & Timelines: At the baseline visit, prior to randomisation, consenting patients will be asked by research nurses to complete FACT B+4. These will be placed in sealed envelopes to be sent to the Surgical & Interventional Trials Unit (SITU). Thereafter all questionnaires will be sent out at the appropriate time-points 6, 12, 18, and 24 months, then annually until 5 years, by post with a pre-paid envelope. This system has ensured excellent compliance in previous studies.

Health Economics

This data will be assessed using Euroqol 5 dimensional 5 level (EQ5D-5L) questionnaires. EQ-5D is primarily designed for self-completion by respondents and is ideally suited for use in postal surveys, in clinics and face-to-face interviews. It is cognitively simple, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire.

These questionnaires consider descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses. The responses record five levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within each particular EQ-5D dimension.

EQ5D will be given out, and collected/returned, at the same time points as FACT B+4, and via the same collection method, to save costs.

Cost Data

Cost data will be collected at patient level.

The purpose of the cost diary is to keep a record of all types of health care resource use. It will allow for the calculation of both the cost to the NHS and patient specific costs, incurred as a result of receiving this treatment. All records will be combined to calculate the cost of Targit Boost to both the NHS and patients.

Simple cost diaries will be sent to each patient after randomisation, these instruments will be sent out by the TARGIT Trials Office and returned to the TARGIT Trials Office. Cost data will be collected only during the first three years of the study. Please see questionnaire schedule for data collection points. Diaries will be sent out at the beginning of the appropriate time window.

Questionnaire Schedule:

	Baseline (before surgery)		6	12	18	24			36	48	60
EQ5D & FACTB+4	√		√	√	√	√			√	√	√
		0-3	3-6	6-12	12-18	18-24	24-30	30-36			
Cost diary		√	√	√	√	√	√	√			

9. Subject selection

The trial will accrue from the centres already participating in the TARGIT-A trial, although many more centres are keen to participate. The TARGIT-A trial accrued patients from around the world (21% from UK, 56% from Europe, 13% from Australia and 10% from North America) but both the trials have been conceptualized, designed, initiated, administered and published from the UK. With the trial inclusion criteria being selective for high risk women, we conservatively estimate the accrual rate to be 5 patients per week (250 per annum) after one year.

Inclusion criteria

Patients diagnosed with breast cancer and suitable for conserving surgery and whole breast radiotherapy, with a histological confirmation of carcinoma can be included in the study once a written informed consent is obtained. All patients should be available for regular follow-up (according to local policies) for at least ten years.

At least one of these criteria must be satisfied:

1. Less than 46 years of age
2. More than 45 years of age and with one or more of the following poor prognostic factors:

   a) Grade 3
   b) ER and/or PgR negative
   c) lobular carcinoma
   d) extensive intraductal component (EIC)
   e) lymphovascular invasion
   f) axillary nodal involvement
   g) more than one tumour in the breast but still suitable for breast conserving surgery through a single specimen
   h) any factor or a combination of factors that puts the patient at a higher risk of local recurrence as per the current local guidelines : e.g., those who need a tumour bed boost or those *not* suitable for TARGIT-Alone as standard treatment.

3. Those patients with large tumours which have responded to neo-adjuvant chemo- or hormone therapy that is given in an attempt to shrink the tumour, and are now suitable for breast conserving surgery as a result.

   Note. It is recommended that hormone receptor status (at least ER) is known before randomisation. Patients with either HER2 positive or HER2 negative tumours can be included. The initial determination of characteristics of the tumour should be made by core biopsy, or fine needle aspiration cytology (FNAC) if this is local practice.

Exclusion criteria

1. Bilateral breast cancer at the time of diagnosis.
2. Patients with any severe concomitant disease that may limit their life expectancy
3. Previous history of malignant disease does not preclude entry if the expectation of relapse-free survival at 10 years is 90% or greater (e.g., non-melanoma skin cancer, CIN etc.).

10. Subject recruitment

Suitable patients will be identified by members of the hospital clinical team (e.g. during the multi-disciplinary meeting) and approached during a clinic visit. No additional tests are required to assess trial suitability. Participants will not be paid for their involvement.

The Patient Information Leaflet (see Appendix B1) will be given to the patient during the recruitment process. Written informed consent will then be obtained using the Consent Form (see Appendix B2), which will also be signed by the physician who explained the study to the patient.

Patients will be issued with a study participant card, so that patients can provide this card whenever they are asked about what type or how much radiation treatment they have received.

A log of patients eligible but not recruited into the trial will be kept at each participating site. A summary of these data will be used in publications requiring adherence to the CONSORT guidelines.

11. Trial interventions

11.1. General information

Only clinical centres with the Intrabeam® or those who are able to refer patients to such a centre may enter the trial. Centres with newly acquired equipment must consult the TARGIT Trial Operations Centre prior to entering patients into the trial. A minimum of Five "pilot" cases (non-randomised patients suitable to receive TARGIT) will be performed followed by an audit by a member of the Steering Committee (or an appointed delegate). A confirmation of the quality control of the system set up must be received at the Operations Centre before randomisation can begin.

Surgery: All patients will have local excision of the primary tumour following appropriate clinical work-up. No special assessments prior to randomisation will be required although mammography and ultrasound are recommended.

