Extended follow up of the TARGIT-A trial

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236431

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PROTOCOL VERSIONS

Version Stage	Versions No	Version Date	Protocol updated & finalised by;	Appendix No detail the reason(s) for the protocol update
Current	1.0	10/11/2017	Haroon Miah Trial Coordinator	

DECLARATIONS

The undersigned confirm that the following protocol has been agreed and accepted and that the investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the Research Governance Framework 2005 (as amended thereafter), the Trust Data & Information policy, Sponsor and other relevant SOPs and applicable Trust policies and legal frameworks.

I (investigator) agree to ensure that the confidential information contained in this document will not be used for any other purposes other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I (investigator) also confirm that an honest accurate and transparent account of the study will be given; and that any deviations from the study as planned in this protocol will be explained and reported accordingly.

Chief Investigator:

Signature:..... **Date** 19/12/2017

Print Name(in full): Prof JAYANT S VAIDYA

Position: Professor of Surgery and Oncology

On behalf of the Study Sponsor:

Signature:..... **Date** 19/12/2017

Print Name(in full): Tabitha Kawo

Position: Research Governance manager

STUDY SUMMARY

Identifiers	
IRAS Number	236431
R&D / Sponsor Reference Number(s):	17/0774
Other research reference number(s) (if applicable)	
Full (Scientific) title	Extended follow up of the TARGIT-A trial
Health condition	Early breast cancer
Study Type	Observational cohort study
Target sample size	714
STUDY TIMELINES	
Study Duration/length	Five years
Expected Start Date	01 January 2018
End of Study definition and anticipated date	Follow-up information on all patients to at least 10 years.
FUNDING & Other	
Funding	NIHR HTA
Other support	None
STORAGE of SAMPLES	No samples will be collected.
KEY STUDY CONTACTS	
Chief Investigator	Professor Jayant S Vaidya MBBS MS DNB FRCS PhD Professor of Surgery and Oncology, Division of Surgery and Interventional Science, University College London

KEY ROLES AND RESPONSIBILITIES

SPONSOR: The sponsor is responsible for ensuring before a study begins that arrangements are in place for the research team to access resources and support to deliver the research as proposed and allocate responsibilities for the management, monitoring and reporting of the research. The Sponsor also has to be satisfied there is agreement on appropriate arrangements to record, report and review significant developments as the research proceeds, and approve any modifications to the design.

FUNDER: The funder is the entity that will provide the funds (financial support) for the conduction of the study. Funders are expected to provide assistance to any enquiry, audit or investigation related to the funded work.

CHIEF INVESTIGATOR (CI): The person who takes overall responsibility for the design, conduct and reporting of a study. If the study involves researchers at more than once site, the CI takes on the primary responsibility whether or not he/she is an investigator at any particular site.

The CI role is to complete and to ensure that all relevant regulatory approvals are in place before the study begins. Ensure arrangements are in place for good study conduct, robust monitoring and reporting, including prompt reporting of incidents, this includes putting in place adequate training for study staff to conduct the study as per the protocol and relevant standards.

The Chief Investigator is responsible for submission of annual reports as required. The Chief Investigator will notify the RE of the end of the study, including the reasons for the premature termination. Within one year after the end of study, the Chief Investigator will submit a final report with the results, including any publications/abstracts to the REC.

PRINCIPAL INVESTIGATOR (PI): Individually or as leader of the researchers at a site; ensuring that the study is conducted as per the approved study protocol, and report/notify the relevant parties – this includes the CI of any breaches or incidents related to the study.

KEY WORDS

TARGIT IORT, TARgeted Intraoperative radiotherapy, breast conserving therapy, lumpectomy, wide local excision, randomised clinical trial, follow up.

LIST OF ABBREVIATIONS

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

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1 INTRODUCTION

Breast cancer remains the commonest female malignancy and its incidence continues to rise. The common conventional treatment of early breast cancer involves surgical excision of the tumour, surgery to the axillary lymph nodes. This breast conserving surgery needs to be followed by external beam radiotherapy given over several weeks of daily treatments, given with the intention of reducing the rate of further cancer developing within the operated breast. Whilst this is an effective treatment with a low rate of local recurrence of cancer, our own laboratory work and its clinical correlation has suggested that radiation to the whole breast may not be necessary in all cases and radiotherapy to the tissue only around the tumour within a risk-adapted approach may be as effective.

The TARGIT-A randomised clinical trial, compared a risk-adapted approach with use of single dose targeted intra-operative radiotherapy (TARGIT IORT) vs. conventional external beam radiotherapy (EBRT) given as a daily course over 3 to 6 weeks.

The initial and 5 year results have been published[5,6] and found that TARGIT-IORT is non-inferior to EBRT.

For the patients, the biggest benefit of having TARGIT-IORT during their lumpectomy procedure, under the same anaesthetic, is that they complete their local treatment in one session and with lower toxicity.

For any healthcare system including the NHS, TARGIT-IORT has been shown to be cost effective and incurs a lower overall cost to the NHS. It also reduces the journey times for patients who would otherwise need to travel, on average, 730 miles for their EBRT treatment.

The recruitment in the trial was completed in June 2012. This extended follow up study enables collection of longer term outcomes by direct patient contact and by data from national records such as the Office for National Statistics (ONS).

2 BACKGROUND AND RATIONALE

The TARGIT-A randomised clinical trial, compared a risk-adapted approach with use of single dose intra-operative radiotherapy vs. conventional radiotherapy. The biological and clinico-pathological arguments[1, 2] for avoiding unnecessary treatment to the whole breast are as follows: In large studies of breast conserving therapy more than 90% of early breast recurrences have been found to occur at the site of the original primary tumour site. This is true whether or not radiotherapy is given and whether or not the margins are involved. Furthermore, when detailed examination of mastectomy specimens are performed using radiological-histological correlational methods, small additional invasive or in-situ cancer foci are found in over 60% of patients, with 80% of these situated remote from the index quadrant. The relative distribution of primary tumour and these occult foci in the four breast quadrants is significantly different. Thus, these occult cancer foci probably remain dormant and do not in general give rise to local recurrence, which more probably develops in the tissues that surround the primary tumour- and it is solely this area that may need radiation.

