Open Surgery versus Minimally invasive vacuum-Assisted excision for smaLL screen-detected breast cancer – a phase III randomised multi-centre trial

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SIGNATURE PAGE

SMALL Trial Protocol, version 2.0 31st July 2019

This protocol has been approved by:

Name:	Mr Stuart McIntosh	**Trial Role:**	Chief Investigator
Signature:	_____	**Date:**	DD / MON / YYYY

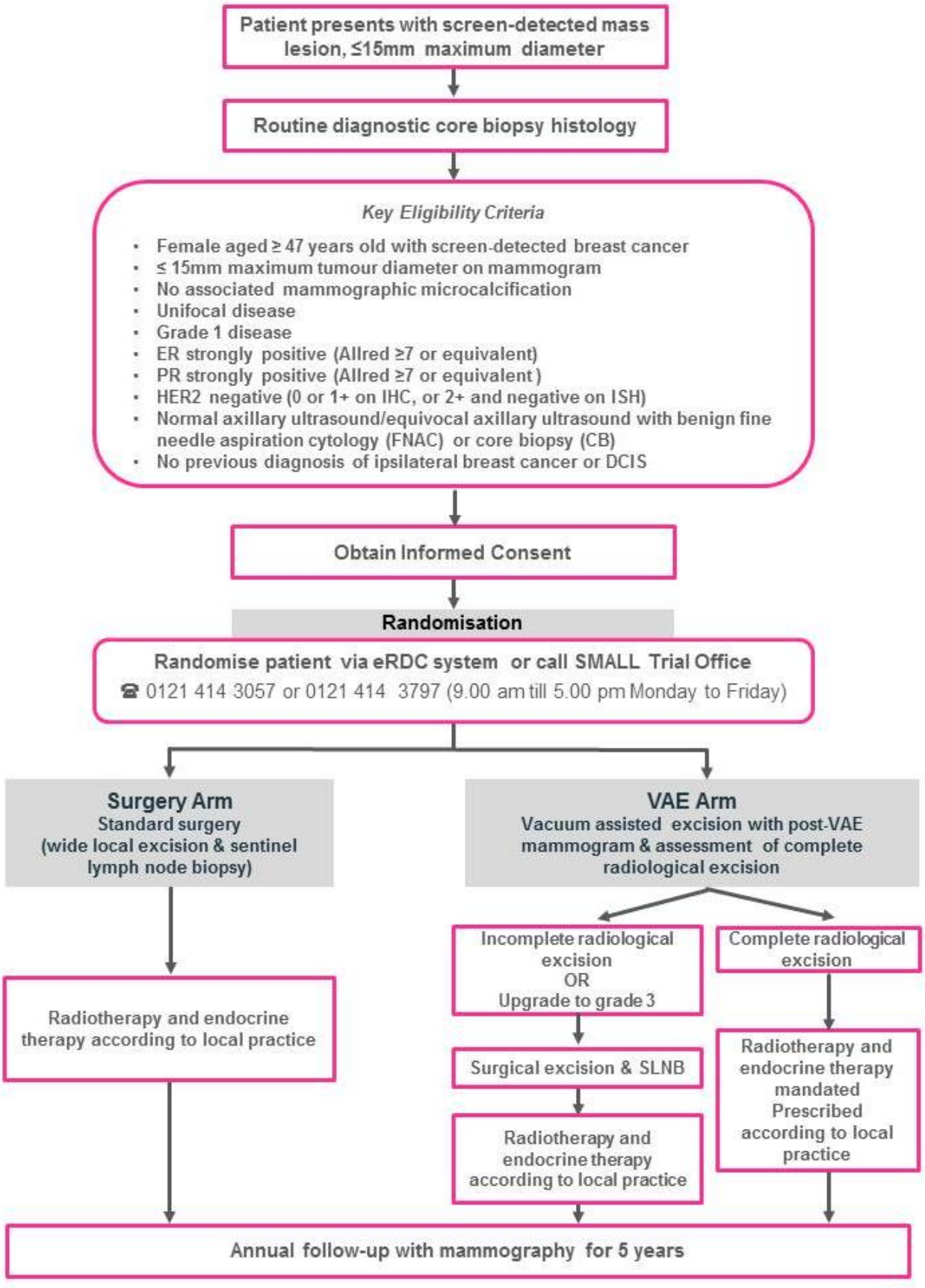
This protocol describes the SMALL trial and provides information about procedures for patients taking part in the SMALL trial. The protocol should not be used as a guide for treatment of patients not taking part in the SMALL trial.

TRIAL SYNOPSIS

Title:	Open surgery versus minimally invasive vacuum-assisted excision for small screen-detected breast cancer – a phase III randomised multi-centre trial
Chief Investigator:	Mr Stuart McIntosh
Sponsor:	University of Birmingham
ISRCTN No.	TBC
Trial Design:	Multi-centre, randomised (1:2) phase III trial of surgery versus minimally invasive vacuum assisted excision of patients with small, biologically favourable screen-detected breast cancer, incorporating an 18 month internal pilot study with a QuinteT Recruitment Intervention (Information Study) to optimise recruitment
Primary Objectives:	**Internal Pilot Study** • To demonstrate that a sufficient number of eligible patients can be identified and recruited over the course of the main trial **Main Study** • To determine whether the extent of surgical treatment can be reduced in the context of standard adjuvant radiotherapy and endocrine therapy
Secondary Objectives:	To determine the impact of minimally invasive treatment with VAE on: • Post-procedure complication • Breast cancer recurrence • Quality of life • Quality adjusted life years
Primary Outcome Measure:	• Re-excision following initial procedure • Local recurrence free survival time for VAE
Secondary Outcome Measures:	• Complications arising from surgery or VAE • Time to ipsilateral breast cancer recurrence • Time to development of contralateral invasive breast cancer • Overall survival time • Quality of life • Quality-adjusted life year (QALY)
Patient Population:	Women with small, biologically favourable breast cancer detected through the NHS Breast Screening Programme
Sample Size:	800 women
Eligibility Criteria:	**Inclusion Criteria** • Female aged ≥ 47 years old with screen-detected breast cancer • ≤15mm maximum tumour diameter on mammogram and ultrasound • No associated indeterminate, suspicious or malignant mammographic microcalcification associated with or extending beyond the mass • Unifocal disease • Grade 1 disease on diagnostic core biopsy • ER strongly positive (Allred score of 7 or 8, or equivalent e.g. at least moderate positivity in >66% of tumour cell nuclei)

	• PR strongly positive (Allred score of 7 or 8, or equivalent, e.g. at least moderate positivity in >66% of tumour cell nuclei) • HER2 negative (0 or 1+ on immunohistochemistry, or 2+ and negative by in situ hybridisation (FISH or DISH)) • Normal axillary ultrasound, or indeterminate ultrasound with benign fine needle aspiration cytology (FNAC) or core biopsy (CB) • Willing to be randomised • Able to provide written informed consent • Willing and able to undergo standard surgical treatment • Willing and able to undergo radiotherapy • Willing and able to take standard endocrine therapy • No previous diagnosis of ipsilateral breast cancer or DCIS (contralateral DCIS or invasive disease permitted if surgically treated ≥ 5 years previously and disease-free) **Exclusion Criteria** • Lesions with associated mammographic microcalcification outwith the lesion • Bilateral breast cancer • Invasive lobular carcinoma • Grade 2 or grade 3 on core biopsy assessment • ER or PR negative or HER2 positive tumour • Unable to provide informed consent • Any serious and/or unstable pre-existing medical, psychiatric or other condition that would prevent compliance with the trial or consent process • Unfit or unwilling to undergo standard surgical treatment • Contra-indications to standard adjuvant therapies (radiotherapy, endocrine therapy) • Previous ipsilateral invasive breast cancer or DCIS • Other invasive malignancy treated within the last 5 years • High risk group for developing breast cancer (as defined by NICE guidance)
Study Treatment:	**Surgery Arm:** • Standard surgical treatment as deemed appropriate by local MDT, including axillary sentinel lymph node biopsy • Adjuvant radiotherapy/endocrine therapy as per local treatment guidelines **Vacuum Excision Arm:** • Image-guided vacuum excision of breast cancer • No axillary surgery • Adjuvant radiotherapy to breast • Adjuvant endocrine therapy
Study Duration:	Recruitment: 4 years Follow-up: 5 years (extended follow-up to be obtained via routine NHS data linkage)
Trial Office Contact Details:	SMALL Trial Office, CRCTU, Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, B15 2TT, UK ☎ 0121 414 9021 🖷 0121 414 8392 ✉ SMALL@trials.bham.ac.uk

TRIAL SCHEMA



SCHEDULE OF EVENTS

Assessment	Screening	Trial Entry	Trial Treatment (within 31 days of randomisation)	Following Trial Treatment	Additional Surgical Treatment as Indicated	Post Completion of Trial Treatment	6-Month Follow-up	Annual Follow-up Years 1-5
Diagnostic biopsy and histology	X		**Appropriate surgery according to local protocol, including axillary sentinel lymph node biopsy**		**Re-excision of margins or mastectomy for Surgery Arm patients**			
Axillary US scan +/- FNAC or core biopsy	X							
Molecular markers ER PR HER2	X X X							
Medical history and physical examination including height and weight	X							
Informed consent for Information Study (optional)#	X							
Informed consent for trial entry		X						
Baseline Quality of Life questionnaires*		X						
Randomisation		X						
Tumour sample collection (VAE arm only)						X		
Related Adverse Event review			**OR**		**Surgical excision for VAE Arm patients with radiological evidence of incomplete excision plus sentinel lymph node biopsy**	X	X	X
Reporting of: survival, disease progression, development of new breast disease							X	X
Tumour sample collection for confirmed recurrence (VAE arm only)							X	X
Post-VAE mammogram (VAE arm only)			**Vacuum assisted excision and insertion of marker clip**	X				
Radiotherapy as per local guidelines$						X		
Adjuvant endocrine therapy as per local guidelines						X	X	X
Quality of Life questionnaires*							X	X
Annual mammography								X
Investigations for and treatment of ipsilateral/contralateral disease as per local protocol							X	X

Discussions with patients will be audio recorded as part of the Information Study (consenting patients only)

* Patients consenting to the Quality of Life Sub-study only. Baseline QoL Questionnaire Booklets completed at clinic, subsequent questionnaires will be sent from the SMALL Trial Office

$ Radiotherapy should commence within 8 weeks following breast conserving surgery and ideally within 31 days

ABBREVIATIONS

CB	**Core biopsy**
CRCTU	**Cancer Research UK Clinical Trials Unit**
CRF	**Case Report Form**
ER	**Oestrogen receptor**
ERDC	**Electronic Remote Data Capture**
ET	**Endocrine therapy**
FNAC	**Fine needle aspiration cytology**
GCP	**Good Clinical Practice**
H&E	**Haematoxylin and eosin**
HBRC	**Human Biomaterials Resource Centre**
HER2	**Human epidermal growth factor receptor type 2**
ISF	**Investigator site file**
LR	**Local recurrence**
MDT	**Multidisciplinary team**
NBSS	**National Breast Screening Computer System**
NCRI	**National Cancer Research Institute**
NHS	**National Health Service**
NHSBSP	**National Health Service Breast Screening Programme**
NICE	**National Institute for Health and Care Excellence**
PIL	**Patient information leaflet**
PR	**Progesterone receptor**
QA	**Quality Assurance**
QALY	**Quality-Adjusted Life Year**
QoL	**Quality of Life**
QRI	**QuinteT Recruitment Intervention (Information Study)**
REC	**Research Ethics Committee**
RT	**Radiotherapy**
RTQA	**Radiotherapy Quality Assurance**
RTTQA	**Radiotherapy Trials Quality Assurance**
SAE	**Serious Adverse Event**
SLNB	**Sentinel lymph node biopsy**
SS&DL	**Site signature and delegation log**
TNO	**Trial number**
TMG	**Trial Management Group**
TSC	**Trial Steering Committee**
US	**Ultrasound**
VAB	**Vacuum assisted biopsy**
VAE	**Vacuum assisted excision**
WLE	**Wide local excision**
WMA	**World Medical Assembly**

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1. BACKGROUND AND RATIONALE

1.1 Background

Overdiagnosis and overtreatment in the NHS Breast Screening Programme

The National Health Service Breast Screening Programme (NHSBSP) was established in the United Kingdom in 1988, and in recent years there has been extensive debate around the risks and benefits associated with breast cancer screening. This resulted in an independent review of the NHSBSP, which concluded that although breast screening reduces mortality from breast cancer, there is undoubtedly overdiagnosis within the programme[1]. Overdiagnosis can be considered the diagnosis of breast cancer in women who would never have received such a diagnosis had they not attended for screening. Overtreatment results from the treatment of such cancers. The Marmot Independent Review estimated that for 10,000 UK women invited for screening from 50-70 years, about 681 breast cancers will be diagnosed, of which 129 will represent overdiagnosis, and 43 breast cancer deaths will be prevented. Thus, for every one death prevented, three women will be overdiagnosed and consequently overtreated.

Current management of screen-detected breast cancer

Conventionally, screen-detected breast cancer has been treated surgically, under general anaesthesia; such surgical treatment has remained largely unchanged in the three decades since screening began. Treatment has been extrapolated from the management of symptomatic breast cancer, rather than being based on prospective evidence obtained from a population of women with screen-detected disease. Recent data suggests that small breast cancers with favourable biological features have an extremely good prognosis, and may account for a significant proportion of the overdiagnosis seen within the screening programme[2]. There is therefore a need to address the overtreatment of such small tumours with favourable biology in a way which is acceptable to patients.

Currently, patients with screen-detected oestrogen receptor (ER) positive breast cancer undergo surgical excision (usually image-guided), under general anaesthesia, together with sentinel lymph node biopsy (SLNB) to establish whether there is any axillary lymph nodal disease. Surgery is generally breast conserving surgery, and is carried out on a day-case basis in the majority of patients, with axillary SLNB carried out at the same time. Following surgery, the tumour is evaluated by histopathology to determine complete excision, as denoted by the absence of tumour cells at the margin of the removed breast tissue (clear resection margins). However, in the UK, up to 20% of patients have histopathological involvement of the resection margins, necessitating a second procedure to ensure that these are cleared[3]. Similar rates of re-excision have been reported worldwide[4]. The need for re-excision is based on the finding that historically, in older breast cancer studies, positive margins have been associated with an increased risk of local recurrence of tumour within the breast. However, after much debate about what constitutes a “clear” margin, many international centres accept the pathological definition of “no tumour at the inked resection margin”, and have demonstrated excellent long-term local recurrence rates[5]. Following successful breast conserving surgery, the vast majority of patients will receive adjuvant radiotherapy to the breast and systemic hormonal therapy[6]. However, breast conserving treatment may have significant associated complications, with early complication rates of up to 25% reported in a recent meta-analysis[7]. Furthermore, breast conserving surgery may have poor cosmetic outcomes[8], which may adversely impact on patient satisfaction and quality of life[9,10].

