CLINICAL TRIAL PROTOCOL

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Sponsor:

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Reducing Re-excisions After Breast Conserving Surgery: A Randomised Controlled Trial Comparing the MarginProbe Device in Addition to Standard Operating Procedure versus Standard Operating Procedure Alone in Preventing Re-excision

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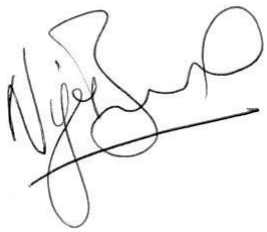
This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP) guidelines and regulatory requirements.



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1. SUMMARY OF TRIAL

Of the 48,000 breast cancers diagnosed annually in UK, almost 60% of patients undergo breast conserving surgery (BCS). Surgical removal of the cancer aims to reduce the risk of local recurrence and patient mortality. In order to minimise the amount of tissue removed, excision up to the cancer-free area (margins) is undertaken. Further surgery following BCS is required in 25% of patients with invasive cancers with surrounding DCIS and 30% of DCIS patients because of disease found at the edges of the tissue removed.

Reducing the need for further operations benefits patients (by reducing the number of operations required, minimising anxiety) and the NHS (by realising economic benefits).

MarginProbe, a disposable probe which measures the margins of tissue removed during BCS surgery, allows the surgeon to remove further tissue during the same surgical procedure to clear any involved margins, minimising subsequent re-operations.

Four hundred and sixty patients in 6 specialist Breast Units will be randomly allocated per-operatively after BCS (and specimen radiology), by telephone randomisation, to either:

- MarginProbe assessment of the surgical specimen with re-excision of margins if required;
- Standard BCS (clinical and radiological clear margins) whereby the wound will be closed and the surgery completed (standard UK practice).

The primary aim of the study is to determine whether the MarginProbe device reduces the need for second surgical procedures (and improves margin clearance by $\geq$1mm) by enabling the removal of involved margins during the same procedure.

Main outcome: number of people requiring second re-excision surgery within 9 months of their first BCS. We will also look at the impact on quality of life, cosmetic appearance and the results of laboratory assessments of removed tissues.

The health related quality of life and cosmetic appearance of the surgery (photographs of 2 views - front/side) will be compared by researchers who do not know which treatment people received.

AIM

Surgical excision of breast cancer and surrounding ductal carcinoma in situ (DCIS) aims to reduce the risk of a local recurrence and increased mortality of the patient, by excising the cancer with cancer-free margins. Surgical practice in the USA allows for examination of frozen tissue section taken during breast conserving surgery to identify involved or close cancer margins.

In Europe and the UK, the shortage of specialist breast pathologists and the recognised difficulties of diagnosing DCIS on frozen tissues, often leads to additional surgical procedures being required to re-excise residual breast cancers. This policy, endorsed by UK National Guidelines, can result in re-excision or mastectomy in up to 30% of DCIS and 25% of invasive cancers with admixed DCIS. This often leads to poorer cosmetic outcomes, increased patient anxiety and increased NHS costs.

This proposal will address whether a new CE-marked technology, MarginProbe, used to assess completeness of excision during surgical therapeutic excision of breast cancers, can reduce the number of patients having to undergo re-excision surgery and therefore reduce the number of NHS repeat surgical operations in this group of patients.

This study will identify and validate a cost effective, new technology which can reduce NHS costs, reduces the number of re-excision surgical procedures and will benefit patients.

Primary aims:

1.To determine if the use of the MarginProbe device, after surgical tumour excision and tissue specimen radiography of a breast cancer (with surrounding ductal carcinoma in situ [DCIS]) or DCIS reduces rates of further surgical re-excision operations, when compared to control/standard practice (whereby the wound is closed after radiography showing clear margins).
2.To compare the total number of re-excision procedures required in both groups following BCS because of positive margins less than 1mm (circumferentially).
3. To compare the number of patients in both groups presenting with excision margins greater than 1mm circumferentially clear after BCS, judged by histopathological assessment.

Secondary aims:

1.To determine the effect of intraoperative margin assessment using the MarginProbe device (when compared to standard practice) on quality of life, Patient Related Outcome Measures and cosmetic outcomes (using digital photography assessment [2 views; front and side]).
2. To determine Quality of life and health related facility measures (EQ5D) between patient groups.
3. Impact on patients and carers of use of MarginProbe in terms of patient preference, satisfaction, convenience, discomfort and financial costs.
4. Resource utilisation and cost of each strategy.
5. Clinical and cost-effectiveness of both management techniques.
6. The cost and implications of adopting MarginProbe use intraoperatively compared with standard of care.

TRIAL OBJECTIVES

Primary Objectives:

1. To determine if intraoperative margin assessment after excision of a cancer reduces re-excision procedures, compared to standard surgical practice by 9 months after primary surgery.2. To compare the total number of re-excision procedures required between groups and tissue weight resected after BCS, because of positive margins.

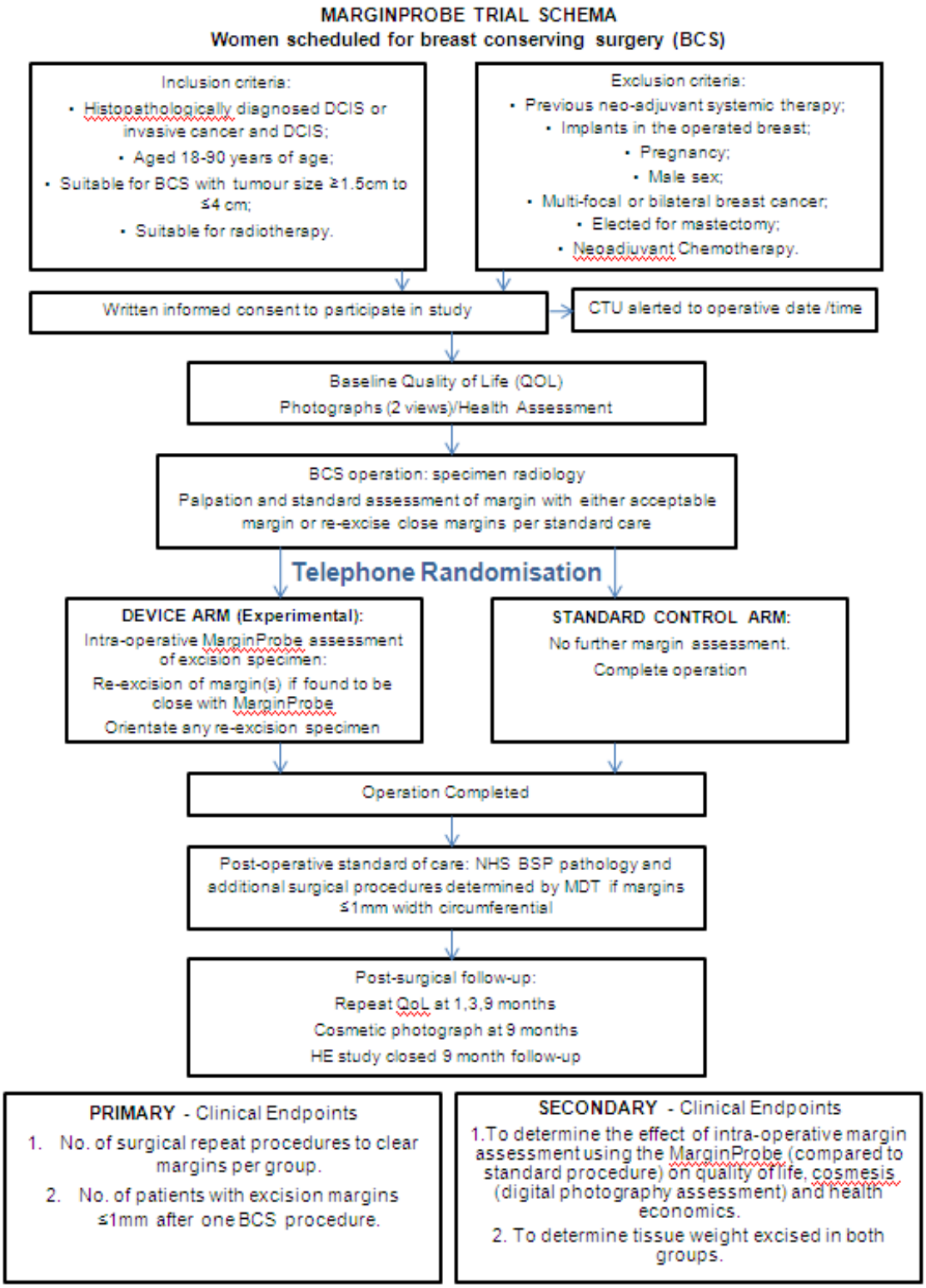
Secondary objectives:

1. To determine the effect of margin assessment on a) quality of life (QOL), b) cosmetic outcomes and cost-effectiveness (EQ5D).

a) QOL in each group will be measured by using validated self-completion disease specific and generic instruments, FACT-B[11], HADS[12], health-related utility (EQ5D) and the body image scale of SABIS[13] administered at baseline (pre-surgery) and postal follow-up at 1,3,9 months post-surgery to permit calculation of Trial Outcome Index (FACT-B TOI). This assessment will permit area under the curve approach to analysis of differences between arms in QoL.[C1] Quality of life is a crucial variable if we are to understand the impact of MarginProbe, especially if the effect on re-excision rates is not of marginal significance. The effect of avoiding re-excision or mastectomy on the quality of life of women may act as a multiplier which makes the procedure worth (or alternatively not worth) undertaking even if the actual numbers of excisions and mastectomies avoided is marginal.

b) Cosmetic evaluation, blind to randomisation assignment will be conducted at baseline and 9 months by observer using a symmetry based scale[14] and photographic measurements compared by observers blinded to randomisation. Two independent observers will use the symmetry-based ratings and undertake the photographic measurements to assess cosmetic outcomes. Inter-rater agreements will be calculated to check reliability of observations. Patient related outcomes will be measured using the Harvard Cosmesis Scale[21].

2. Qualitative study of women's experience: Early during the trial we will undertake a qualitative sub-study of some 30 women (an estimate based on previous studies when data saturation is reached) to investigate women's experience of the two surgical approaches. This study has 3 related purposes: (i) To permit us to describe any differences in "lived experience" of women across groups who receive MarginProbe or not (perhaps related to expectations of benefit from receiving a new hi-tech surgical approach) and between women with or without re-excision. (ii) To provide qualitative accounts of participating in the trial which will help us in understanding trial outcomes as recommended by MRC 2008. (iii) To generate items for use in a questionnaire assessing experience and satisfaction with procedures. Purposive sampling across sites, study arms, age, re-excision or not etc, will be undertaken. Semi-structured interviews exploring concerns, expectations, preferences, satisfaction and awareness of procedural differences will also be carried out. Interviews will be audio-recorded and transcribed. Constant comparative approach[18] will be used and thematic framework analysis (facilitated by use of NVivo) will be used to identify main themes for comparison between groups[19].



2. BACKGROUND

Breast cancer is diagnosed in over 48,000 women per year in the United Kingdom, with at least 60-70% undergoing breast conservation surgery (BCS)[1,2]. Standard management requires BCS to achieve histologically-negative margins (>1mm circumferential clearance)[2] prior to radiotherapy because if margins are involved, the risk of subsequent local recurrence and

mortality is increased[3-6,11]. The presence of microcalcification in surrounding DCIS is a predictor of margin involvement for cancers detected by screening mammography (20-25% of new breast cancers)[3-6].

Meta-analysis shows that for every five women who develop local recurrence, one will die of breast cancer, thus prevention of local recurrence by complete surgical excision with histopathologically-clear margins after BCS has become an essential part of oncological treatment[11].

NICE guidelines for BCS advise either re-excision or mastectomy in patients where margins are involved with cancer cells after BCS[2]. Prospective data are lacking on margin width clearance required, but three retrospective analyses of margin width within large DCIS trials suggest width of 1mm clearance is sufficient[6] and a large metaanalysis of invasive breast cancer identified a 1mm margin as adequate to prevent recurrence[20]. Re-excision procedures occur 5-6 weeks after initial BCS, producing social and economic costs to the patient (reduced cosmesis, increased risk of infection and additional time off work/recovery time) and to the NHS in terms of surgical time and in-patient care.

A recent Association of Breast Surgeons Audit suggests that 16% of invasive cancers go on to require re-excision and 9%, mastectomy, after initial BCS, as well as up to 37% of non-invasive breast cancer (DCIS) because of circumferential margin involvement[1]. At least 1 in every four DCIS and breast cancer with surrounding DCIS diagnosed on core biopsy/mammotome surgery need second re-excision operations[1].

Re-excision operations on average cost £2,885 and mastectomy with breast reconstruction costs around £6,714, thus considerable savings are possible if 2nd operations are avoided.

Margin status is assessed histopathologically according to the NHS Breast Screening Programme Quality Assurance Pathology Guidelines[17] and its width is measured with a micrometer. Specimen radiography is routinely used to identify the closest margin and surgeons re-excise during the initial operation if a margin is close on specimen radiography. NICE guidelines mean most Breast Units schedule a re-excision operation if the margin circumferentially is less than 1mm from any edge on final histopathology, at additional costs to patient and NHS[2].

For DCIS and cancers with surrounding DCIS identified on core biopsy and/or mammography, the re-excision rate ranges between 23-37%. Nationally after BCS, despite specimen radiology showing clear margins and this is the group to be studied in this trial. As re-excision rates may differ between Trusts, we will stratify randomisation for each Breast Unit and for the presence or absence of invasive cancer with DCIS. Additionally, each Unit has agreed to use 1mm as the clear margin cut-off when deciding the need for re-excision in the MDT meeting.

The MarginProbe device utilises a probe which when placed on an excised specimen in theatre, detects involved margins, thereby allowing immediate re-excision during the same surgical procedure and optimising surgical outcome by reducing the need for repeat operations to achieve clear margins[7]. The device measures a tissue area of 7mm to a depth greater than 1mm which, requiring repeated margin measurements, allows multiple points of the specimen to be sampled in approximately 10 minutes.

In a randomised, prospective, multi-centre trial carried out in Israel encompassing 300 patients, device use produced a 56% reduction in re-excision rate[9] when excluding patients who underwent subsequent mastectomy and positive margin width assessment was not different at

1mm or 2mm thresholds. There was no significance in device sensitivity for different cancer types including DCIS, invasive, ductal and lobular cancer[7,9] and no significant difference in long-term cosmetic outcome between groups when evaluating patients in both groups.

A US RCT of 600 patients, published as an Abstract, indicated a 50% reduction in re-excision rate and Health Economic assessment suggested a cost benefit from the use of the probe. In a small non-randomised, prospective German study of DCIS of 27 patients, breast re-excision rates were reduced from a retrospective (historical) 31% to 12% with the use of the MarginProbe device[12]. In all three studies, re-excision rates varied between centres involved and were 18.6% in the control arm of the Israeli study, 30% in the control arm of the US study and thus re-excision rates partly vary dependent on patients enrolled in the study and country-specific practice.

The margins surrounding core biopsy-diagnosed DCIS and lobular cancer can be difficult to define and this device therefore provides an method by which surgical operations can be reduced and cosmesis in women with early breast cancer of these subtypes can be improved. In the UK, NICE recommends a 2mm margin but surgical literature[6,20] indicate a 1mm clearance to be sufficient to prevent local recurrence and most UK Units do not re-excise with 1mm clear margins. All 6 Units involved have predefined re-excision criteria at 1mm circumferential margins agreed for the study.
It is essential we understand whether the device (which is already kite-marked) will have clinical utility in the UK before ad hoc use occurs in the NHS.

Several new margin assessment devices are being developed worldwide and thus, meta-analysis of these trials will be important in the future. However, given the cost of the probes (300 to 400 Euro) and the console necessary to interpret the data (£30,000), unless at least 10 in every 100 re excisions are prevented, it may not be cost-effective.