In the TARGIT-A trial, the experimental arm used the targeted intraoperative radiotherapy (TARGIT) technique using the Intrabeam device to give radiotherapy to the tissues around the tumour, during the lumpectomy procedure. The control arm received whole breast external beam radiotherapy given according to local policy, usually 40 to 50 Gy in 15 to 25 fractions, with a boost to the tumour bed. The technique of giving targeted intraoperative radiotherapy (TARGIT) using INTRABEAM™ (now manufactured by Carl Zeiss Surgical, Oberkochen, Germany) was developed in University College London in collaboration with the specialised manufacturers. It allows the patient to receive a single fraction of radiotherapy as soon as the primary tumour is excised, during the same anaesthetic[1-4]. Advantages of this approach include: delivering

the radiation immediately, ensuring the radiation is delivered to the tumour bed under direct vision, thus avoiding a "geographical miss"; and decreased costs to the healthcare providers and patients.

INTRABEAM™ uses a mobile, miniature x-ray generator powered by a 12-volt supply. Accelerated electrons strike a gold target at the tip of a 10 cm long drift tube with a diameter of 3 mm, resulting in the emission of low-energy x-rays (50 kV) in an isotropic dose distribution around the tip. The irradiated tissue is kept at a fixed, known distance from the source by spherical applicators to ensure a more uniform dose distribution. The tip of the electron drift tube sits precisely at the epicentre of a spherical plastic applicator, the size of which is chosen to fit the cavity after the tumour is excised. Using this method, the walls of the tumour cavity are irradiated to a biologically effective dose (20 Gy to the tissue in contact with the applicator) that rapidly attenuates over a distance of a few centimetres. As a result, vital organs (such as the heart and the lungs) are spared. Since these are soft x-rays, the biologically effective dose attenuates rapidly so that the highest radiation dose is received by tissue nearest the primary tumour, and a much lower dose by the skin and other normal tissues. It also means that there is no need for a specialised operation theatre and TARGIT can be given in a standard unmodified operating theatre with no need for lead shielding other than a mobile shield to protect the equipment operators.

The published results[5,6] of the TARGIT-A trial show that compared with conventional external beam radiotherapy given over several weeks, TARGIT given at the time of lumpectomy within a risk-adapted approach achieves much the same results in terms of breast cancer control (locally and systemically). Interestingly, TARGIT was found to have a significantly lower mortality from causes other than breast cancer due to fewer deaths from cardiovascular causes and other cancers.

Although the current results are convincing enough for the treatment to be adopted worldwide (over 20,000 women have now had this treatment in about 300 centres in 35 countries), it is essential that all the 3451 patients are followed up over a longer period of time and data analysed as per the original protocol.

This extended follow up study will enable timely recording of additional local recurrences and deaths. With a higher number of events, it would be possible to perform meaningful subgroup analysis using predictive factors such as hormone receptors (available data suggests that these have a predictive value), tumour grade and lymph node involvement that would allow fine tuning of patient selection criteria. Furthermore the effect on non-breast-cancer and overall mortality will also be ascertained.

We expect these new data will significantly influence wider and enthusiastic adoption of this approach that will be greatly welcomed by patients. As a large proportion of such patients are screen-detected, their overtreatment would be avoided by such adoption.

3 OBJECTIVES

The objective of this protocol is to obtain follow-up information including details of diagnosis and treatment of any disease relapse, other cancer incidence, or death (including the cause of death) in all enrolled patients as per the TARGIT A Trial protocol.

4 STUDY DESIGN

This protocol gives the details of the additional approaches to the follow up of patients randomised in the TARGIT-A Trial. The design of the TARGIT-A trial is given in the appendix.

5 STUDY SCHEDULE

The study has been divided into two Work Packages.

Work Package 1: Continue to gather efficacy, safety and follow-up data to year 10, all centres, using the current methods as per protocol.

Aim and rationale

The latest analysis of the TARGIT-A trial, includes a very large number of patients (1222) with a median follow up of 5-years and our analysis suggests that the results remain the stable for cohorts of patients with increasing periods of follow up. However, for the whole trial, the median follow up is 2.6 years, and one the barriers to widespread adoption of the new treatment could be the perception that we should have a 5-year follow up of all the patients in the trial – this will mean that a substantial number will also have a 10 year follow-up, a milestone that is now considered essential in many trials. Importantly, follow up to 10 years was stipulated in the original protocol. The work package WP1 will deliver this.

Primary & secondary objectives

To evaluate in the longer term, primary outcome i.e., local recurrence in the conserved breast and secondary outcomes of the main trial, including complications/side effects, breast cancer and non-breast-cancer survival.

Brief description of methods and statistical analysis

All patients recruited in the trial (n=3451) from 33 centres in 11 countries will be followed up as defined in the original protocol (6 monthly for 5 years and annually thereafter until 10 years). The analysis of the updated database will be directed by a statistical analysis plan (SAP) appended to this application. The higher number of events with longer follow up will also give more robustness to the planned subgroup analysis (e.g., effect of hormone receptor status) to inform further individualization of the treatment. Analysis will be performed as per the submitted Statistical Analysis Plan that has been signed off by the Chair of the DMC (Professor Martin Bland). As usual, any modifications of the SAP, based on new information such as data from other trials and biological insights, will be finalized and signed off BEFORE unblinding of the database. The current plan is to analyse as per the two pre-pathology and post-pathology strata as well as subgroup analysis as per hormone receptor status and hormone therapy. Multivariate analysis will also be performed for assessing the predictive value of other tumour and patient factors such as age, tumour size, grade, lymph node status, margins, lymphovascular invasion, time since randomization, etc.