Surgery will be according to usual local practice but complete macroscopic excision of the tumour is required. The aim of the local excision should be to achieve the widest margin of excision whilst maintaining a good cosmetic outcome (aim for margins of >10mm). The final histological margin should be at least 1mm clear of all invasive and in-situ disease, or 'no ink on margin' as per local practice. For superficial tumours an ellipse of overlying skin should be excised. The depth of resection will depend on the position of the tumour within the breast and the size of the breast but in most instances will extend to the pectoral fascia. The exact size of the tumour free margin and specimen weight will be recorded to assess equality between the two groups.

In all patients, but especially in those women with impalpable tumours where pre-operative localisation has been performed, the specimen should be well orientated with sutures or clips according to local protocols and x-rayed intra-operatively. The specimen x-ray should be examined in theatre to ensure complete excision of the lesion and to help with the assessment of adequacy of the margins. Further tissue should be taken (and marked) from a margin if the x-ray abnormality extends near the margin.

Either a standard sentinel node biopsy or at least level II axillary lymph node dissection must be performed in all patients. Similar surgical techniques must be employed in all patients regardless of the randomisation. Wound closure must be performed meticulously (air and water-tight) as described [9 18] and sutures (if non-absorbable), should remain in place for 14 days.

Patients who are not randomised to the TARGIT arm should have the tumour bed localised with two titanium clips in each available face (posterior. medial/lateral, superior and inferior) before closure of the skin.

11.2. Use within the trial

Patients with positive margins: If final pathology shows involved or close margins (evidence of invasive or in situ tumour at, or within 1mm, of an excision margin or 'ink-on-margin' as per local practice and multidisciplinary team discussion) re-excision is strongly recommended. In some cases, this may necessitate a mastectomy. Decision about re-excision or mastectomy should not be influenced by whether the patient had received TARGIT-Boost or not. For patients who have already received TARGIT, such re-excision to clear margins should be followed by external beam radiotherapy excluding the boost. Intraoperative radiotherapy or EBRT boost of the re-excised tumour bed which had previously received TARGIT should not be done because we have had no experience regarding its safety.

The procedure for delivering the TARGIT is described below, including the administration of a prophylactic antibiotic just after the induction of anaesthesia. In this group of patients, special care should be taken to ensure the wound closure is meticulous, air- and water-tight and sutures are not removed for at least 2 weeks. If an absorbable suture is used it should be at least 3-0 in thickness, should not be absorbable within 2 weeks and Steristrips should be used and left in situ for 2 weeks. Also, in this group the antibiotic cover should be for 5 days.

Pathological Examination: Data from pathological examinations should be recorded on the appropriate data collection forms and all reporting of pathological findings are to be in accordance with the TNM Classification.

Radiotherapy

TARGeted Intra-operative radioTherapy (TARGIT): The technique of the operation and the delivery of radiotherapy have been described in a video available from the TARGIT Trial Operations Office and at http://www.youtube.com/watch?v=GVlHGpvRf8A. We have established a standard training protocol before any centre is allowed to recruit into the trial. We shall ensure that the doses are standardized between all centres.

Preparation of the Intrabeam: TARGIT will either be delivered in the operating theatre immediately after the removal of the tumour or as a subsequent procedure, a short time later. The procedure has been described in detail [8 9 18]. The device and the arm of the stand are wrapped in a sterile clear plastic cover. The individual applicators are sterilised prior to the theatre session. The size of the sphere is determined at surgery by the surgeon and/or the radiation oncologist. An appropriately sized

Intrabeam applicator fits comfortably without tension in the surrounding tissue so that the skin and subcutaneous tissues can be gathered with a purse string suture over the sphere. Any other apparatus to assist this apposition may also be used.

It is essential that complete haemostasis is achieved before insertion of the applicator sphere, because even a small ooze of blood can distort the cavity around the sphere and significantly change the target dose. The applicator sphere is inserted into the surgical cavity and a deep surgical purse string suture is inserted in the breast tissues to bring together the target breast tissue so that it applies well to the surface of the Intrabeam applicator sphere and holds it in place during treatment. The skin, but not the breast tissue, can be slightly everted and held away from the delivery device by surgical sutures to prevent direct contact with the sphere. It is important to keep the skin at a distance of at least 1cm from the applicator. However, at no point should anything (such as a piece of gauze) be placed between the target breast tissue and the applicator surface thus making sure not to inadvertently shield the areas of tissue that require radiation treatment. If the skin is coming too close then it may need to be excised. Also the breast tissue should not be dissected off the skin as it could reduce its blood supply reducing the effectiveness of radiotherapy. The tumour bed should have no or minimal disturbance.

If necessary, protective caps (made from tungsten impregnated rubber available from Carl Zeiss) may be fashioned by the surgeon to protect deep or superficial structures. If the deep margin of excision is such that left anterior descending branch of the coronary artery could receive significant radiation dose, then the surface of the applicator sphere should be covered with a protective cap at the chest wall. However, in most patients the normal thickness of the chest wall (muscle and rib cage) would provide adequate shielding and such a protective cap is not required.