This study will ascertain the value to patients and cost-effectiveness to the NHS of device use in early breast cancer (including DCIS) in a multi-centre NHS Breast Unit setting, determining the extent to which surgical re-excisions can be avoided by employing its use.

3. TRIAL DESIGN

In women with Ductal Carcinoma in Situ (DCIS) or invasive cancer with surrounding DCIS on mammogram/core biopsy undergoing BCS to undertake a randomised non-blinded controlled trial, comparing standard operating procedure followed by use of the MarginProbe device to:

- assess excision margins and where necessary undertake additional margin tissue excision (experimental arm), versus;
- standard operating procedure alone (randomisation ratio 1:1)

Study setting: Specialist Breast Units.

Target population: Women aged 18 to 90 years, with early breast cancer (invasive breast cancer with surrounding DCIS or DCIS alone, histologically diagnosed by core biopsy) and scheduled to undergo BCS. (See flow diagram)

Inclusion criteria:

1. Women aged 18-90 years with DCIS, Invasive Breast cancer containing DCIS or HER2 positive invasive breast cancer(with or without DCIS) diagnosed histopathologically.
2. Histologically diagnosed DCIS or invasive lobular cancer in core biopsy (B5a or B5b). Invasive lobular carcinoma does not require concomitant DCIS.
3. Tumour size 1.5cm - 4cm and undergoing BCS.
4. Written informed consent.

Exclusion criteria:

1. Unsuitable for BCS on basis of tumour size (>4cm) or stage.
2. Radiotherapy contraindicated.
3. No histopathological evidence of DCIS, invasive lobular cancer or HER2 positive invasive breast cancer.
4. Small invasive cancers ($\leq$1.5cm)
5. Multicentric Disease (histologically diagnosed cancer in two different quadrants of the breast), unless resected in a single specimen
6. Bilateral disease (diagnosed cancer in both breasts)
7. Neoadjuvant systemic therapy
8. Previous radiation in the operated breast
9. Implants in the operated breast
10. Pregnancy
11. Lactation
12. Cryo-assisted localisation

Sample size: The ABS 2011 Audit[1] found the average re-excision rate for DCIS is 30% and that for invasive cancers is 25%. It is estimated that approximately 20% of recruited patients will have DCIS and 80%, invasive cancer. The estimated average re-excision rate for the whole study group is 26%. Specialist Centres are expected to have a slightly lower re-excision rate, if we assume a 25% re-excision rate in the control arm and predict that the device will give a 50% reduction in the re-excision rate (i.e. to 12.5%), it is estimated that 219 patients will be required to be recruited in each group (90% power using a simple chi-square test with continuity correction). It is proposed to recruit 230 per group to allow for drop-out and loss to follow-up.

With this number of patients, the study would have 80% power to detect a 44% relative reduction from 25% to 14% in re-excision rate and a 50% relative reduction from 20% to 10% in re-excision rate.

This number of patients would also lead to 90% power to detect differences in TOI of 4.5 or more between the two groups and 80% power to detect differences in TOI of 3.9 or more (using an estimated SD of 15 from the ALMANAC trial and a simple two-sample t-test with the conventional 5% significance level).

The Breast Screening Centres selected treat over 2,600 cancers each year of which over 1,800 will require BCS. In this group of patients, 50% agree to participate in treatment trials, however, we would expect a higher rate as this trial does not involve patients having to take additional trial medication and similar non-medical intervention trials have recruited up to 60% in Manchester. Thus we expect to recruit the required number of 460 patients within one year from the participating centres. We would not expect loss of population due to death as these patients will be fit for anaesthetic and survival is in excess of 98% at 10 years.

Surgery: All surgeons will perform standard wide local excision (BCS) using localisation of the lesion for impalpable lesions where required. The aim will be to excise the lesion with a 5mm-1cm microscopic margin of clear tissue. Following excision and orientation of the excision specimen, specimen radiography will be carried out to ensure all margins are radiologically clear, per standard NHSBSP practice[17].

It should be the aim of conservation surgery to achieve clear excision margins. Any patients who do not have a clear excision require re-excision. Patients should be counselled about this possibility at the time of diagnosis. Because of the difficulty of assessing margins, all patients undergoing breast-conserving surgery should have directed cavity biopsy shavings taken to assess excision (See Surgical Principles under 'Trials Procedures').

Randomisation procedure: Simple individual randomisation will be undertaken by telephone, after prior arrangement via The MAHSC-CTU. Women will be randomised in theatre, by call to the CTU after completion of excision and specimen radiology, to either standard procedure (no further surgery, close wound) or the use of the MarginProbe device on the excised specimen to determine whether margins are involved and further re-excision is required.

Patients must be randomised between 9am-4.30pm Monday-Friday. If there are any changes to the MAHSC-CTU randomisation line opening hours, sites will be informed. It is important that sites take this into consideration when approaching patients/ planning surgery lists.
Randomization will take place immediately after the main ex-vivo lumpectomy specimen has been excised, oriented, centre marked, inspected, palpated, and additional cavity shavings performed and documented.

Blinding and bias: Leaving randomisation until after excision will minimise bias that may occur in surgical procedure and thus also removes need for using a cluster design. Clearly, we cannot blind the surgical team to allocation once it occurs and we will not blind women to whether or not they received MarginProbe as this is likely to be viewed unfavourably by an Ethics Committee and it is only through knowing allocation that any expectation effect may occur amongst those who do receive MarginProbe. We recognise that a disappointment bias may affect the control group and we will guard against this by ensuring information about benefits to taking part in RCTs are available to both groups. After written informed consent, the surgical team will liaise with the MAHSC-CTU so telephone randomisation in theatre can be planned and without delays.

Histopathological assessment of margin status will utilise micrometer measurement of margin clearance according to standard NHSBSP pathology guidelines protocols[17]. NHSBSP minimal pathology datasets requires margin width to be measured at specimen margins and all centres have agreed they will only offer further surgery if margins are less than 1mm width at a circumferential (radial) margin. CRFs will record margin width, pathological size, extent of surrounding DCIS, grade and steroid receptor status, HER2 status (invasive cancers), together with the Multidisciplinary Meeting decisions about need and reason recorded for any further surgery being offered to the patient. All specimens will be weighed and total specimen weight compared between groups. Fidelity checks for probe use according to randomisation and correct, probe-guided re-excision will be made. Independent review of pathology and fidelity checks will be supervised by the Lead Pathologist, Dr Howe.

Pathology

Pathology assessment is identical for both study arms. Histological examination of all tissue removed during the initial lumpectomy procedure and during any repeated surgery (repeat lumpectomy or mastectomy) will be blinded to subjects' treatment arm. Surgeons should coordinate with pathologists in order to ensure that orientation conventions are agreed upon and that pathologists' interpretation of margin boundaries (Medial, Lateral, Inferior, Superior, Anterior and Deep) are similar to those of the surgeon.

Each margin shall be inked in different colour, using the boundaries marked by the surgeon.

Routine processing will be performed on all tissue removed during the initial lumpectomy procedure. The pathology report will include the following:

a) Microscopic margin width ("D") as well as the exact orientation, malignant content, and margin status of all tissue removed during the initial lumpectomy. D will be noted in increments of at least 0. 5 mm up to 2 mm, and in increments of at least 1 mm in the range 2-10 mm.
b) Dimensions of all specimens (main ex-vivo lumpectomy and Shavings)

Pathology data for ipsilateral breast surgical procedures (repeat lumpectomy / mastectomy procedures) will be also collected. In mastectomy procedures, margin status is not required; however all other data shall be included.

Specific harmonized study related requirements for pathology examination and for pathology data reporting are detailed in the pathology Standard Operating Procedure (Appendix 2).

A positive margin by histology is defined in this study as a margin microscopically measured and reported in the histology report to have cancer within 1 mm or less of the inked surface.

Cold ischemia time should be kept to less than 1 hour based on ASCO guidelines.

Data Collection

Each research site is responsible for maintaining source data for their trial patients in their medical notes, and for transcribing this data onto a trial specific case report form (CRF). All entries on the CRF, including corrections, must be made by an authorised member of trial staff. Research site staff will also provide trial patients with copies of the relevant questionnaires for completion at each required time-point.