Detailed Methods of Data Collection

With many trusts in the UK stopping clinical follow up after 5 years, it will be more effective to use different follow approaches for obtaining follow up information. All follow-up data will be chased via site (hospital) and directly from the patient every 6 months for the first five years, and then annually thereafter. After ten years all follow up will be directly through patient contact. A case report form (CRF) has been specifically designed for direct-to-patient contact. As in the previous analysis, an independent reviewer (Mr Steve Ebbs) will specifically deal with assessment of cause of death supported by a cause-of-death committee. Case record forms, death certificates and case notes will be used to ascertain the cause of death, blinded to the randomisation arm. Special attention will be paid to cardiovascular and other-cancer mortality. CRFs will be sent out at scheduled timepoints. Should a CRF fail to arrive at SITU after 6 weeks, a reminder will be sent out. For the 6 monthly CRFs, only one reminder will be sent, for annual CRF, two reminders will be sent 6 weeks apart. As per protocol, follow-up (clinical examination and mammogram) will continue annually at least until the 10th year after randomization. Annual mammograms are normally performed as part of usual care for 10 years following breast cancer surgery. All follow-up data will be collected via site (hospital) and directly from the patient every 6 months for the first five years, and then annually thereafter. In addition to contacting sites, this extension will enable us to (i) contact patients directly (following appropriate permissions being obtained), and (ii) obtain information on new primary cancers and death from the ONS. Should either of these methods reveal anything other than "healthy" follow-up, site staff will be contacted directly to obtain further information.

Work Package 2: Collect death & new primary cancer data from UK patients through ONS.

Collection of death & new primary cancer data from UK patients through ONS will help improve the completeness of the data, and will support WP1.

Detailed Methods of Data Collection
All UK patients will be registered with the Office for National Statistics (ONS), for cohort event notifications. These reports will be sent quarterly and will show Exits from the NHS, Embarkations, Re-entries into the NHS, Deaths and new primary cancer registrations. Cause of death reports will be requested for each patient.

Statistical considerations
The original sample size of 2232 was powered at 80% to prove non inferiority with a 2.5% absolute difference (the non-inferiority margin) in local recurrence. A two-year extension to accrual means that the follow-up of 3451 patients for 5 years has increased the power to 92.6% (based on the same original assumptions). In addition, we have found a borderline-significant overall survival advantage with TARGIT with a hazard ratio of 1.43 (p=0.099). We would need 243 events to have statistical power to demonstrate superiority in overall survival with 95% confidence. We expect to record this number in the proposed follow up period.

Study Activities

See Figure for an illustration of the patient progress though the study.

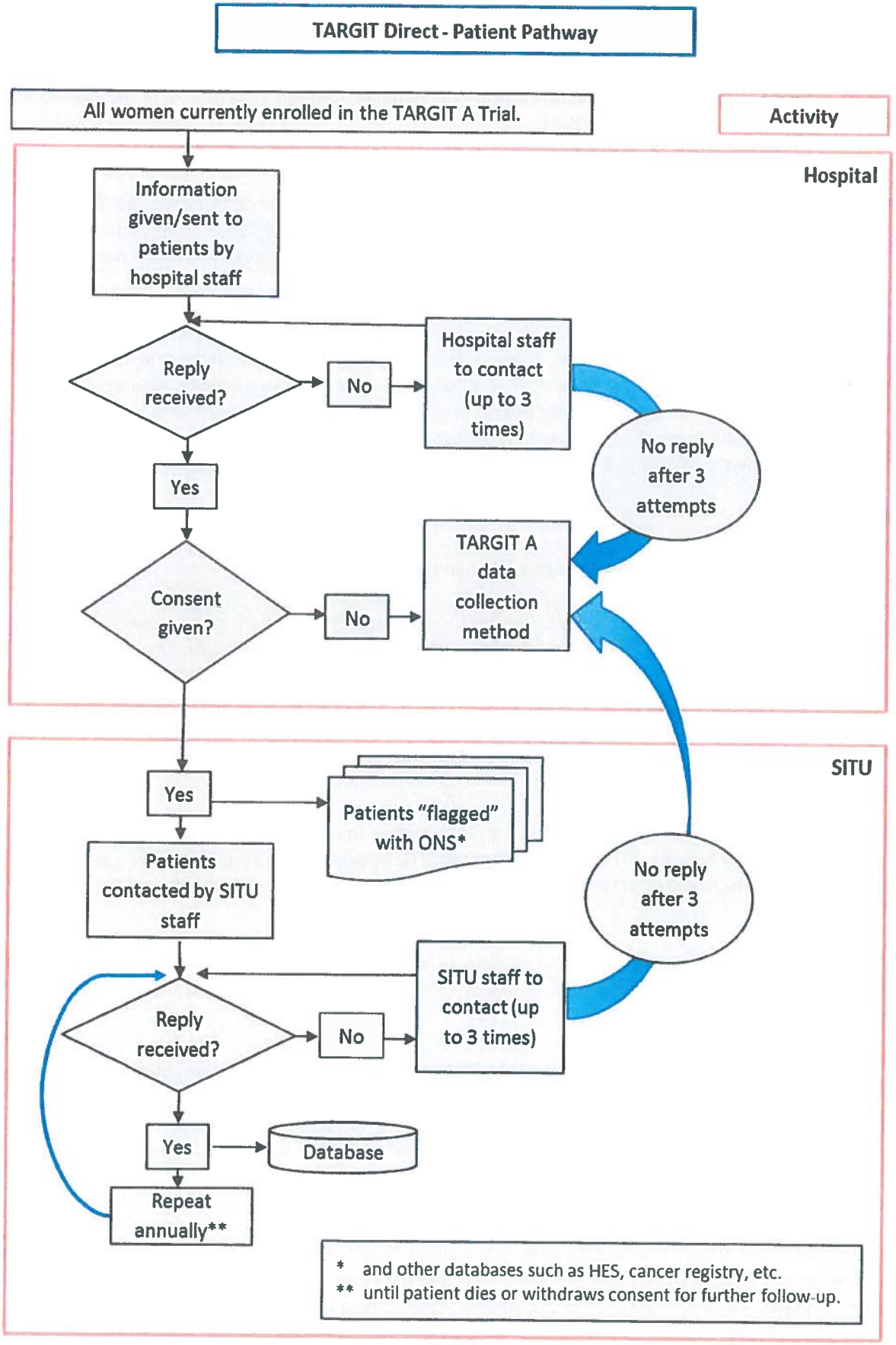
The clinical trials unit (SITU) will send to each Principal Investigator (PI) a list of patients who meet the eligibility criteria as per information held on the database (alive, not withdrawn consent). The PI will review the list to ensure the information is up-to-date. The PI will make the initial approach to the patient. He/she will send the approved letter (on local letterhead) to each patient, together with the participant information leaflet, consent form, contact details form, and follow-up (questionnaire) form. If the patient has any questions, she can telephone the office of the PI (contact details will be provided), or have a face-to-face discussion at her next clinic visit.

