Manchester University
NHS Foundation Trust

Study Title: Cost Effectiveness and benefits of Magtrace® versus Technetium in sentinel node biopsy for breast cancer

Protocol Short Title/Acronym:	Costs and benefits of Magtrace® in breast surgery
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Sponsor Number:	**B01337**
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Sponsor:	Manchester University NHS Foundation Trust, Southmoor Road, Manchester, M23 9LT.
Funder (if applicable):	Endomagnetics Ltd, The Jeffreys Building, Cowley Road, Cambridge. CB4 0WS

This project will be conducted in accordance with the study protocol and the ethical principles outlined by Good Clinical Practice (GCP) and the Declaration of Helsinki in its most current version

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Role of Sponsor and Funder

Manchester University NHS Foundation Trust is acting as sponsor for this study and is assuming overall responsibility for the initiation and management of the

study. The Trust will provide permission to conduct the research and monitor the progress of that research. The research team all hold substantive or honorary contracts with the Trust and therefore the sponsor has influence over all aspects of the study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results which are the responsibility of the research team.

The funder Endomagnetics Ltd have provided funding to conduct the trial, reviewed the study design, a representative will sit on the trial steering committee and be sent a copy of the results at the end of the trial.

Signatures

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

_____ _____

Chief Investigator signature Date

Print name:

_____ _____

Sponsor Representative signature Date

Print name:

Contents.

Study Summary

Title:	Cost Effectiveness and benefits of Magtrace® versus Technetium in sentinel node biopsy for breast cancer
Short title:	Cost benefit of Magtrace® in breast surgery
Medical Device:	Magtrace®
Phase of trial:	IV
Objectives:	Primary Endpoint Cost effectiveness of Magtrace® compared to Technetium in the identification of sentinel nodes in breast cancer. Secondary Endpoint: • Patient time spent in hospital and in transit in total over pre-operative and perioperative journey • Patient anxiety on day of surgery – as measured using State trait anxiety questionnaire STAI-Y given on ward on morning of surgery. • Number and length of patient hospital visits – comparing preoperative visits (clinic visits, preoperative assessment, tracer injection visits, ward visits and operative visits). • Safety of Magtrace® and efficacy – adverse events relatable to tracers, number of nodes removed, number of nodes containing tracer, % of patients with detectable tracer in the axillary sentinel nodes, can surgeons differentiate Magtrace® and Magseed signal®. • Cost per episode and for total care. • Surgical start time, days of week of operating, and delays to getting patient to theatre. Delays will be

	recorded by asking the theatre team directly pre-operatively whether they had to wait for the patient to arrive, and what the reason was, and also whether the list had to be rescheduled/ moved to accommodate a delay. • To map the current pathways of patient care. • Evaluation of the key aspects of care pathways important to patients and healthcare professionals in the management of breast cancer. • Preferences/overall satisfaction with care package for Magtrace vs. Technetium, from the perspective of patients and healthcare providers.
Type of trial:	Single site, case control study investigating the healthcare costs of Magtrace®, and a discrete-choice qualitative experiment of the perceived value of Magtrace® vs. the current standard of care

Trial design and methods:

Magtrace® is a Superparamagnetic iron oxide (SPIO) nanoparticles, and is a novel tracer for detection of sentinel lymph nodes (SN) in patients with breast cancer. Magtrace®, 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 the sentinel lymph nodes in breast cancer surgery.

The magnetic tracer is proven to be non-inferior to the standard method of sentinel node detection in two meta-analyses [(Teshome M, 2016 May, 23(5))][(Karakatsanis A, 2016 Jun; 157(2))]. This Phase IV study is designed to assess the cost-effectiveness of using the CE marked Magtrace® device in the UK healthcare system.

The study will be carried out two parts; Part I - a health economic analysis informed by a time in-motion study, and, Part 2 – a Discrete-Choice Experiment (DCE) to elicit preferences for, and satisfaction with Magtrace vs. the current

standard of care. The two methodologies would occur in parallel and not sequentially. Methods: 1. Part 1. Cost-implications and efficiency gains from using Magtrace® vs the current standard of care: A time-in-motion study 2. Part 2. Managing Breast Cancer: What matters when treating breast cancer? Focus Group and Survey Patient and Healthcare provider preferences towards the management of breast cancer: A Discrete-choice experiment	
Trial duration per participant:	8 weeks maximum
Estimated total trial duration:	14 months
Planned trial sites:	Single Centre – Wythenshawe Hospital
Total number of participants planned:	Part 1: 50 (5-10 pilot patients, 20 under Magseed, 20 under the current SOC). Part 2: Managing Breast Cancer: What matters? A focus-group, will include 5-10 patients to help design the discrete choice experiment. Managing Breast Cancer: What Matters? Survey. Discreet Choice Experiment will include: • 150 patients • 50 healthcare professionals
Part 1 Main inclusion/ exclusion criteria:	Part 1 Inclusion: • 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) requiring Magseed® localisation and sentinel node biopsy

	• Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the study; • Undergoing breast conserving surgery with sentinel node biopsy • Surgeons may only operate on the Magtrace arm of the study if they have completed a minimum of five training cases with Magtrace. Part 1 Exclusion criteria: • Patients with a Pacemaker or implanted device in the chest wall; • Patients who are pregnant or lactating; • Patients who have received Magtrace® (iron oxide) injection in the previous six months; • Patients with previous ipsilateral axillary surgery • Patients whose breast and axillary surgery are not due to be performed synchronously. • Patients following neoadjuvant chemotherapy • Patients who require MRI follow-up of the ipsilateral breast in the year following surgery (as Magtrace® may interfere with MRI) • Patients requiring an interpreter • Patients involved in current research or have recently been involved in any research prior to recruitment •

Part 2 inclusion/ exclusion criteria	Part 2 Inclusion criteria: – mixed recruitment of HCP and patients • Over 18 • Must be fluent English speaker. HCPs- must be involved in the day-to-day care of patients surgical pathways. Patients – can be naïve to the surgical pathway or have experience of having undergone breast conservation surgery within the last two years. Part 2 Exclusion criteria: • Under 18

2. Glossary of Terms

AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CT	Clinical Trials
DCIS	Ductal carcinoma in situ
DSMB	Data Safety Monitoring Board
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
MRI	Magnetic resonance imaging
NHS	National Health Service
HRA	Health Research Authority
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&I	NHS Trust R&I Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SIL	Subject Information Leaflet (see PIL)
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. During surgery for breast cancers, surgeons will often perform a sentinel node biopsy to check the draining lymphatic glands for signs of early cancer spread.