With respect to the management of the axilla in this patient population, the incidence of axillary nodal disease is known to be low, and ultrasound +/- core biopsy/fine needle aspiration cytology of the axilla has been shown to have an extremely high negative predictive value in the NHSBSP[3]. Furthermore, even in the context of a positive SLN, excellent regional control can be achieved in the axilla without further surgical dissection[11], and information on the extent of nodal status does not usually influence treatment selection[12], nor indeed change long-term prognosis[13]. Data supporting the omission of axillary

surgery in a selected low-risk patient population has suggested that this approach is safe with acceptable recurrence-free survival[14], and this is currently being further investigated in the SOUND trial[15] in a comparable patient group. Taken together, this data suggests a lack of evidence to justify routine use of SLNB in this setting, given that it has an attendant (albeit low) morbidity in terms of lymphoedema, numbness and paraesthesia[16,17].

Minimally invasive approaches to the treatment of small breast cancers

Given that many of the biologically favourable small tumours in the population eligible for the SMALL trial are likely to represent overdiagnosis, there is no prospective evidence that conventional open surgery is required. Thus, it is increasingly important that novel, minimally invasive techniques be developed for use in this setting. Such techniques may potentially reduce the morbidity and complication rates outlined above, as well as healthcare costs. A recent meta-analysis of minimally-invasive image-guided percutaneous ablation techniques for the treatment of breast cancer concluded that such techniques have a high rate of technical success, with relatively low complication rates[18]. However, many of the techniques described in this review are not in general use within the UK, and would not be available for routine use in the context of the NHSBSP. Furthermore, evidence from prospective randomised trials will be required to support the adoption of such techniques into clinical practice, enabling women of screening age to make informed choices about their treatment.

The vacuum-assisted biopsy (VAB) technique is one such minimally-invasive technique which is widely available within the UK. The VAB device is equipped with a large calibre needle, and the procedure is carried out under image-guidance (either ultrasound or X-ray guided). It is generally carried out under local anaesthesia during a brief out-patient stay. Initially used for diagnostic purposes following its development in 1995, VAB has evolved and been utilised as a tool for the non-surgical excision of benign lesions[19-21]. More recently, vacuum-assisted excision (VAE) has been described in the management of breast lesions of uncertain malignant potential (B3 lesions) I[22], and in a prospective study it has been demonstrated that post-VAB imaging can accurately estimate complete removal of masses in 90% of cases[23]. Vacuum-assisted sampling of breast lesions has been shown to be generally well- accepted by patients[24], and the technique is approved by National Institute for Health and Care Excellence (NICE) for excision of benign breast lesions.

Thus, the efficacy and acceptability of VAB in the benign biopsy field is proven, and there is sufficient evidence at this time to support its repurposing for the excision of small, impalpable, screen-detected breast cancers with favourable biological characteristics. The indolent nature of such tumours[2] means that annual surveillance mammography following VAE will allow early detection of residual or recurrent disease. The introduction of VAE following a prospective randomised trial would represent a significant step forward in the management of screen-detected breast cancer, with benefits to patients and the NHS alike as outlined below.

Following conventional surgical treatment with adjuvant radiotherapy and endocrine therapy, these patients have an excellent prognosis. The risk of local recurrence of tumour within the breast is estimated from the recently published IMPORT LOW[25] results at around 1% at 5 years (median follow-up 72 months). This pivotal UK study has established the non-inferiority of partial breast radiotherapy compared with adjuvant whole breast radiotherapy. In light of these results, the SMALL trial aims to establish whether, in a population of women with a lower local recurrence risk than that seen in IMPORT LOW, the extent of surgical treatment can be further reduced in the context of partial breast radiotherapy and endocrine therapy. This builds on the results of the IMPORT LOW study, showing a strategic, step-by-step approach to studies examining the de-escalation of breast cancer treatment in women with good prognosis screen-detected disease. It also complements the ongoing PRIMETIME study[26] evaluating the omission of radiotherapy in a good prognostic group, and the combined results from these trials may provide the basis for subsequent studies assessing the possibility of further treatment de-escalation in highly selected groups.

Thus, there is a strong argument at the present time for the need for treatment de-escalation studies in patients with good prognosis, screen-detected disease[27].

1.2 Trial Rationale

1.2.1 Justification for patient population

The patient population are women of NHSBSP age or above (as these women can still access the screening programme) who have had a small, good-prognosis tumour detected mammographically. It is now possible to identify women with screen-detected breast cancers who have an extremely good prognosis (low grade, ER positive, progesterone receptor (PR) positive and human epidermal growth factor receptor type 2 (HER2) negative tumours), and this is the patient population most likely to be overtreated by conventional surgical excision. The recent IMPORT LOW trial has demonstrated that with surgery followed by standard adjuvant therapies extremely low local recurrence rates can be achieved[25]. It is now necessary to investigate whether the extent of surgical intervention in this patient group can be further reduced, by utilising a minimally-invasive radiologically guided technique for the excision of these primary tumours and omitting axillary surgery. This approach has the potential to benefit patients by avoiding a general anaesthetic and an open procedure (as well as being a more convenient treatment option), together with the possibility of reducing surgical complications and the side effects associated with surgery. Furthermore, there are potential important benefits to the NHS, in terms of reducing theatre time requirements (freeing up operating time for other procedures), and cost savings associated with both the avoidance of surgery and possibly also from the avoidance of the need to manage long-term surgical complications such as lymphoedema.

1.2.2 Justification for design

It is appropriate to address the issue of overtreatment of screen-detected early breast cancer through a prospective randomised trial. In order for this trial to be practice-changing, it will be necessary to demonstrate that not only is there an acceptable local recurrence (LR) risk associated with VAE followed by radiotherapy (RT) and endocrine therapy (ET), but also that there is no excess requirement for additional procedures in the case of radiologically-determined incomplete excision. It is possible there may be fragments of microscopic disease remaining in the breast following VAE, but what is important is not their presence, but their impact on long-term clinical outcomes (LR in this context). It is well-recognised that following surgical excision a negative pathological margin does not indicate no residual tumour within the breast[28], but rather that the residual disease burden is likely to be sufficiently low to be controlled by adjuvant therapy. The role of both RT and adjuvant systemic therapies in maintaining local disease control are well documented[29,30]. Furthermore, a large Dutch cohort study demonstrated that omission of re-excision for focally involved margins (where microscopic foci of residual malignancy may be seen) was associated with a 5-year local recurrence rate of 2.9%, when whole-breast RT was given following surgery. Although this local recurrence rate was reduced by surgical re-excision, this did not impact 5-year disease free or overall survival[31].

Consequently the study is designed with co-primary endpoints, to demonstrate non-inferiority of VAE in terms of requirements for a second procedure, and to demonstrate acceptable long-term local recurrence rates following VAE in these tumours.

Thus, the rationale for adjuvant therapies following breast surgery is based on the premise that there may be an undetected microscopic cancer burden likely to benefit from additional treatment, and this principle has underpinned the safe introduction of breast conserving therapy for early breast cancer.

A QunteT Recruitment Intervention (QRI), also known as the Information Study, has been included in the recruitment stages (pilot phase and main recruitment phase) of the trial in order to identify potential barriers to recruitment and to suggest changes to improve levels of informed consent and randomisation. The QRI will monitor recruitment rates and assess patient and clinician preferences. In doing so, an action from the QRI may be to make recommendations for strategies to improve recruitment.

1.2.3 Choice of treatment

The control arm of the study is necessarily standard surgical treatment, which for the population eligible for this trial will be image-guided wide local excision and sentinel lymph node biopsy. The selection of image-guided VAE for the minimally-invasive arm of the study is based on the fact the VAE is a well-established technology for managing benign and indeterminate breast lesions within the NHSBSP, and is in widespread use within UK breast units, with extensive experience already in place, unlike many of the other minimally invasive radiologically techniques currently available.

2. AIMS, OBJECTIVES AND OUTCOME MEASURES

2.1 Internal Pilot Phase

2.1.1 Aims and objectives

The aim of the internal pilot phase of the trial is to demonstrate that a sufficient number of eligible patients can be identified and recruited over the course of the main trial, in order to answer robustly the trial objectives. This will be evaluated from the following factors:

- Number of sites open
- Number of patients randomised

2.1.2 Outcome measures

1. Number of sites open: defined as the total number of sites open to recruitment with at least one patient recruited by the end of month 18
2. Number of patients randomised: total number of patients randomised from all sites opened to recruitment during the pilot phase

2.2 Main Trial

2.2.1 Aims and objectives

The aim of the main trial is to determine whether the extent of surgical treatment can be reduced in the context of standard adjuvant radiotherapy and endocrine therapy.

2.2.2 Outcome measures

2.2.2.1 Primary outcome measures

Primary outcome 1: Re-excision following initial procedure

Primary outcome 2: Local recurrence-free survival time for VAE

2.2.2.2 Secondary outcome measures

1. Complications arising from surgery or VAE
2. Time to ipsilateral breast cancer recurrence
3. Time to development of contralateral invasive breast cancer
4. Overall survival time
5. Quality of life: will be assessed using the following tools:
    - o EORTC QLQ-C30 and BR23
    - o EuroQoL EQ-5D
    - o BREAST-Q (breast conserving therapy module)
6. Quality-adjusted life year (QALY)

2.2.2.3 Exploratory outcome measures

- Assessment of predictive biomarkers of ipsilateral tumour recurrence

3. TRIAL DESIGN

SMALL is a prospective, multi-centre, randomised (1:2) phase III trial of surgery versus minimally invasive vacuum-assisted excision of patients with small, biologically favourable screen-detected breast cancer. It incorporates an 18 month Internal Pilot Study with a QuinteT Recruitment Intervention (Information Study) to optimise recruitment, and is designed to determine whether:

- The extent of surgical treatment can be reduced in the context of standard adjuvant radiotherapy and endocrine therapy.
- Vacuum-assisted excision is non-inferior to conventional surgery in terms of the requirement for a second operation to achieve complete resection of the cancer.
- There is an acceptable local recurrence risk in the VAE arm with long-term follow up.

Patients will be recruited over a 4 year period and will be followed-up for 5 years from randomisation. Long-term follow-up information will be obtained via data linkage.

Please also refer to the Trial Schema on page vii.

4. ELIGIBILITY

4.1 Inclusion Criteria

1) Female aged ≥ 47 years old with screen-detected breast cancer
2) ≤15mm maximum tumour diameter on mammogram and ultrasound
3) No associated indeterminate, suspicious or malignant mammographic microcalcification associated with the lesion or extending beyond the mass
4) Unifocal disease
5) Grade 1 disease on diagnostic core biopsy
6) ER strongly positive (Allred score of 7 or 8, or equivalent, e.g. at least moderate positivity in >66% of tumour cell nuclei)
7) PR strongly positive (Allred score of 7 or 8, or equivalent, e.g. at least moderate positivity in >66% of tumour cell nuclei)
8) HER2 negative (0 or 1+ by immunohistochemistry, or 2+ and negative by in situ hybridisation techniques (FISH or DISH))
9) Normal axillary ultrasound axillary, or equivocal ultrasound with benign fine needle aspiration cytology (FNAC) or core biopsy (CB)
10) Willing to be randomised
11) Able to provide written informed consent
12) Willing and able to undergo standard surgical treatment
13) Willing and able to undergo radiotherapy
14) Willing and able to take standard endocrine therapy
15) No previous diagnosis of ipsilateral breast cancer or DCIS (contralateral DCIS or invasive disease permitted if surgically treated ≥ 5 years previously and disease-free)

4.2 Exclusion Criteria

1) Lesions with associated mammographic microcalcification outwith the lesion
2) Bilateral breast cancer
3) Invasive lobular carcinoma
4) Grade 2 or grade 3 on core biopsy assessment
5) ER or PR negative or HER2 positive tumour
6) Unable to provide informed consent
7) Any serious and/or unstable pre-existing medical, psychiatric or other condition that would prevent compliance with the trial or consent process
8) Unfit or unwilling to undergo standard surgical treatment
9) Contra-indications to standard adjuvant therapies (radiotherapy, endocrine therapy)
10) Previous ipsilateral invasive breast cancer or DCIS
11) Other invasive malignancy treated within the last 5 years
12) High risk group for developing breast cancer (as defined by NICE guidance)

5. SCREENING AND CONSENT

Potential patients will be identified via clinic referrals from Breast Units or Screening Units, or from Multidisciplinary Team (MDT) meetings. The screening requirements defined in this protocol are standard practice in many sites and can therefore be commenced prior to obtaining trial consent.

5.1 Screening

The screening procedures detailed below should be undertaken. The reason for screening failures should be captured on the Patient Screening/Enrolment Log which will be reviewed by the SMALL Trial Office in order to monitor uptake and identify issues with eligibility.

5.1.1 Involvement of local NHS breast screening unit

Patients enrolling in the trial will have recently attended their local NHS Breast Screening Unit following recall for assessment of a mammographic abnormality identified on routine screening mammograms. Eligible patients will be those with a discrete mammographic abnormality up to and including 15mm in maximum diameter, without associated indeterminate, suspicious or malignant microcalcification extending beyond the lesion. Where possible, the local Screening Unit should supply potential patients with a copy of the brief Patient Information Leaflet (PIL) and Information Study Patient Information Leaflet either with the invitation to attend for assessment, or when attending for biopsy. This PIL aims to provide information to prepare patients for the possibility of being invited to participate in a research study at an early stage in their pathway. Please refer to the SMALL Radiology Manual for further details.

A pre-operative diagnosis of grade 1 carcinoma (of any morphological type) should be confirmed by percutaneous biopsy, in accordance with the Royal College of Pathologists: Guidelines for Non-operative Diagnostic Procedures and Reporting in Breast Cancer Screening[32]; and this is a pre-requisite for trial entry. Percutaneous biopsy may be either small volume (14G) needle core biopsies or by diagnostic vacuum assisted biopsy (any gauge). Axillary ultrasound (US) should be carried out at screening assessment and only patients with either normal axillary US, or equivocal US with benign FNAC or CB will be considered eligible for study entry.

