Study Title: Phase I Safety and Feasibility Study of the use of Magnetic Marker Seeds to localise breast cancers

Protocol Short Title/Acronym:	Magnetic seed localisation of breast cancers
Ethics Ref:	Insert
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Version No and Date:	V2, 18th March 2016
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Sponsor:	UHSM, Southmoor Road, Manchester, M23 9LT.
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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, the Sponsoring Trust's R&D Office (or a Southern Sector R&D Office, regulatory authorities, and members of the Health Research Authority or Local Research Network).

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Signatures

The approved protocol should be signed by author(s) and/or person(s) authorised to sign the protocol

The Chief Investigator and UHSM as the Sponsors have discussed this protocol. The investigator agrees to perform the investigations and to abide by this protocol

The investigator agrees to conduct the trial in compliance with the approved protocol, EU GCP and UK Regulations for CTIMPs (SI 2004/1031; as amended), the UK Data Protection Act (1998), the Trust Information Governance Policy (or other local equivalent), the Research Governance Framework (2005' 2nd Edition; as amended), the Sponsor's SOPs, and other regulatory requirements as amended.

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Chief Investigator signature Date

Print name:

_____ _____

Sponsor Representative signature Date

Print name:

Contents

1. Summary

Title:	Safety and feasibility study of Magnetic Seed markers to localise breast cancers for surgical excision
Short title:	Magnetic seeds to localise breast cancers
Trial medication:	N/A
Phase of trial:	I
Objectives:	The Primary Endpoint An evaluation of the distribution of seed migrations to estimate the risk of markers migrating • A clinically significant distance (10mm or greater) • A clinically unsafe distance (40 mm or greater) Marker (seed) location will be compared radiographically between the post-placement image and the pre-operative image. The position of the marker (seed) will be assessed in relation to anatomical landmarks and any change recorded in mm. Secondary research questions include; • Accuracy of initial placement – distance of the marker (seed) on radiographic imaging from the intended site of placement (e.g. lesion, marker clip, calcification); • Percentage magnetic markers (seeds) within target area; ○ The target area will be detected by mammography on the day of surgery and is defined as within 10mm of the target lesion. • Relationship between depth of marker (seed) and ease of transcutaneous detection;

- Marker (seed) depth to the nearest skin surface will be estimated sonographically
- Ease of detection measured by ability to detect the marker (seed) with Sentimag detector and the time to detect marker (seed) in seconds;

Other End-points

- Safety and tolerability
  - Tissue responses as assessed by gross pathology and histology will be described
  - Adverse Effects profile will be monitored
- Seed integrity post excision;
- Number of days the marker (seed) was in place;
- Mastectomy weight
- Relationship between clinical characteristics and movement of the markers -- If any markers migrate a clinically significant distance, a qualitative assessment will be carried out to see if there is a possible relationship between clinical characteristics seen in patients and movement of the marker. (e.g. Haematoma, placement of seed into fatty rather than soft tissue)

Type of trial: Single site, single arm, open label safety and feasibility cohort study of using magnetic marker seeds to localise breast tumours.

Trial design and methods: The magnetic marker system (Sentimark® Magnetic Marker System) is a sterile, single use device composed of a magnetic marker (seed) preloaded in a delivery system. The magnetic seed is approximately 5mm long and 0.9mm in diameter.

The seed is intended to be temporarily placed within the breast and removed within 28 days. The seed, when used in conjunction with the Sentimag® System (base unit and probe), can be used as a guide for the surgeon to facilitate excision of tissue. The Tissue

Marker (seed) is visible using ultrasound and mammography.

The study is a first-in-human study using this particular magnetic seed and designed to test the feasibility and safety of using the marker (seed) in breast cancer patients. The data will support the application for a CE mark.

The study will be carried out in patients requiring a mastectomy. In this population, the full cycle of marker (seed) deployment and removal can be evaluated, but as the breast is being removed as part of the planned cancer treatment, patient treatment will be unaffected should the magnetic seed not perform as intended.

Methods:

The marker (seed) will be inserted by trained and qualified healthcare professionals under image guidance (ultrasound or radiography) and removed with the surgical mastectomy (breast) specimen.

Sentimark will be placed in the lesion for which a patient is scheduled to have a mastectomy, a minimum of 2 days prior to surgery.

The depth of lesion and marker will be recorded by the radiologist

Confirmation of initial detectability with magnetometer immediately after placement and time to detection (seconds).

Assessment of distance of the magnetic marker (seed) from lesion on pre-operative mammography.

Check mammogram on morning of surgery to ensure Sentimark is still visible.

Surgeon checks that Sentimark can be detected transcutaneously during surgery.