Research sites will submit original completed copies of the CRF and patient completed questionnaires to MAHSC CTU, keeping a copy at site with the Investigator Site File.

Patient diaries should be returned to the Sponsor site for analysis.

Follow up and data collection; MarginProbe use starts and ends during the primary lumpectomy procedure. Thus, patient management differs between the two study arms only during the procedure. Following the procedure, pathological assessment and any other patient management aspects are identical for both study arms. The device will not be used in any repeated surgery, even in patients randomised to the "Device" arm.

Data will be collected regarding all ipsilateral breast surgical procedures and their respective permanent section histological data. Patients will be followed until evaluation of cosmetic status, performed at 6 +/- 1 month following the end of surgical treatment (either conversion to mastectomy, or the latest ipsilateral repeat lumpectomy procedure).

In the event a repeat lumpectomy procedure or mastectomy has occurred during the data collection period, additional information will be recorded in the case report form.

Data will be collected on any repeated ipsilateral breast surgical procedure, including axillary lymph node dissection (ALND), and sentinel lymph node biopsy (SLNB), including permanent histopathology data. Surgical procedures performed in the contralateral breast will be also documented.

We are hoping that a CRN Clinical Trials Research Administrator/ Research Nurse at each site will be utilised to consent the patient, with the aid of the surgeon, and to record the data from the MarginProbe/excision specimen assessment. RfPB approval will allow use of CRN Research Administrators as the study will be registered on the NIHR Portfolio. Once consent has been gained, the CTU will be informed of the date and time of surgery to facilitate telephone randomisation in theatre.

Data Handling at MAHSC-CTU: Completed CRFs and questionnaires submitted to MAHSC CTU will be entered onto a trial database by the trial data manager. The trial database will be stored on a secure server with controlled access, regular back-up of data and an audit trail of changes made to the data.

Data provided to the MAHSC-CTU will be checked for errors, inconsistencies and omissions. If missing or questionable data are identified, the MAHSC-CTU will request that the data be clarified. All aspects of data collection and handling throughout the life cycle of the trial will be described in trial-specific documents held in the trial master file at MAHSC CTU.

Health Economic Analysis: Specialists treating breast disease claim that the rate of re-excision and mastectomy to ensure the surgical margins are clear is unacceptably high, given their comparatively low risk of developing local recurrence. Second surgical operations are associated with increased morbidity and lead to poorer cosmetic results with reduced Body Image scores if more than 10% breast tissue is removed. If the amount of surgery can be reduced by the use of the MarginProbe device, there would be important benefit to patients and the NHS.

The resource data will be validated using Unit costs at each centre involved, from hospital finance data using appropriate and explicit assumptions regarding staff time and equipment use. Extensive sensitivity analysis will be carried out where assumptions are made. The data should enable a comprehensive comparison of the total costs to the NHS and the two groups, to be made. Any savings to the NHS will be identified. Indicative costs for breast conservation re-excision are £2,885 and mastectomy with reconstruction approximately £6,714. If reduced surgery is possible with the use of MarginProbe device, this trial will be practice-changing, with cost savings and improved quality of life for patients and the NHS.

Under the assumption that there is a halving in the re-excision rate (from 25% to 12.5%) including a halving in the mastectomy rate (from 10% to 5%), we estimate there will be an approximately 20% reduction in costs.

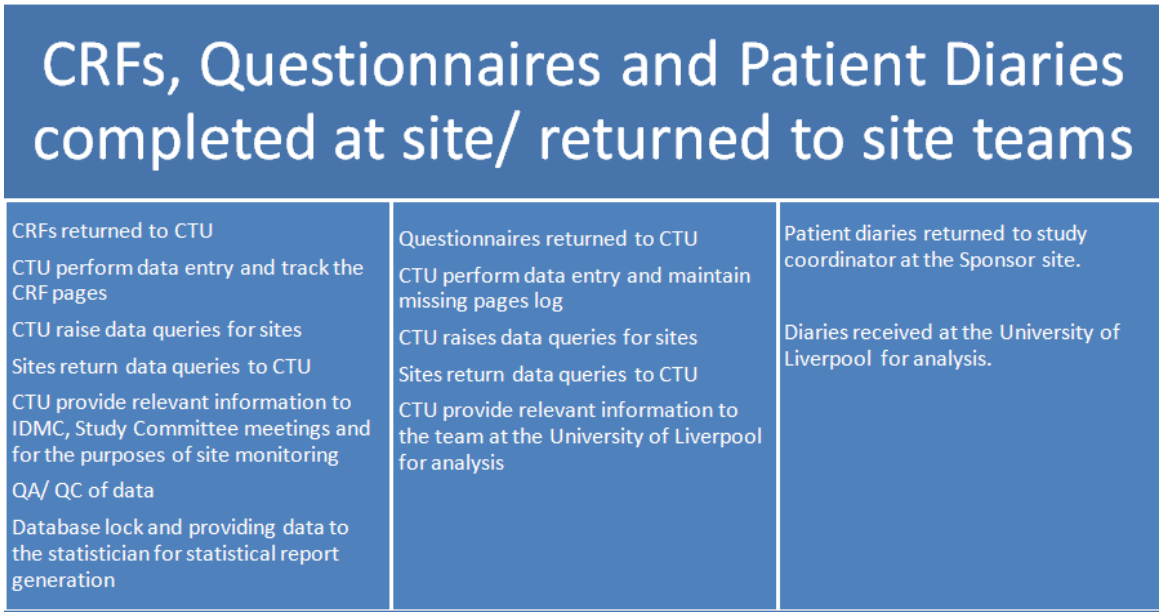
In addition to a cost-effectiveness analysis, we will estimate the budget and service impact of day case surgery to the NHS based on the experience of the trial and include the possibility of extending this treatment service to non-specialist centres.
The appropriate economic evaluation technique is a cost effectiveness analysis, in which any outcome benefits are compared to cost differences between the two strategies. To facilitate this, a comprehensive comparison of the costs of the two groups will be undertaken. For each patient group, the following resource data will be collected using hospital records for in-patient resource use and patient-held diary cards for care in the immediate discharge period:

1. Length of pre- and post-operative hospital stay (in days/nights).
2. Number of outpatient clinic visits (planned and unplanned).
3. Use of capital equipment and supplies (e.g. probes).
4. Number of consultations with GP (at home or in surgery).
5. Number of contacts with District Nurses and/or breast specialist Nurses.
6. Resources used in therapy (e.g. surgery, MarginProbe, Radiation treatment: WBRT; IORT; none)
7. Patient carer trips associated with hospital care (mode of transport and cost).
8. Other costs associated with treatment (e.g. meals, loss of earnings, etc.).

Quality of Life assessments: QoL will be measured in each group by using validated self-completion disease specific and generic instruments, FACT-B[11],HADS[12] and EQ5D for health-related utility, together with the body image scale of SABIS[16]. These will be administered at baseline (pre-surgery) and by postal follow-up at 1,3,9 months post-surgery, permitting calculation of Trial Outcome Index (FACT-B TOI).

If women are scheduled for chemotherapy before re-excision procedures, the final assessment at 9 months will ensure all have completed therapeutic surgery. A window of +3 months for the collection of details regarding re-excision procedures is provided.

Data Flow Diagram:



Initiation Meeting and Study Training: An initiation meeting at each site will occur after relevant staff from participating sites have attended a training day where they are trained by Prof. Bundred and Dune Medical Device representatives in the use of the Probe.

The CI, or an appropriate delegate, intends to visit each site when the study is due to commence there, to observe the first two patients undergoing surgery for the trial. This will ensure that the same operating procedure is used in each centre. Agreed Protocols for re-excision according to standardised margin width will also be standardised across all sites.
Please see Appendix B for further information about the MarginProbe Device.