If the patient consents to take part in the study, she must complete the consent form, contact details form, and follow-up (questionnaire) form. These should be sent to SITU by post in the pre-paid envelope provided. One copy of the consent form will be returned to the patient, one copy will be sent to the PI, and the original will remain in SITU.

If the patient explicitly states that she refuses to participate, no further contact will be made. If the patient does not reply, the PI will be asked to send a reminder to the patient. If no contact is made after three attempts, no further contact will be made.

Patients who have consented to be in the study will be "flagged" with administrative databases such as ONS and the Cancer Registry. In addition, the patient will be contacted annually directly by SITU and asked to update the contact details form (if necessary), and complete a follow-up (questionnaire) form, and return by post in the pre-paid envelope provided. Patients will be followed up until death or withdrawal of consent. Patients can refuse consent at any time by contacting either SITU or the PI, in which case no further contact will be made.

Data will be added to two databases. One database will contain identifiable data (patient name and contact details), the other will contain pseudonymised (de-identified) data and will eventually be sent to the Trial Statistician for analysis. The information on the databases will be linked by a unique, anonymous identifier.


TARGIT Direct - Patient Pathway
All women currently enrolled in the TARGIT A Trial.
Activity
Hospital
Information given/sent to patients by hospital staff
Reply received?
No
Hospital staff to contact (up to 3 times)
No reply after 3 attempts
Yes
Consent given?
No
TARGIT A data collection method
SITU
Yes
Patients "flagged" with ONS*
Patients contacted by SITU staff
No reply after 3 attempts
SITU staff to contact (up to 3 times)
Reply received?
No
Yes
Database
Repeat annually**
* and other databases such as HES, cancer registry, etc.
** until patient dies or withdraws consent for further follow-up.

6 CONSENT

Eligible patients have already given consent for participation in the TARGIT-A trial. We shall seek consent from each patient for direct patient contact, and collection of information from national records such as the Office for National Statistics (ONS).

7 ELIGIBILITY CRITERIA

7.1 Inclusion Criteria

All patients who participated in the TARGIT-A trial.

7.2 Exclusion Criteria

Any patient who has withdrawn consent for further follow-up, or died.

8 RECRUITMENT

All eligible patients who participated in the TARGIT-A trial (from March 2000 to June 2012) will be included. Patients will be identified from the TARGIT-A database, and lists of eligible patients will be sent to Principal Investigators at each site. Each patient will be given an information sheet and consent form, either when they attend clinic, or by post. Completed consent forms will be returned to the Trials Office, who will then contact patients directly for subsequent follow-up.

9 STATISTICAL METHODS

This protocol only relates to continuing collection of follow up information from patients already in the TARGIT-A trial. Formal statistical analysis will be performed as per the original TARGIT-A trial. In brief, analysis will be performed as per the submitted Statistical Analysis Plan (SAP) that has been signed off by the Chair of the DMC (Professor Martin Bland). As usual, any modifications of the SAP, based on new information such as data from other trials and biological insights, will be finalized and signed off BEFORE unblinding of the database. The current plan is to analyse as by pre-pathology and post-pathology strata as well as subgroup analysis as per hormone receptor status and hormone therapy. Multivariate analysis will also be performed for assessing the predictive value of other tumour and patient factors such as age, tumour size, grade, lymph node status, margins, lymphovascular invasion, time since randomization, etc.

10 PATIENT AND PUBLIC INVOLVEMENT (PPI)

A patient sits on the Trial Steering Committee and has been involved in discussions about the management of the research, analysis of results and dissemination of findings.

In addition, a minimum of one patient focus group meeting per annum will be held. Items to be discussed include responding to feedback from patient-completed questionnaires, informing the group of study progress, and addressing more general questions. At the end of recruitment, the patient focus group meeting will be mainly concerned with the dissemination plan.

11 FUNDING AND SUPPLY OF EQUIPMENT

The study funding has been reviewed by the UCL/UCLH Research Office, and deemed sufficient to cover the requirements of the study. NHS costs will be supported via UCLH and/or the Local Clinical Research Network.

The research costs for the study have been supported by the NIHR HTA programme.

12 DATA HANDLING AND MANAGEMENT

The clinical trials unit (SITU) will send to each Principal Investigator a list of patients who meet the eligibility criteria as per information held on the database (alive, not withdrawn consent). The PI will review the list to ensure the information is up-to-date.