5.1.2 Local diagnosis of grade 1 invasive breast carcinoma

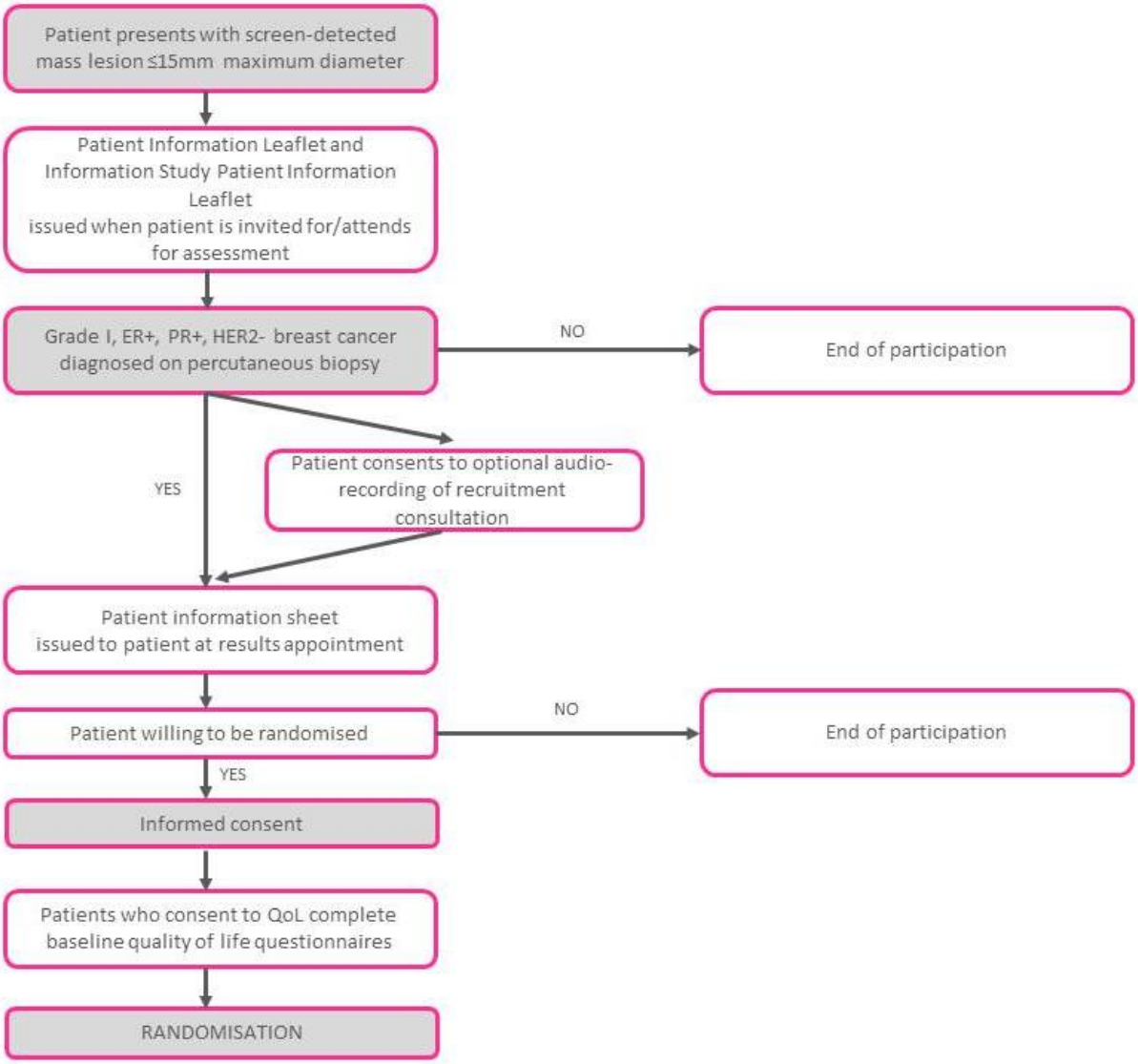
All biopsy specimens should be immediately fixed in 10% buffered formalin and processed as per local practice, through to paraffin wax, and should be handled and reported in accordance with the Royal College of Pathologists: Guidelines for Non-operative Diagnostic Procedures and Reporting in Breast Cancer Screening[32]. Histological grade will be ascertained by the local reporting pathologist. ER, PR and HER2 status should be ascertained according to local practice and national guidelines; all laboratories undertaking receptor status tests must participate in appropriate external quality assurance schemes (such as NEQAS ICC and ISH, or equivalent) with satisfactory results.

All patients diagnosed with grade 1, ER and PR positive and HER2 negative invasive carcinoma, who meet the specified eligibility criteria may be approached about the trial.

5.1.3 Medical history and full physical examination

A full medical history and physical examination including height and weight should be carried out.

5.1.4 Flowchart 1: Patient pathway to randomisation



Discussions with the patient will be audio recorded if the patient has given informed consent for the Information Study

5.2 Informed Consent

It is the responsibility of the Investigator to obtain written informed consent for each patient prior to performing any trial related procedure. The Investigator may delegate responsibility for obtaining written informed consent to other appropriately qualified members of the site research team (e.g. specialist trainees, radiologists, clinical research nurses) who are trained in obtaining informed consent and in Good Clinical Practice (GCP). However, assessing patient suitability and the final confirmation of the patient eligibility is the responsibility of the Investigator. Delegation of responsibility for obtaining written informed consent must be clearly indicated on the Site Signature and Delegation Log (SS&DL).

5.2.1.1 Informed consent for the QuinteT recruitment intervention (Information Study)

It is recommended that all sites participate in the QuinteT Recruitment Intervention (QRI), also known as the Information Study. The Information Study Patient Information Leaflet can be issued to patients when they attend for their biopsy result, if they have not received the leaflet previously. Procedures for the Information Study will be explained to the patient by the Investigator or healthcare professional. If the patient has consented to participate in the Information Study, any further discussion between the patient and the Investigator and/or healthcare professional may be audio recorded.

Further information on the Information Study can be found in Appendix 6 and detailed instructions for participating sites are supplied in the SMALL QuinteT Recruitment Intervention (Information Study) Instructions).

5.2.2 Informed consent for trial entry

A Patient Information Sheet is provided to facilitate the informed consent process, and this may be provided to patients following confirmation of eligibility. Investigators must ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the patient. The Investigator should also stress that the patient is completely free to refuse to take part or withdraw from the trial at any time. If the patient (and Investigator and/or healthcare professional) has consented to participate in the Information Study, the discussion between the patient and the Investigator and/or healthcare professional will be audio recorded. The patient should be given ample time (e.g. 24 hours) to read the Patient Information Sheet and to discuss their participation with others outside of the site research team. The patient must be given an opportunity to ask questions which should be answered to their satisfaction. Eligible patients who decline randomisation will be requested to indicate the reason for this, and this will be recorded on the Patient Screening/Enrolment Log. The right of the patient to refuse to participate in the trial without giving a reason must be respected.

If the patient expresses an interest in participating in the trial they should be asked to sign and date the latest version of the Informed Consent Form. The Investigator or designate must then sign and date the form. The patient's Trial Number (TNO) should be entered on the Informed Consent Form. A copy of the Informed Consent Form should be given to the patient, a copy should be filed in the hospital notes, and the original placed in the Investigator Site File (ISF). Once the patient is entered into the trial the patient's trial number should be entered on the Informed Consent Form maintained in the ISF. In addition, if the patient has given explicit consent a copy of the signed Informed Consent Form must be sent in the post to the SMALL Trial Office for review.

Details of the informed consent discussions should be recorded in the patient's medical notes, this should include date of, and information regarding, the initial discussion, the date consent was given, with the name of the trial and the version number of the Patient Information Sheet and Informed Consent Form. Throughout the trial the patient should have the opportunity to ask questions about the trial and any new information that may be relevant to the patient's continued participation should be shared with them in a timely manner. On occasion it may be necessary to re-consent the patient in which case the process above should be followed and the patient's right to withdraw from the trial respected.

Electronic copies of the Patient Information Sheet and Informed Consent Form are available from the SMALL Trial Office and should be printed or photocopied onto the headed paper of the local institution.

Details of all patients approached about the trial should be recorded on the Patient Screening/Enrolment Log.

6. TRIAL ENTRY

6.1 Patient Recruitment

Eligible patients should be invited to take part in the trial by the site research team at the earliest opportunity. This will usually be when the patient returns to the local Breast Clinic or Breast Screening Unit (depending on local organisation) to discuss their diagnostic biopsy report. An Eligibility Checklist should be completed for each patient.

6.2 Randomisation

6.2.1 Timeframe for randomisation

Patients who are deemed eligible should be consented for trial entry as soon as possible.

Advice from the Cancer Waiting Times (CWT) Team regarding trial participation and CWTs states that a patient should not be denied the opportunity to participate in a trial purely in order to avoid a breach. If a patient breaches a 31/62 CWT target as a result of necessary steps, such as additional screening tests, introduced by the trial protocol, this will indeed register as a breach. However, since the patient will have been fully informed of (and consented to) the delay, this is acceptable.

6.2.2 Randomisation

Patients may be randomised into the trial upon completion of the written Informed Consent Form.

Following consent, patients who have consented to the Quality of Life (QoL) and Health Economics sub-study will be asked by a member of the site research team to complete the baseline QoL questionnaires prior to randomisation. The person providing the questionnaires should ensure that all questions and all pages of each questionnaire have been completed.

Investigators must be registered with the SMALL Trial Office before they are permitted to enter patients into the trial (see Section 15.1 Site Set-up and Initiation).

The Investigator (or person delegated this responsibility) should randomise the patient into the trial using the SMALL electronic Remote Data Capture (eRDC) system accessed via the CRCTU Systems Portal or via completion of the Randomisation Form followed by a telephone call to the SMALL Trial Office. The randomisation line will be open during office hours (9:00am to 5:00pm, Monday to Friday).

Randomisation via the CRCTU Systems Portal:

http://www.cancertrials.bham.ac.uk/CRCTUPortal/

Or via the Trial Office: ☎ 0121 414 9021 or 0121 414 3604

(9.00 am till 5.00 pm, Monday to Friday)

The site will be asked to confirm the patient's details and eligibility and provide the following information:

- Name of site and responsible Investigator
- Forename and surname
- Patient's full address (if participating in QoL and Health Economics sub-study)
- Date of birth
- Hospital number
- Patient's NHS number or in Scotland Community Health Index (CHI) number, or H&C number in Northern Ireland
- Date of informed consent

Patients will be randomised at a ratio of 1:2 in favour of the VAE arm using computerised minimisation technique.

Patients will be allocated to one of the treatment arms:

- **Arm A:** surgery
- **Arm B:** vacuum-assisted excision

On completion of the randomisation process, the site will be immediately notified of the treatment allocation. The site research team will then:

- Ensure that the patient's TNO is added to the Informed Consent Form before taking 3 photocopies (original to be kept in the ISF, 1 copy in hospital notes, 1 copy to the patient, 1 copy to be sent to the SMALL Trial Office)
- Inform the patient of their randomised allocation without delay
- Add the patient's TNO to the completed baseline QoL questionnaires (if applicable) and return the completed questionnaires to the SMALL Trial Office using the pre-paid envelopes provided
- Update the Patient Screening/Enrolment Log
- Add the patients details to the Patient Identification Log
- With the patient's prior consent, their General Practitioner (GP) should be informed that they are taking part in the trial. A GP Letter is provided electronically for this purpose and should be forwarded to the patient's GP
- The completed Eligibility Checklist (and Randomisation Form if trial entry completed via call to the Trial Office) should be returned via post to the SMALL Trial Office

The SMALL Trial Office will send the responsible clinician confirmation of the patient's entry into the trial via email.

7. TREATMENT DETAILS AND SCHEDULED ASSESSMENTS

Patients will be randomised to one of the treatment arms:

- Arm A: surgery
- Arm B: vacuum-assisted excision

See Section 7.1 and 7.2 for details.

Please also refer to the Schedule of Events, page viii.

7.1 Surgery Arm Patients

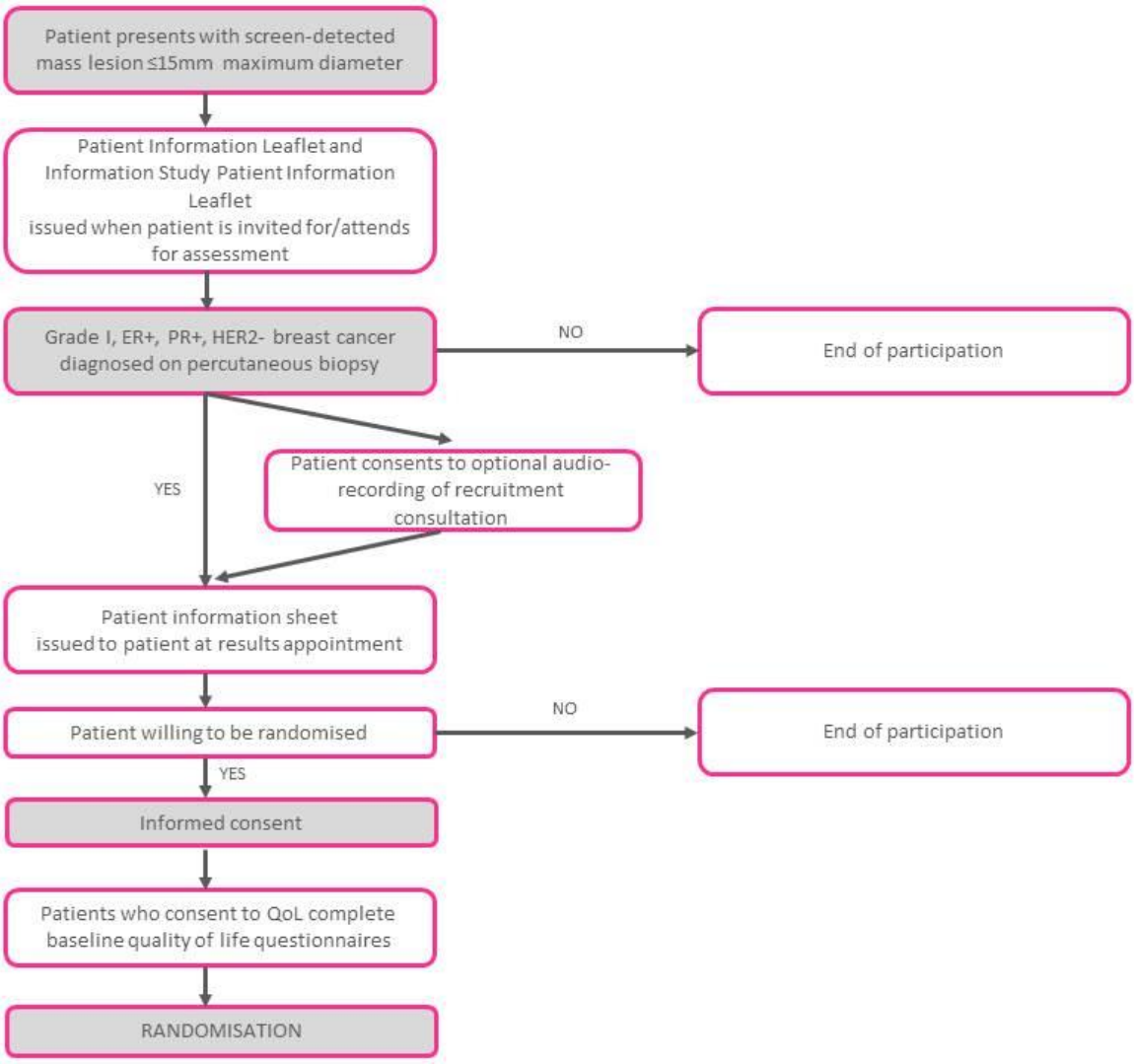
7.1.1 Baseline

Baseline data will be collected, to include details of the radiological findings and diagnostic biopsy histology including tumour type, grade, and biomarker status (ER/PR/HER2).