TARGIT Dose Prescription and Delivery: The surgeon and radiation oncologist should choose the largest possible suitable applicator in order to ensure the highest dose is delivered to the tumour bed tissue. Radiation protection shielding material may also be used, which is sterile and suitable for both internal and external use.

A dose of 20Gy (in water) calculated at the applicator surface should be prescribed by the radiation oncologist and delivered to the breast tissue. This takes typically 30 minutes depending on the size of the applicator. This dose has superior radiobiological advantages as it ensures that tumour beds from larger tumours receive a higher dose than small tumours [19 20].

During the radiation treatment, the anaesthetist, clinician and physicist may remain in the room. To avoid unnecessary exposure we recommend that as many people as possible vacate the operating theatre and those remaining, either wear a lead apron or remain behind a shielded screen. It is important to emphasise that the operation theatre itself needs to be initially checked that its walls

provide adequate shielding for radiation- although this does not need to be more than that required for routine operative fluoroscopy.

Completion of TARGIT: After completion of radiation, the conforming stitches are removed. Strict haemostasis should be obtained following the removal of the Intrabeam device. The skin is sutured meticulously to achieve a water-tight closure and a good cosmetic result. If non-absorbable- sutures are used, they should be left in situ for 14 days and if absorbable sutures are used, Steristrips covering the entire wound should be left in place for 14 days [9].

TARGIT Physics: Prior to entering any patient into the trial, centres will be expected to submit data for each x-ray source (XRS) probe and applicator set in use. Each centre will be responsible for measuring data for the probe and applicator set, and shall submit the data supplied by the manufacturer for comparison with measured data together with a copy of the letter of acceptance supplied by Carl Zeiss.

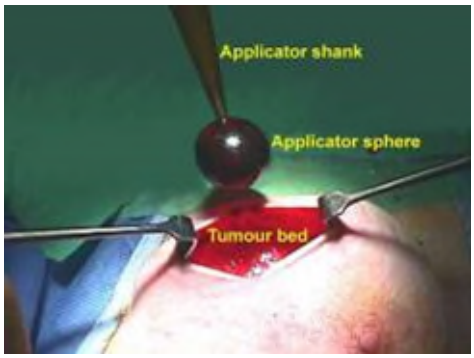
External beam radiotherapy: Planning protocols for the conventional whole breast radiotherapy will vary from centre to centre but for each centre a written policy will be required and should follow acceptable protocols (e.g., 40Gy in 15 fractions or 50Gy in 25 fractions). Patients with previously irradiated adjacent fields for example, those with previous contra-lateral breast cancer, will need to have the radiotherapy fields modified according to local policies. EBRT tumour bed boost should only be delivered to those patients who are randomised to the EBRT boost arm and they should preferably receive this in the form of 16Gy in 8 fractions over 1.5 weeks with electrons of appropriate energy [2]. We believe that external beam radiotherapy planning should be image guided using tumour bed localisation clips as described in the IMPORT trials [21]. Although a centre would not be excluded from the study if this is not being practised (as stratification of randomisation will balance the two arms), we shall strongly recommend its use. VBH or a similar technique can be used to reduce exposure of internal organs to unnecessary radiation.

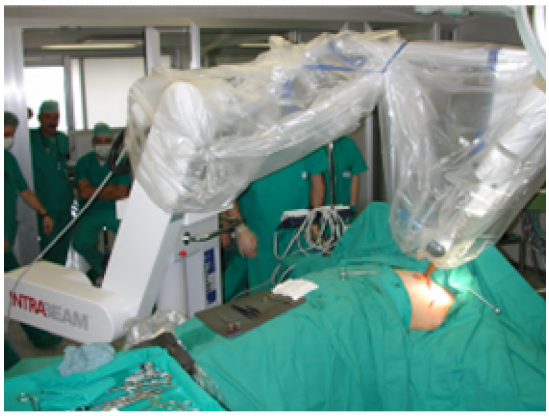
Adjuvant Systemic Therapy: Trial patients may be recommended appropriate adjuvant systemic therapy according to local practice or trial protocols. The sequencing of these other therapies is not governed by this protocol, but the policy for such treatment-sequencing should be declared in the Policy Statement (e.g. it should be declared whether the EBRT will be delivered before or after chemotherapy).

Patient Compliance: Compliance is likely to be high because the treatment is given during surgery. Some patients will refuse the allocated therapy between randomisation and surgery, but based on our experience with more than 3000 patients from the TARGIT A Trial we think the number will be minimal.

The Technology

The recent development of a new method has made possible the delivery of radiation directly to the tissues at the site of the primary tumour. The Intrabeam® (originally developed by the Photoelectron Corporation in Massachusetts, USA, but now manufactured by Carl Zeiss, Germany) is a simple but ingenious device, in essence a miniature electron beam-driven X-ray source which provides a point source of low energy X-rays (50kV maximum) at the tip of a 3.2mm diameter tube. The radiation source can be inserted into the area of interest immediately after excision of the tumour (Figure 1) and switched on for 20-35 minutes to provide intra-operative radiotherapy accurately targeted to the tissues that are at highest risk of local recurrence. The physics, dosimetry and early clinical applications of this soft x-ray device have been well studied and the probe has already been used for treatment of human malignant brain tumours. [8 9 22]





Figures 1 (a) and (b)

Figure 1 (a): The applicator being placed in the tumour bed, immediately after the excision of the tumour.
Figure 1 (b): The x-ray source is delivered to the tumour bed utilizing a surgical support stand. The sterile applicator is joined with a sterile drape that is used to cover the stand during treatment delivery.