Cosmetic evaluation: The cosmetic outcome assessment will be performed using objective evaluation. The objective evaluation will be performed by two evaluators blinded to arm assignment. The evaluation will be based on pictures taken, under standardized photographic conditions, which will be conducted at baseline and 9 months (. Only the breast and torso (excluding the head and neck) will be photographed. The pictures will be provided to the lead study site electronically and all be evaluated together by clinicians who were not involved in the initial research. The scoring will be performed using a symmetry based scale[14] and photographic measurements (two views; front and side) compared by observers blinded to group allocation. The validated 4-point Harvard Breast Cosmesis Scale will be used[21]. This scale classifies the overall aesthetic results in four categories:

- Excellent - Treated breast almost identical to untreated breast.
- Good - Minimal difference between the treated and untreated breasts.
- Fair - Obvious difference between the treated and untreated breasts.
- Poor - Major functional and esthetic sequel in the treated breast

Minimizing loss to follow up

Loss to follow up that will influence the collection of valid data for the co-primary endpoints is not expected in this study. The co-primary endpoint data is obtained during the (initial) surgery and during a period of up to two weeks following it. Additionally, this data is collected routinely as part of the subject's standard treatment. In the pivotal study there was no loss to follow-up.

Loss to follow up that will influence the collection of patient questionnaires and diaries at 1, 6 and 9 months following the end of surgical treatment, will be minimized by letters and reminder phone calls to the patients, and also by providing patients with stamped addressed envelopes.

Sites will also be provided a 3 month window in order to collect data and complete photographs for the 9 month period; these can be completed up to 12 months post-surgery.

3. Trials Procedures

Baseline/screening visit:

- Eligibility criteria
- Informed consent
- Demographics Baseline characteristics(height, weight, bra cup and band size)

- Relevant medical history
- Pre-operative information
- Disease characteristics
- FACT B +4, HADS, EQ5D and SABIS Questionnaires administered

Operative visit:

- Procedural characteristics
    - Surgery information
    - Device use information, including failures and malfunctions
    - Lumpectomy cavity shavings performed based on visual inspection and palpation
    - Lumpectomy cavity shavings performed based on device use (Device arm only)
- Intraoperative imaging use
    - Performed (Y/N)
    - Imaging technique
    - Imaging result (when applicable)
    - Lumpectomy cavity shavings performed based on intraoperative imaging assessment
- Pathology
    - Tumour type
    - Margin status – main ex-vivo lumpectomy specimen and lumpectomy cavity shavings
    - Margin depth
    - Specimen dimensions
- Adverse events and Serious Adverse Events

Follow up visits (month 1, 3 and 9):

- FACT B +4, HADS and EQ5D Questionnaires and Patient Diary Cards Administered

MarginProbe Device

In patients randomised to the device arm, the MarginProbe will be used after radiological examination of the operative specimen and ensuring that the margins are radiologically clear. The MarginProbe will then be used to examine all six outer surfaces of the lumpectomy specimens with five to eight measurements per face..

A single positive reading identifying a margin as positive: The device output is recorded and Surgeons will be required to excise additional tissue from the corresponding surface of the lumpectomy cavity from every device identifying positive margins.

Additional tissue removed following analysis by the device will not be examined by the device, nor will the lumpectomy cavity. The device should be used within 20 minutes after specimen excision. In both study arms, the main lumpectomy specimens will be orientated and shaves will also be orientated.

Specimens will be interpreted by the Surgeon for the presence and absence of tissue abnormalities registered during surgery and compared to the Pathologists' interpretation of the permanent section pathology slides.

The agreement between the Surgeon's interpretation of MarginProbe positivity and the pathology results will be recorded and the potential reduction of repeat surgery will be assessed by including additional shavings taken and their weight, based on the reading of the device images and the NHS BSP QA reporting of the pathology.

The Pathologists will record tissue dimensions, margin status and margin distance, using micrometer for all surfaces. Specimen volume will be calculated based on the ellipsoid formula (π/6xLxWxD). All patients will be followed (including additional surgical procedures) until the completion of surgical treatment and nine months thereafter.

No restrictions will be placed on Surgeons in terms of performance or additional surgical procedures but additional surgical procedures should be decided by the Breast MDT in the Surgical Units and for the purpose of this study, a positive margin will be considered to be disease less than 1mm from the inked edge of the tissue and diagnostic measures including false-negative and false-positive rates will be evaluated by comparison of device readings so pathology is the gold standard of margin by margin basis.

The molecular phenotype of all tumours will be recorded, to assess whether MarginProbe accuracy is affected by molecular phenotype.

Components:

The MarginProbe System is comprised of two distinct components: a probe and a console, described in more detail below. The console is a reusable, closed-system component consisting of various electrical components, a vacuum system, pre-installed software, and a monitor with a user interface system, including a display, audio components and operation buttons. The probe is a detachable, sterile, single-use, single-patient component. It is connected to the console by two RF cables and a vacuum tube, via a single connector. The probe and the console are packaged and intended to be sold separately.

<u>Console:</u>

The console is reusable and has a user interface system with display, audio components and operation buttons. The console is a freestanding unit that is designed for use in a surgical environment. The unit is supplied ready for use and requires no special installation procedures, other than plugging the unit into the power supply. The console does not require periodic maintenance or calibration. The RF signal generator and analyzer unit is housed within the console. The software on the system operates the system, provides the interface with the user, and classifies the tissue readings as positive or negative via a memory module.

Probe:
The probe is a detachable, sterile, single-use, single-patient component. It is connected to the console by two RF cables and a vacuum tube, via a single connector. The probe is 1.6 cm in diameter with an effective measurement area of 7 mm diameter.

Device use – "Device" arm only

- If the patient is randomized into the "Device" arm, a sterile probe will be opened in the sterile field and connected to the console.
- MarginProbe will be used on the outer final surface, not on the initial specimen
- The MarginProbe will be applied in the sterile field. The outer final lumpectomy specimen surface shall be perceived as being divided into 6 margins: Lateral, Medial, Inferior, Superior, Anterior and deep, each margin defined by its borders marked by the surgeon. The device shall be applied to all 6 margins sequentially. Readings from multiple locations within each margin will be grouped using the console Graphical User Interface. The probe should be applied to tissue with care not to attach to sutures, clips, or any orientation markings such as ink.
- The entire surface area of every margin of the outer final surface should be sampled. MarginProbe sampling shall be evenly spread, usually 5-8 points per margin, depending on the specimen size, or up to 12 points per margin in larger specimens.
- Each single site reading is performed as follows: The surgeon positions the hand-piece tip perpendicular to the relevant tissue section. The system automatically performs a full cycle of measurement. The site result, "Positive" or "Negative", is displayed on the monitor in real time along with audio indication.
- Once the device has been applied to all margins, all margins indicated by the MarginProbe as positive (a margin is indicated positive if there is one or more positive readings on it) should be shaved from the cavity.
- Additional cavity shavings performed based on device use will be documented.
- If the shaving is taken after the x-ray, take the shaving from the outer final surface.

Intraoperative Imaging assessment - both arms of the trial

- If part of routine practice, specimen imaging by ultrasound or radiography should be performed.
- Results of imaging assessment will be documented.
- Additional cavity shavings performed based on intraoperative imaging assessment will be documented.

Concomitant patient management

- Use of saline and/or ultrasound gel and/or local anesthetic on the main ex vivo lumpectomy specimen before performing the MarginProbe measurements is precluded. Sterile water can be used instead.

Additional lumpectomy cavity shavings handling - both arms of the trial

- All lumpectomy cavity shavings should be appropriately oriented, marking with a suture the new margin and clearly noting for pathology the orientation of the shaving relative to the main ex-vivo lumpectomy specimen.
- The shaving name as reported by the surgeon to the pathologist shall be documented
- If a lumpectomy cavity shaving encompasses more than one margin in one main ex-vivo lumpectomy specimen, this should be documented by the surgeon and mentioned in the pathology report.
- If more than one shaving is taken from the same face, it shall be documented if the shaving is the outermost cavity shaving or not.

Conclusion of procedure - both arms of the trial

- The procedure will be concluded in the routine practice.
- All tissue removed during the initial lumpectomy procedure will be submitted for routine permanent histology analysis.

Surgical Principles – WLE for palpable or impalpable lesions:

These may be either through the UK screening programme from the Nightingale Centre or lesions on mammograms requested for other reasons. Ultrasound guided surgery or needle localisation surgery is used. In the former the surgeon removes the area of breast tissue at a depth calculated by the scan, consistent with the scan findings. At needle localisation a volume of tissue is removed together with the wire.