7.1.2 Treatment

The surgical arm treatment pathway is summarised in Flowchart 2: Surgical Arm Treatment Pathway.

Flowchart 2: Surgical Arm Treatment Pathway



7.1.2.1 Surgery

Patients randomised to the surgery arm should undergo appropriate surgery according to local guidelines following MDT review. This should include axillary SLNB. It is expected that patients will undergo surgery within 31 days of randomisation.

Following surgical excision and axillary sentinel node biopsy, the excision specimen should be reported in accordance with the NHSBSP/Royal College of Pathologists guidance[33]. Resection margins should be deemed involved or clear according to local protocol and the need for re-excision of margins or

mastectomy determined at post-operative MDT review. A copy of the patient's anonymised pathology report for the VAE should be forwarded to the SMALL Trial Office.

Data on all surgical procedures will be collected on the electronic Case Report Form (eCRF). This will include data on second procedures and any subsequent surgery, including the requirement for mastectomy together with any immediate breast reconstruction surgery, if performed.

7.1.2.2 Endocrine therapy

Adjuvant endocrine therapy in the surgery arm of the trial should be given according to pre-defined local guidelines. Data on the use of endocrine therapy will be captured on the eCRF.

7.1.2.3 Radiotherapy

The use of post-surgical radiotherapy in the surgery arm of the trial should be in accordance with local MDT recommendation. Radiotherapy may be prescribed according to agreed local protocols. Data on radiotherapy use including regimen and fractionation will be collected on the CRF. As radiotherapy in the standard surgery arm of SMALL may be omitted, this arm of the study is compatible with the PRIMETIME study and therefore patients may be offered entry to PRIMETIME.

7.1.3 Annual follow-up

Patients should have annual follow-up mammography carried out until 5 years post-randomisation. Where local protocol dictates that patients are not reviewed in clinic on an annual basis, arrangements should be made to contact the patient by telephone following the outcome of surveillance mammography. Any planned additional follow-up for patients in the surgery arm of the trial will be in accordance with local guidelines.

7.1.3.1 Mammography

Patients must be invited to attend for annual mammography for 5 years following randomisation. Beyond 5 years follow-up will be in accordance with local guidelines. In the majority of cases it is anticipated that this will be in the NHSBSP.

Following annual mammography, patients should be informed of the outcome of their mammogram as soon as possible and ideally within two weeks of the mammogram being carried out.

If a patient fails to attend for a mammogram appointment, a second appointment should be sent. If the patient fails to attend the second appointment, the patient's GP should be contacted to ensure that the patients address is correct. If the address is correct, a letter should be sent to the patient and their GP by the site research team, asking them to contact their research nurse. If a patient does not respond to this invitation, the patient should be contacted by telephone. The site research team must make every effort to ensure that patient contact details are up to date.

7.1.4 Investigations and treatment of ipsilateral breast disease

Suspected new disease in the ipsilateral breast should be investigated and treated according to local protocol. Details of confirmed disease will be collected on the CRF.

7.1.5 Investigations and treatment of contralateral breast disease

Suspected new disease in the contralateral breast should be investigated and treated according to local protocol. Details of confirmed disease in the contralateral breast will be collected on the CRF.

7.1.6 Related adverse event review

Protocol-related adverse events (AEs) will be collected post trial treatment, at 6-months post randomisation and annually from randomisation on the CRF from years 1-5, with reference to the defined Surgical Complications and Definitions (see Appendix 4) for events occurring within 30 days of trial treatment or CTCAE thereafter. Serious Adverse Events (SAEs) will be reported from trial entry until 5 years post-randomisation in accordance with Section 12 Adverse Event Reporting.

7.1.7 Survival

Sites should report patient deaths by completing the Death Form immediately upon being made aware of the event.

7.2 Vacuum-assisted Excision Arm Patients

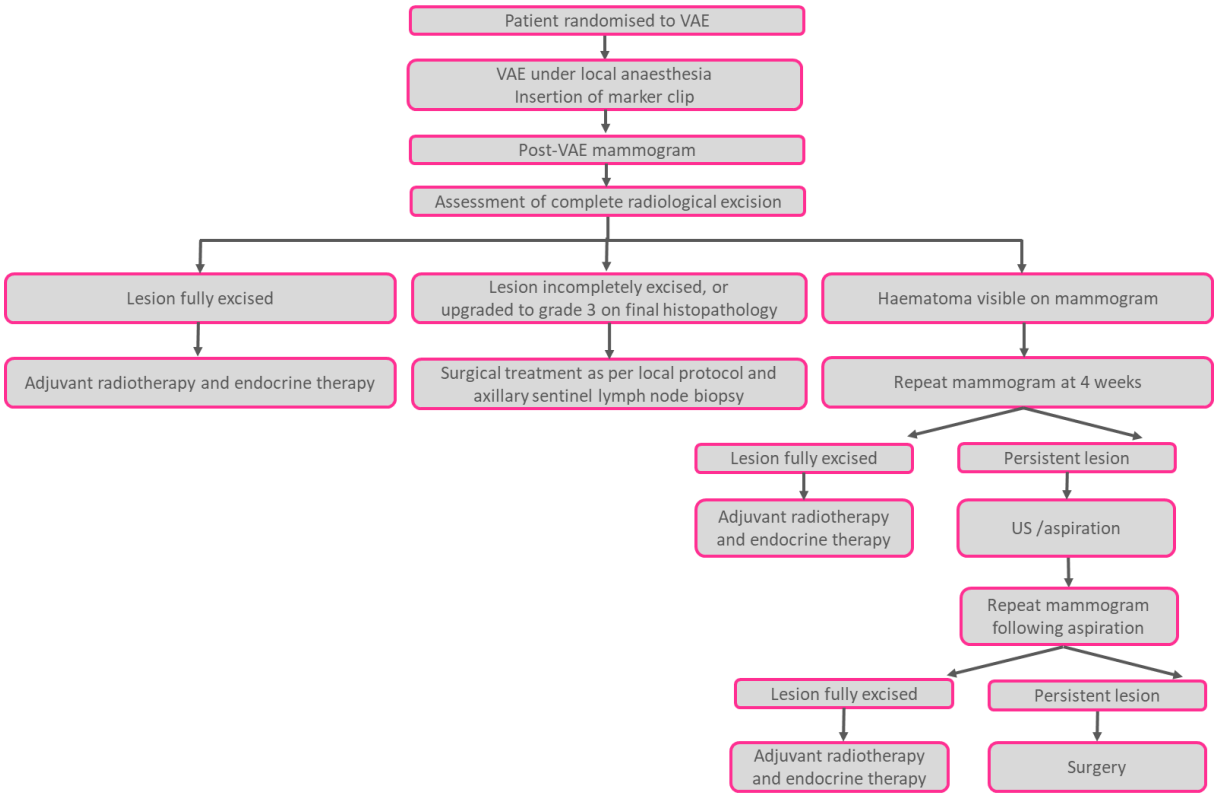
7.2.1 Baseline

Baseline data will be collected, to include details of the radiological findings and diagnostic biopsy histology including tumour type, grade, and biomarker status (ER, PR and HER2).

7.2.2 Treatment

The VAE arm is summarised in Flowchart 3: VAE Arm Patient Pathway.

Flowchart 3: VAE Arm Patient Pathway



7.2.2.1 Vacuum assisted excision

Please refer to the SMALL Radiology Manual for detailed guidance on the VAE procedure. Patients randomised to this arm of the trial will undergo VAE of their breast cancer under local anaesthesia as an out-patient procedure. It is expected that VAE will be performed within 31 days of randomisation. VAE may be carried out under either ultrasound or stereotactic guidance. All cores taken at VAE should be submitted for histopathological assessment, with number of cores and total weight recorded on the CRF. VAE should be carried out by appropriately-trained individuals carrying this out as part of their routine clinical practice. Post-VAE a marker clip should be inserted and a post-VAE mammogram carried out (lateral/mediolateral oblique and cranio-caudal views). The procedure report should stipulate the needle gauge used, number of cores taken and the type of marker clip placed in the breast, together with the operator's impression of the completeness of excision. The post-VAE mammogram report should state whether the lesion remains visible. If no lesion is visible then complete excision of the lesion is assumed. If the lesion remains visible then surgical excision will be required, in these cases please also forward a copy of the patient's anonymised pathology report to the SMALL Trial Office.

If interpretation of the post-VAE mammogram is unclear due to the presence of haematoma then a repeat mammogram should be carried out at 4 weeks post-procedure. If haematoma remains present at this stage then repeat ultrasound should be carried out with aspiration of the haematoma. Subsequently a further repeat mammogram should be carried out. If at this stage the lesion is resolved then complete excision is assumed. A persistent lesion should be assumed to be residual disease and the patient should proceed to surgical excision.

Where there is uncertainty at a local level regarding completeness of excision, a radiological second opinion can be provided through the Radiological Second Opinion Service (see below, Section 7.2.3.3).

Patients undergoing VAE only in the VAE arm will not undergo any axillary procedure in addition to their axillary ultrasound carried out as part of their diagnostic assessment. Patients proceeding from VAE to surgical treatment due to radiological assessment of incomplete excision should undergo axillary staging using sentinel lymph node biopsy.

Pathological review of VAE samples may result in re-assignment of tumour grade in some cases. Patients where tumour grade is re-assigned from grade 1 to grade 2 will remain in the VAE arm of the study. However, in the small number of cases where a tumour grade is re-assigned from grade 1 to grade 3, these cases will be treated with standard surgery and axillary SLNB, as such higher grade tumours may be more biologically aggressive than grade 1 or grade 2 tumours and therefore do not constitute low-risk tumours that are considered suitable for minimally invasive treatment.

A copy of the patient's anonymised pathology report for the VAE should be forwarded to the SMALL Trial Office.

7.2.2.2 Radiological second opinion service

A radiological second opinion service will be provided where local radiologists wish a second opinion regarding the assessment of completeness of excision. When a radiological second opinion is required, the current images and any prior images (if not previously captured) will be locally anonymised and uploaded for review via Image Exchange Portal or the local equivalent, to enable the images to be reviewed via an NHS computer. Participating sites which are unable to transfer images in this way should submit anonymised images for review on CD via post, including the patient's TNO, date of birth and date of mammogram only as identifiers. A request for the radiology second opinion service should be emailed to the SMALL Trial Office.

The outcome of the radiology review will be notified via email to the main contact, reporting radiologist and nominated lead radiologist within 7 days of the images being uploaded.

Please refer to the SMALL Radiology Manual for further details.

7.2.2.3 Endocrine therapy

Adjuvant endocrine therapy is mandated within the VAE arm of the trial. Therefore, all patients should receive adjuvant endocrine therapy according to pre-defined local guidelines. Data on the use of endocrine therapy will be captured on the CRF.

7.2.2.4 Radiotherapy

The use of post-surgical radiotherapy is mandated within the VAE arm of the trial. Radiotherapy may be prescribed according to agreed local protocols. Data on radiotherapy use including regimen and fractionation will be collected on the CRF.

7.2.2.4.1. Radiotherapy treatment timelines

Radiotherapy should commence within 8 weeks following VAE and ideally within 31 days following breast conserving surgery as recommended by NICE. Occasionally, this will need to be delayed to allow treatment for breast infection or persistent seroma. It is anticipated that partial breast radiotherapy will

be discussed/offered as per NICE guidelines 2018, although omission of radiotherapy is not appropriate in the VAE arm as radiotherapy is mandated for these patients.

7.2.2.4.2. Radiotherapy planning and delivery

Radiotherapy planning and delivery should be carried out in accordance with the best current routine practice, as exemplified in the IMPORT and FAST-Forward planning and delivery guidelines.

7.2.2.4.3. Supportive care guidelines

All required supportive care should be delivered according to local practice.

7.2.2.4.4. Radiotherapy Quality Assurance

A radiotherapy quality assurance (RTQA) program will be instigated to ensure the safety and consistency of radiotherapy delivery at participating sites. For further information please see Appendix 5.

7.2.3 Annual follow-up

Patients should have annual follow-up mammography carried out until 5 years post-randomisation. Where local protocol dictates that patients are not reviewed in clinic on an annual basis, arrangements should be made to contact the patient by telephone following the outcome of surveillance mammography. Any planned additional follow-up for patients in the surgery arm of the trial will be in accordance with local guidelines.

7.2.3.1 Mammography

Patients must be invited to attend for annual mammography for 5 years following randomisation. Beyond 5 years follow-up will be in accordance with local guidelines. In the majority of cases it is anticipated that this will be in the NHSBSP.

Following annual mammography, patients should be informed of the outcome of their mammogram as soon as possible and ideally within two weeks of the mammogram being carried out.

If a patient fails to attend for a mammogram appointment, a second appointment should be sent. If the patient fails to attend the second appointment, the patient's GP should be contacted to ensure that the patients address is correct. If the address is correct, a letter should be sent to the patient and their GP by the site research team, asking them to contact their research nurse. If a patient does not respond to this invitation, the patient should be contacted by telephone. The site research team must make every effort to ensure that patient contact details are up to date.

7.2.3.2 Ipsilateral mammographic indications for patient recall

Mammographic changes which would warrant recall for further investigation are:

- Developing asymmetry or mass around the marker clip at the VAE site
- A new non-calcified lesion in either breast which is not definitively benign
- A new cluster of microcalcification in either breast which is not definitively benign

7.2.4 Relapse

All relapses will be treated as per local practice. As soon as definite confirmation has been obtained that a patient has relapsed or has developed a new second primary cancer, the applicable form should be completed and submitted to the SMALL Trial Office; Ipsilateral Breast Disease (please also forward a copy of the patient's anonymised pathology report to the SMALL Trial Office), Contralateral Breast Disease or Distant Metastases Form. See Table 1 for definitions of relapse.

Patients who relapse or develop a new second primary cancer should remain on follow-up.

Table 1: Definition of Relapse

Type of Relapse	Definition
Loco-regional relapse (invasive or in situ)	A loco-regional relapse is defined as a recurrence of breast cancer (either invasive or in situ) in the ipsilateral breast/chest wall, axillary lymph nodes and/or ipsilateral supraclavicular fossa and/or internal mammary nodes
Distant relapse	Distant recurrence is defined as a recurrence (metastasis) of breast cancer developing beyond the ipsilateral breast/chest wall, axillary lymph nodes and/or ipsilateral supraclavicular fossa and internal mammary lymph nodes
New primary	Confirmation of the presence of a second unrelated and new cancer. For the purposes of SMALL this will include contralateral malignant breast disease (either invasive or in situ)

7.2.5 Related Adverse Event Review

Protocol-related AEs will be collected post trial treatment, at 6-months post randomisation and annually from randomisation on the CRF from years 1-5, with reference to the defined Surgical Complications and Definitions (see Appendix 4). Serious Adverse Events (SAEs) will be reported from study entry until 5 years post-randomisation in accordance with Section 12 Adverse Event Reporting.

7.2.6 Survival

Sites should report patient deaths by completing the Death Form immediately upon being made aware of the event. Every effort should be made to obtain a date and cause of death.