	Surgeon performs mastectomy Record mastectomy weight. 25 patients (range of breast sizes (a minimum of three of each of small (<250g), and medium (250-500g), and five large (>500g) breasts). Perform pathology assessment of mastectomy tissue and record any unexpected tissue reaction to the Sentimark device (minimum 10 patients) All adverse events will be recorded from when the patient signs the informed consent until the final study visit. 25 patients
Trial duration per participant:	6 weeks maximum
Estimated total trial duration:	Ten months
Planned trial sites:	Single – University Hospital of South Manchester
Total number of participants planned:	25
Main inclusion/exclusion criteria:	Inclusion criteria: • Participant is willing and able to give informed consent for participation in the study; • Female, aged 18 years or above; • Diagnosed with breast cancer (invasive or DCIS); • Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the study; • Undergoing mastectomy breast surgery. Exclusion criteria: • Patients with a Pacemaker or implanted device in the chest wall; • Patients requiring an MRI scan prior to surgery; • Patients with known coagulopathy or receiving anticoagulant medication including warfarin,

heparin, clopidogrel or rivaroxaban;
- Patients receiving Neoadjuvant chemotherapy;
- Patients who are pregnant or lactating;
- Patients who have received Sienna (iron oxide) injection in the previous six months;
- Patients with an existing breast haematoma close to the target lesion.
- Patients with known hypersensitivity to stainless steel

Statistical methodology and analysis:

This protocol has been developed with Julie Morris Medical Statistician at Manchester University. Simple descriptive summary statistics of the main parameters will be derived together with a graphical presentation of the raw data. Percentages for categorical variables, means, standard deviations, medians and range values for quantitative factors will be calculated as appropriate. 95% confidence intervals will also be presented to provide a measure of accuracy for the estimates.

The relationship between breast size and detectability of the seed by the magnetometer will be assessed using simple correlational analysis.

The statistical software package, SPSS version 22, will be used for the statistical analysis.

Sources of measurement error will be graphically displayed, reviewed and discussed as appropriate.

2. Glossary of Terms

AE	Adverse Event
AR	Adverse Reaction
CRF	Case report form
CI	Chief Investigator
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trials
CTA	Clinical Trials Authorisation
DCIS	Ductal carcinoma in situ
DSMB	Data Safety Monitoring Board
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Products
IRB	Independent Review Board
MHRA	Medicines and Healthcare Products Regulatory Agency
MRI	Magnetic resonance imaging
NHS	National Health Service
HRA	Health Research Authority
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SIL	Subject Information Leaflet (see PIL)
SmPC/SPC	Summary of Products Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
U/S	Ultrasound
WLE	Wide Local Excision (lumpectomy surgery)

3. Background and Rationale

Breast Cancer

Breast cancer is a heterogeneous disease, with great diversity in the site, size and progression of tumours. Some are palpable and discovered by the patient, though many are first detected during mammogram screening. For such cancers, localisation is necessary prior to surgery, to guide surgeons to the target excision site.

Wire Guided Localisation

Traditionally, localisation involves radiographic-guided insertion of a wire into the breast, with positioning of the wire tip at the centre of the lesion. However, this procedure carries several logistical limitations[i,ii] stemming from the fact that wire localisation must be performed on the day of surgery. This is to minimise risk of wire migration or dislodgement[iii], a significant possibility due to the external section of wire left protruding from the breast. Same-day appointments demand excellent coordination between radiological departments and operating theatres to ensure that disruption to procedure scheduling is minimised. Delays may result from technically difficult procedures[iv], leading to over-running radiology appointments that have a knock on effect on operating lists. Additionally, cancelled operations can result in preceding wire guidance procedures becoming unnecessary, resulting in wasted staff hours.

Another limitation of wire guidance occurs because the wire directs surgeons along a linear route. Lesions are found at a point along the wire, though it can be difficult to determine how far along they are found. For this reason, surgeons making initial incisions may be dictated by the visual trajectory of the wire, rather than the location of the lesion[i]. This can lead to excessive dissection and sub optimal cosmetic results.

Radioactive Seed Localisation

Radioactive seed localisation (RSL) is a localisation technique that is less commonly used in the UK. A radioactive seed can be inserted up to 5 days before surgery, thus eliminating the requirement for radiology appointments on the same day as the patient's operation. The seed is detected in theatre using a handheld gamma probe. The gamma probe directs the surgeon to a single specific point via the shortest route, whereas, wires often transect the breast, meaning that surgeons commonly end up dissecting across normal tissue to locate the tip of the wire. In addition, with RSL, there is no distraction from external projections of wire, so the surgeon is guided purely by the audible response to the seed. It is hypothesised that the

advantages of RSL will lead to improved surgical techniques and reduce pressures on theatre schedulingi.