It was developed for use for breast cancer and was first piloted at University College London [8 18 23]. The device has subsequently received FDA approval for use in any part of the body. For use in the breast, the radiation source is surrounded by a spherical applicator (see Figures 1 (a) and 2). The spherical applicator is specially designed to produce a uniform field of radiation at its surface, enabling delivery of an accurately calculated dose to a prescribed depth. It is inserted in the tumour bed and apposed to it with surgical sutures and/or other means. Since the radiation consists of soft X-rays, the beam rapidly attenuates reducing the dose to more distant tissue. Full measurements and calibration are carried out in a water phantom and/or in materials that simulate the radiation absorption properties of the breast. Depending upon the size of the surgical cavity, various sizes of applicator spheres are available. The radiation received is proportional to the time the machine is

switched on. The precise dose rate depends on the diameter of the applicator and the energy of the beam, both of which may be varied to optimise the radiation treatment. For example, a dose of about 20Gy can be delivered in about 20 minutes to the tumour bed apposing the applicator. Following the treatment delivery, the radiation is switched off, the applicator removed from the wound, and the wound closed in the normal way.

The x-ray source is small and lightweight (weight =1.8 Kg; dimensions: X-ray generator body 7 x 11 x 14 cm; applicator: 16 cm long conical applicator shank with a 2 to 5 cm sphere at the tip) and is mounted on the surgical stand and balanced for ease of delivery and support during treatment. With this elegant approach the pliable breast tissue around the cavity of surgical excision wraps around the radiotherapy source, i.e. the target is 'conformed' to the source. This simple, effective technique avoids the unnecessarily complex and sophisticated techniques of using interstitial implantation of radioactive wires to provide high dose radiotherapy to the tumour bed or the even more complex techniques necessary for conformal radiotherapy by external beams from a linear accelerator. The quick attenuation of the radiation dose allows the treatment to be carried out in the routine theatre. The walls usually incorporate shielding for microwave radiation from electronic equipment such as mobile phones and as such provide enough protection to the staff. Furthermore, the dose attenuates rapidly, so that the highest radiation dose is received by tissue nearest the primary tumour and a much lower dose at the skin. Thus in theory, the biological effect and cosmetic outcome could be improved.

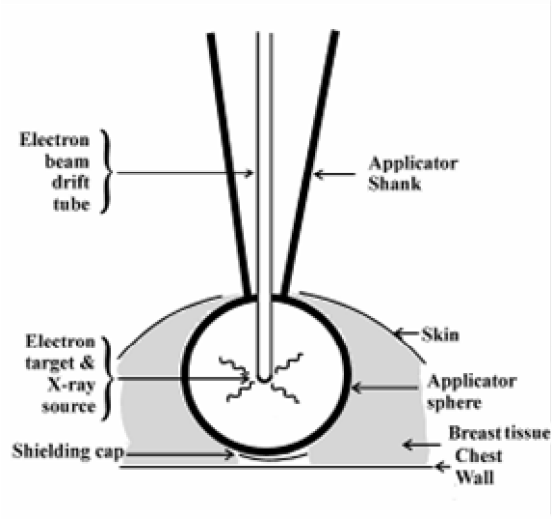


Figure 2: The Intrabeam System (PRS). The electrons are generated and accelerated in the main unit and travel via the electron beam drift tube which is surrounded by the conical applicator sheath such that its tip lies at the epicentre of the applicator sphere. Once the electrons hit the inner surface of the hemisphere at the tip, x-rays are generated. Thus a uniform radiation dose rate is available at the surface of the applicator sphere [8]. The details of operative technique are available at http://www.targit.org.uk.

12. Randomisation

Randomisation schedules will be prepared using a bespoke SAS program, blocked and stratified by centre and stratum, with equal allocation between treatment arms, by the Trials Operations Office. The schedules will be accessible by authorised staff only. Requests for randomisation can be made by either fax (receipt of a completed inclusion/exclusion criteria checklist) or telephone. A trained member of staff will confirm eligibility and perform the randomisation, according to the Standard Operating Procedure. The turnaround time for faxed randomisations is next working day, for telephone randomisations immediate provided the call is made between 09.00 and 17.30 UK time.

The randomisation codes will be included in the data sent to the Trial Statistician for analysis.

13. Blinding & other measures taken to avoid bias

13.1. Blinding

The randomised treatment allocation will not be blinded to physician or patient, but participating centres will only be unblinded to treatments given in their own site. Summary details of randomised allocation and outcomes will not be made available (unless specifically authorised by the TSC and/or DMC), in order to maintain the overall blind of the trial.

The statistical analysis of the primary and secondary endpoints will be performed on an intention-to-treat basis, which will provide an unbiased assessment of the efficacy of the intervention.

13.2. Other measures taken to minimise / avoid bias

The statistical analysis will include checks on potential bias in the extent of surgery, as surgeons will be aware of randomised treatment before beginning the operation. Specifically, the specimen weight and total specimen size will be compared between the treatment arms.