Iron Oxide Use in Breast Surgery

Several studies have investigated the use of liquid injections of iron oxide (Magtrace®) rather than traditional radioisotope and blue dye injections, in sentinel node identification. Following iron oxide injections, a handheld magnetometer (Sentimag®) 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. Magtrace® can be injected up to seven days prior to the date of surgery which allows the injection to be given simultaneously when the patient attends for a pre-existing hospital visit in the week prior to surgery (e.g. coinciding with a pre-operative anaesthetic assessment or at the same time as placement of the Magseed®) or on the day of surgery. Currently we perform this most often on the day of surgery and this will be the intention during this study. If the patient has received localisation of the cancer (by Magseed®) prior to the date of surgery and Magtrace® for the sentinel node then the patient requires no further preparations prior to surgery. The patient can arrive in the hospital at the scheduled time and be prepared for theatre. Technetium injections have by contrast, a half-life meaning that injection has to occur in the 16 hours prior to surgery. This can be given on the day prior to surgery (Two day protocol), but this means an extra visit for the patient, or on the day of surgery (but this means the patient has to have an injection on the morning of surgery and have two hours for the technetium to move to the nodes prior to surgery). Logistically this means a challenge to get the patient ready in time for the first half of a morning list as the injection should be done two hours prior to surgery, and is even more challenging on a Monday morning as

Technetium is not available for weekend injection in most sites. Technetium is also in short supply worldwide and is becoming increasingly difficult to source. Magtrace® has the potential to make the perioperative pathway simpler for the patient, less stressful around the time of surgery and to avoid delays in the perioperative setting.

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.

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.

Magseed® Magnetic Localisation

The localisation method with which this project is concerned has similar principles to radioactive seed localisation) RSL. However, instead of radioactive seeds, a soft magnetic seed called Magseed®, 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 Magseed® seed. The magnetometer produces an audible response when held close to the Magseed® seed and can be used by surgeons to locate target excision sites. Magseed® is inserted well before the operation, ideally tied in with a pre-operative anaesthetic appointment, for patient convenience.

Magseed® is a novel method of localisation that has been validated in Manchester for use in breast conservation surgery. It is widely adopted across the UK in 45 units (Nov 2019) and has been audited nationally in an audit led in Manchester to compare its performance to wire localisation.

Summary of Localisation and sentinel node 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 of breast lesions and sentinel nodes. Magseed® is currently used as the standard of care in Manchester University NHS Foundation Trust for lesion localisation. Technetium +/- blue dye is currently used as the standard for care for sentinel node localisation. Part 1 of this study would aim to assess the cost-effectiveness of using Magtrace® for sentinel node localisation compared to a control group of patients receiving Technetium. Part 2 will be a Discrete choice experiment for patients and health care professionals to ascertain the values of Magseed® and Magtrace® compared to wire localisation and Technetium sentinel node localisation.

3.1 Study Population

Adult women with capacity to consent who have a proven breast cancer requiring breast conserving surgery requiring localisation with a Magseed®, and who also require a sentinel node biopsy on the same date.

3.2 Potential Risks to Patients

- All processes and technologies have previously been proven to be efficacious and effective.
- Technetium sentinel node injection is often combined with a blue dye to increase nodal yield. The blue dye has a small risk of anaphylaxis of approximately 1 in 10,000 and can stain the skin of the breast blue for several months. Magtrace® does not have a risk of anaphylaxis but can stain the skin of the breast brown for several months post-operatively.

- Magtrace® is used as a single tracer whereas Technetium is either used as a single tracer or as a dual tracer with blue dye. Both methods are standard of care and their utility is dependent on the availability of one of the two dyes. I.e. if technetium not available Magtrace is used and vice versa. The number of nodes removed during Magtrace® localisation is slightly lower than that with Technetium , as proven on Meta-analysis (on average 1.9 nodes removed vs 2 with Technetium). This difference in tracer performance has not been shown to be clinically relevant or to increase the risk of lymphoedema in patients' index arm's as a result of removing slightly more lymph nodes in the case of Technetium.

3.3 Potential Benefits

The potential benefits of using Magtrace® will be in simplifying the patient pathway in the pre-operative period. Magtrace® will be given on the day of surgery, whereas Technetium would be given on the day of surgery or the day before. This means around the time of surgery there will be less stress for the patient, they will be ready to have their surgery at any time of the day (rather than having to wait until they have a Technetium injection). Technetium requires aliquoting out from the Christie and transporting across to the Nuclear medicine department on a daily basis, and following radioactive licences, must be given by two trained professionals in a very controlled manner. Magtrace® can be given by any trained member of staff without the need for ARSAC radioactivity licences. It will negate the need for the complex process of transferring the Nuclear medicine across the city and the need for staff to make up the injections every morning and give them to patients. Magtrace® will therefore simplify the pathway and remove multiple steps freeing up staff for other jobs. Magtrace® will make theatre scheduling in the morning easier as any patient will be available for theatre, potentially making less waiting for theatre staff and more efficient operating. It is unlikely that extra cases will be done as a result of the change but it may avoid overruns and delays in theatre.

4. Trial Objectives and Design

4.1. Trial Objectives

Primary and Secondary Endpoints/Outcome Measures

The Primary Endpoint:

Cost effectiveness of Magtrace® compared toTechnetium in the identification of sentinel nodes in breast cancer. (Part 1).

Secondary Endpoints

- Patient time spent in hospital and in transit in total over pre-operative and perioperative journey (Part 1)
- Patient anxiety on day of surgery – as measured using State trait anxiety questionnaire STAI-Y given on ward on morning of surgery (Part1).
- Number and length of patient hospital visits – comparing preoperative visits (clinic visits, preoperative assessment, tracer injection visits, ward visits and operative visits) (Part 1).
- Safety of Magtrace® and efficacy – adverse events relatable to tracers, number of nodes removed, number of nodes containing tracer, % of patients with detectable tracer in the axillary sentinel nodes (Part 1), can surgeons differentiate Magtrace® and Magseed signal®.
- Cost per episode and for total care (Part 1).
- Surgical start time, days of week of operating, and delays to getting patient to theatre. Delays will be recorded by asking the theatre team directly pre-operatively whether they had to wait for the patient to arrive, and what the reason was, and also whether the list had to be rescheduled/ moved to accommodate a delay (Part 1).
- To map the current pathways of patient care (Part 1).
- Evaluation of the key aspects of care pathways important to patients and healthcare professionals in the management of breast cancer (Part 2).
- Preferences/overall satisfaction with care package for Magtrace vs. Technetium, from the perspective of patients and healthcare providers (Part 2).