7.3 Protocol Deviations and Patient Withdrawal

7.3.1 Protocol deviations

The details of the protocol deviation (date, reason and type of deviation) should be clearly documented in the source data. A Deviation Form should be completed to notify the SMALL Trial Office of the deviation.

Patients will continue to be followed-up on an intent-to-treat basis.

7.3.2 Withdrawal of consent

Patients may withdraw consent at any time during the trial. For the purposes of this trial, three different types of withdrawal are defined:

- The patient would like to withdraw from the randomised allocation, but is willing to be followed up according with the Schedule of Assessments (i.e. the patient has agreed that data can be collected and used in the trial analysis)
- The patient would like to withdraw from the randomised allocation and does not wish to undergo study assessments in accordance with the Schedule of Events but is willing to be followed up at standard clinic visits (i.e. the patient has agreed that data can be collected at standard clinic visits and used in the trial analysis)
- The patient would like to withdraw from the randomised allocation and is not willing to be followed-up for the purposes of the trial at any further visits (i.e. only data collected prior to the withdrawal of consent can be used in the trial analysis)

The details of withdrawal (date, reason and type of withdrawal) should be clearly documented in the source data. A Withdrawal of Consent Form should be completed to notify the SMALL Trial Office of the patient's withdrawal.

7.4 Concurrent Studies

Investigators wishing to enrol patients into another trial should contact the SMALL Trial Office in the first instance. The SMALL Trial Management Group (TMG) will consider the enrolment of SMALL patients into other trials that do not interfere with the analysis of the primary outcome or introduce bias. Examples may include trials of imaging or supportive treatment. The SMALL Trial Office will maintain a contemporary record of trials approved by the TMG. Where a trial has not been considered, the SMALL Trial Chief Investigator will provide advice based on the above principles.

8. QUALITY OF LIFE

8.1 Quality of life

The primary QoL aspect of the trial examines the hypothesis that the psychological well-being of women undergoing minimally-invasive VAE of small screen-detected breast cancers is not adversely affected by this approach, when compared standard surgical treatment. In addition, these QoL outcomes will inform future women diagnosed with small, good prognosis invasive breast cancer through the NHSBSP. Patients will be asked to complete questionnaires at different time-points, which will assess quality of life outcomes including psychological adjustment, anxiety and depression, body image and satisfaction with breasts, These will be completed at the time points summarised in Table 2.

8.1.1 EORTC QLQ-C30 and BR 23

The EORTC QLQ-C30 is a validated instrument for evaluating quality of life in patients participating in clinical trials. The core module incorporates nine multi-item scales (functional, symptomatic and a global health and quality of life scale)[34]. The breast- specific module (QLQ BR23) was designed to be used in conjunction with the QLQ-C30 and consists of 23 items covering symptoms and side-effects related to different treatment modalities (including both the breast and arm), as well as body image, sexuality and future perspectives[35].

8.1.2 EuroQoL EQ-5D

The EQ-5D is a health status measure comprised of 5 attributes or dimensions - mobility, self-care, usual activity, pain/discomfort and anxiety/depression[36]. The single summary scores derived from the EQ-5D can be used in QALY analysis and in cost- effectiveness and cost-utility analysis.

8.1.3 BREAST-Q (breast conserving therapy module)

The BREAST-Q is a patient-reported outcome instrument designed to evaluate outcomes among women undergoing different types of breast surgery and includes a BCT (breast conserving therapy) module appropriate to the patient population in this study[37]. The BREAST-Q comprises two over-arching themes, which are patient satisfaction and health-related quality of life. Body image is an important concept for many women undergoing treatment for breast cancer, and it is possible that there may be differences in body image perception and satisfaction with breasts between the conventional surgery arm and the VAE arm, which is the rationale for utilising the BREAST-Q in this study.

Table 2: Timeline for Quality of Life Questionnaires

	Time points (months from randomisation)						
Questionnaires	**Baseline**	**6**	**12**	**24**	**36**	**48**	**60**
EORTC QLQ-C30 & BR23	✓	✓	✓		✓		✓
BREAST-Q	✓		✓	✓	✓	✓	✓
Euro-QoL EQ-5D	✓	✓	✓	✓	✓	✓	✓

With the exception of the baseline QoL questionnaires, which will be completed by the patient prior to randomisation, all other questionnaires will be distributed directly to the patients' home address by the SMALL Trial Office for completion at the designated time points.

Site research teams should inform the SMALL Trial Office immediately upon becoming aware of any changes to patient contact details by completing and returning the Change of Patient Contact Details Form.

9. HEALTH ECONOMICS

9.1 Form of the Health Economic Evaluation

If VAE is found to be an effective approach to help de-escalate the need for surgery in the treatment of small screen-detected breast cancer then it is likely that there will be important cost implications for the health care sector. For example, the patient will avoid initial standard surgery but will still receive adjuvant radiotherapy or endocrine treatment (according to local protocol) and will undergo mammographic surveillance, so the impact on resources and quality of life may or may not compare favourably to current standard treatment. If inpatient stay and resources associated with more invasive treatment are deemed unnecessary, then overall, resources may be saved. However, VAE may or may not incur unexpected or unscheduled costs due to additional appointments for reassurance using health care resources (for example, in providing counselling). Therefore, all associated resource use costs incurred by both approaches need to be assessed in conjunction with measures of effectiveness.

The aim of the economic evaluation is to determine the cost-effectiveness of VAE compared with standard surgery for small screen- detected breast cancer. The most appropriate type of analysis is a cost-effectiveness analysis which will be determined in two ways: a cost-effectiveness analysis will be undertaken based on a number of outcomes including the cost re-excision rate avoided at 10 years and cost per local recurrence of breast cancer avoided utilising the clinical outcome data collected within the trial. In addition, a cost-utility analysis will be undertaken to calculate the cost per additional quality-adjusted life year (QALY) gained. The utility values required to calculate QALYs will be obtained by administering the EuroQol EQ-5D questionnaire at the time points described in the PRO section. In the first instance, the evaluation will consider costs incurred by the health service in the delivery of both treatment pathways. However, information on costs incurred by patients will also be collected in order that an evaluation from a wider societal perspective can also be undertaken.

9.2 Cost Data Collection

Data collection will be undertaken prospectively for all trial patients so that a stochastic cost analysis can be undertaken. The process of collecting resource use data will be undertaken separately from data collection on unit costs.

The main resource uses to be monitored from the trial by trial staff (but not directly from the patients) include the following:

- Consultation time required to explain each procedure for explanation and consent (captured in a staff questionnaire or trial data collection sheet)
- VAE and surgical procedures (identification of procedures will be collected as part of the trial data collection; resource use associated with alternative procedures will be collected from time and motion study where appropriate or staff/expert opinion)
- Adjuvant therapy (which is provided according to local protocols and will differ across centres; this will be captured by a survey of protocols from the range of centres and the full range will be tested in the probabilistic sensitivity analysis)
- Resource use involved with mammography procedures (from a staff survey questionnaire and/or HRG cost data for mammography)
- Costs involved with other related procedures, including level of health care professional involvement in the procedure, equipment required, overheads, consumables and drugs including anaesthesia (procedures used will be identified from staff and trial data collection sheet; resource use will be collected from health care professionals in the various centres via time and motion study or expert opinion as appropriate)
- Any additional procedures required where initial treatment is unsuccessful or incomplete (Trial participating staff)
- Duration of inpatient stay for the surgical procedure (Trial data collection sheets)

Information on additional related primary or secondary care contacts will also be collected from women to ensure any resulting resource use from additional complications is recorded. The best approach to this data collection is likely to be the cross-sectional approach to investigate community-based healthcare and participant resource use for the first 5 years post randomisation, which follows that used by the ProtecT study. A patient resource use questionnaire is used to collect patient data, on private travel for hospital appointments and time off work, for example, with the aim of obtaining cross-sectional

community based healthcare and participant resource use for the first 5 years post randomisation. However, to achieve this, a specific resource use questionnaire is distributed to all women at one time point. This approach will capture some women at year one post-randomisation, some at 2 years etc. The approach can be used to ensure that no woman receives more than one questionnaire. The questionnaire will be issued at one time point and for the targeted women it will be at 4 months, 8 months and 12 months post-randomisation, depending on when they were randomised. In each case the requested information will relate to their resource use in the previous 4 months. In the 18-60 months questionnaires women can be asked about resource use in the previous 6 months. This approach would capture specific resource use for all women randomised into the study for complete coverage of five years, and follows the success of capturing the analogous data for men in the NIHR-HTA funded ProtecT and CAP studies currently in progress for prostate cancer. Unit costs will be obtained and attached to resource items in order that a cost can be calculated for each trial patient. Published sources for these costs will include Unit Costs of Health and Social Care and NHS Reference costs. Also, some primary cost data will be collected from a representative sample of participating hospitals. In addition, the set-up costs of the trial will be estimated and additional analyses will be undertaken including these costs. In order to consider the wider cost implications of the interventions, a patient cost questionnaire will be administered to all trial patients at the suggested year 5 time-points. The questionnaire will contain questions to determine out of pocket expenses incurred (e.g. transport costs) when attending for treatment and private time costs including time lost from work.

9.3 Analyses

The main analysis will be undertaken at completion of the project, using the data analyses from the trial. There will be two components to the analysis: a within trial analysis and a model-based analysis.

Model-based analysis - a preliminary modelling exercise will be carried out at the beginning of the study and will be populated and refined during the pilot to prepare for the end of trial analysis.

A decision analytic model will be used to allow the extrapolation of cost and effectiveness parameters beyond the data observed in the clinical trial (and to allow extrapolation to other settings). The model will, therefore, consider treatment over total disease duration and will include surgical treatments provided in the longer term. An individual sampling model (such as a Markov model) or similar model to ensure time to event can be analysed. A preliminary model-based analysis will be conducted during the initial months of the study, using all available data and highlighting areas of uncertainty to be targeted during the trial – this will be revisited during the pilot stage and draw upon follow-up data up to 18 months. This will utilise published data and assumptions to predict costs and benefits into the long-term. The analysis will then be repeated in the last 12 months of the study using the main trial and follow-up data, but still predicting costs and effects beyond the trial end.

Results of all economic analyses will be presented using cost-effectiveness acceptability curves to reflect sampling variation and uncertainties in the appropriate threshold cost-effectiveness value. We shall also use simple and probabilistic sensitivity analyses to explore the robustness of these results to plausible variations in key assumptions and variations in the analytical methods used, and to consider the broader issue of the generalisability of the results.

10. TISSUE SAMPLE COLLECTION

Tissue samples must be collected in accordance with the SMALL Trial Tissue Sample Collection Guidelines.

Principal Investigators are asked to nominate one individual at their site to act as a Lead Pathologist. The Lead Pathologist will be provided with the SMALL Trial Tissue Sample Collection Guidelines describing the labelling and shipment of samples.

A representative formalin fixed paraffin embedded tumour block from the VAE will be collected for all consenting patients recruited to the VAE arm of the trial, plus a representative block from any subsequent confirmed ipsilateral recurrence will be submitted to the Human Biomaterials Resource Centre (HBRC) for future ethically approved research.

For further details please refer to the SMALL Trial Tissue Sample Collection Guidelines.

All material must be sent to:

Dr Jane Steele
Human Biomaterials Resource Centre (HBRC)
University of Birmingham
Hospital Drive
Birmingham, B15 2TT

☎ 0121 414 7668
✉ J.C.Steele@bham.ac.uk

If the tissue sample is urgently needed for subsequent re-assessment by the local Pathology Department, please contact the SMALL Trial Office who will arrange for immediate retrieval of the material and return.

Please be aware that it will be the responsibility of the local research team to obtain their patient's pathology material if the material is stored at a separate site to the registering hospital.

Pathology Departments will receive a per-patient payment for supplying the requested samples.

11. MAMMOGRAPHIC IMAGE LIBRARY

The trial will generate a library of anonymised mammographic and ultrasound images. The aim of any future image studies would be to identify potential radiological features that might identify cases where minimally invasive treatment was associated with early local recurrence (i.e. features predicting for possible incomplete excision with VAE).

Retrospective collection of radiological images is notoriously complex and incomplete and the raw (unprocessed) images, which are not routinely stored on hospital Picture Archive Computer Stores (or a local equivalent platform) are needed for any computer based analysis, therefore data needs to be captured in real time, as much as possible. Sites will be supplied with bespoke image collection software tools[38]. This will provide:

- De-identification with a pseudonym, Digital Imaging and Communications in Medicine (DICOM) Supplement 142 compliant, de-identification process that recognises the primary identifier (usually the NHS number) and always replicates the original pseudonym. This means that any new images from a recognised trial patient will always be allocated to the correct file within the data store
- Automatic uploading via N3, the secure NHS network
- Mark up and remote reading on any PC connected to the internet but specifically the diagnostic quality monitors attached to the work stations regularly used and quality assured for the breast screening programme

SMALL trial patients will be appropriately tagged within the store to ensure that images can be subsequently associated with outcome data from the trial site.

The image library is maintained and managed by the Scientific Computing section based at Royal Surrey County Hospital. The de-identified image and data will be stored on the cloud.

Participating sites which do not use Picture Archiving Computer Stores or an equivalent platform, should submit de-identified images for review on CD via post to the Scientific Computing section at Royal Surrey County Hospital, including the patient's TNO, date of birth and date of mammogram only as identifiers.

12. ADVERSE EVENT REPORTING

The collection and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care Research and the requirements of the National Research Ethics Service (NRES). Definitions of different types of AE are listed in Appendix 2. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the protocol.

12.1 Reporting Requirements

12.1.1 Adverse Events

AEs (see Appendix 2 for definitions) are commonly encountered in patients receiving treatment for breast cancer. The safety of these treatments is already well characterised, therefore only related AEs experienced as a direct result of the trial protocol will be reported.

12.1.2 Serious Adverse Advents

Investigators should report AEs that meet the definition of an SAE (see Appendix 2 for definition) and are not excluded from the reporting process as described below.

12.1.2.1 Expected Serious Adverse Events

The following are regarded as expected SAEs for the purpose of the trial and should not be reported on an SAE form:

- Hospitalisation for primary surgery
- Haematoma, wound infection or seroma, as a result of primary breast surgery, unless the condition is life threatening or proves fatal
- SAEs relating to breast reconstruction
- SAEs relating to adjuvant treatment for breast primary cancer or recurrence
- SAEs that are related to symptoms or progression of the patient's cancer
- Death from cancer or from a pre-existing medical condition

This is not an exclusive list and Investigators should only report SAEs which are attributable to the trial protocol.

12.1.3 Reporting period

Details of all AEs (except those listed above) will be documented and reported from the date of commencement of protocol defined treatment until 5 years post-randomisation.

12.2 Reporting Procedure

12.2.1 Site

12.2.1.1 Adverse Events

Protocol-related AEs should be recorded in the AE section of the Treatment Form and Annual Follow-up Form with reference to the defined Surgical Complications and Definitions (see Appendix 4).