The PI will send the approved letter (on local letterhead) to each patient, together with the participant information leaflet, consent form, contact details form, and follow-up (questionnaire) form. If the patient has any questions, she can telephone the office of the PI (contact details will be provided), or have a face-to-face discussion at her next clinic visit.

If the patient consents to take part in the study, she must complete the consent form, contact details form, and follow-up (questionnaire) form. These should be sent to SITU by post in the pre-paid envelope provided. One copy of the consent form will be returned to the patient, one copy will be sent to the PI, and the original will remain in SITU.

If the patient explicitly states that she refuses to participate, no further contact will be made. If the patient does not reply, the PI will be asked to send a reminder to the patient. If no contact is made after three attempts, no further contact will be made.

Patients who have consented to be in the study will be "flagged" with administrative databases (such as ONS and the Cancer Registry). In addition, the patient will be contacted annually directly by SITU and asked to update the contact details form (if necessary), complete a follow-up (questionnaire) form, and return by post in the pre-paid envelope provided. Patients can refuse consent at any time by contacting either SITU or the PI, in which case no further contact will be made.

All data obtained will be held securely in UCL. Patient identifiers (such as name, address, etc.) will be held on a separate Data Safe Haven which has been certified to the ISO27001 information security standard and conforms to NHS Digital's Information Governance Toolkit. This has been built using a walled garden approach, where the data is stored, processed and managed within the security of the system, avoiding the complexity of assured end point encryption. A file transfer mechanism enables information to be transferred into the walled garden simply and securely.

Long term arrangements will be as per the sponsors SOP. On publication of the final analysis and closure of all sites, the main REC (HRA) will be notified using the appropriate forms. All essential documentation, CRFs and electronic records will be catalogued and boxed up. All duplicates and non essential documentation will be confidentially destroyed. These boxes will be held off site within UCLs commercial storage, provided by Iron Mountain. These data will be held for 20 years, at the end of which they will also be confidentially destroyed.

The principal investigator at each participating site agrees to archive his/her respective site's study documents for 20 years and in line with all relevant legal and statuary requirements.

13 MATERIAL/SAMPLE STORAGE

No tissue or samples will be collected from patients as part of this study.

14 PEER AND REGULATORY REVIEW

The Sponsor considers the procedure for obtaining funding from the NIHR HTA programme to be of sufficient rigour and independence to be considered an adequate peer review.

15 ASSESSMENT AND MANAGEMENT OF RISK

There is a risk that some patients might feel upset at being reminded about their diagnosis and treatment for breast cancer. The initial letter from the treating hospital will include contact details of the team and breast care nurses for easy access.

16 RECORDING AND REPORTING OF EVENTS AND INCIDENT

As the last treatment occurred more than 5 years ago, this section (16) will be relevant in the rare case of any adverse event that is being reported retrospectively, or a rare event that occurs in the course of longer follow up that may be attributed to radiation therapy (e.g. lung cancer, oesophageal cancer, angiosarcoma, ischaemic heart disease, rib facture, etc.).

16.1 Definitions of Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or study participant, which does not necessarily have a causal relationship with the procedure involved.
Serious Adverse Event (SAE).	Any adverse event that: • results in death, • is life-threatening*, • requires hospitalisation or prolongation of existing hospitalisation**, • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect
*A life- threatening event, this refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** Hospitalisation is defined as an in-patient admission, regardless of length of stay. Hospitalisation for pre-existing conditions, including elective procedures do not constitute an SAE.	

16.2 Assessments of Adverse Events

Each adverse event will be assessed for severity, causality, seriousness and expectedness as described below.

16.2.1 Severity

The generic categories below are given for use as a guide.

Category	Definition

Mild	The adverse event does not interfere with the participant's daily routine, and does not require further procedure; it causes slight discomfort
Moderate	The adverse event interferes with some aspects of the participant's routine, or requires further procedure, but is not damaging to health; it causes moderate discomfort
Severe	The adverse event results in alteration, discomfort or disability which is clearly damaging to health

16.2.2 Causality

The assessment of relationship of adverse events to the procedure is a clinical decision based on all available information at the time of the completion of the case report form.

If a differentiated causality assessment which includes other factors in the study is deemed appropriate, please add/amend the following wording to specify:

It is of particular importance in this study to capture events related to the treatment. The assessment of relationship of an adverse event to this/these additional safety issue(s) will also be carried out as part of the study.

The following categories will be used to define the causality of the adverse event:

Category	**Definition**
Definitely:	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
Probably:	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
Possibly	There is some evidence to suggest a causal relationship (e.g. the event occurred within a reasonable time after administration of the study procedure). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant events).
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study procedure). There is another reasonable explanation for the event (e.g. the participant's clinical condition).
Not related	There is no evidence of any causal relationship.
Not Assessable	Unable to assess on information available.

16.2.3 Expectedness

Category	Definition
Expected	An adverse event which is consistent with the information about the procedure defined in the TARGIT A Trial protocol.
Unexpected	An adverse event which is not consistent with the information about the procedure defined in the TARGIT A Trial protocol*.

* this includes listed events that are more frequently reported or more severe than previously reported

16.3 Recording adverse events

All adverse events will be recorded in the medical records in the first instance.

All adverse events will be recorded with clinical symptoms and accompanied with a simple, brief description of the event, including dates as appropriate.

All adverse events will be recorded in the CRF until the participant completes the study.

16.4 Procedures for recording and reporting Serious Adverse Events

All serious adverse events will be recorded in the medical records and the CRF. The sponsors AE log is used to collate SAEs and AEs so that the CI can review all in one place for trend analysis. This data will be collated on a database throughout the study, from which a line listing of the SAEs can be extracted for review; therefore an AE log will not be required.