4.2 Study Design

Single site, case control study of the cost implications of Magtrace® and a discrete-choice qualitative experiment of the value of localisation devices. There are two approaches required to gather this data and demonstrate the value that Magtrace®/Magseed® combination usage could provide, namely (Part 1) a time-in-motion study, otherwise known as a time-driven and activity-based costing to demonstrate health-economic benefits, and (Part 2) a discrete-choice experiment, to demonstrate patient and healthcare provider benefits.

Study design (Part 1)

For Part 1, time-driven and activity-based costing (TDABC) will be utilised. TDABC is a bottom-up approach to healthcare pathway mapping and costing, which records pathways observed during routine clinical practice, identifies all points and durations of interaction with healthcare providers therein; and assigns time-dependent costs to each constituent. This method of costing is far more granular than reference costing[v] and enables not only an estimation of the economic impact of care pathways, but also the implications for healthcare professionals and service planning. This is due to the ability to monitor the extent of patient-HCP interactions, and to determine the true 'time cost' of existing and novel care pathways. The costs of non-time-dependent activities, including tariff-based ancillary investigations, radiography, and outpatient services, are subsequently added, based on reference costs, to provide a representative activity-weighted cost per completed treatment episode.

This approach is common in health service research.[vi] The methodology is the most thorough and comprehensive way to determine the real-world impact of Magtrace® on both patient flow, and clinical involvement with patients vs. the current standard of care, highlighting differences in both resource use and care pathways therein. Highly accurate and internally valid, this approach would enable the comparison of both the efficiency of breast cancer excision, and the workload of healthcare providers, whether clinical, clerical, or simply observation. Combined, these factors will combine a holistic estimate of the expected difference between existing care, and a switch to widespread use of Magtrace®.

Prior to recruitment, research staff will begin by mapping the current pathways for breast cancer excision at Wythenshawe Hospital and providing a preliminary

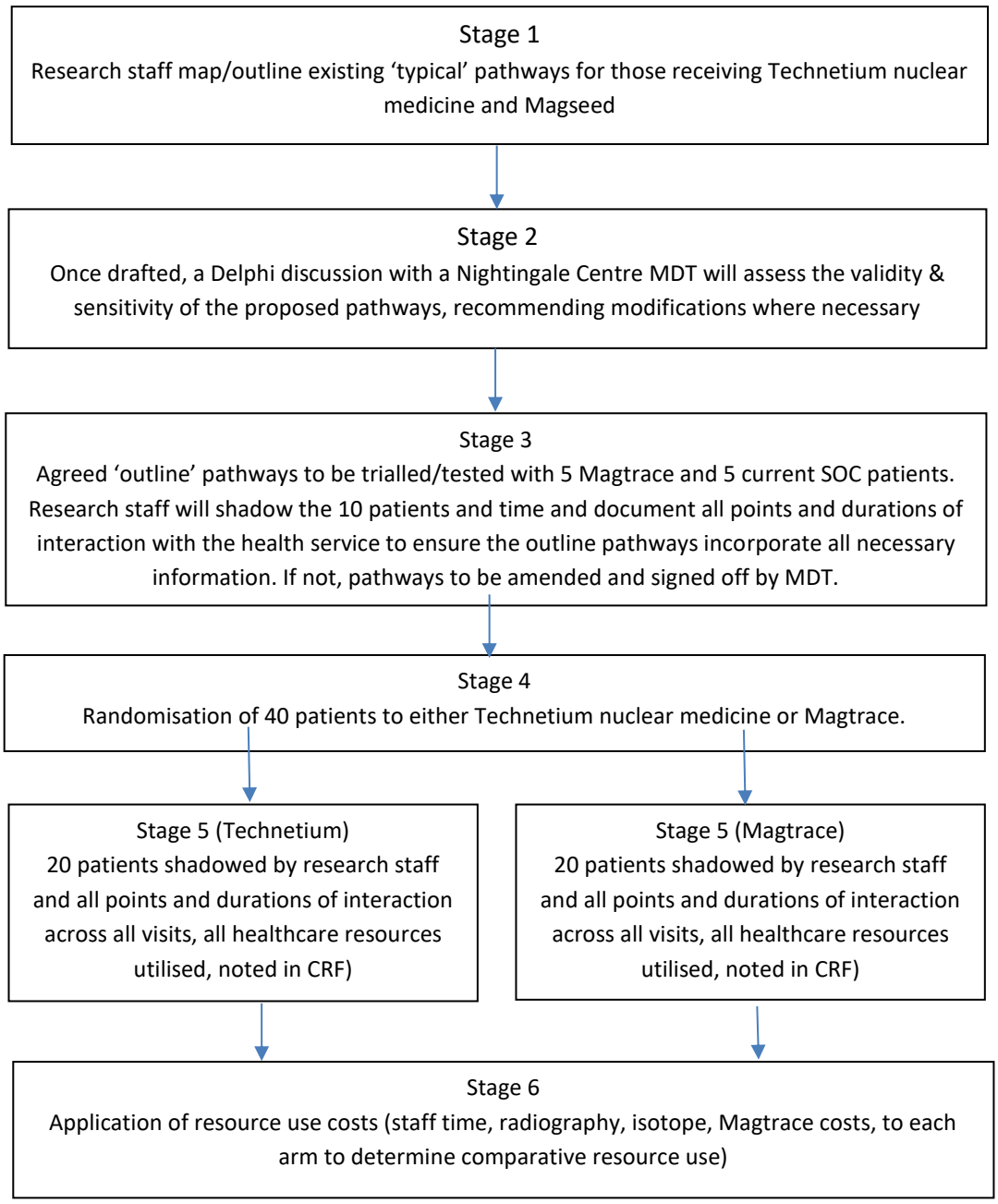
assessment of the workload of all members of staff involved in the patient pathway, from the decision-to treat appointment through to completion of surgery. Using a Delphi-approach, and coordination with staff from the Nightingale centre they will determine an outline of the basic resources involved, including staff costs (time, grade), radiography, inpatient and add-on costs.