1 In both cases liga-clips must orientate the specimen. One clip is used superiorly, two clips laterally and three inferiorly – if this is written fully on the card then the radiologist will be able to ascertain the orientation of the specimen. It must also be recorded on the operation note.
2 The biopsy cavity site must be orientated with 4 ligaclips, superiorly, inferiorly, medially, laterally. This is important for the planning of adjuvant radiotherapy.
3 The excised specimen must be weighed and recorded in the operation note
4 Shavings must be taken from the adjacent breast tissue and sent separately. The shavings may have a sutures placed on the biopsy (inner) cavity surface to allow the pathologist to orientate the shaving itself. Ligaclips cannot be used as they would interfere with the device.
5 All impalpable lesions must be visualized radiologically by the operating surgeon on the in-theatre X-Ray machine. The specimen should be radiographed in two perpendicular planes for a radiological assessment of the completeness of excision. A comment on the completeness of excision based on the intraoperative image must be made in the operation note by the surgeon. If the biopsy is undertaken for microcalcification a comment must be made in the operation note relating to the presence of microcalcification in the X-Ray image of the excision specimen. Any concerns should be discussed with a Consultant intraoperatively.
6 It is mandatory to obtain an intraoperative X-Ray image of a radiologically guided WLE.
7 It is expected that intraoperative images of WLE specimens in palpable cancers will also be obtained. It is not routinely required to obtain an intraoperative images of biopsy cavity shavings but this may be helpful in cases where the main specimen radiograph does not show the malignancy.
8 Intraoperative images should be electronically sent to Radiology for formal radiological assessment and to inform the MDT discussion of the case and complete radiological assessment of the lesion.
9 The patient should remain anaesthetised until confirmation of removal of the targeted lesion.
10 If cytology or corecut biopsy has produced malignant cells a therapeutic biopsy may be undertaken. If not, a diagnostic biopsy weighing less than 20g must be carried out. Wherever possible a therapeutic rather than a diagnostic operation should be done.
11 Axillary node surgery should be carried out in association with localisation surgery only if a diagnosis of invasive carcinoma has been proven preoperatively.
12 It is the responsibility of the operating surgeon to ensure the pathology forms are concordant and record accurately the specimens submitted for histopathological examination. The specimens sent for histology should be recorded in the operation notes as stated in the Royal College of Surgeons publication “Good Surgical Practice”.
13 The operation note should record the specimen weight and whether or not the specimen was x-rayed and the lesion was present in the specimen.

Fidelity checks will be instigated to ensure telephone randomisation time fits with theatre records and probe use.

Intraoperative surgical resection correctness using the probe will be checked between probe results recorded on the console and resection specimens.
Please see Appendix B for further information about the MarginProbe Device.

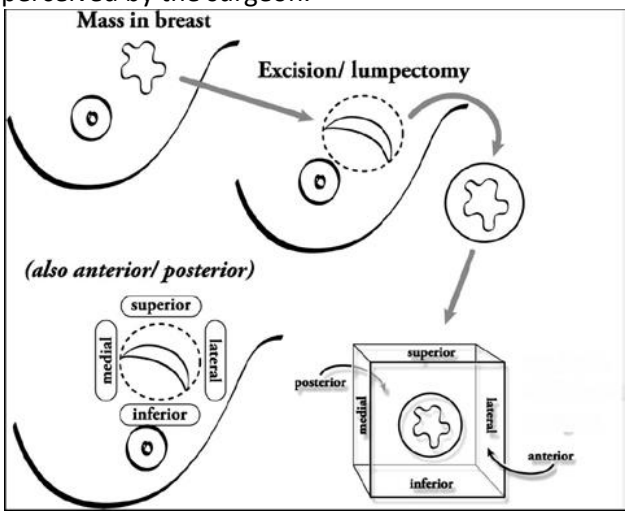
Intraoperative

General:

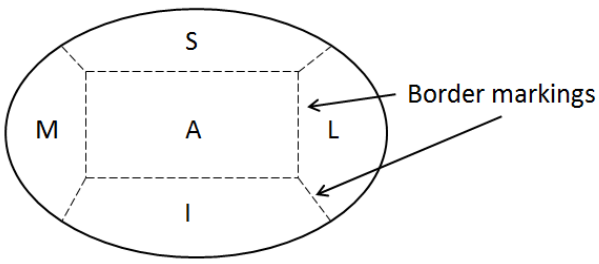
- Use of the device will take place during a lumpectomy procedure only in patients randomized to the "Device" arm.
- The console will be set-up in the OR and turned on. This is in preparation for the randomization phase, and so as not to lose time if the patient is randomized into the "Device" arm.

Pre-Randomization:

- The main ex-vivo lumpectomy specimen will be excised in the surgeon's routine surgical manner.
- All main ex-vivo lumpectomy specimens will be suture oriented (using standard of care techniques), so as to uniquely define the aspects of the specimen relative to the body (lateral, medial, superior, inferior, deep, anterior; see also figure below). The orienting suture (clip, or other similar means) should be placed in the centre of the margin, as perceived by the surgeon.



- In all main ex-vivo lumpectomy specimens, the borders of each of 6 margins should be marked by the surgeon by thin ink markings (see figure below), for further assist in pathology assessment.



- Intraoperative assessment by visual inspection and palpation will be performed by the surgeon.
- Additional lumpectomy cavity shaving is performed by the surgeon, as deemed necessary, based on this intraoperative assessment.
- Lumpectomy cavity shavings performed based on visual inspection and palpation shall be documented.

Please see Appendix B for further information about the MarginProbe Device.

MarginProbe Schedule of Assessments

2.1

Assessment	Baseline/ screening visit	Operative visit	1 month post surgery	3 months post surgery	9 months post surgery
Informed Consent	X				
Eligibility criteria	X				
Demographics	X				
Baseline characteristics	X				
Relevant Medical History	**X**				
Procedural characteristics		X			
Intraoperative imaging use		X			
Pathology assessment		X			
FACT-B, HADS, EQ5D, SABIS Questionnaires	X		X (by post)	X (by post)	X (by post)
Randomisation		X			
Photographic measurements	X				X
Adverse events assessed		X	X		
Health Economic Diaries			X (by post)	X (by post)	X (by post)

NB: Adverse events and Serious Adverse events should be recorded, as appropriate, at all points of contact.

4. Data Analysis and Statistical Considerations

Sample size: The ABS 2011 Audit[1] found the average re-excision rate for DCIS is 30% and that for invasive cancers is 25%. It is estimated that approximately 20% of recruited patients will have DCIS and 80%, invasive cancer. The estimated average re-excision rate for the whole study group is 26%. Specialist Centres are expected to have a slightly lower re-excision rate, if we assume a 25% re-excision rate in the control arm and predict that the device will give a 50% reduction in the re-excision rate (i.e. to 12.5%), it is estimated that 219 patients will be required to be recruited in each group (90% power using a simple chi-square test with continuity correction). It is proposed to recruit 230 per group to allow for drop-out and loss to follow-up.

With this number of patients, the study would have 80% power to detect a 44% relative reduction from 25% to 14% in re-excision rate and a 50% relative reduction from 20% to 10% in re-excision rate.

This number of patients would also lead to 90% power to detect differences in TOI of 4.5 or more between the two groups and 80% power to detect differences in TOI of 3.9 or more (using an estimated SD of 15 from the ALMANAC trial and a simple two-sample t-test with the conventional 5% significance level).

The Breast Screening Centres selected treat over 2,600 cancers each year of which over 1,800 will require BCS. In this group of patients, 50% agree to participate in treatment trials, however, we would expect a higher rate as this trial does not involve patients having to take additional trial medication and similar non-medical intervention trials have recruited up to 60% in Manchester. Thus we expect to recruit the required number of 460 patients within one year from the participating centres. We would not expect loss of population due to death as these patients will be fit for anaesthetic and survival is in excess of 98% at 10 years.