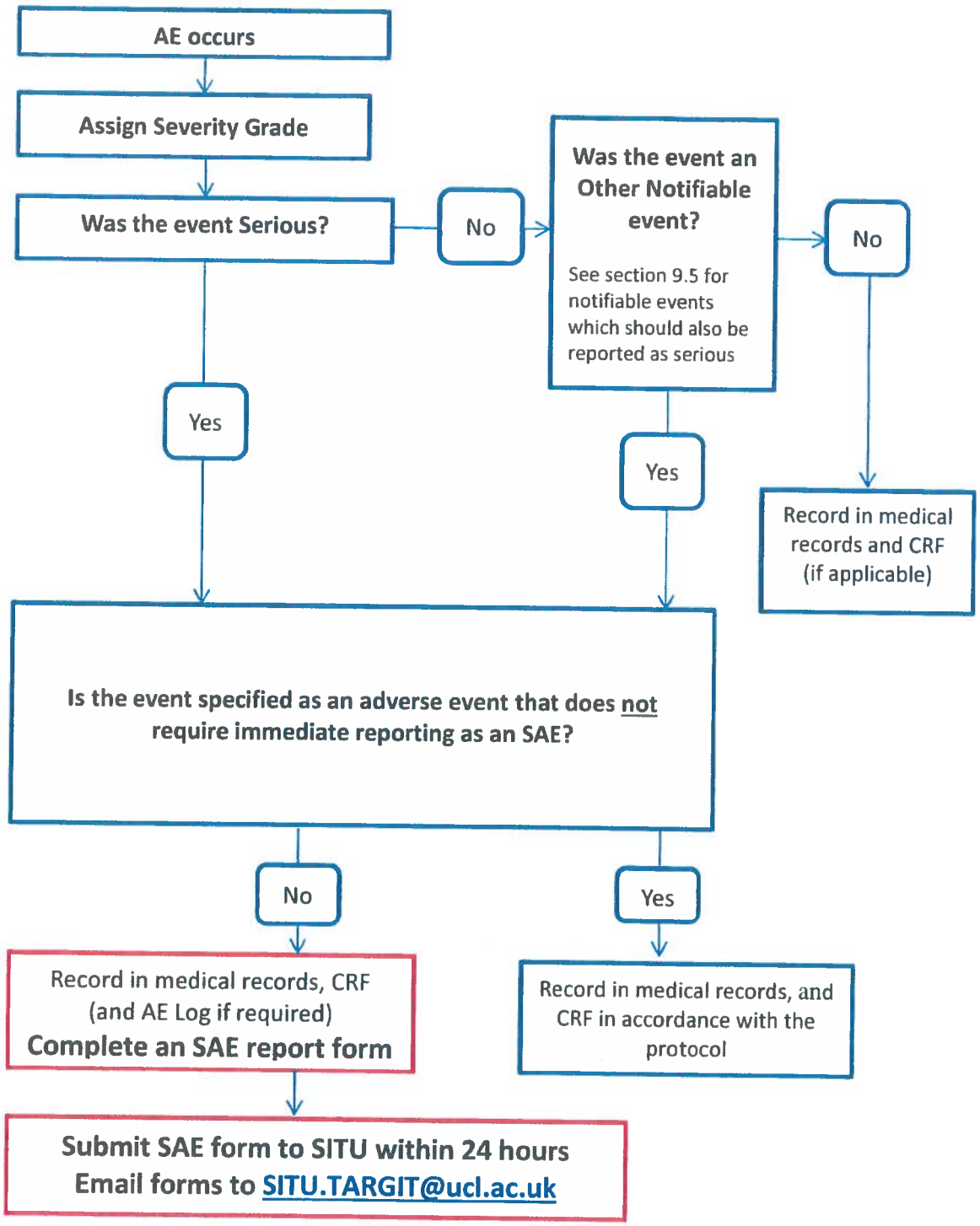
All SAEs (except those specified in section 16.5 as not requiring reporting to the Sponsor) must be recorded on a serious adverse event (SAE) form. The CI/PI or designated individual will complete an SAE form and the form will be preferably emailed to the Sponsor within 5 working days of becoming aware of the event. The Chief or Principal Investigator will respond to any SAE queries raised by the sponsor as soon as possible.

Where the event is unexpected and thought to be related to the procedure this must be reported by the Investigator to the Health Research Authority within 15 days.

Completed forms for unexpected SAES must be sent within 5 working days of becoming aware of the event to the Sponsor

Email forms to Research-incidents@ucl.ac.uk

Flow Chart for SAE reporting



16.5 Serious Adverse Events that do not require reporting

As treatment occurred more than 5 years ago, the only reportable adverse events are those that that occur in the course of longer follow up that may be attributed to radiation therapy (e.g. lung cancer, oesophageal cancer, angiosarcoma, ischaemic heart disease, rib facture, etc.).

16.6 Reporting Urgent Safety Measures

If any urgent safety measures are taken the CI/ PI shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC and Sponsor of the measures taken and the circumstances giving rise to those measures.

16.7 Protocol deviations and notification of protocol violations

A deviation is usually an unintended departure from the expected conduct of the study protocol/SOPs, which does not need to be reported to the sponsor. The CI will monitor protocol deviations.

A protocol violation is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the study; or
(b) the scientific value of the study.

The CI and sponsor will be notified immediately of any case where the above definition applies during the study conduct phase.

16.8 Reporting incidents involving a medical device

Any adverse incident involving a medical device should be reported to the manufacturer of the device.

This is especially important where the incident has led to or, was it to occur again could lead to an event classified as serious (see section 9.1 for definition of SAE). Other minor safety or quality problems should be reported along with incidents that appear to be caused by human error.