It will be the responsibility of the research assistants to provide a 'learned' assessment, of what they believe represents a 'typical' pathway at the Nightingale centre. A multidisciplinary team will then assess the validity of this pathway and voice any concerns/objections/potential additions. Once an accurate representation of the existing care pathway has been generated (as agreed by research staff and clinical leads), this will be pilot tested among a group of 10 patients (5 current SOC and 5 Magtrace), in order to ensure that all relevant points of interaction with healthcare staff, and utilisation of health services, are captured, the pathway will be amended as necessary. Using a stopwatch, research staff would have the ability to consent and then actively monitor (shadow around the hospital) a group of ~20 patients in each treatment group (Magtrace® vs. routine care using Technetium nuclear medicine). It is critical prior to recruitment that key covariates and factors likely to influence not only outcomes, but also health economic factors of care are identified. These factors will require consideration before randomisation to Magtrace or routine care, with randomisation recommended to take place using sealed envelopes in blocks of ten. If imbalances in key covariates occur following randomisation, adjustment of health economic outcomes will be performed to mitigate these imbalances using gold-standard two-stage bootstrapping for cost-effectiveness analyses.

Once data is collected for 20 patients undergoing Magtrace, and 20 patients undergoing routine care, it will be possible to multiply NHS resource utilisation by representative NHS unit costs (staff salaries per minute, radiography, inpatient, nuclear medicine) and determine the array of health economic outcomes listed above. The result will be a health-economic comparison of Magtrace® over Technetium nuclear medicine (Figure 1). Sensitivity analyses will be performed on this dataset to measure the robustness of the findings to changes in the values of the parameters measured during the TDABC stopwatch exercise. Rather than relying on point-estimates, this will enable the derivation of credible intervals, and determine

how specific factors such as time in the hospital, number of visits, requirement for isotopes etc. each individually affect the overall cost per completed treatment episode. This way, if there are imbalances across treatment groups (whether systematic, for example Magtrace leading to reduced expectation to visit the department repeatedly), or stochastic, due to sampling, these factors will be accounted for in the costing. Furthermore, because it is not necessary to monitor and time every patient over a one-year period (or more), to model the expected annual health-economic benefits of Magtrace®, results observed in this cohort of 40 patients (representative sample) may then be extrapolated to all expected patients/caseload over the course of a calendar year, with the 40 patients observed closely, serving as an estimation set. This is common in cost-effectiveness modelling, and bootstrapping from this cohort of patients to a larger group representative of the full spectrum of clinical caseload over a calendar year, will enable determination of the expected return-on-investment of switching from Technetium nuclear medicine to Magtrace® at the Trust level (or at various levels of implementation/caseload, from 0 to 100%. A previous example of this approach is provided in the reference list [vii].

Figure 1: Study flow for health-economic assessment



The Magtrace® will be inserted by trained and qualified healthcare professionals. The Magtrace® will be injected into the index breast on the day of surgery. The technetium will be injected as per the current pathway on the day of surgery or the day before, technetium is generally used with or without blue dye. Blue dye is injected by the surgeon at the time of surgery and can be used as ab additional tracer with Technetium. It is up to the clinicians' discretion if they use the blue dye at the time of surgery.

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

Identification of potentially eligible patient – done by medical and research team in the breast MDT

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 (by medical team/breast care nurse/breast research nurse).

- Follow-up phone call to patient more than 24 hours after invitation (by breast research nurse);
- Study visit 1 – Consultation with patient – consent taken for study. Eligibility confirmed and baseline data recorded. Randomisation occurs. Placement of Magseed® device, and anaesthetic assessment performed.
- Study visit 2a – day before surgery – patients in the control group will receive their technetium on the afternoon prior to surgery if they are in a Two day protocol.
- Study visit 2 – day of surgery. Patient will receive Technetium injection if in the control group and on a One day protocol and will receive blue dye in theatre if deemed clinically necessary. Patients in the Magtrace group will receive their Magtrace® injection. All patients will receive breast surgery. Participants will be asked to complete a single anxiety questionnaire on day of surgery.

- Study visit 3 – Routine follow-up done remotely without patient – Adverse effects recorded, oncological outcomes recorded.

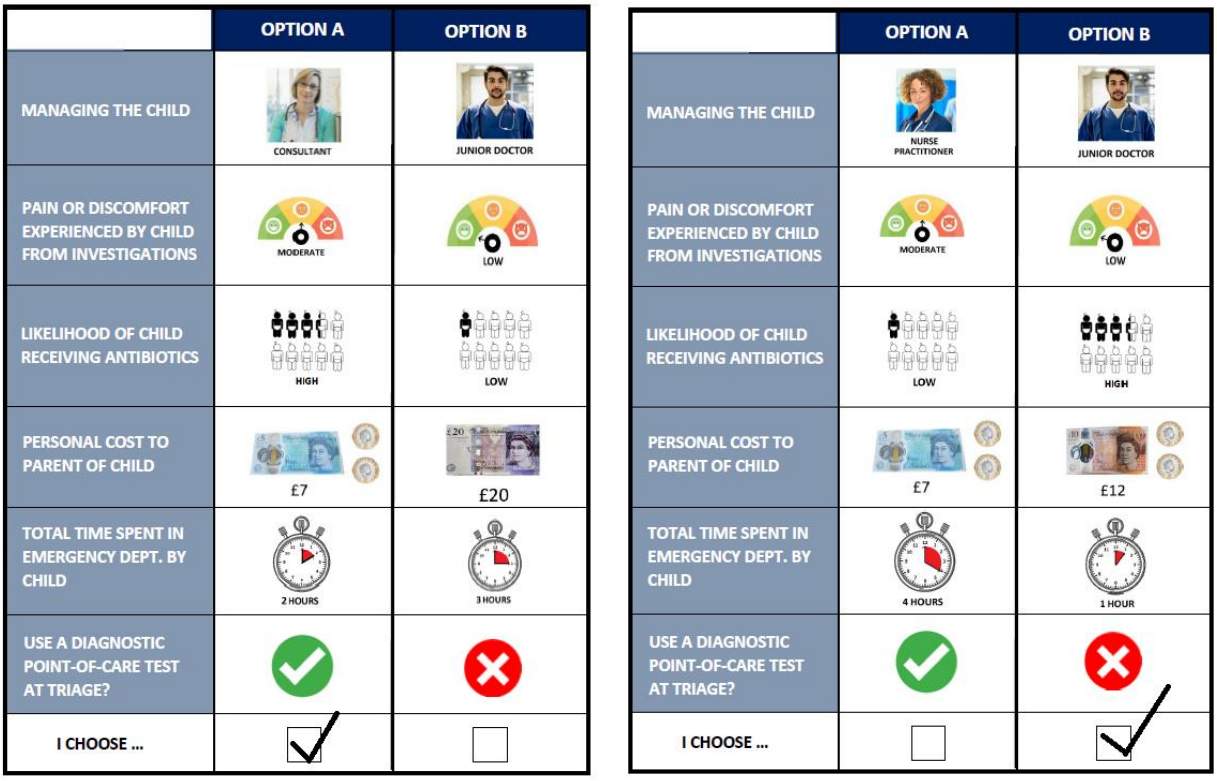
Study design & analysis (Part 2)