14. Data

14.1. Data to be collected

Data will be collected on case record forms (CRFs), including baseline, follow-up and safety data. All CRFs are mandatory, except those that are required on an "as and when" basis (for example, the local recurrence form).

Patient Follow-up and recording of events, notification of recurrence, adverse events and death

Patients should be followed according to local guidelines and these should be noted on the Policy Statement prior to entry into the trial. However, case report forms will be required for each patient at 6 monthly intervals for the first three years and annually thereafter until at least 10 years.

Wherever possible each patient should be seen within a six week window of the anniversary of the date of randomisation (e.g. at 12 months ± 6 weeks). At each visit the patient should be offered a physical examination and asked whether she has experienced any adverse events.

We recommend that mammography occurs annually. Any other examination is at the discretion of the local clinician.

Recording of recurrence/new malignancies

Recurrence includes any new occurrence of breast cancer apart from new disease in the opposite breast in the absence of previous recurrence (which is classified as a contralateral breast cancer). Local recurrence, for the purposes of this protocol, is defined as recurrence in the ipsilateral breast. Loco-regional recurrence is defined as recurrence either in the ipsilateral breast and/or in the axilla. Ipsilateral supraclavicular and intramammary node recurrence are not classified as local recurrence since the prognosis of patients with recurrence at these sites is more similar to distant than loco-regional disease.

Confirmation of ipsilateral recurrence must be by histology or unequivocal cytology. Clinical examination and imaging are not sufficient. Careful recording of the site of the recurrence is required to determine whether it is at the site of the original tumour and/or within the treatment field.

Recurrence at any other site must be confirmed by appropriate imaging and/or biopsy. Details of both first ipsilateral local, loco-regional (breast and axilla) and first distant recurrence are required as well as the status of the patient with regard to active disease when treatment for local disease has been completed.

Development of new malignancy (including the contralateral breast) must be reported on the case report forms once a diagnosis has been confirmed. Cause of death must be recorded accurately.

Guidelines for the Management of Recurrence

The management of recurrent disease will be left to the discretion of the participating institution/investigator. If appropriate, patients having had TARGIT alone are able to have conventional irradiation as part of the management of a recurrence. It may also be possible for patients who have received external beam treatment to have TARGIT after surgical excision of the recurrence, particularly if they wish to avoid mastectomy.

14.2. Adverse Events

This section describes the minimum reporting procedures for the trial, based on current UK and European Union legislation. Local and national policies may require additional reporting of safety data, including adverse events.

The Trial Steering Committee and the DMC will review data on adverse events and complications. If a local or national policy requires a summary of this review (e.g. for an annual report), please contact the TARGIT Trial Operations Office.

Acute and late radiation morbidity must be graded according to established criteria such as LENT-SOMA and RTOG; the criterion 'pain due to radiation' will be graded according to the Common Toxicity Criteria [24]. These are the only expected adverse events and would cover most events, any other adverse events must be recorded on the 'Adverse Event' log (TB29.0). Adverse events may be recorded at any time following the surgery and a new form should be completed for each episode. Any complications following surgery (± TARGIT) must also be reported on the complication forms.

Serious Adverse Events

Serious adverse events (SAEs) are defined as any event that is fatal; life threatening; causes or prolongs hospitalisation; causes disability or incapacity or requires medical intervention to prevent permanent impairment or damage, any grade 4 toxicity.

Reporting Requirements

Immediate reporting of any SAEs must be made directly to the TARGIT Trial Operations Office as soon as possible and at least within 5 working days of the investigator becoming aware of the occurrence of the event. The TARGIT Trials Office will email all SAE forms to research-

incidents@ucl.ac.uk. SAEs must be reported whether or not considered related to the treatment under investigation. An early report can be followed up by a more detailed report.

SAEs directly caused by chemotherapy (e.g. febrile neutropenia) do not need to be reported to the trial centre.

All serious adverse events that occur during the period of observation (see next section) must be documented on the 'Serious Adverse Event Form'. It is also the investigators' responsibility to report them to the local institutional ethics committee as required by local regulations.

- For all serious adverse events, the following must be assessed and recorded on the SAE reporting form: intensity/severity; relationship to treatment; action taken; outcome to date.
- Adverse events must also be recorded in the subject's medical records.

The clinical course of the serious adverse event should be managed according to accepted standards of medical practice until a satisfactory explanation is found or the investigator considers it medically justified to terminate follow-up of this event. Should the adverse event result in death, a full pathologist's report should be supplied, if possible.

Period of Observation

For the purpose of this trial the period of serious adverse event (SAE) observation extends from the time of registration onto the trial until 90 days after the completion of randomised treatment. Trial follow-up should continue according to schedule once the SAE is resolved.

SSARs (Suspected Serious Adverse Reactions)

Suspected Serious Adverse Reactions are adverse reactions (or events) that are thought to be related to the research procedure. For the purpose of this trial the following is a list of potential SSARs:

Fibrosis
Delayed wound healing
Wound infection
Wound breakdown
Haematoma in breast or axilla
Seroma
Dermatitis associated with radiation
Telangiectasia
Pain in irradiated field
Oedema

SSARs should be reported as described in 14.2

SUSARs (Suspected Unexpected Serious Adverse Reactions)

Suspected Unexpected Serious Adverse Reactions are adverse reactions (or events) that are thought to be related to the research procedure but do not appear on the list of SSARs. SUSARs should be reported within 24 hours as described in 14.2.