Randomisation: Allocation of patients to either standard procedure or the use of the Margin Probe device in a 1:1 ratio will be made using the method of simple permuted block randomisation (with random block sizes) .Patients will be individually randomised by telephone via the MAHSC-CTU.

Baseline data: Patient characteristics will be summarised using numbers and percentages for qualitative data, medians and ranges for ordinal qualitative data and non-Normal continuous data, and means and standard deviations for Normally distributed continuous data. Normality will be assessed by inspection of distribution graphs and skewness/kurtosis statistics.

Primary Endpoints: The re-excision rate (at least one further surgical re-excision operation by 9 months) between the two groups will be compared initially using the simple chi-square test followed by logistic regression analysis (to adjust, if necessary, for any potential confounding factors e.g. Centre; DCIS vs invasive). Total numbers of re-excisions will be compared using generalised linear models with Poisson or Negative Binomial regression. The percentage of patients with excision margins ≤ 1 mm after one BCS procedure will be compared using logistic regression analysis.

Secondary Endpoint: Tissue weight excised will be compared initially between the two groups using the simple t test followed by linear regression analysis (to adjust, if necessary, for any potential confounding factors e.g. Centre; DCIS vs invasive). Ordinal regression will be used to compare the cosmetic evaluation scales.

Quality of Life assessments: QoL will be measured in each group by using validated self-completion disease specific and generic instruments, FACT-B[11],HADS[12] and EQ5D for health-related utility, together with the body image scale of SABIS[16]. These will be administered at baseline (pre-surgery) and by postal follow-up at 1,3,9 months post-surgery, permitting calculation of Trial Outcome Index (FACT-B TOI).). Analyses of covariance will be used to compare QOL scores between the groups at 6 months follow-up, adjusting for baseline scores and other potential confounding factors (e.g. Centre, chemotherapy use). In addition, longitudinal regression analysis, using generalised estimating equations, will be used to compare the QOL scores between groups over the whole follow-up period (1, 3 and 9 months post randomisation).

Missing data: Missing QOL data at follow-up time points will be adjusted for in the statistical analysis using multiple imputation procedures.

Statistical Approach: All analyses will be by intention-to-treat using the conventional two-sided 5% significance level. The statistical software packages SPSS and STATA will be employed to carry out the statistical analyses.

5. REPORTING PROCEDURES

ADVERSE EVENTS

Definitions

Where the definition indicates 'device', it refers to any device used in the study. This might be the device under investigation, or any market released component of the system.

AE – Adverse Event: Any untoward medical occurrence unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device

- This definition includes events related to the IMD
- This definition includes events related to the procedures involved
- For users or other persons, this definition is restricted to events related to IMD (ISO 14155:2011, 3.2)

ADE - Adverse Device Effect : Adverse event related to the use of an IMD

- This definition includes AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation of operation, or any malfunction of the IMS
- This definition includes AE resulting from an error use or from intentional misuse of the IMD (ISO 14155:2011, 3.1)
-

DD – Device Deficiency: inadequacy of a MD with respect to its identity, quality, durability reliability, safety or performance.

- Device deficiencies include malfunctions, use errors and inadequate labelling

(ISO 14155:2011, 3.15)

a.

SAE- Serious Adverse Event:Any untoward medical occurrence that:

- Results in death;
- Is life-threatening*;
- Requires in-patient hospitalisation or prolongation of existing hospitalisation**;
- Results in persistent or significant disability or incapacity, or;
- Consists of a congenital anomaly or birth defect;
- Other important medical events***.

*'life-threatening' in the definition of 'serious' 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 which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

General

- The MarginProbe is a low-risk device. In previous intended use studies the observed rates for adverse events, including serious adverse events (SAEs), were low and there were no differences observed between the device and the control groups. There were no Probable or Definite device-associated adverse events.
- As is reported in the literature, a significant proportion of patients undergoing lumpectomy procedures are expected to have positive margins and undergo additional breast and axillary procedure(s). Further, some patients are expected to undergo additional breast procedures in the contralateral breast as a result of the workup. Therefore, breast and axillary surgical procedures and hospitalizations are expected to occur in the study population. Thus, breast or axillary procedures, including the associated hospitalization, will **not** be considered as an AE or as a SAE and will not require reporting to authorities.
- Adverse Events (AE) will be followed until the end of the initial lumpectomy procedure. Because adverse events potentially related to the use of the MarginProbe are very limited, and any such events would be likely to arise in the surgery or the immediate postoperative period, only those adverse events observed at surgery or the one month post-study visit will be followed. All such events will be followed until resolution or the final follow-up visit, whichever occurs first.
- Serious Adverse Events (SAE) (as a subset of those AEs defined in (e) above) will be followed until the final (9 month) follow-up visit or resolution of the SAE, whichever occurs first.
- The investigator shall report any SAE or UADE immediately, within 24 hours, to the sponsor. The site should contact the relevant person by telephone to provide the initial notification. For this study, UADEs will include device failure or device malfunction resulting in device not being used during surgery.
- The investigator shall provide a written report by facsimile or mail describing the SAE or UADE to the sponsor.
- Reports relating to the patient's subsequent medical course must be submitted to the sponsor until the event has subsided or, in the case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.
- The investigator is required to comply with applicable regulations regarding the notification of SAE to the reviewing IRB consistent with any IRB conditions of approval.

Assessment of AE Relationship to Study Proceedure

The investigator's assessment of an AE's relationship to the study device is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the study device in causing or contributing to the AE will be characterized as one of the following:

Unrelated - suggests the AE can be attributed to something other than the study device.

Possible - suggests that the association of the AE with the study device is unknown. However, the AE is not reasonably supported by other conditions.
Probable - suggests that a reasonable temporal sequence of the AE with the study device exists and, based upon the investigator's clinical experience, the association of the AE with the study device seems likely.
Definitely - suggests that a definite temporal sequence of the AE with the study device exists.

Device Failures and Malfunctions

All device malfunctions will be documented and reported. Devices that malfunctioned during the procedure will be returned to the sponsor for analysis, after appropriate decontamination per hospital guidelines.

Device Malfunction: A device malfunction is an unexpected change to the device that is contradictory to the labeling and may or may not affect device performance.

Device Failure: A device has failed if it does not perform according to labeling and negatively impacts the treatment while used according to the labeling.

Potential anticipated adverse effects

There are no known anticipated device related AEs or SAEs.