Discrete-choice experiment (DCE) methodology is well described in existing published literature; and used extensively to measure patients', and more recently healthcare providers', preferences for various aspects of healthcare services.[viii] In DCEs, respondents are given a hypothetical care scenario, typically comparing one package of care or pathway to another, and asked to choose which of the available options they prefer, by placing a tick in a box. In some cases, an 'opt-out' option is included, however this is unlikely, although not unheard of, in the case of non-palliative oncology. The options provided to respondents typically vary with respect to several characteristics which have previously been deemed to be important to the respondents undertaking the survey. This study will follow methodological guidelines from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)[ix], identifying attributes of potential importance through discussions with experts in breast cancer excision and focus-groups.

For this research therefore, these attributes will be determined following focus-groups with representative patients and healthcare providers alike (n = 4-10 representatives per focus group and 2 focus groups). Examples of attributes of care which may be important to patients and healthcare providers, and may impact on satisfaction with care, include time spent in the department (1 hour, 2 hour, 4 hours, 8 hours), number of injections received during treatment episode (0,1,2,4), exposure to radioactive substances, or the number of separate visits to the hospital in the week prior to surgery (1,2,4). Once these attributes have been determined following focus-groups a DCE survey is developed, with several hypothetical care pathways presented, all differing slightly with regard to the attributes identified during the focus groups. This process is repeated with the values (levels) of the characteristics (attributes) changing randomly each time. The choices respondents make, i.e. which option they prefer and tick the box of, can be used to infer preferences for each level of each of the attributes included. For example if respondents, more often than not,

prefer the option with a lower number of visits to the hospital, all things being equal, we can identify that this is a factor affecting their satisfaction with care. An example DCE from an unrelated disease area is provided in Figure 2

Figure 2: Example DCE



Generally, each respondent is given between 12 and 20 discrete choice tasks, with the levels of the attributes to choose from changing each time. It is not uncommon in DCE application to include at least one, if not two tests of rationality. One is usually provided as the first task to test understanding of the problem (and ensure rationality of the responses received), and one as the final task to ensure that respondents have been paying attention all the way through the survey and not simply rushing through, or alternatively suffering from survey fatigue. These are usually choice tasks with one very obviously preferable situation (i.e. 1 hospital visit, no injections, and only 2 hours on site) vs. a clearly inferior alternative (4 hospital visits, 8 injections and 24 hours on site). If respondents fail either test of rationality by saying that they prefer the option which is inferior, their responses are excluded from formal analysis.

As a full factorial approach to the DCE, where respondents are asked to choose between each one of thousands of possible management scenarios is implausible, a D-optimal approach to designing the DCE will be taken with the use of the gold-standard DCE software, nGene. Once developed, all choice sets will be reviewed by the Principal Investigator (PI) for the study before being checked for understanding, interpretation, and grammatical errors by research staff. At this point, choice tasks may be supplemented with imagery and colour in order to improve retention and minimise cognitive burden. This has proved useful in other DCEs where the literary capabilities or perceived attention span of respondents may be limited, as may be the case in the event of illness x. It will also be necessary at this point to perform a pilot test among a small group of research staff, to ensure the survey can be completed in less than 15 minutes. Once all checks have been performed, choice-sets will be converted into an interactive PDF format, for use on laptops or tablet-PCs.

Once the cohort of respondents have filled in the survey using a tablet-PC, a mixed-logit regression (in the assumed case of expected heterogeneity in preferences), performed using Stata 14, is proposed to estimate preferences for the management of breast cancer excision, owing to the likelihood of significant intra-respondent heterogeneity, due to the wide-ranging epidemiology of breast cancer and the likelihood of widely differing ages and other baseline characteristics. As such, each individual preference observed is considered as a random draw from the underlying general population distribution. In addition to the main-effects model, sub-group models differentiated by characteristics such as patient age (patients), or healthcare provider role (in the case of healthcare providers) will also be estimated. As the experiment is yet to be finalised, with levels and attributes yet to be determined, the sample size required to detect statistically significant preferences, is currently difficult to pinpoint. In general, the rule of thumb for DCEs is that 100 responses (per group, HCPs and patients), is usually sufficient[xi]. However, using a conservative set of assumptions and applying Louviere's non-parametric assessment, we anticipate, based only on preliminary discussions with the PI, that a sample size of 22 to 55 patients and healthcare providers, as demonstrated in Figure 3 below:

Figure 3: Sample size calculation for DCE

$$N \geq \frac{1-p}{Tp(a^2)}\left[\Phi^{-1}\left(\frac{1+\alpha}{2}\right)\right]^2$$

N = Sample size

P = Expected choice proportion (i.e. 50% if two choices to pick from, 33.3% if three choices, 25% if four choices). **IN OUR CASE 2**

T = Number of choice tasks performed by each respondent **RANGE 12 to 20**

α = Confidence level (i.e. 95%, 99%) **RANGE 95 to 99**

a = accuracy level (i.e. observed proportion within 10% of true one) **95%**

Φ^{-1} = Inverse normal distribution

=

22 (optimistic) > N > 55 (conservative)