All adverse incidents must be reported to Carl Zeiss, Oberkochen, Germany.

Incidents should be reported as soon as possible (usually within 24 hours).

Local trust reporting procedures may also need to be followed. It is the responsibility of the PI and study site team to ensure they are aware of any specific local requirements for reporting device incidents.

16.9 Trust incidents and near misses

An incident or near miss is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a. It is an accident or other incident which results in injury or ill health.
b. It is contrary to specified or expected standard of patient care or service.
c. It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d. It puts the Trust in an adverse position with potential loss of reputation.
e. It puts Trust property or assets in an adverse position or at risk.

Incidents and near misses must be reported to the Trust through DATIX as soon as the individual becomes aware of them.

A reportable incident is any unintended or unexpected event that could have or did lead to harm, loss or damage that contains one or more of the following components:

a) It is an accident or other incident which results in injury or ill health.
b) It is contrary to specified or expected standard of patient care or service.
c) It places patients, staff members, visitors, contractors or members of the public at unnecessary risk.
d) It puts the Trust in an adverse position with potential loss of reputation.
e) It puts Trust property or assets in an adverse position or at risk of loss or damage.

17 MONITORING AND AUDITING

The Chief Investigator will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol, procedures for consenting and ensure adequate data quality.

The Chief Investigator will inform the sponsor should he/she have concerns which have arisen from monitoring activities, and/or if there are problems with oversight/monitoring procedures.

18 TRAINING

The Chief Investigator will review and provide assurances of the training and experience of all staff working on this study. Appropriate training records will be maintained in the study files

19 INTELLECTUAL PROPERTY

Any foreground IP generated during the programme of work proposed within this grant application will belong to UC). The background IP pertaining to the registered trade mark TARGIT already vests with UCL and as no external IP will be required to run this project - no third party access rights will be required to commercialise the outputs from said project.

A brief Freedom-to-Operate (FTO) was performed prior to registering the name TARGIT. No other significant registered trademarks were identified that could prevent the commercialisation of the UCL TARGIT trademark.

Clinical knowhow involving the INTRABEAM Technology and how to optimise patient outcomes using said technology will most probably be generated during the course of this study. This data will be owned by UCL and may be on interest to the owners of the INTRABEAM technology.

UCL Business (UCLB) has assigned an experienced Business Manager to oversee and manage the commercial and IP aspects of this project. Should any new IP be developed during this study then necessary steps to protect said IP will be instigated with a view to commercialising the technology at a later date.

Any exploitable knowledge will be identified and presented at the project meetings prior to any public disclosure/s and the applicants will work with UCLB to pursue appropriate protection of such knowledge - if relevant. There is potential for IP to be generated during the performance of this study that will support the approach being developed by the applicants. This includes results and know how and perhaps some process modifications to the technology.

This technology has already been CE marked and has the relevant regulatory approval required for clinical use. No further barriers to adoption or commercial exploitation are envisaged for this technology in its current iteration.

20 INDEMNITY ARRANGEMENTS

University College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. 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.

21 ARCHIVING

UCL and each participating site recognise that there is an obligation to archive study-related documents at the end of the study (as such end is defined within this protocol). The Chief Investigator confirms that he/she will archive the study master file at University College London for the period stipulated in the protocol and in line with all relevant legal and statutory requirements. The Principal Investigator at each participating site agrees to archive his/her respective site's study documents for 20 years and in line with all relevant legal and statutory requirements.

22 PUBLICATION AND DISSEMINATION POLICY

The publication policy of the TARGIT A Trial will be used.

23 REFERENCES

1. Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *The Lancet* 2010; **376**(9735): 91-102.
2. Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *The Lancet* 2014 (e-pub 11 Nov 2013); **383**(9917): 603-13 DOI:10.1016/ S0140-6736(13)61950-9.
3. Vaidya JS, Wenz F, Bulsara M, et al. An international randomised controlled trial to compare targeted intra-operative radiotherapy (TARGIT) with conventional post-operative radiotherapy after conservative breast surgery for women with early stage breast cancer (The TARGIT-A trial). *Health technology assessment* 2016; **20**(73).
4. Vaidya JS, Vyas JJ, Chinoy RF, Merchant N, Sharma OP, Mittra I. Multicentricity of breast cancer: whole-organ analysis and clinical implications. *British journal of cancer* 1996; **74**(5): 820-
5. Baum M, Vaidya JS, Mittra I. Multicentricity and recurrence of breast cancer. *Lancet* 1997; **349**(9046): 208.
6. Vaidya JS, Baum M, Tobias JS, et al. Targeted intra-operative radiotherapy (Targit): an innovative method of treatment for early breast cancer. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2001; **12**(8): 1075-80.
7. Vaidya JS, Baum M, Tobias JS, Morgan S, D'Souza D. The novel technique of delivering targeted intraoperative radiotherapy (Targit) for early breast cancer. *European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology* 2002; **28**(4): 447-54.

24 APPENDICES

Appendix 1 - Schedule of assessments

Appendix 2 – TSC membership

Appendix 3 – DMC membership

Appendix 4 – TMG Membership

Appendix 5 – Summary of the TARGIT A Trial

Appendix 1 - Schedule of assessments

	Consent	Direct patient contact	
Visit No:	1	2, 3, 4, etc.	-
	Day 1	Annually, on the anniversary of day 1	Death, withdrawal of consent, or loss of contact (after three attempts)
Window of flexibility for timing of visits:	-	+/- 3 months	-
Informed Consent	X		
Eligibility confirmation	X		
Health status	X	X	X
Adverse Events review	X	X	X

Appendix 2 – TSC membership

TARGIT Extension Trial Steering committee (TSC)