However, up to now, there is little evidence demonstrating clear superiority in surgical outcome of one localisation technique. Several studies have found lower positive margin rates in patients undergoing RSL versus wire guidance[v,vi,vii]. This means that edges of excised tissues less commonly involves cancerous tissue, suggesting that RSL more accurately localises cancerous lesions. Conversely, many more studies, including one of the largest trials to date, conclude there is no variability in surgical outcome[i,v,viii,ix.]

Regardless of stance on surgical outcome, all studies noted that RSL offers significant improvements in scheduling of appointments and patient convenience[i,ii,v-ix.]

However, radioactive techniques are not without limitations. Several studies have evaluated the use of standard radioisotope and blue dye injections for sentinel node biopsy[x,xi,xii]. Each study commented on the complex legislation regulating use of radioisotopes, particularly with regards to operator training and correct disposal and handling. In addition, radioisotope use increases patient and healthcare worker radiation exposure which, though minimal, would be preferable to avoid.

Iron Oxide Use in Breast Surgery

Several studies have investigated the use of liquid injections of iron oxide rather than traditional radioisotope and blue dye injections, in sentinel node identification[x,xi,xii]. Following iron oxide injections, a handheld magnetometer was used to detect the location of iron oxide in the lymph nodes. All studies concluded that iron oxide particles performed equally as well as standard radioisotope & blue dye injections in sentinel node identification, demonstrating potential for more widespread use of the technique.

In addition, Ahmed et al tested localisation of cancerous lesions using a magnetic tracer injection. The tracer successfully localised all tumours and resulted in appropriate excisional margins, without excess tissue excision[x]; thus demonstrating the feasibility of magnetic tracer localisation of tumours.

Sentimark Magnetic Localisation

The localisation method with which this project is concerned has similar principles to RSL. However, instead of radioactive seeds, a soft magnetic seed called Sentimark, is placed into the breast. The seed is similar to a biopsy clip and can be detected using a handheld magnetometer called Sentimag. The Sentimag probe

emits an alternating magnetic field that detects the magnetic response of the Sentimark seed. The magnetometer produces an audible response when held close to the Sentimark seed and can be used by surgeons to locate target excision sites. Sentimark is inserted about a week before operation, ideally during a biopsy appointment, for patient convenience.

This study will be the first to investigate magnetic seed localisation of tumours. It is hypothesised that using magnetic seeds rather than injections with a magnetic tracer will allow more accurate detection and localisation using the Sentimag probe. This is because the probe is detecting the magnetic field produced by a single discrete object, rather than a collection of iron oxide-containing liquid which may disperse throughout the breast.

Summary of Localisation Techniques

The coordination and scheduling difficulties encountered in wire guided localisation, alongside the logistical and safety issues of radioisotope usage, highlight a requirement for further innovation and acquisition of new technologies in the field of localisation. It is hoped that magnetic seed localisation can act as a feasible alternative to existing technologies. Use of magnetism in localisation techniques offers a potential alternative to wire guidance and RSL.

An important consideration with the deployment of the new seed is whether the size and shape of the seed are sufficiently similar to previous designs to show similar migration patterns, as movement of the seed prior to surgery can cause incomplete lesion excision with en-suing requirements for re-operation or an increased risk of recurrence.

The migration performance of Sentimark in an implantation trial in goats, mean migration of 0.95mm with a range 0 to 3.6mm (N=10), was very similar to that observed by Alderliesten, et al.[xiii] who report a mean migration of 0.8mm, range 0 to 2.8mm (N=10) for RSL seeds which was considered “clinically negligible” in RSL of human breast lesions. However, confirmation is required that the magnetic marker performs as expected in the clinic.

The study will test a soft magnetic seed (Sentimark) and its accompanying handheld magnetic probe (Sentimag) with particular consideration for its safety and performance once placed into human breast tissue.

Device

The device to be studied is a small (5mm x 0.9mm) metal magnetic marker (seed) that has soft magnetic properties. This means that when exposed to a magnetic field it becomes magnetic. The magnetism can then be detected using a magnetometer and probe which gives an audible and visual signal of the strength of response from the seed and as it is directional this can accurately guide the user to the site of the magnetic seed. The magnetometer is a CE approved device and is used worldwide for detecting iron oxide in sentinel lymph node biopsy procedures, and is proven in clinical practice. The seed itself will be deployed by a radiologist into the centre of the tumour site using a similar technique to that used to currently place a wire into the breast. The seed itself is cylindrical and in *in vivo* studies in goats have shown similar migration performance to that seen with radioactive seeds in human breast tissue.