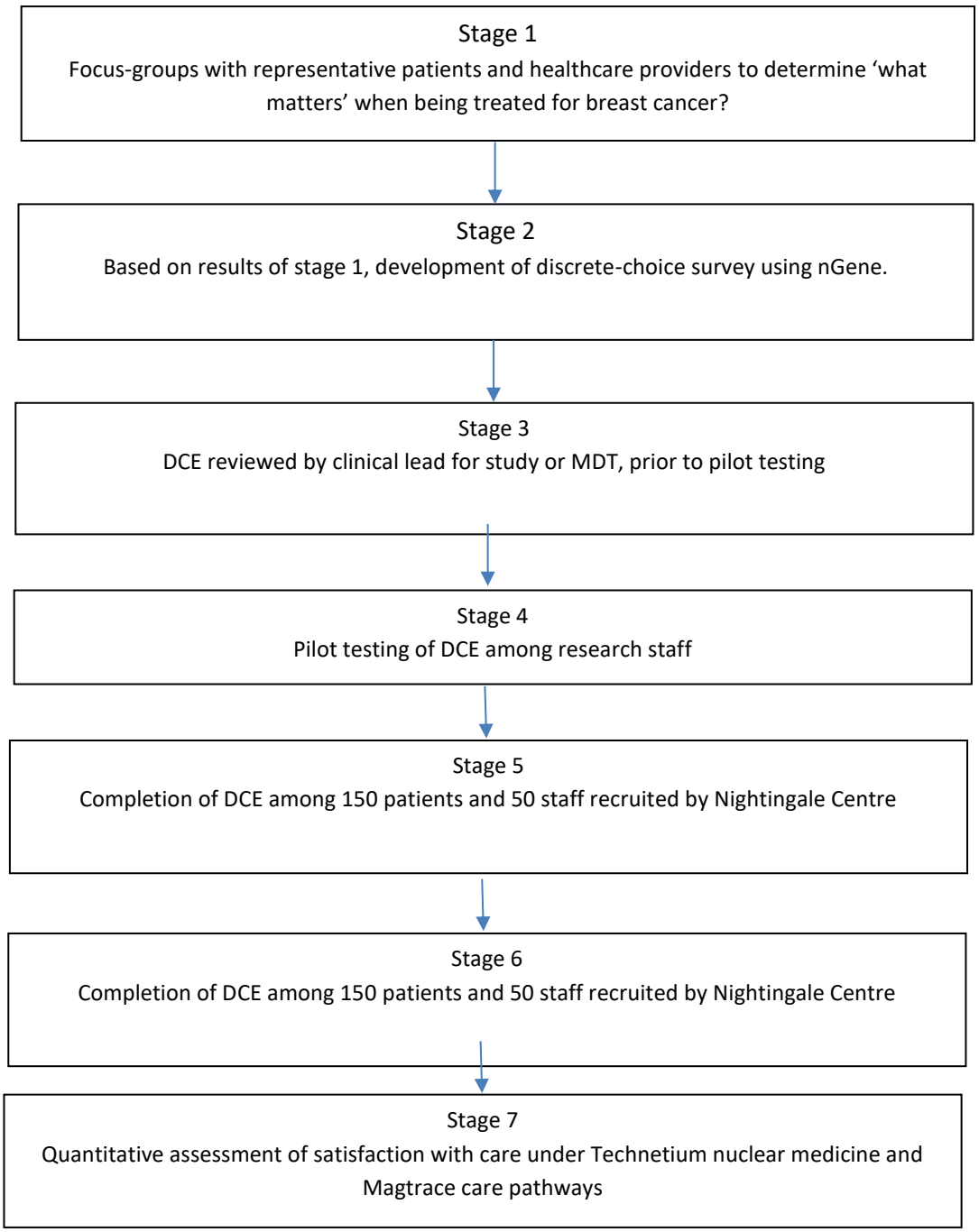
This number of participants answering the DCE will provide information regarding which attributes, and therefore which features of existing and future care pathways, are most important to respondents, and which cause them the most dissatisfaction. The results are expressed as relative preferences, thereby indicating which of the attributes including are more important than the others, and by what magnitude. By providing the survey to both patients and healthcare providers involved in the delivery of care it will be possible to determine which things are most important to both groups, and determine the level of satisfaction (measured quantitatively), with existing care pathways (Technetium nuclear medicine) and using Magtrace. This may in turn make adoption and uptake of Magtrace easier or help assuage concerns from commissioners regarding non utilisation; if the evidence suggests that a change in care provision would constitute an improvement for patients and healthcare providers alike. Similarly, by sub-grouping patients and healthcare providers into smaller groups (by age (patients), or role (healthcare providers) for example), it can be possible to hone-in on what really matters most to each group, and where resistance to adoption of the technology is likely to be greatest. Combining the utility estimates for various aspects of care pathways, it will be possible to say that a move from the current standard of care to Magtrace, would result in an increase in utility/satisfaction with care of X% for patients and Y% for healthcare providers.

Part 2 - Survey recruitment

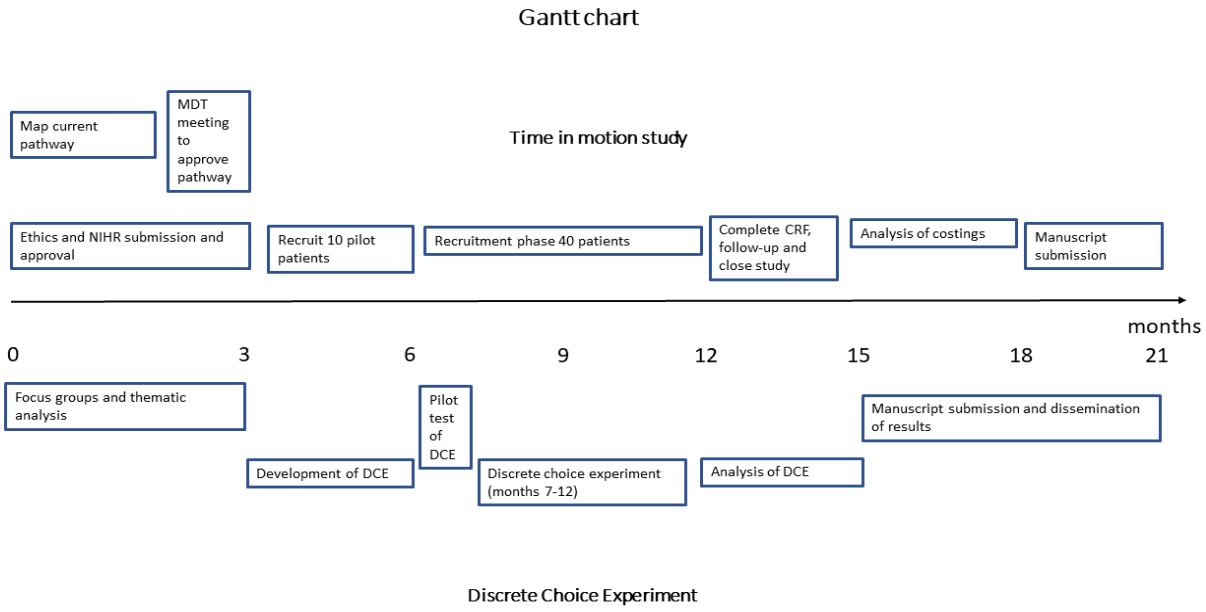
Both healthcare providers and patients will be invited to take part in the Discrete Choice Experiment, sample size is 200 with a minimum of 50 responses being by health care professionals. We will invite up to 150 patients who attend the Manchester University NHS Foundation Trust Breast Service to participate in the study. These will be patients who have undergone breast cancer surgery and so have some insight into the treatment pathway. The patients will be invited either before or after their clinic appointment to complete the survey. Participants will be recruited by research staff while present for a clinical appointment in the Nightingale centre. Upon consenting to hear about the study, patients and healthcare providers will be given a short synopsis of the study detailing the aims and providing a brief example of the survey questions, in the form of a patient information leaflet (paper or electronic). Following consent (either by paper forms or using a Tablet-PC) , respondents will be asked to spend 10-15 minutes completing the survey. Informed consent will be implied via completion of the survey both online and paper. No patient identifiable information will be collected for the survey, only very basic baseline demographics including age (patients), role (in the case of healthcare providers) and how far they have travelled to the department that day (patients).