Professor Freddie Hamdy Nuffield Professor of Surgery Nuffield Department of Surgical Sciences University of Oxford	Independent Chair
Professor Ian Fentiman Surgery Guys & St Thomas Hospital	Independent Ordinary Member
Dr Mangesh Thorat Research Fellow Centre for Cancer Prevention Wolfson Institute of Preventive Medicine Barts & The London School of Medicine and Dentistry Queen Mary University of London	Independent Ordinary Member
Ms Carolyn Murphy Operational Director King's Clinical Trials Unit at KHP Kings College	Independent Ordinary Member
Ms Ann Millman Principal, Anne Millman Associates Anne Millman Associates	Independent Ordinary Member
Professor Martin Bland Emeritus Professor Department of Health Sciences University of York	Independent Ordinary Member
Dr David Dommett Consultant Clinical Scientist Radiotherapy Physics Southend University Hospital NHS Foundation Trust	Independent Ordinary Member
Dr David Morgan Radiation Oncologist Oncology Sherwood Forest Hospitals NHS Foundation Trust	Independent Ordinary Member
Professor Max K. Bulsara Chair in Biostatistics Institute of Health Research University of Notre Dame	Non-Independent Ordinary Member
Professor Jayant S. Vaidya Consultant Surgeon & Professor of Surgery and Oncology Surgical & Interventional Trials Unit - Division of Surgery University College London - UCL	Non-Independent Ordinary Member

Appendix 3 – DMC membership

Independent Data Monitoring Committee (IDMC)

There is no DMC.

Appendix 4 – Trial Management Group (TMG) Membership

Professor Jayant S Vaidya

Professor Jeffrey S Tobias

Professor Max Bulsara

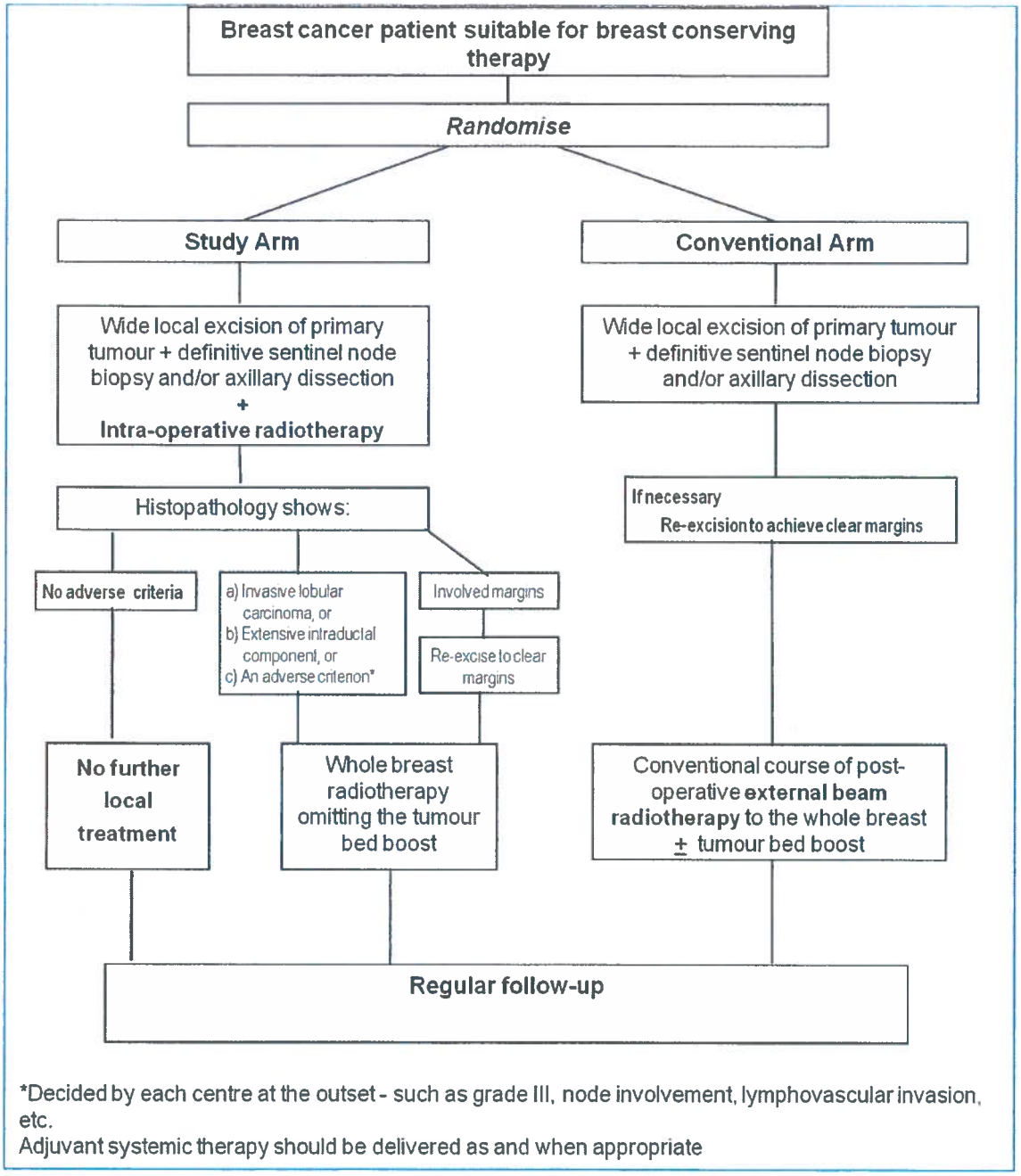
Ms Chris Brew-Graves

Dr Norman Williams

Dr Ingrid Potyka

Mr Haroon Miah

Appendix 5 – Summary of the TARGIT A Trial



*Decided by each centre at the outset - such as grade III, node involvement, lymphovascular invasion, etc.
Adjuvant systemic therapy should be delivered as and when appropriate