The seed has also been tested in animal tissue models by UHSM radiologists and surgeons, and in these models it can be safely deployed by the radiologists using existing techniques. The device was detected and surgical resection was performed with 100% accuracy on all specimens. There is no radiation exposure from this device.

Study Population

Adult women with capacity to consent who have a proven breast cancer requiring breast removing mastectomy surgery.

Potential Risks to Patients

The device itself is a small piece of metal and in itself does not offer a likely safety risk.

- Migration of the seed – the seed is cylindrical and therefore once placed in the breast it has the potential to migrate along the path of the needle that was used to deploy it. When deployed into mammary soft tissue in animal models the device has not migrated. This study will involve placing the device in women having mastectomy so even if the device migrates it will not affect patient's cancer care (as the whole breast will be removed along with the device no matter where it is located in the breast).
- Failure to detect the seed – the seed is small and the magnetic field generated is proportional to the size of the seed. This study aims to assess whether the seed can be detected in all sizes of breast as in some cases it

may be possible that the seed lies too deep in the breast to be detected using the magnetometer. To ensure safe resection of the cancer, each patient in this study will be under-going a planned mastectomy, to ensure that the device is fully removed even if detection should fail.

- Tissue acceptance – the seed is produced from a single material and has demonstrated biocompatibility through ISO-10993 biocompatibility evaluation including demonstration of tissue acceptance in mammary tissue of goats (28-day implantation period). Bone wax is used as a terminal plug for Sentimark device. Bone wax is commonly used for the same purpose in brachytherapy and RSL needles. Some reaction to bone wax may occur, such as an allergic reaction or foreign body reactions (e.g. granulomas), as bone wax is a minimally resorbable implantable substance.

Potential Benefits

The study will be carried out in patients requiring a mastectomy. In this population, the full cycle of marker (seed) deployment and removal can be evaluated, but as the breast is being removed as part of the planned cancer treatment, patient treatment will be unaffected should the magnetic seed not perform as intended. However, there will be no direct benefit for patients taking part in the study and the potential benefits of this study are limited to the advancement of medical knowledge. If the study confirms that the magnetic marker (seed) is safe and the method is feasible, the device has the potential to be used for localisation of breast cancers for lumpectomy surgery.

4. Trial Objectives and Design

4.1. Trial Objectives

Aims of the feasibility study:

- Assess migration of Sentimark magnetic marker (seed) between deployment and surgery;
- Investigate the accuracy of magnetic marker (seed) placement;
- Assess the ability to transcutaneously detect the Sentimark device;
- Examine the safety profile and Adverse Effects of Sentimark device use;
- Explore the relationship between mastectomy weight, depth of lesion and ability to detect the magnetic seed using Sentimag probe;
- Determine marker seed integrity in vivo.

4.1.1 Primary and Secondary Endpoints/Outcome Measures

The Primary Endpoint:

An evaluation of the distribution of seed migrations to estimate the risk of markers migrating

- A clinically significant distance (10mm or greater);
- A clinically unsafe distance (40 mm or greater).

Marker (seed) location will be compared radiographically between the post-placement image and the pre-operative image. The position of the marker (seed) will be assessed in relation to anatomical landmarks and any change recorded in mm.

Secondary research questions include:

- Accuracy of initial placement – distance of the marker (seed) on radiographic imaging from the intended site of placement (e.g. lesion, marker clip, calcification);
- Percentage magnetic markers (seeds) within target area.
    - The target area will be detected by mammography on the day of surgery and is defined as within 10mm of the target lesion.
- Relationship between depth of marker (seed) and ease of transcutaneous detection;
    - Marker (seed) depth to the nearest skin surface will be estimated sonographically

- Ease of detection measured by ability to detect the marker (seed) with Sentimag detector and the time to detect marker (seed) in seconds

Other Endpoints:

- Safety and tolerability;
  - Tissue responses as assessed by gross pathology and histology will be described
  - Adverse Effects profile will be monitored
- Seed integrity post excision;
- Number of days the marker (seed) was in place;
- Mastectomy weight;
- Relationship between clinical characteristics and movement of the markers -- If any markers migrate a clinically significant distance, a qualitative assessment will be carried out to see if there is a possible relationship between clinical characteristics seen in patients and movement of the marker. (e.g. Haematoma, placement of seed into fatty rather then soft tissue).

4.2 Study Design

This is a single site, single arm, unblinded safety and feasibility cohort study investigating the use of magnetic marker seeds to localise breast tumours.

Expected duration of patient participation – Four to six weeks. This will equate to a 2-4 week period between invitation to join study and Study visit 2 when surgery occurs. And a 2-3 week period between surgery and the final follow-up Study visit 3.