A minimum of 50 Healthcare providers will be invited to complete the survey electronically, this will be a mixture of breast surgeons, breast care nurses and breast radiologists. They will be invited via email, directly from the study team. This is a survey to establish their preferences towards the healthcare scenarios provided to them, as such their answers will be critical to understanding the perceived added value of Magtrace. These individuals will be given written information about the study as with the patients, in the form of a participant information sheet, and asked to complete a consent form to take part in the study (either by paper forms or using a Tablet-PC). Informed consent will be implied via completion of the survey both online and paper. No identifiable information will be collected about the respondent with the exception of some simple descriptors and demographics. A full step by step guide to this process is provided in Figure 4

Figure 4: Study flow for DCE



4.3 Gantt Chart



5. Selection and Withdrawal of Subjects

5.1 Informed Consent

Consent for Part 1 of the study will be taken by a Consultant Breast Surgeon or Research Nurse. This consultant or research nurse 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, for Part 1 patients, more than 24 hours after initial invitation to take part in the study. Consent for Part 2 (Focus Group & Survey) will be undertaken by the same staff members but will be taken at the time of introduction of the study to the patient or healthcare professional.

5.2 Inclusion Criteria – Part 1

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

- Undergoing breast conservation surgery requiring Magseed® localisation and sentinel node biopsy
- All MRIs must be completed prior to Magseed® insertion

5.3 Exclusion Criteria – Part 1

- Patients with a Pacemaker or implanted device in the chest wall;
- Patients who are pregnant or lactating;
- Patients who have received Magtrace® (iron oxide) injection in the previous six months;
- Patients with previous ipsilateral axillary surgery
- Patients whose breast and axillary surgery are not due to be performed synchronously.
- Patients following neoadjuvant chemotherapy
- Patients requiring an interpreter
- Patients involved in current research or have recently been involved in any research prior to recruitment

Patients who require MRI follow-up of the ipsilateral breast in the year following surgery (as Magtrace® may interfere with MRI)

All individuals will be considered for inclusion in this study regardless of age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion and belief, sex, and sexual orientation except where the study inclusion and exclusion criteria EXPLICITLY state otherwise

5.4 Screening and Eligibility Assessment

Potential participants for Part I will be identified at the Breast Multidisciplinary Meeting which occurs every morning in the Nightingale Breast Unit, MFT. 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;

Part 2 – Focus Groups

Potential participants will be identified by the Research nurses and surgical team at the Breast Multidisciplinary Meeting which occurs every morning in the Nightingale Breast Unit, Manchester University NHS Foundation Trust. Patients will be approached during their appointment at Manchester University NHS Foundation Trust for the study design part of the discrete choice experiment. Healthcare professionals will be approached via either direct contact with the research team or by electronic invitation from the Chief Investigator. Informed consent will be taken on paper at time of introduction to the study.

Part 2 - Survey

Patient participants will be recruited by research staff while in waiting room of the Nightingale centre. Upon consenting to hear about the study, patients and healthcare providers will be given a short synopsis of the study detailing the aims and providing a brief example of the survey questions. Following verbal consent to complete the survey, respondents will be asked to spend 10-15 minutes completing the survey. Informed consent will be implied via completion of the survey both online and paper. No patient identifiable information will be collected for the survey, only very basic baseline demographics including age (patients), role (in the case of healthcare

providers) and how far they have travelled to the department that day (patients). Healthcare providers will be recruited by direct and email approach from the research team and by electronic invitation to complete the study online.

Please note the survey will be designed as part of the Focus Group meetings, the REC and HRA will be notified when the survey has been created via non-substantial amendment and a copy of the survey before being given to any participant for completion. The survey will not collect any personal information.

5.5 Selection of Participants

Case control study of 40-50 patients in the time in motion study and 200 (150 patients, 50 healthcare providers) in the Discrete-Choice Experiment (DCE). 5-10 patients will be invited to participant in the study design part of the discrete choice experiment.

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 study as all of the interventions are now established in large studies with good safety profiles. Magtrace® has a risk of causing staining to the skin of the breast in the months following injection and that it appears as a brown stain that fades over time. This is similar to the blue dye that is often used in conjunction with Technetium to help identify the sentinel nodes in existing practice. The blue dye stains the skin Blue/grey compared to the brown of Magtrace®. The blue dye has a 1 in 10,000 risk of anaphylaxis, a risk not seen in Magtrace® injection.

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, patients will asked for a reason for withdrawal if they wish to offer one.

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 in Part 1 – Four to eight weeks. This will equate to a 1-4 week period between invitation to join study and Study visit 3 when post-surgery histology is discussed. Study visit 1 will occur a minimum of 1 day prior to surgery. Surgery will not be delayed beyond 31 days from decision to treat the cancer. 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.