SAEs will be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (see Appendix 3). Any SAEs experienced by the patient but not included in the CTCAE should be graded by an Investigator and recorded on the AE Form using a scale of (1) mild, (2) moderate or (3) severe. For each sign/symptom, the highest grade observed since the last visit should be recorded.

12.2.1.2 Serious Adverse Events

For more detailed instructions on SAE reporting refer to the SAE Form Completion Guidelines contained in section 5 of the Investigator Site File (ISF).

AEs defined as serious and which require reporting as an SAE (excluding events listed in Section 12.1.2 above) should be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE which should be documented using the CTCAE version 4.0.

On becoming aware that a patient has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be faxed together with a SAE Fax Cover Sheet (or emailed where fax facilities are not available) to the SMALL Trial Office using one of the numbers listed below as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, fax the completed SAE Form with an SAE Fax Cover Sheet to:

🖷 0121 414 8392 or 🖷 0121 414 3700

Or email to:

✉ reg@trials.bham.ac.uk

On receipt the SMALL Trial Office will allocate each SAE a unique reference number. This number will be transcribed onto the SAE Fax Cover Sheet which will then be faxed back to the site as proof of receipt. If confirmation of receipt is not received within 1 working day please contact the SMALL Trial Office. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE Fax Cover Sheet completed by the SMALL Trial Office should be filed with the SAE Form in the ISF.

For SAE Forms completed by someone other than the Investigator, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the SMALL Trial Office in the post and a copy kept in the ISF.

Investigators should also report SAEs to their own Trust in accordance with local practice.

12.2.1.3 Provision of follow-up information

Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

12.2.2 Trial Office

On receipt of an SAE Form seriousness and causality will be determined independently by a Clinical Coordinator. An SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the trial treatment will be regarded as a related SAE. The Clinical Coordinator will also assess all related SAEs for expectedness. If the event is unexpected (i.e. is not defined in the protocol as an expected event) it will be classified as an unexpected and related SAE.

12.2.3 Reporting to the main Research Ethics Committee

12.2.3.1 Unexpected and Related Serious Adverse Events

The Trial Office will report all events categorised as Unexpected and Related SAEs to the main Research Ethics Committee (REC) and Sponsor within 15 days.

12.2.3.2 Other safety issues identified during the course of the trial

The main REC and Sponsor will be notified immediately if a significant safety issue is identified during the course of the trial.

12.2.4 Investigators

Details of all Unexpected and Related SAEs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the ISF.

12.2.5 Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review all SAEs.

13. DATA HANDLING AND RECORD KEEPING

13.1 Data Collection

The Case Report Form (CRF) will comprise the following forms:

Form	Summary of data recorded	Schedule for submission
Eligibility Checklist	Confirmation of eligibility	As soon as possible after randomisation
Randomisation	Patient details; confirmation of diagnosis of grade 1 ER-pos, PR-pos, HER2-neg breast cancer	As soon as possible after randomisation
Baseline	Details of biopsy histology; details of planned surgery, concomitant medications	Within 1 month of randomisation
Surgical Procedure for Surgery Arm	Details of type of surgery performed, surgical complications Details of any additional procedure performed, surgical complications	Following completion of planned primary surgery (allow 30 days to report surgical complications) Following completion of any additional procedures
Pathology – Planned Randomised Surgery	Pathology details of surgical excision specimen (including margin status) and axillary node status, (with copy of pathology report)	As soon as possible following surgery
Pathology – Incomplete Surgical Excision	Pathology details of any re-excision of margins (with copy of pathology report)	As soon as possible following re-excision procedure
VAE	Details of VAE, including needle gauge used, post-procedure radiology (including any repeat imaging or haematoma aspiration)	Following completion of planned VAE and post-VAE mammogram (allow 30 days to report surgical complications)

Radiological Second Opinion Service Request	Details of imaging submitted and reason for second opinion request	As required
Pathology – Planned Randomised VAE	Pathology details following planned randomised VAE (with copy of pathology report)	As soon as possible following VAE
Surgical Procedure for VAE Arm	Details of type of surgery performed, surgical complications Details of any additional procedure performed in VAE arm, surgical complications	Following completion of any additional procedures
Pathology – Following Incomplete VAE	Pathology details for any surgery following radiological diagnosis of incomplete excision or upon upward grade migration post VAE (with copy of pathology report)	As soon as possible following procedure
Adverse Event	Complications related to planned randomised treatment	As soon as possible following 30 days after completion of randomised treatment
Adjuvant Treatment	Details of adjuvant endocrine therapy and radiotherapy, targeted therapy and chemotherapy. Details of any related adverse events.	Within 1 month of the 6-month follow-up
Annual Follow-up	Survival, outcome of annual mammogram, concomitant medications (HRT, endocrine therapy, NSAIDs), persisting protocol related adverse effects, record of related interventions and referrals, new breast disease, other clinical trials	Within 1 month of patient annual mammogram or as soon as possible following investigations or treatment if indicated
Ipsilateral Invasive Breast Cancer	Date confirmed, disease type and nature (e.g. in situ or invasive), including grade and type (with copy of pathology report)	Immediately upon confirmation of disease
Pathology – Invasive Ipsilateral Breast Cancer	Details of pathology of ipsilateral breast cancer	As soon as possible following confirmation of ipsilateral invasive breast cancer
Contralateral Invasive Breast Cancer	Date confirmed, disease type and nature including grade and type	Immediately upon confirmation of disease
Death Form	Date and cause of death	Immediately upon notification of patient's death
Deviation Form	Completed in the event of a deviation from the protocol	Immediately upon discovering deviation
Withdrawal Form	Used to notify the Trial Office of patient withdrawal from the trial	Immediately upon patient withdrawal
Serious Adverse Event	See Section 12	Complete and return form immediately on discovering the patient has experienced an SAE

The study will use an eRDC system (as described in Section 6.2) for completion of CRFs. If the eRDC system is unavailable for an extended period of time a paper based CRF should be completed and forms returned to the SMALL Trial Office. The Investigator and site staff must ensure all data from scheduled visits are promptly entered into the eRDC system in accordance with the SMALL electronic CRF (eCRF) Completion Guidelines. The SMALL eRDC system can be accessed via the following link:

http://www.cancertrials.bham.ac.uk

SAE reporting will be paper-based. Paper CRFs must be completed, signed/dated and returned to the SMALL Trial Office by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log) within the timeframe listed above. The exceptions to this are the SAE Form and Withdrawal of Consent Form which must be co-signed by the Investigator. Entries on the CRF should be made in ballpoint pen, in blue or black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported within the eRDC system or on paper should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. All missing and ambiguous data will be queried. All sections are to be completed before returning to the SMALL Trial Office.

In all cases it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data are accurate.

Where paper CRFs have been used, the completed original forms must be sent to the SMALL Trial Office. A copy of all CRFs should be retained in the ISF.

Study CRFs may be amended by the SMALL Trial Office, as appropriate, throughout the duration of the study. Whilst this will not constitute a protocol amendment, new versions of the form must be implemented by participating sites immediately on receipt.

13.2 Archiving

It is the responsibility of the Principal Investigator to ensure all electronically stored data, essential trial documentation and source records (e.g. signed Informed Consent Forms, Investigator Site Files, Pharmacy Files, patients' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 10 years after the end of the trial or following the processing of all biological material collected for research, whichever is the later. Do not destroy any documents without prior approval from the CRCTU Document Storage Manager.

14. QUALITY MANAGEMENT

14.1 Site Set-up and Initiation

All sites will be required to sign a Clinical Study Site Agreement and complete a Site Registration Form prior to participation. In addition, all participating Investigators will be asked to complete a Registration Form and supply a current CV to the SMALL Trial Office. All members of the site research team will also be required to sign the Site Signature and Delegation Log, which should be returned to the Trial Office. Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, Adverse Event reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The Trial Office must be informed immediately of any change in the site research team.

14.2 On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the SMALL Quality Management Plan. Additional on-site monitoring visits may be triggered for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of patient withdrawals or deviations. If a monitoring visit is required the Trial Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the SMALL trial staff access to source documents as requested.

14.3 Central Monitoring

Where a patient has given explicit consent, sites are requested to send in copies of signed Informed Consent Forms for in-house review.

Trial staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trial staff will check CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will receive Data Clarification Forms requesting missing data or clarification of inconsistencies or discrepancies.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group, Trial Steering Committee and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the main Research Ethics Committee (REC).

14.4 Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents.

Sites are also requested to notify the Trial Office of any inspections.

14.5 Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial or;
- The protocol relating to that trial, within 7 days of becoming aware of that breach

For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trial; or
- The scientific value of the trial

Sites are therefore requested to notify the SMALL Trial Office of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trial Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trial Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.

15. END OF TRIAL DEFINITION

The end of trial will be 6 months after the last data capture, or the final analysis of predictive biomarkers, whichever is later. This will allow sufficient time for the completion of protocol procedures, data collection and data input.

The duration of time for which patient follow-up data will be collected is dependent on future funding arrangements. Current funding is secured for this to continue for 5 years after randomisation of each patient and further funding will be sought to continue this in the longer term.

The Trial Office will notify the main REC that the trial has ended and a summary of the clinical trial report will be provided within 12 months of the end of trial.

16. STATISTICAL CONSIDERATIONS

16.1 Internal Pilot Study

The first part of the SMALL trial is an internal pilot study of 18 months duration. The aim of the internal pilot study is to demonstrate that sufficient eligible patients can be identified and recruited over the course of the study to robustly answer the main trial objectives. The patients randomised during the internal pilot phase will form part of the total number of patients (800) included in the main study.

16.1.1 Definition of outcome measures

The outcome measures in the internal pilot study will be assessed at the end of the 18 month pilot:

- Adequate recruitment is defined in terms of the number of sites open and the number of patients randomised at conclusion of the internal pilot phase

16.1.2 Analysis

No formal statistical testing will take place during the feasibility phase. Recruitment and site opening will be monitored by the Trial Management Group throughout the pilot phase. The specific progression criteria are detailed below in Section 16.1.3.

16.1.3 Specific progression criteria from internal pilot to main trial

- 141 patients recruited by end of month 18
- 44 sites activated for recruitment by the end of month 18

16.2 Main Trial

16.2.1 Definition of Primary outcome measures

Primary Outcome 1: *Re-excision following initial procedure*

The requirement for a second procedure in both arms will be ascertained.

Following VAE, patients will undergo radiological assessment of completeness of excision of their primary tumour. Where there is radiological evidence of residual disease, patients will undergo standard surgical excision (wide local excision and sentinel lymph node biopsy).

In the standard surgery arm of the trial, histopathological assessment of resection margin status will be carried out. The need for re-excision of margins will be determined by local MDT policy.

Primary Outcome 2: *Local recurrence free survival time for VAE*

This is defined in whole days as the time from randomisation until first report of ipsilateral invasive breast cancer. Patients without recurrence will be censored at the date of last clear mammogram or date of death.

16.2.2 Definition of Secondary outcome measures

Complications arising from surgery or VAE

This is defined as complications occurring within 30 days of protocol defined surgery or VAE. Possible complications are expected to include seroma, haematoma, wound infections, delayed wound healing, skin flaps necrosis, nipple necrosis, wound dehiscence, in hospital complications, hospital readmission and unplanned re-operations, and these are defined in Appendix 4.

Time to ipsilateral breast cancer recurrence

This is defined in whole days as the time from randomisation until first report of ipsilateral invasive disease. Randomised patients with no evidence of disease will be censored at the date of last clear mammogram or date of death.

Time to development of contralateral invasive breast cancer

This is defined in whole days as time from randomisation until first report of contralateral invasive disease. Randomised patients with no evidence of disease will be censored at the date of last clear mammogram or date of death.

Overall survival time

This is defined in whole days as time from randomisation until date of death from any cause. Patients who remain alive during the course of the study will be censored at the date last known to be alive.

Quality of life

The assessment utilities being used are defined in Section 8.1. These will all be scored at each timepoint utilising the specific scoring schemes for each type of questionnaire which will produce scores across multiple themes and domains.

QALY

This will be calculated from the EQ5D QoL questionnaire and will be utilised in the Health Economic analysis (see Section 9).

16.3 Analysis of Outcome Measures

Key aspects of the analysis methods to be utilised are detailed below and the statistical analysis plan will provide details of the selection of subjects to be included in each analysis in addition to procedures accounting for missing, unused or spurious data.

Primary Outcomes

Re-excision following initial procedure

Once all patients have undergone surgery the proportion of patients requiring re-excision will be compared between the trial arms. A 2-sided 95% confidence interval around the difference in proportions will be calculated. If the upper bound of the confidence interval is below 10 then non-inferiority will be declared. If non-inferiority is declared then a pre-specified but unpowered analysis of superiority will also be undertaken, to investigate whether superiority has also been demonstrated.

Local recurrence free survival time for VAE

The point estimate for local recurrence free survival at 5 years will be calculated with 2-sided 95% confidence interval using the Kaplan-Meier method. No hypothesis testing will be performed. This will be interpreted both with reference to the same rate calculated for the surgery arm of the trial and in relation to the undesirable local recurrence rate of 97%. Sensitivity analysis will be conducted utilising exact methods for calculating the proportion of recurrence at 5 years to explore the appropriateness of the Kaplan-Meier method.

Secondary Outcomes

Time to ipsilateral breast cancer recurrence, time to development of contralateral invasive breast cancer and overall survival will be analysed as per local recurrence free survival time above. Complications arising from surgery or VAE will be reported descriptively for both treatment arms (see Appendix 4 for complications and definitions). No hypothesis testing will be conducted.

QoL will be analysed using standardised area under the curve and appropriate repeated measures modelling techniques to compare treatment arms.

16.4 Planned Sub Group Analyses

No subgroup analyses are planned.

16.5 Planned Interim Analysis

No formal interim analysis is planned. Cumulating data will be reported to an independent data monitoring committee at 6, 12, 18 and 24 following trial opening and then annually, as required. Data presented will include trial recruitment and conduct, data completeness, compliance, safety and complications data relating to randomised allocation, subsequent procedures, radiotherapy, endocrine therapy and all adverse events. The DMC will also monitor local recurrence events to ensure that it does not exceed an acceptable threshold. The acceptable threshold has been set at 3% per year which was established in close consultation with the PPI members of the trial development group, and is set in recognition of the fact that local recurrence is not a life-threatening condition and is salvageable with further surgical treatment.

16.6 Planned Final Analyses

The final analysis of re-excision following initial procedure will be conducted 3 months following the completion of recruitment. This will ensure all patients have undergone randomised procedures and been assessed for re-excision. The analysis of complications arising from surgery or VAE will also be conducted at this point. Analysis of the local recurrence free survival and all remaining secondary outcomes will be conducted 3 months after all patients have completed 3 years of annual mammography following randomisation.