Deaths

All deaths, with date and cause, must be reported as soon as possible to the TARGIT Trial Operations Office on the appropriate CRF. Deaths which also meet the SAE criteria should additionally be reported as described in 14.2.

14.3. Data handling and record keeping

The dataset will be used for the sole purpose of the TARGIT-B trial.

Only authorised individuals will have access to person identifiable data. The TARGIT Operations Group makes a commitment to maintaining the confidentiality, safety, security and integrity of all confidential and sensitive data, which is held under its guardianship.

Staff in the TARGIT Operations Group are obliged to fully comply with The Data Protection Act 1998, together with all relevant rules of the sponsor organisation (UCL, London).

Where patients are willing, at randomisation they can provide mobile phone numbers and email addresses for long term follow up. All such electronic identifiable data is kept in a dedicated database in a secure data vault, separate from anonymised data. The study database is held on a dedicated database server. The Surgical & Interventional Trials Unit network, a subnet of the UCL network, is protected by a firewall and is behind UCL's institutional firewall. Both firewalls are managed by UCL's network group. Access to server and the Surgical & Interventional Trials Unit network is password & access right controlled. Access to identifiable data is controlled by staff roles and passwords.

Data transfer and storage

The data will be sent to the TARGIT Operations Group via one of three routes: (1) a secure online file transfer system, (2) to a fax machine located in a locked room within a locked building, (3) through the post. Note that the TARGIT Operations Group can only accept responsibility for the data after it has arrived in their custody.

The data will be retained by the TARGIT Operations Group until 20 years after the final publication from the trial.

Specific details regarding data storage and destruction are covered in a separate document available from the TARGIT Operations Group on request.

15. Statistical considerations

The Trial Statistician has primary responsibility for the statistical aspects of the trial.

15.1. Sample size calculation

In the Oxford overview of December 2005 [25] of 10 BCS trials that started in 1995, patients who were node positive had a local recurrence rate of 11%. In the more recent EORTC trial, the boost arm [2 26-28] had a local recurrence rate for patients <41 at 5 yrs of 9.5% and at 10 years of 13.5% and for patients 41-50, 8.7% at 10 years. Although the overall 10-year local recurrence rate was 6.2%, the recurrences were "concentrated" in the younger patients. Furthermore, the trial population was at low risk of recurrence- most tumours were <2cm and 91.9% were node negative. On the other hand, the TARGIT-B trial will focus on patients aged 45 or less, or with adverse features. Considering that local recurrence rates are reducing substantially with modern systemic therapy, we have estimated that the local recurrence rate in the conventional arm will be 5.64%.

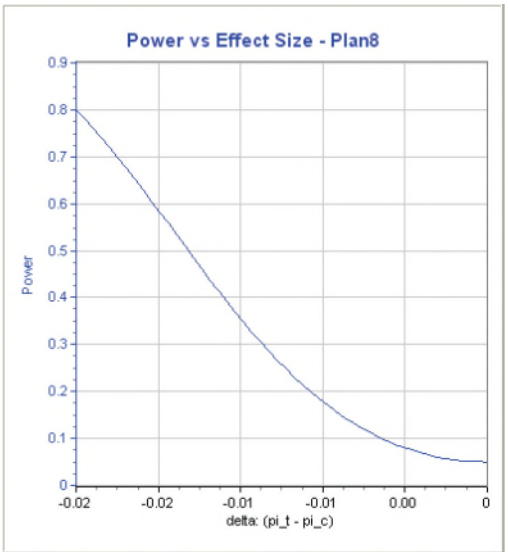
In the long term results of our pilot series of 299 patients which received the proposed experimental treatment had even higher risk tumours (29% node positive vs. 20% node positive in the overview), but had the actuarial 5 year local recurrence rate of 1.73%[11 12],which was about half of the expected recurrence rate in this unselected group of patients. In women <50, this study had a local recurrence of 2.1% (SE 1.5). Thus we shall take the conservative estimate of 2.9% (2.1+0.5xSE=2.9%) as the expected recurrence in the experimental arm.

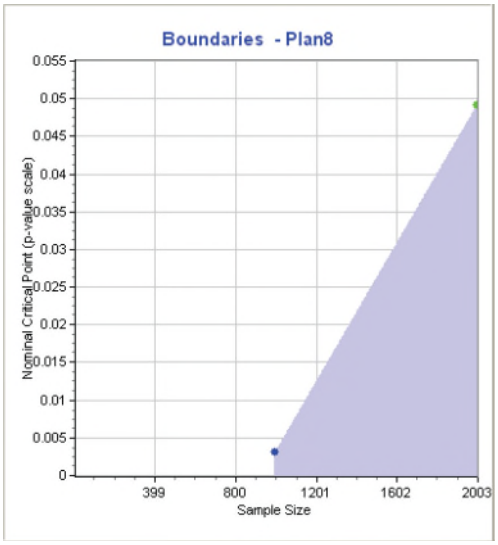
Therefore, the study will be powered to detect a difference between 5.64% and 2.9% (OR=0.5, exponential hazard rate of 0.80) and will need 1707 patients. (Two sided RCT with alpha=0.05 and power=80%. Assuming an attrition of 5%, we shall aim towards an accrual goal of 1796 patients, i.e., a sample size of 898 in each group.