Invitation – occurs immediately after surgical discussion on the patient's surgical plan for removal of the breast cancer. Patient given an information leaflet about study.

- Follow-up phone call to patient more than 24 hours after invitation;
- Study visit 1 – Consultation with patient – consent taken for study. Eligibility confirmed and baseline data recorded. Placement of Sentimark device, mammogram taken to check placement, detectability of device confirmed, ultrasound performed to confirm depth of clip;
- Study visit 2 – day of surgery – check mammogram (this can occur on the day before surgery if the patients requires attendance for Sentinel Node

Biopsy as part of routine clinical care the day before surgery), check detectability of Sentimark seed, surgery performed;

- Study visit 3 – Routine follow-up appointment – Adverse effects recorded, oncological outcomes recorded and mastectomy weight.

5. Selection and Withdrawal of Subjects

5.1 Informed Consent

- Consent for the study will be taken by a Consultant Breast Surgeon. This consultant will be authorised to take consent by the Chief Investigator of the study and will have received training about the study and written information about the study. This consent process will take place at Study Visit 1, more than 24 hours after initial invitation to take part in the study.

5.2 Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study;
- Female, aged 18 years or above;
- Diagnosed with breast cancer (invasive or DCIS);
- Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the study;
- Undergoing mastectomy breast surgery.

5.3 Exclusion Criteria

- Patients with a Pacemaker or implanted device in the chest wall;
- Patients requiring an MRI scan prior to surgery[i];
- Patients with known coagulopathy or receiving anticoagulant medication including warfarin, heparin, clopidogrel or rivaroxaban;
- Patients receiving Neoadjuvant chemotherapy;
- Patients who are pregnant or lactating;
- Patients who have received Sienna (iron oxide) injection in the previous six months;
- Patients with an existing breast haematoma close to the target lesion.
- Patients with known hypersensitivity to stainless steel.

5.4 Screening and Eligibility Assessment

- Potential participants will be identified by the Research nurses at the Breast Multidisciplinary Meeting which occurs every morning in the Nightingale

[i] If the patient requires a MRI scan for another reason, the scan can be performed safely in line with the MRI conditional information provided for Sentimark

Breast Unit, UHSM. Potential study participants will be patients who are newly diagnosed with breast cancer and screening will occur in this pre-clinic MDT meeting to see if they meet the eligibility criteria for the study. These patients will have a clinical consultation with a Breast Care Nurse and Breast Surgeon later the same day and their cancer diagnosis and care will be discussed. At the end of this discussion they will be offered further discussion about this study which they could be eligible for. The study will be briefly introduced by the clinician and then if the patient is potentially interested, they will be given a Patient Information Leaflet about the study and made aware that the study is completely optional and in the next few days the Research Nurse will contact them to ask if they are potentially interested in taking part.

- Patients interested in taking part in the study will return for a further follow-up visit to discuss the study further and to confirm eligibility and to consent to the study at this point.
- The screening process will include collection of the following data;
- Demographics – age, sex, BMI;
- Current medications including anticoagulant medication;
- Pre-operative histology of the breast cancer;
- Oncological information – size and location of lesion on imaging, clinical findings, radiological score;
- Medical history – including implantable devices such as pacemakers or defibrillators;
- Confirmation from Surgical team that pre-operative MRI will not be required.
- Pregnancy test for premenopausal women.

5.5 Selection of Participants

Potential participants will be identified by the Research nurses at the Breast Multidisciplinary Meeting which occurs every morning in the Nightingale Breast Unit, UHSM.

5.6 Withdrawal of Subjects

Safety of the study participants will be monitored by the Chief Investigator. It is unlikely there will be Serious Adverse Events directly related to the Sentimark as it is similar to devices currently in use to mark breast cancer location. The study involves an intervention of Sentimark placement within the breast. Patients may withdraw consent to have this procedure performed in which case this will be recorded and the patient will be withdrawn from the study and will be replaced by another subject. If a patient withdraws consent to the study once the Sentimark has been placed, they will be withdrawn from the study but information on the cancer

excision surgery will be recorded to ensure the Sentimark magnetic marker (seed) was removed as part of the breast cancer surgery.

Each participant has the right to withdraw study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospective having been overlooked at screening);
- Significant protocol deviation;
- Significant non-compliance with treatment regimen or study requirements;
- An adverse event which requires discontinuation of the study medication or results in inability to continue to comply with study procedures;
- Disease progression which requires discontinuation of the study medication or results in inability to continue to comply with study procedures;
- Consent withdrawn;
- Lost to follow up.

It is understood by all concerned that an excessive rate of withdrawals can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible.