Adverse Event Reporting

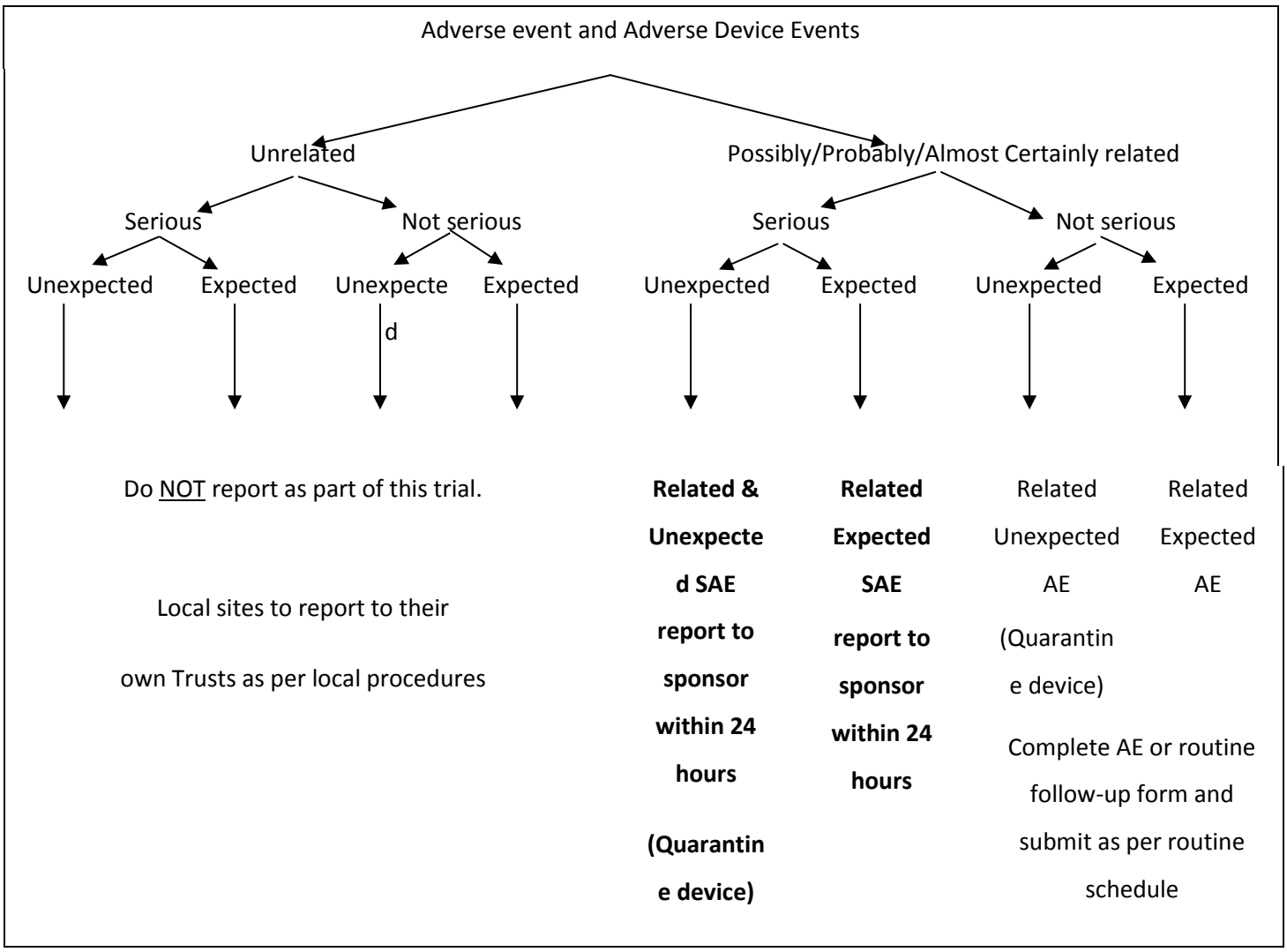
Only adverse events **specifically related to the device** should be reported.
Do not report any complications or side effects commonly associated with cancer and/or chemotherapy e.g. septicaemia, neutropenia, deep vein thrombosis and hospitalisation due to viral illness or complications/ events related to surgical procedure.

All device-related SAEs must be reported immediately by the local Investigator to the Chief Investigator. The site should:

- Either, complete the SAE case report form, signed and dated and send immediately (within 24 hours or the next working day, preferably by fax on 0161 291 5771) to the sponsor together with relevant treatment forms and anonymised copies of all relevant investigations.
- Or, contact the sponsor by telephone and then send the completed SAE form to the sponsor within the following 24 hours as above.

The form asks for nature of event, date of onset, severity, corrective therapies given, outcome and causality The responsible investigator should sign the causality of the event. Additional information should be sent within 5 days if the event has not resolved at the time of reporting.

The sponsor will notify the Main REC of all UADEs occurring in the trial within 15 days of notification, and will provide the Main REC with an annual report of all SAEs. Investigators should report any SAEs as required by their Main Research Ethics Committee and/or Research & Development Office.



NB. Only adverse events e.g. illness, injury and accident <u>specifically related to the device</u> should be reported.

Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance. Please see appendix A for further information.

To report an SAE, an SAE form must be completed and returned **within 24 hours** of the clinician becoming aware of the event.

Fax: 0161 291 4651 for the attention of Faye O'Keeffe

5. INFORMED CONSENT, ETHICAL AND REGULATORY CONSIDERATIONS

Ethical Approval

This trial will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, GCP, the Data Protection Act and other regulatory requirements, as appropriate.

Multicentre Research Ethics Committee (MREC) approval has been obtained for this trial, and Site Specific Assessments (SSAs) will be performed at participating centres. The trials centre will maintain contact with NRES and will submit any protocol amendments. The trials centre will forward any resulting documentation to local centres.

Patient Informed Consent

The local investigator is required to explain the nature and purpose of the trial to the patient prior to trial entry. A detailed patient information sheet and consent form will be given to the patient and written informed consent obtained before entry to the trial.

Protocol Compliance

MAHSC-CTU data management staff will be in regular contact with local centre personnel to check on progress and to help with any queries that may arise, with regards to data related matters. Incoming forms will be checked for completeness, consistency, timeliness and compliance with the protocol.

The data management team will liaise primarily with the trial project manager to escalate issues, trends and any non-compliance identified by the trial data. The project manager will have an overall view of the study and maintain regular contact with sites. Trial PM is responsible for identifying all relevant protocol deviations that merit recording and actioning, and maintaining oversight of site compliance.

Decisions relating to significant and/or persistent issues with sites are made by the CI//Sponsor, and any issues identified and escalated by the project manager. Centres may be withdrawn from further recruitment in the event of serious and persistent non-compliance.

Data Protection

All data will be kept strictly confidential according to Good Clinical Practice (GCP) Guidelines. At the end of the study, all study data will be stored by the Manchester University NHS Foundation Trust in a secure fashion for 20 years in accordance with the ICH GCP. During the study period, the Case Report Forms will be stored at the MAHSC-CTU.

Source data will be stored at the relevant clinical sites in line with respective Trust policies. Please note, original Questionnaires, diaries and CRF pages are to be sent to be processed; copies of these are to be retained at sites. The trials centre will act to preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner and our trials are registered in accordance with the Data Protection Act 1998 with the Data Protection Officer at the relevant NHS Trusts.

Publication Policy

Data from all centres will be analysed together and published as soon as possible after the analysis time point has been achieved; after the last patient has completed their 9 month assessment. Individual participants may not publish data concerning their patients that are directly relevant to questions posed by the trial until the Trial Management Group (TMG) has published its report. The TMG will form the basis of the Writing Committee and advise on the nature of publications.

All publications shall include a list of participants, and if there are named authors, these should include the principal investigator, clinical trial coordinator(s), and statistician(s) involved in the trial and contributors of more than 10% of participants. If there are no named authors then a writing committee will be identified.

TRIAL GOVERNANCE

Independent Data Monitoring and Ethics Committee (IDMC), Independent Trial Steering Committee (TSC) and Trial Management Group (TMG)

The trial will have an IDMC with an independent Chairman. In addition, the Trial Steering Committee includes 2 patient representatives.

The data will be reviewed six monthly by an IDMC, consisting of at least two clinicians not entering patients into the trial and an independent statistician. The IDMC will be asked to recommend whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients. The IDMC would make a decision to discontinue recruitment, in all patients or in selected subgroups. However, thiswill be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. If a decision is made to continue, the IDMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDMC will make confidential recommendations to the TSC.

The role of the TSC is to act on behalf of the funder, to provide overall supervision for the trial, to ensure that it is conducted in accordance with GCP, and to provide advice through its independent Chairman. This independent committee will review the recommendations from the IDMC and will decide on continuing or stopping the trial, or modifying the protocol.

The Trial Management Group, under the chairmanship of the Chief Investigator, will coordinate and manage the trial's day-to-day activities. It will include all of the Grant co-applicants, all of the PIs or

their representatives, the Study Coordinator and representatives from the MAHSC CTU. We currently aim to hold these face-to-face meetings at six monthly intervals.

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7. APPENDIX A – CAUSALITY

The assignment of causality of adverse events should be made using the definitions in the table below.

If any doubt about the causality exists the investigator should inform the trials centre who will notify the Chief Investigators. The device manufacturer and/or other clinicians may be asked to advise in difficult cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. If a difference of opinion remains between the PI and the CI, then both should be reported.

Relationship	Description	RESPONSE
Unrelated	There is no evidence of any causal relationship.	Yes or No
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after trial procedure/ surgery). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).	Yes or No
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial procedure/ surgery). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).	Yes or No
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes or No
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes or No
Not assessable	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.	Yes or No

8. Appendix B - MarginProbe Device

Indications for use, including contra-indications should be taken from the EU version of the IFU/UM