The study is powered for a 5 year- recurrence rate. The hazard of local recurrence peaks between 2-3 years hence we have chosen the 3-year time point for the interim analysis. An interim analysis will be performed at a median follow up of 3 years, or after 41 events, whichever is earlier. At this point may revise the sample size by considering both efficacy and futility analysis. The DMC will of course regularly review the data for both safety and efficacy as per MRC guidelines.

Using Lan-DeMets Alpha spending function with O'Brien-Fleming Boundary to reject null hypothesis.

Cumulative Patient Accrual	Alpha Spent
~1000 (41 events)	0.003
1796	0.035





15.2. Statistical analysis

Planned Statistical Analysis: The primary endpoint is the incidence of local recurrence. All comparison will be done on an "intent to treat" basis where all randomised patients will be included in the statistical analysis. Between-treatment group comparisons of proportion of local recurrence will be compared using simple Chi-squared test. Kaplan-Meier curves and log-rank test will be used to compare the time to local recurrence in the two treatment arms. Proportional Hazard regression models will control for possible confounding variables when comparing local recurrence in the treatment groups. We will report 95% confidence intervals for all reported proportions and hazard ratios.

Interim Analysis: Interim analyses will be carried out when 41 events occur or at a median follow up of 3 years, whichever is earlier. We have chosen 3 years because it will include the peak of hazard of local recurrence. This analysis will include the assessment for the need to change the sample size, as well as futility analysis about the continuation of the trial.

In addition, analysis of data will be carried out regularly by the DMC as per MRC guidelines.

Handling of loss to follow up or missing data: In order to carry out an Intent To Treat (ITT) analysis and avoid potential bias resulting from missing data, multiple imputation methods will be used after the missingness mechanisms are established. A full report of the patterns of missing data will be reported based on the recent CONSORT guidelines[29]. Sensitivity analysis will be carried out and reported.

Planned subgroup analyses: This will include immediate vs. delayed boost (as a second procedure), pre- vs post- menopausal chemotherapy vs. no chemotherapy, neo-adjuvant vs. other, ER, PgR, HER2 status, Oncotype DX score. Further factors will be decided before unblinding of the data.

16. Compliance and withdrawal

16.1. Subject compliance

Compliance to randomised treatment will be assessed by monitoring the completion of appropriate forms, e.g. the intra-operative radiotherapy form and the external beam radiotherapy form.

16.2. Withdrawal / dropout of subjects

The statistical analysis of the primary and secondary endpoints will be performed on an intention-to-treat basis, which will provide an unbiased assessment of the efficacy of the intervention.

Withdrawal of Consent

Patients may "opt out" of the trial at any time. Rarely, patients may also wish to withdraw consent for further data collection. Such cases should be reported to the TARGIT Trial Operations Office so that no further data are entered onto the database, as specified in the patient information leaflet and appropriate Standard Operating procedure. Data captured before consent was withdrawn will be used in the study, but no further data, beyond this date will be collected or used in any analysis.

The TSC and in particular the DMC will monitor compliance and withdrawal data to determine the effect on the power of the study.

17. Interim analysis and data monitoring

17.1. Stopping / discontinuation rules and breaking of randomisation code

There are no formal stopping rules in this trial. The TSC (with or without the recommendation of the DMC) may decide to stop the trial prematurely, particularly if there are unforseen safety issues.

17.2. Monitoring, quality control and assurance

Essential data will be verified using manual and electronic validation checks. The validation is carried out at and/or after completion of data entry of each case record form (CRF). Any missing or ambiguous data will be queried with site staff.

Quality Assurance

Quality assurance (QA) in radiotherapy is defined as "[the set of] procedures that ensures consistency of the medical prescription and the safe fulfilment of that prescription as regards dose to the target volume, together with minimal dose to normal tissue, minimal exposure to personnel, and adequate patient monitoring aimed at determining the end result of treatment" [30]. In the UK the Department of Health issues a mandatory standard. It is based on a formal quality management system issued by the International Standards Organisation [31]. This is a multidisciplinary responsibility to ensure consistency in absolute dosimetry, dose delivery, volume definition and reproducibility are paramount in radiotherapy QA and have become even more important with the advent of conformal therapy. Formal procedures should ensure that every "non-conformity" (i.e., a failure of any element of the system or its procedures) is identified and controlled, and that corrective action is taken to deal with the underlying causes. The quality system itself must be formally audited at regular intervals to ascertain whether it is working as intended. We expect that all investigators joining the TARGIT trial will be working to local or national standards which conform to the international guidelines. The Trial Steering Committee therefore is content that no additional quality assurance exercise is necessary for conventional external beam radiotherapy provided that the investigators at each site are subject to local/national guidelines similar to those quoted above. If no such scheme operates at an investigator site the principle investigator must inform the TARGIT Operations Office who will inform the Trial Steering Committee to determine an appropriate course of action.