Withdrawal from the study will result in exclusion of the data for that participant from analysis.

The reason for withdrawal will be recorded in the CRF.

If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

5.7 Expected Duration of Trial

Expected duration of patient participation – Four to six weeks. This will equate to a 2-4 week period between invitation to join study and Study visit 2 when surgery occurs. Study visit 1 will occur a minimum of 2 days prior to surgery. Surgery will not be delayed beyond 31 days from decision to treat the cancer with mastectomy. There will be a 2-3 week period between surgery and the final follow-up Study visit 3, the end of the study will be confirmed as when post-operative histology has been recorded and any plans for re-excision surgery are known.

6. Trial Procedures

Assessments	Baseline Visit 1	Surgery Visit 2	Post surgery Visit 3 (2-3 wks post surgery)
Informed consent	X		
Medical history	X		
Pregnancy test (if pre menopausal)	X		
CRF/eCRF completion including data transfer and query resolution	X	X	X
Concomitant medication check	X	X	X
Review/reporting of patient AEs/SAEs		X	X
Place sentimark lesion and ultrasound	X		
Localise lesion during surgery		X	
Check detectability of seed with magnetometer	X	X	
Data collection in theatre		X	
Record migration of clip		X	
Mammogram	X	X	
Mastectomy specimen x-ray		X	

7. Assessment of Efficacy

7.1 Primary Efficacy Parameters

The Primary Endpoint:

An evaluation of the distribution of seed migrations to estimate the risk of markers migrating

- A clinically significant distance (10mm or greater);
- A clinically unsafe distance (40 mm or greater).

Marker (seed) location will be compared radiographically between the post-placement image and the pre-operative image. The position of the marker (seed) will be assessed in relation to anatomical landmarks and any change recorded in mm.

Formally the 95% CI if 0 out of 25 seeds migrate >10mm is 0-13%. However, findings will be considered in conjunction with other observations:

- The observed distribution of migration (e.g. how variable is this distribution and how close does it lie to the limits)
- For any seeds migrating >10mm, a qualitative assessment of underlying characteristics such as haematoma or placement into fatty tissue (both reported as causes of migration in RSL procedures)
- Abnormal tissue responses will be assessed by gross pathology and histology, as part of the safety endpoint.

7.2 Secondary Efficacy Parameters

Secondary Research Questions:

- Accuracy of initial placement – distance of the marker (seed) on radiographic imaging from the intended site of placement (e.g. lesion, marker clip, calcification);
- Percentage magnetic markers (seeds) within target area;
    - The target area will be detected by mammography on the day of surgery and is defined as within 10mm of the target lesion
- Relationship between depth of marker (seed) and ease of transcutaneous detection;
    - Marker (seed) depth to the nearest skin surface will be estimated sonographically
    - Ease of detection measured by ability to detect the marker (seed) with Sentimag detector and the time to detect marker (seed) in seconds

8. Source Data

- Medical records;
- Histopathology reports;
- Specimen x-rays and mammograms;
- CRF.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

9. Assessment of Safety

9.1 Specification, Timing and Recording of Safety Parameters.

All Serious Adverse Events (SAEs) will be reported immediately to the Sponsor of the study. Refer to SOP 2a Safety Reporting for clinical trials conducted at UHSM.

European Commission guidance on Medical Devices MEDDEV 2.7/3 Revision 3 May 2015 will be used for reporting all Adverse Events under directives 90/385/EEC and 93/42/EEC.

Serious Adverse Events are defined as:

- Adverse Event that:
    - Led to a death,
    - Led to a serious deterioration in health that either:
        - Resulted in a life-threatening illness or injury, or
        - Resulted in a permanent impairment of a body structure or a body function, or
        - Required in-patient hospitalization or
        - Prolongation of existing hospitalization,
        - Or resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
    - Led to foetal distress, foetal death or a congenital abnormality or birth defect

NOTE 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made

or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

NOTE 2: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered to be a serious adverse event.

Device deficiency
Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

Adverse Device Effect (ADE)
Adverse event related to the use of an investigational medical device.
NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.
NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report

REPORTABLE EVENTS UNDER ANNEX 7 AND ANNEX X OF DIRECTIVES 90/385/EEC AND 93/42/EEC RESPECTIVELY

For the purpose of this guidance and based on the definitions above, the following events are considered reportable events in accordance with Annex 7, section 2.3.5 and Annex X, section 2.3.5 of the above mentioned Directives 5 :
- any SAE,
- any Device Deficiency that might have led to a SAE if:
a) suitable action had not been taken or
b) intervention had not been made or
c) if circumstances had been less fortunate
- new findings/updates in relation to already reported events.