16.7 Power Calculations

The total number of patients to be recruited with an allocation ratio of 2:1 is 800 (533 VAE, 267 surgery). The total number of patients required for the re-excision comparison was 762[39] which has been inflated by 5%. This will ensure that we have sufficient patients for the single arm investigation into local recurrence rates with VAE, and allow for possible drop-outs. To ensure that the trial as a whole only has 5% alpha the significance level for each of the co-primary outcomes has been set at 2.5% with 90% power. The probability of success in both the surgery arm and the VAE arm is expected to be 80% (20% re-excision). The maximal acceptable difference between the two has been set at 10% which was defined as acceptable by PPI bearing in mind that this is salvageable by a second procedure and has no survival sequelae. The total number required for the local recurrence free survival outcome is 511[40] (VAE). This assumes that the expected survival probability at 5 years is 99%[25] and that an undesirable survival probability for VAE is 97% at 5 years. Allowing for 4 years recruitment and following all patients for a minimum of 3 years post randomisation.

17. TRIAL ORGANISATIONAL STRUCTURE

17.1 Sponsor

The study is sponsored by the University of Birmingham.

17.2 Coordinating Centre

The trial is being conducted under the auspices of the Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham according to their local procedures.

17.3 Trial Management Group

The Chief Investigator, Co-investigators, Trial Statistician, Senior Trial Manager and Trial Coordinator will form the TMG (members are identified in the introductory pages). The TMG will be responsible for the day-to-day conduct of the trial. They will be responsible for the clinical set-up, promotion, on-going management of the trial, the interpretation of the results and preparation and presentation of relevant publications. The TMG will meet every 3 months (usually by teleconference).

17.4 Trial Steering Committee

The TSC will be set up to provide overall supervision of the study, safety monitoring and to ensure the study is being conducted in accordance with the principles of GCP. Membership will be composed of the TMG, independent clinicians, invited Principal Investigators, representatives from the funders, an independent chair and at least one patient advocate. The TSC will meet shortly before commencement of the trial and then annually (usually by teleconference); they will supervise the conduct of the trial, monitoring progress including recruitment, data completeness, losses to follow-up, and deviations from the protocol. They will make recommendations about conduct and continuation of the study.

17.5 Data Monitoring Committee

Data analyses will be supplied in confidence to an independent Data Monitoring Committee (DMC), which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further patients. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMC will is scheduled to meet 6, 12 18 and 24 months after the trial opens to recruitment and then annually during the main recruitment phase and subsequently as and when required. Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the TMG who will convey the findings of the DMC to TSC, funder, and/or Sponsor as applicable. The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise patient safety. The trial would also stop early if the interim analyses showed differences between treatments that were deemed to be convincing to the clinical community.

17.6 Finance

SMALL is a clinician-initiated and clinician-led trial funded by the National Institute for Health Research Health Technology Assessment Programme. The study has been independently peer reviewed and has been adopted by the National Institute for Health Research (NIHR) Clinical Research Network (CRN) Portfolio.

The Sponsor will pay Research Costs, as defined in the Clinical Site Agreement, to participating sites.

18. ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, 1964, amended by the 48th WMA General Assembly, Somerset West, Republic of South Africa, 1996.

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and the General Data Protection Regulation and Human Tissue Act 2018 if appropriate) and Good Clinical Practice (GCP). The protocol will be submitted to and approved by the main Research Ethics Committee (REC) prior to circulation.

Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain local R&D approval. Sites will not be permitted to enrol patients until written confirmation of R&D approval is received by the Trial Office.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

19. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the General Data Protection Regulation and the Data Protection Act (2018). With the patient's consent, their full name, date of birth, National Health Service (NHS) number, or in Scotland the Community Health Index (CHI), address, post code and hospital number will be collected at trial entry to allow the Trial Office to send patient questionnaires to the patient's home address and for the purposes of tracing through NHS Digital. Patients will be identified using only their unique TNO, initials and date of birth on the Case Report Form and correspondence between the Trial Office and the participating site. However, patients are asked to give permission for the Trial Office to be sent a copy of their signed Informed Consent Form which will not be anonymised. This will be used to perform in-house monitoring of the consent process and may also be forwarded to other health care professionals involved in the treatment of the patient (e.g. patient's GP).

The Investigator must maintain documents not for submission to the Trial Office (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

The Trial Office will maintain the confidentiality of all patients' data and will not disclose information by which patients may be identified to any third party other than those directly involved in the treatment of the patient and organisations for which the patient has given explicit consent for data transfer (e.g. Cancer Registries, laboratory staff. Representatives of the SMALL trial team may be required to have access to patient's notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

20. INSURANCE AND INDEMNITY

University of Birmingham employees are indemnified by the University insurers for negligent harm caused by the design or co-ordination of the clinical trials they undertake whilst in the University's employment.

In terms of liability at a site, NHS Trust and non-Trust hospitals have a duty to care for patients treated, whether or not the patient is taking part in a clinical trial. Compensation is therefore available via NHS indemnity in the event of clinical negligence having been proven.

The University of Birmingham cannot offer indemnity for non-negligent harm. The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation.

21. PUBLICATION POLICY

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the Trial Management Group (TMG) and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the University of Birmingham. Intellectual property rights will be addressed in the Clinical Study Site Agreement between Sponsor and site.

22. REFERENCE LIST

1. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. *Lancet* 2012; **380**(9855): 1778-86.

2. Lannin DR, Wang S. Are Small Breast Cancers Good because They Are Small or Small because They Are Good? *The New England Journal of Medicine* 2017; **376**(23): 2286-91.

3. Public Health England and the Association of Breast Surgery. NHS Breast Screening Programme and Association of Breast Surgery: An audit of screen-detected breast cancers for the year April 2015 to March 2016., 2017.

4. Wilke LG, Czechura T, Wang C, et al. Repeat surgery after breast conservation for the treatment of stage 0 to ii breast carcinoma: A report from the national cancer data base, 2004-2010. *JAMA Surgery* 2014.

5. Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *Annals of Surgical Oncology* 2014; **21**(3): 704-16.

6. Bloomfield DJ, Core Group facilitated by The Royal College of R. Development of Postoperative Radiotherapy for Breast Cancer: UK Consensus Statements – a Model of Patient, Clinical and Commissioner Engagement? *Clin Oncol (R Coll Radiol)* 2017.

7. Losken A, Dugal CS, Styblo TM, Carlson GW. A meta-analysis comparing breast conservation therapy alone to the oncoplastic technique. *Annals of Plastic Surgery* 2014; **72**(2): 145-9.

8. Clough KB, Cuminet J, Fitoussi A, Nos C, Mosseri V. Cosmetic sequelae after conservative treatment for breast cancer: classification and results of surgical correction. *Annals of Plastic Surgery* 1998; **41**(5): 471-81.

9. Al-Ghazal SK, Fallowfield L, Blamey RW. Does cosmetic outcome from treatment of primary breast cancer influence psychosocial morbidity? *European Journal of Surgical Oncology* 1999; **25**(6): 571-3.

10. Waljee JF, Hu ES, Ubel PA, Smith DM, Newman LA, Alderman AK. Effect of esthetic outcome after breast-conserving surgery on psychosocial functioning and quality of life. *Journal of Clinical Oncology* 2008; **26**(20): 3331-7.

11. Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Annals of Surgery* 2010; **252**(3): 426-32; discussion 32-3.

12. Straver ME, Meijnen P, van Tienhoven G, et al. Role of axillary clearance after a tumor-positive sentinel node in the administration of adjuvant therapy in early breast cancer. *Journal of Clinical Oncology* 2010; **28**(5): 731-7.

13. Giuliano AE, Ballman KV, McCall L, et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. *JAMA* 2017; **318**(10): 918-26.

14. O'Connell RL, Rusby JE, Stamp GF, et al. Long term results of treatment of breast cancer without axillary surgery – Predicting a SOUND approach? *European Journal of Surgical Oncology* 2016; **42**(7): 942-8.

15. Gentilini O, Veronesi U. Abandoning sentinel lymph node biopsy in early breast cancer? A new trial in progress at the European Institute of Oncology of Milan (SOUND: Sentinel node vs Observation after axillary UltraSouND). *Breast* 2012; **21**(5): 678-81.

16. Purushotham AD, Upponi S, Klevesath MB, et al. Morbidity after sentinel lymph node biopsy in primary breast cancer: results from a randomized controlled trial. *Journal of Clinical Oncology* 2005; **23**(19): 4312-21.

17. Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. *Journal of the National Cancer Institute* 2006; **98**(9): 599-609.

18. Mauri G, Sconfienza LM, Pescatori LC, et al. Technical success, technique efficacy and complications of minimally-invasive imaging-guided percutaneous ablation procedures of breast cancer: A systematic review and meta-analysis. *Eur Radiol* 2017; **27**(8): 3199-210.

19. Sperber F, Blank A, Metser U, Flusser G, Klausner JM, Lev-Chelouche D. Diagnosis and treatment of breast fibroadenomas by ultrasound-guided vacuum-assisted biopsy. *Archives of surgery* 2003; **138**(7): 796-800.

20. Baez E, Huber A, Vetter M, Hackeloer BJ. Minimal invasive complete excision of benign breast tumors using a three-dimensional ultrasound-guided mammotome vacuum device. *Ultrasound Obstet Gynecol* 2003; **21**(3): 267-72.

21. Fine RE, Boyd BA, Whitworth PW, Kim JA, Harness JK, Burak WE. Percutaneous removal of benign breast masses using a vacuum-assisted hand-held device with ultrasound guidance. *Am J Surg* 2002; **184**(4): 332-6.

22. Strachan C, Horgan K, Millican-Slater RA, Shaaban AM, Sharma N. Outcome of a new patient pathway for managing B3 breast lesions by vacuum-assisted biopsy: time to change current UK practice? *J Clin Pathol* 2016; **69**(3): 248-54.

23. Fine RE, Israel PZ, Walker LC, et al. A prospective study of the removal rate of imaged breast lesions by an 11-gauge vacuum-assisted biopsy probe system. *Am J Surg* 2001; **182**(4): 335-40.

24. Eller A, Janka R, Lux M, et al. Stereotactic vacuum-assisted breast biopsy (VABB)–a patients' survey. *Anticancer research* 2014; **34**(7): 3831-7.

25. Coles CE, Griffin CL, Kirby AM, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. *Lancet* 2017; **390**(10099): 1048-60.

26. Kirwan CC, Coles CE, Bliss J, Group PPW, Group PPW. It's PRIMETIME. Postoperative Avoidance of Radiotherapy: Biomarker Selection of Women at Very Low Risk of Local Recurrence. *Clin Oncol (R Coll Radiol)* 2016; **28**(9): 594-6.

27. Wallis MG. How do we manage overdiagnosis/overtreatment in breast screening? *Clin Radiol* 2017.

28. Holland R, Veling SH, Mravunac M, Hendriks JH. Histologic multifocality of Tis, T1-2 breast carcinomas. Implications for clinical trials of breast-conserving surgery. *Cancer* 1985; **56**(5): 979-90.

29. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; **366**(9503): 2087-106.

30. Fisher B, Dignam J, Bryant J, et al. Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. *Journal of the National Cancer Institute* 1996; **88**(21): 1529-42.

31. Vos EL, Siesling S, Baaijens MHA, et al. Omitting re-excision for focally positive margins after breast-conserving surgery does not impair disease-free and overall survival. *Breast Cancer Research and Treatment* 2017; **164**(1): 157-67.

32. Lee AHS, Carder P, Deb R, et al. Royal College of Pathologists. Guidelines for non-operative diagnostic procedures and reporting in breast cancer screening.June 2016., 2016. www.rcpath.org (accessed 4/7/18).

33. Ellis IO, Carder P, Hales S, et al. Royal College of Pathologists. Pathology reporting of breast disease in surgical excision specimens incorporating the dataset for histological reporting of breast cancer.June 2016, 2016. www.rcpath.org (accessed 19/7/18).

34. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute* 1993; **85**(5): 365-76.

35. Sprangers MA, Groenvold M, Arraras JI, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. *Journal of Clinical Oncology* 1996; **14**(10): 2756-68.

36. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; **20**(10): 1727-36.

37. Pusic AL, Klassen AF, Scott AM, Klok JA, Cordeiro PG, Cano SJ. Development of a new patient-reported outcome measure for breast surgery: the BREAST-Q. *Plastic & Reconstructive Surgery* 2009; **124**(2): 345-53.

38. Patel M, Looney P, Young K, Halling-Brown M. A National Digital Mammography Image Database and Associated Observer Study Software. Symposium Mammographicum; 2014; Bournemouth: British Institute of Radiology; 2014. P. 26.

39. Machin D, Campbell MJ. Sample size tables for clinical studies. Oxford: Blackwell Publishing; 2009.

40. Lawless JF. Statistical models and methods for lifetime data. New York: John Wiley & Sons; 2003.

41. Donovan JL, Lane JA, Peters TJ, et al. Development of a complex intervention improved randomization and informed consent in a randomized controlled trial. *J Clin Epidemiol* 2009; **62**(1): 29-36.

42. Donovan JL, Rooshenas L, Jepson M, et al. Optimising recruitment and informed consent in randomised controlled trials: the development and implementation of the Quintet Recruitment Intervention (QRI). *Trials* 2016; **17**(1): 283.

43. Donovan J, Mills N, Smith M, et al. Quality improvement report: Improving design and conduct of randomised trials by embedding them in qualitative research: ProtecT (prostate testing for cancer and treatment) study. Commentary: presenting unbiased information to patients can be difficult. *BMJ* 2002; **325**(7367): 766-70.

44. Donovan JL, Paramasivan S, de Salis I, Toerien M. Clear obstacles and hidden challenges: understanding recruiter perspectives in six pragmatic randomised controlled trials. *Trials* 2014; **15**: 5.

45. Wilson C, Rooshenas L, Paramasivan S, et al. Development of a framework to improve the process of recruitment to randomised controlled trials (RCTs): the SEAR (Screened, Eligible, Approached, Randomised) framework. *Trials* 2018; **19**(1): 50.

46. Glaser B, Strauss A. The discovery of grounded theory. Chicago: Aldine Publishing Co.; 1967.

47. Wade J, Donovan JL, Lane JA, Neal DE, Hamdy FC. It's not just what you say, it's also how you say it: opening the 'black box' of informed consent appointments in randomised controlled trials. *Soc Sci Med* 2009; **68**(11): 2018-28.

48. Paramasivan S, Strong S, Wilson C, Campbell B, Blazeby JM, Donovan JL. A simple technique to identify key recruitment issues in randomised controlled trials: Q-QAT – Quanti-Qualitative Appointment Timing. *Trials* 2015; **16**: 88.

APPENDIX 1 – WMA DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964 and amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, 35th World Medical Assembly, Venice, Italy, October 1983, 41st World Medical Assembly, Hong Kong, September 1989 and the 48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the WMA binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the WMA has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

7. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

8. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

9. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

10. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

11. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

12. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

13. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

14. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

15. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

16. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

17. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

18. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE

(Clinical Research)

1) In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

19. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

20. In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

21. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

22. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I,

23. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

2) In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

24. The subject should be volunteers – either healthy persons or patients for whom the experimental design is not related to the patient's illness.

25. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

26. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

APPENDIX 2 – DEFINITION OF ADVERSE EVENTS

Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject participating in the trial which does not necessarily have a causal relationship with the treatment received.