Quality assurance for the Intrabeam

All the evidence to date supports the description of the Intrabeam as delivering an accurate and reliable dose. The local physics departments are responsible for verifying the miniature X-ray source is operational prior to use, and setting up the parameters within the control console software for

treatment delivery. During the procedure, the control console monitors the system for safe and accurate dose delivery.

The Intrabeam System includes a full set of quality assurance tools. These, combined with the operator interface of the control console allow complete verification of all of the performance functions in minutes and constant monitoring of critical treatment parameters throughout the treatment period. The sites are responsible for QA according to the manufacturer's instructions and these data should be made available to the trial centre. Recalibration of the output of the X-Ray Source must be performed at least annually and a report this needs to be sent to the trial centre. Carl Zeiss offers contracts for annual manufacturer service. We strongly recommend all centres to use this service.

Parameters to be collected for QA Audit

For each trial treatment delivered the following will be collected: Applicator diameter, prescribed dose (should usually be the same in each case) and treatment time.

17.3. Assessment of safety

Data on safety will be gathered by the following methods:

- From serious adverse event forms.
- From the protocol violation/deviation form.
- From the complication forms.
- From data missing or contained within other CRFs.

Procedures for dealing with the above are contained in relevant Standard Operating Procedures.

18. Ethical considerations

Risks and benefits

The mature pilot study has confirmed that it is safe and feasible to give intraoperative radiotherapy with the TARGIT technique [32 33]. There is no significant acute toxicity as long as attention is paid to the meticulous surgical approach. For example, the skin needs to be at least one cm away from the applicator and protected from the radiation so that there is no delay in wound healing. We have also demonstrated that this technique can be adopted in over 30 worldwide centres safely. We have a robust training and auditing programme that each centre needs to pass before they start recruiting patients in the trial.

The risk of long term toxicity will be assessed carefully. This is mainly in the form of normal tissue reactions such as fibrosis in the tissue receiving the higher dose of radiotherapy. Our clinical experience suggests that this risk is low, and does not appear to be more than conventional treatment. This is not surprising as the volume of tissue receiving the high dose with the TARGIT technique is small, compared to other methods of radiotherapy. Long term results of the phase 2 study (maximum follow up 121 months) [32 33] have also borne out the safety of the technique. A German cohort of patients has also confirmed the long-term safety of the technique [34].

Informing potential trial participants of possible benefits and known risks

Suitable patients will be identified at multi-disciplinary team meetings and approached by a member of the clinical team (usually the breast surgeon). Patients will be informed of the trial and given an information leaflet to take home and discuss with members of their family. Randomisation would take place only after written informed consent has been obtained.

UK ethics approval for this study has already been granted (Main REC 06/S1401/108 Oct 2006).

The Intrabeam device has FDA approval and a CE mark, and in this study, is being used for the purposes for which the approval was given.

The main ethical issue is the necessity of an additional procedure that would be required in those patients who are found to be suitable for the trial after their primary operation has already been performed, and who would otherwise not need a second operation. These patients would be at much higher risk of local recurrence even after routine radiotherapy (about 15-20%) and thus could potentially derive significant benefit from TARGIT-boost. The consenting physician/surgeon will carry out careful discussions about the risk of a second operation (which may not be significant in these patients who would usually be young and fit) vs. the possibility of a superior result and decision

to enrol will be taken on an individual patient basis. We expect that these will constitute about 90 to 120 cases out of the total accrual of 1796.

Research Governance

The sponsor for this clinical trial is UCL. The overall research governance of the trial is determined largely by the sponsor, including Standard Operating Procedures and Data Protection.

Each centre takes responsibility for the collection and management of its own data. Randomisation is performed centrally though the TARGIT Trial Operations Office based in London which is also responsible for the administration of the trial database. Access to the entire dataset is restricted to designated trials staff and the Trial Statistician. Regular electronic reports will be produced and passed to each centre for audit and checking purposes. This not only allows each centre to have full responsibility for its own data, but also ensures there is adequate backup and central auditing of the data. Standard operating procedures are in place for any data management or clinical queries.

The project is managed by a 4-tiered approach: quarterly meetings of the Trial Steering Committee; biannual meetings of the Data Monitoring Committee; monthly meetings of the Trial Operations Group; and weekly meetings of operational staff in the Trial Operations Office. The Trial Operations Group is responsible for the project management and consists of seven members who are all co-applicants of this grant. The Trial Steering Committee's role will be overarching as they are the custodian of the data. The Trial Operations Office is based at UCL and the finances are managed by the University finance office, which ensures propriety.

Data Monitoring Committee (DMC)

An independent DMC has been appointed and their remit agreed. They will regularly review the data collected during the trial and report to the TSC as to whether the trial should continue and make recommendations as to changes in the protocol.

Meetings will probably be scheduled annually for the first two years of the trial whilst accrual gains momentum. More frequent meetings may then be held.

19. Financing and Insurance

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

20. Reporting and dissemination

A publication policy will be written and agreed by the Trial Steering Committee. Presentations and publications arising directly from the pre-planned analyses will be the responsibility of the Trial Steering Committee.

Other members of the medical and scientific community will be encouraged to submit requests for new analysis of the data set. However, the raw data will remain in the custodianship of the Trials Operations Group, apart from the transfer of anonymised data to the Trial Statistician for pre-determined analyses.

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