All SAEs and SARs will be reported immediately to the Chief Investigator of the Study, Mr James Harvey, and the Research & Development Office.

Adverse Events requiring reporting:

- Migration of Sentimark magnetic marker (seed) >10mm from cancer location;
- Haematoma following Sentimark placement surgical treatment;
- Sentimark device not resected from breast during cancer surgery.

9.2 Procedures for Recording and Reporting Adverse Events

All Serious Adverse Events (SAEs) should be reported immediately to the Sponsor. The immediate reports should be followed promptly by detailed, written reports using the MEDDEV Summary Reporting Form. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects' names, personal identification numbers, and/or addresses.

9.2.1Reporting Timelines

Report by sponsor to National Competent Authorities (NCA).

The sponsor must report to the NCAs where the clinical investigation has commenced:

- - for all reportable events as described which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.
- - any other reportable events as described or a new finding/update to it: immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.
- Any other reportable events as described or a new finding/update to the event: immediately, following the date the sponsor becomes aware of the new reportable event or of new information in relation with an already reported event.

9.2.2 Causality Assessment

The relationship between the use of the medical device and the occurrence of each adverse event shall be assessed and categorized. During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the Investigator's Brochure, the Clinical Protocol or the risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.
The above considerations apply also to the serious adverse events occurring in the comparison group.
For the purpose of harmonising reports, each SAE will be classified according to five different levels of causality. The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the investigational medical device.

1) Not related: relationship to the device or procedures can be excluded when:
- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has no temporal relationship with the use of the investigational device or the procedures;
- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
- the event involves a body-site or an organ not expected to be affected by the device or procedure;
- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis 17, when applicable;
- harms to the subject are not clearly due to use error;
- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

2) Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

3) Possible the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
4) Probable the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
5) Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:
- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
a) the investigational device or procedures are applied to;
b) the investigational device or procedures have an effect on;
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;
- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event. The sponsor and the investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of investigational device use/application. In some particular cases the event may be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations. Where the sponsor

remains uncertain about classifying the serious event, it should not exclude the relatedness and classify the event as “possible”.
Particular attention shall be given to the causality evaluation of unanticipated serious adverse (device) events. The occurrence of unanticipated events related to the use of the device (USADE) could suggest that the clinical investigation places subjects at increased risk of harm than was to be expected beforehand.

9.2.3 Reporting Form

The reporting form template for the summary SAE tabulation is given in the Appendix of this document.
The table gives a cumulative overview of the reportable events per clinical investigation and will be updated and transmitted to participating NCAs each time a new reportable event or a new finding to an already reported event is to be reported. More detailed information has to be provided on request of an NCA, if so requested by using the individual reporting form. The sponsor shall identify the new/updated information in the status column of the tabular form featured in the Appendix as:
a = added = new reportable event;
m = modified = new finding/update to an already reported event;
u = unchanged.
Changes in a line should be highlighted in bold and/or colour in the respective column.
The reporting form is study specific and covers only a given clinical investigation, defined by a distinct clinical investigation plan. English is the recommended language for the reporting form. The report should be sent by email in Excel to the participating NCAs, or an equivalent format which allows using the inserted filters.
The reporting to MHRA shall use the form template for the summary SAE tabulation as given in the Appendix of MEDDEV 2.7.3 December 2010.
Safety Oversight:
The Trial Steering Committee will meet once all patients have completed the study or earlier if considered necessary by the Chief Investigator. They will consider all Serious adverse events and adverse events and the main safety and efficacy outcomes. Notably they will discuss:
Morbidity and safety of seed placement – recording of any morbidity as a result of Study visit 1 or 2;
Detectability of the seed in the breast. – measured at Study visits 1 and 2 using the hand-held magnetometer;
Assessment of migration of the seed from time of deployment to time of surgery. Measured on difference in position of magnetic marker (seed) from the cancer

between Study Visits 1 and 2, and assessed on mammograms by a Consultant Radiologist.
If any markers migrate a clinically significant distance, a qualitative assessment will be carried out to see if there is a possible relationship between clinical characteristics seen in patients and movement of the marker. (e.g. Haematoma, placement of seed into fatty rather then soft tissue)
Adverse tissue responses as assessed by gross pathology and histopathology.

9.2.4 Adverse Events that do not require reporting

n/a

9.3 Urgent safety measures (USMs)

For any safety issues during the study, refer to SOP 2d Urgent Safety Measures

10. Statistics

10.1 Sample Size

This protocol has been developed with Julie Morris Medical Statistician at Manchester University.

The sample size has been set at 25 patients to achieve a balance between having sufficient numbers to observe any unexpected patterns of seed migration and keeping to a minimum the number of patients exposed to any risk through participating in the study as no direct benefit is to be expected for participants who consent to taking part in the trial.