Comment:

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Related Event

An event which resulted from the administration of any of the research procedures.

Serious Adverse Event

An untoward occurrence that:

- Results in death (unrelated to original cancer)
- Is life-threatening*
- Requires hospitalisation** or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly/ birth defect
- Or is otherwise considered medically significant by the Investigator***

Comments:

The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

* Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.

*** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

Unexpected and Related Event

An event which meets the definition of both an Unexpected Event and a Related Event.

Unexpected Event

The type of event that is not listed in the protocol as an expected occurrence.

APPENDIX 3 – COMMON TOXICITY CRITERIA GRADINGS

Toxicities which are reportable as a Serious Adverse Event will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The full CTCAE document is available on the National Cancer Institute (NCI) website, the following web address was correct at the time that the protocol was approved:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

APPENDIX 4 – SURGICAL COMPLICATIONS & DEFINITIONS

Post-operative complications occurring within 30 days;

1. Seroma (breast/axilla) – a collection of serosanginous fluid in the wound
   a. Requiring aspiration 1-2 times
   b. Requiring aspiration 3 or more times

2. Haematoma (breast/axilla) – a collection of blood in the wound
   a. Minor (conservative management)
   b. Major 1 requiring evacuation in clinic +/- US guidance (no GA)
   c. Major 2 requiring surgical evacuation (GA)

3. Wound infection (breast/axilla)
   a. Minor (oral antibiotics)(breast/axilla)
   b. Major 1 (iv antibiotics)(breast/axilla)
   c. Major 2 (surgical drainage +/- debridement)(breast/axilla)

4. Delayed wound healing/skin flap necrosis
   a. Minor (conservative management)
   b. Major 1 requiring surgical debridement in clinic (no GA)
   c. Major 2 requiring surgical debridement in theatre (GA)

5. Nipple necrosis
   a. Minor (conservative management)
   b. Major 1 (requiring debridement)
   c. Major 2 (complete NAC loss)

6. Wound dehiscence (breast/axilla)
   a. Minor (conservative management)(breast/axilla)
   b. Major (requiring return to theatre)(breast/axilla)

7. In-hospital complication (including systemic complications
   a. DVT/PE/MI/LRTI/UTI/transfusion/unplanned HDU/ITU admission

8. Readmission to hospital within 30 days
   a. No
   b. Yes, for complication listed above (1-7)
   c. Yes, for other reason

APPENDIX 5: RADIOTHERAPY QUALITY ASSURANCE

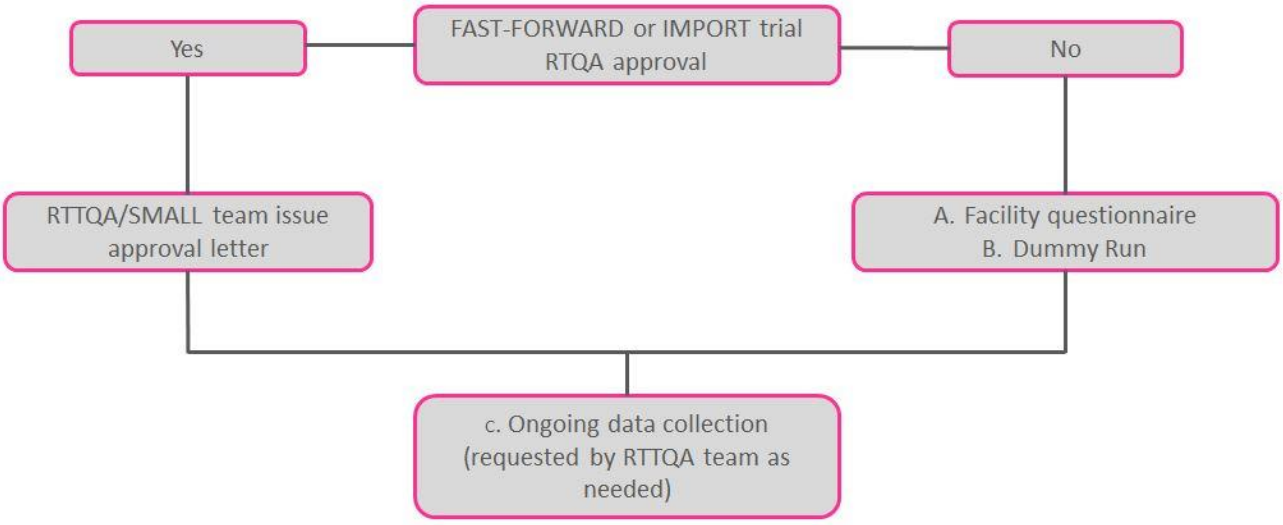
A radiotherapy quality assurance programme is an integral component of any radiotherapy trial. The NCRI Radiotherapy Trials Quality Assurance (RTTQA) group will be responsible for implementing and coordinating the PRIMETIME Radiotherapy Quality Assurance (RTQA) programme.

The planning and delivery of radiotherapy for SMALL will reflect radiotherapy practice developed as part of the IMPORT and FAST-Forward trials which represent the modern standard for breast cancer radiotherapy practice in the UK.

The SMALL Radiotherapy Quality Assurance (RTQA) programme:
The SMALL RTQA programme is comprised of two parts, a pre-study and an on-study component. In light of the comprehensive RTQA programmes associated with the afore mentioned radiotherapy breast cancer trials, radiotherapy centres may be eligible to undertake a streamlined pre-study RTQA programme based on participation in the IMPORT or FAST-Forward trials.

If a radiotherapy centre has undertaken and received pre-trial QA approval for either the IMPORT or FAST-Forward trials, centres will be granted RTTQA approval without any additional QA procedures requested. If a centre has not previously undertaken and received pre-trial RTQA approval for either the IMPORT or FAST-Forward trial, a centre will be required to complete a Facility Questionnaire and submit a 'dummy run' case for review by RTTQA.

Flow diagram summarising RTQA review for SMALL:



***Additional information may be requested by RTTQA.**

Pre-study QA:

A. Facility Questionnaire
The Facility Questionnaire must be completed by a member of the radiotherapy staff and submitted to the QA team. The questionnaire will cover details of treatment technique, immobilisation, verification and dosimetry.

B. Dummy Run
Centres should choose one of their own patients to submit to the RTTQA group for technique review. A patient, where the breast only has been treated with radiotherapy, should be selected.

On-study QA:

C. Ongoing Data Collection
Radiotherapy plans (CT data, structure set, plan and dose files) may be collected electronically by the QA team if requested by the SMALL study team, TMG or DMC based on the recurrence rates seen in the study.

Analysis of Radiotherapy data for QA programme:

The radiotherapy data from the quality assurance programme may be analysed independently from the main study. Discrepancies from standard of care treatment will be audited and discussed with the Chief Investigator and participating centres.

APPENDIX 6 - QUINTET RECRUITMENT INTERVENTION (INFORMATION STUDY)

The SMALL trial will employ an integrated QuinteT Recruitment Intervention (QRI) aimed at optimising recruitment and informed consent[41,42]. The trial aims to recruit across a large number of centres, and the recruitment pathway is likely to be multi-disciplinary. Recruitment challenges may arise in relation to flagging up eligible patients, differences in levels of recruiters' equipoise and patients' preference for open surgery or VAE. The QRI in the SMALL trial is aimed at identifying such recruitment difficulties as they emerge and implementing interventions to address them throughout the recruitment period over four years. The QRI will begin in the internal pilot phase (months 1-6 of active recruitment), and will initially be carried out in a small, diverse sample of centres (in terms of centre size, early recruitment figures/practices, etc.), with concurrent reviews of other centres. This will enable an in-depth understanding of recruitment challenges early on, and the development of tailored solutions, which can be applied to other centres, alongside continued identification of recruitment challenges as they occur in the pilot phase (months 7-18). It is anticipated that this multi-faceted approach to recruitment will enable a smooth transition into the main phase of the trial (months 19-24), which will continue to be carefully investigated employing the QRI methods until recruitment is completed (months 25-48). The QRI has been demonstrated to be most effective at optimising and sustaining recruitment when integrated throughout the recruitment phases of a trial, as proposed for SMALL.

The QRI uses novel qualitative and mixed-method approaches pioneered during the HTA-funded ProtecT study[43]. These methods have since been refined and applied to several other RCTs in different clinical contexts, leading to insights about recruitment issues and development of targeted recruitment strategies[44]. The QRI will proceed in two iterative phases.

Phase I: Understanding Recruitment

Phase I aims to understand the recruitment process in clinical centres and will comprise one or more of the following:

- **Mapping of eligibility and recruitment pathways for clinical centres**

  Detailed pathways will be compiled noting the points at which patients receive information about the trial, which members of the clinical team they meet and the timing/frequency of appointments. These will be compared with details specified in the trial protocol and pathways from other centres to identify practices that are potentially more/less efficient. The QRI researcher will also work closely with the CTU to compose detailed logs of potential participants documenting the numbers of screened, eligible, approached and randomised patients (SEAR approach)[45]. Adherence to treatment allocation amongst those randomised and reasons for non-participations amongst decliners will also be noted. These will help identify points at which patients do not continue with recruitment to the RCT across centres and be considered in relation to estimates specified in the grant application/study protocol.

- **Audio-recording and observations of recruitment discussions**

  Scheduled face-to-face appointments and telephone conversations during which the trial is discussed will be routinely audio-recorded on an encrypted device (and if necessary, observed) with written consent. Recordings will be used to explore information provision in relation to key study concepts and treatment options, recruitment techniques, management of patient treatment preferences, and randomisation decisions to identify recruitment difficulties and improve information provision. Recordings will be collected by trial staff across centres and transferred to/from the University of Bristol through University of Bristol-approved secure data transfer facilities or encrypted flash drives that adhere to NHS Trust policies.

- **In-depth interviews**

  Semi-structured interviews will be undertaken with:

  - Members of the Trial Management Group (TMG), including the Chief Investigator and those involved in design and management of the trial (n=4-5)

- Clinicians/recruiters involved in the patient pathway (n=20-25)
- Eligible patients approached to take part in the trial (n=5-10)

Interviews with TMG members/recruiters will explore key topics such as their perspectives on the trial design, protocol, evidence base for the trial, uncertainty/equipoise in relation to the RCT arms, how the arms/protocol are delivered in their clinical centre, methods for identifying eligible patients, views on eligibility, and examples, if any, of actual recruitment successes/difficulties. Interviews with patients will explore views on the presentation of study information, understanding of trial processes (e.g. randomisation), and reasons underlying decisions to accept or decline the trial. Interview and audio-recording data will be compared to identify differences in reported and actual recruitment practices amongst recruiters and, if necessary, differences in levels of understanding amongst patients. The numbers specified above are estimates based on previous QRIs and the precise numbers will be guided by the concept of data saturation (when no new information is forthcoming) and other pragmatic considerations.

All interviews will be audio-recorded on an encrypted device, and take place at a mutually convenient location, in a suitably private and quiet setting. Participants will be offered the option to be interviewed over the telephone. The University of Bristol's 'lone researcher' safety policies will be adhered to for any interviews taking place in non-public settings (e.g. participants' homes).

- **Observation of TMG and investigator meetings**

  The QRI researcher will regularly observe and make detailed notes of study meetings to gain an overview of trial conduct and overarching challenges. These meetings may be audio-recorded, with informed consent.

- **Study documentation**

  The QRI team will work closely with the CTU to ensure that patient-facing study documents are unbiased and clear. As the study progresses, patient information sheets (PIS) and consent forms will be compared with interviews and recorded appointments, to identify any disparities or improvements that could be made.

Phase II: Development and Implementation of Recruitment Intervention Strategies

The QRI team, with the CI and TMG, will formulate a 'plan of action' to improve recruitment and information provision, grounded in findings from phase I. Generic forms of intervention may include 'tips' documents providing suggestions on how to explain the trial design and processes. Supportive feedback will be a core component of the plan of action, with the exact nature and timing of feedback dependent on issues that arise. Centre-specific feedback may cover institutional barriers, while multi-centre group feedback sessions may address widespread challenges that would benefit from discussion. As the SMALL trial will have a large number of centres, the QRI team may combine them in regional clusters for feedback. All group feedback sessions will be aided by displaying anonymised data extracts from interviews and audio-recorded appointments. Individual confidential feedback will also be offered – particularly where recruiters experience specific difficulties, or where there is a need to discuss potentially sensitive issues. Investigator meetings/teleconferences and site visits from the CI/TMG members may also be employed to discuss technical or clinical challenges related to the trial (e.g. discomfort surrounding eligibility criteria).

Evaluating Changes in Recruitment Figures and Practice

Recruitment figures (numbers of screened, eligible, approached and randomised patients) will be assessed before and after the 'plan of action' is implemented, and regularly monitored thereafter to assess changes. Continued targeted investigation of recruitment issues and delivery of feedback/training will be undertaken as necessary, with particular focus on changes in recruitment practice before and after the intervention.

Consent Processes for the QRI

Healthcare professional consent

Recruiting staff and TMG member consent will be obtained through a 'master' consent form that covers all aspects of the QRI. Research nurses or the QRI researcher will obtain written consent from all staff. This will be a one-off process to cover consent for all future recordings of appointments, interviews, and observations of TMG/investigator meetings throughout the study.

Patient consent

Audio recording/observing recruitment appointments:

Information about the QRI is provided to patients in the Information Study Patient Information Leaflet. Recruiters will check if the patient has any questions about the audio-recording process at the first recruitment appointment, and seek written consent to record the discussion. Patients who agree will sign a one-off QRI consent form that seeks permission to record future discussions about the trial in the lead up to the patient making their decision about participation.

Interviews:

The QRI consent form will include a clause that asks patients if they would be willing to take part in a future research interview ('Yes' or 'No'). Patients who select 'Yes' may then be approached by the QRI researcher.

Analysis of QRI Data

Audio-recordings of interviews and appointments will be transcribed verbatim in full or in parts (targeted) either by a University of Bristol employee or by a University of Bristol approved transcribing service. Transcripts will be edited to ensure anonymity of respondents and stored securely, adhering to the university's data storage policies.

Interview data will be managed using qualitative data analysis software (such as NVivo, QRS International), and analysed thematically using constant comparative approaches derived from Grounded Theory methodology[46]. Audio-recorded recruitment appointments and follow up discussions will be subjected to content, thematic, and novel analytical approaches, including aspects of targeted conversation analysis[47] and appointment timing (the 'Q-QAT method')[48]. There will be a focus on aspects of information provision that are unclear, disrupted, or potentially detrimental to recruitment and/or adherence. Analysis of QRI data will be led by the qualitative RA with the guidance of the QRI lead, with a sample of transcripts independently coded by both researchers.

Key issues identified from the observation notes of appointments and TMG/investigator meetings will be considered alongside other qualitative findings. Findings from all sources will be drawn together in a descriptive account that will be presented to the CI/TMG and will form the basis for the 'plan of action' (Phase II above).

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Or email to:

✉ reg@trials.bham.ac.uk