RSL seeds are a product similar in size and shape to Sentimark, in widespread clinical use in the same indication, and considered to be safe and effective. In the literature Alderliesten[xiii], et al. [2011] report a mean migration of 0.8mm, range 0 to 2.8mm (N=10) for RSL seeds which was considered “clinically negligible” by the authors.

Migration of Sentimark in preclinical studies where the seed is deployed in soft mammary tissue showed a mean migration of 0.95mm, range 0 to 3.6mm (N=10) and no abnormal tissue reaction. Migration observed is substantially similar to that reported by Alderliesten et al for RSL seeds.

From the experience with RSLs, clinically significant migration of radioseeds (greater than 1cm) in larger studies has been reported in 3/456 placements (Gray[xiv] et al [2004], Sung[xv] et al [2013]). However when it does occur the reason is often either a pre-existing or newly formed haematoma or placement of the seed into fatty rather than soft tissue.

For this reason, clinical characteristics of patients in whom a seed migrates more than 1cm will be carefully evaluated.

Formally, the 95% CI if 0 out of 25 seeds migrate >10mm is 0-13%. However, findings will be considered in conjunction with other observations including:

- The observed distribution of migration (e.g. how variable is this distribution and how close does it lie to the limits)
- For any seeds migrating >10mm, a qualitative assessment of underlying characteristics such as haematoma or placement into fatty tissue (both reported as causes of migration in RSL procedures)
- Abnormal tissue responses will be assessed by gross pathology and histology, as part of the safety endpoint.

10.2 Randomisation

No randomisation is required.

10.3 Analysis

Simple descriptive summary statistics of the main parameters will be derived together with a graphical presentation of the raw data. Percentages for categorical variables, means, standard deviations, medians and range values for quantitative factors will be calculated as appropriate. 95% confidence intervals will also be presented to provide a measure of accuracy for the estimates.

The relationship between breast size and detectability of the seed by the magnetometer will be assessed using simple correlational analysis.

The statistical software package, SPSS version 22, will be used for the statistical analysis.

Sources of measurement error will be graphically displayed, reviewed and discussed as appropriate.

11. Trial Steering Committee

The Trial Steering Committee will consist of;

- Lay member who has already been involved in design of the study and of the Patient Information Leaflet.
- Chief Investigator and co-investigators – Mr J. Harvey, Dr Y. Lim, Dr A. Maxwell, Mr J. Murphy.
- Independent Chairman.
- Statistician – Julie Morris.
- Endomag - Scientific Representative.

The function of the committee is to ensure ongoing safety of the study to patients and to monitor ongoing efficacy of the device. The committee will convene after all patients have completed the study (or earlier at the request of the Chief Investigator) to review the primary end-point, discuss the safety of the Study, to perform the qualitative assessment of clinical characteristics for seeds migrating more than 10mm and to evaluate the overall feasibility and safety of the device based on the end-points recorded.

12. Direct Access to Source Data and Documents

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents (e.g. patients' case sheets, X-ray reports, histology reports etc.).

13. Ethics and Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (specifying which amendment), the principles of GCP and all of the applicable regulatory requirements. The study protocol and other documentation will be submitted to the REC. Any subsequent protocol amendments will be submitted to the REC and Regulatory Authorities for approval, and will comply with regulations.

The protocol will be submitted for MHRA approval and assessment as part of CE marking process for the Sentimark device. Results of the study will form part of the CE marking application to Endomag's notified body for the Sentimark device.

The Chief Investigator will submit a final report at conclusion of the trial to the Sponsor and the REC within the timelines defined in the Regulations.

14. Quality Control

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained, by Mr James Harvey and the Trial Steering Committee, as per the study monitoring plan. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

There is a requirement for the maintenance of an updated training record for each member of the research team and retention of GCP training certificates which must be less than 2 years old.

15. Data Handling and Management

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to:

- Patient data will be anonymised.
- All anonymised data will be stored on a password protected computer;
- All trial data will be stored in line with the Medicines for Human Use (Clinical Trials).

Amended Regulations 2006 and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Kings Health Partners Clinical Trials Office Archiving SOP.

Data Management

Given the small number of patients within the study a paper CRF will be maintained for all Study Patients.

16. Publication Policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals.

17. Insurance / Indemnity

NHS indemnity will cover the Indemnity for the study. The provider of the Sentimark device has indemnity to cover use of the Sentimark device.

18. Financial Aspects

Funding to conduct the trial is provided by Endomagnetics Ltd, The Jeffreys Building, St John's Innovation Park, Cowley Road, Cambridge, CB4 0WS.

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