Expected duration of participation in Part 2 Focus Group – 60 minutes.

Expected duration of participation in Part 2 Survey – 15-20 minutes.

6 Trial Procedures – Part I

Assessments		Visit 2a		

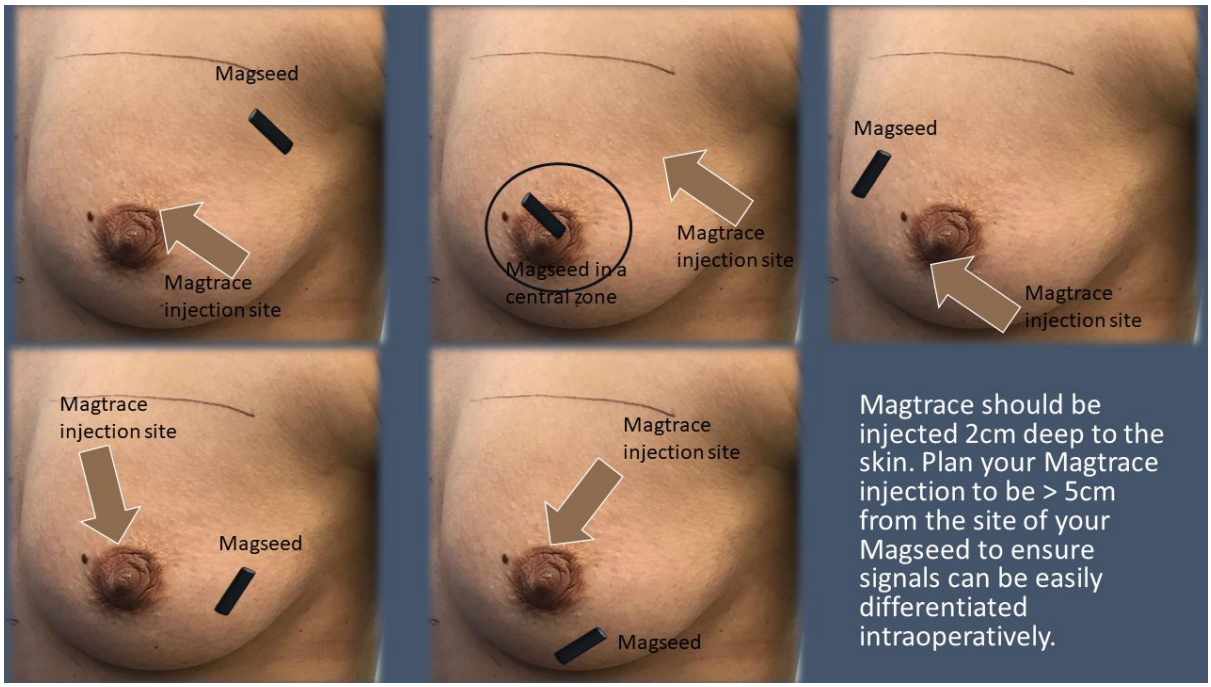
	Baseline Visit 1	Technetium (two day protocol only)	Surgery Visit 2	Post surgery Visit 3
Informed consent and randomisation	X			
Medical history	X			
Magseed® insertion	X			
CRFompletion including data transfer and query resolution	X	X	X	X
Concomitant medication check	X			X
Review/reporting of patient AEs/SAEs			X	X
Anaesthetic assessment	X			
Localise lesion with Magseed® during surgery			X	
Perform sentinel node biopsy			X	
Data collection in theatre			X	
Technetium injection		X	X (one day protocol)	
Magtrace® injection			X	

6.1 Magtrace injection protocol

Magtrace will be injected by the operating surgeon on day of surgery. This injection will occur prior to surgery, on the admitting ward with massage of the area. If the patient arrives in the theatre suite before being seen by a surgeon, the injection will be given by the surgeon prior to general anaesthetic.

Prior to injection, the surgeon giving the injection must check the pre-operative mammograms and Magseed position. The Magtrace injection should be injected 2cm deep in the breast to avoid staining of the skin, and at a distance to the Magseed. This is to ensure that the Magseed signal is not confused with the Magtrace injection site.

Some examples are given in the Figure below;



7. Assessment of Efficacy

7.1 Primary Efficacy Parameters

The Primary Endpoint

Cost effectiveness of Magtrace® compared toTechnetium in the identification of sentinel nodes in breast cancer.

7.2 Secondary Efficacy Parameters

The Secondary Endpoint

- Patient time spent in hospital and in transit in total over pre-operative and perioperative journey
- Patient anxiety on day of surgery – as measured using State trait anxiety questionnaire STAI-Y given on ward on morning of surgery.
- Number and length of patient hospital visits – comparing preoperative visits (clinic visits, preoperative assessment, tracer injection visits, ward visits and operative visits).
- Safety of Magtrace® and efficacy – adverse events relatable to tracers, number of nodes removed, number of nodes containing tracer, % of patients with detectable tracer in the axillary sentinel nodes, can surgeons differentiate Magtrace® and Magseed signal®.
- Cost per episode and for total care.
- Surgical start time, days of week of operating, and delays to getting patient to theatre. Delays will be recorded by asking the theatre team directly pre-operatively whether they had to wait for the patient to arrive, and what the reason was, and also whether the list had to be rescheduled/ moved to accommodate a delay.
- To map the current pathways of patient care.
- Evaluation of the key aspects of care pathways important to patients and healthcare professionals in the management of breast cancer.
- Preferences/overall satisfaction with care package for Magtrace vs. Technetium, from the perspective of patients and healthcare providers.

8. Source Data

- Medical records;
- Histopathology reports;
- Data capture worksheets 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) for participants undergoing randomised treatment will be recorded for as long as the participants is on the trial. . All SAEs should be reported immediately to the Sponsor and where appropriate the regulatory authorities following the Trust SOPs. The immediate reports should be followed promptly by detailed, written reports. 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.

SAEs are defined as any untoward medical occurrence that:

- Results in death,
- Is life-threatening*
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is otherwise considered medically significant by the investigator

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.

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.

All SAEs and SARs will be reported immediately to the Chief Investigator of the Study, Mr James Harvey, and the Research Office at adverse.events@mft.nhs.uk.

The following common post-operative complications will be recorded as Adverse Events but not serious adverse events as they are unlikely to be related to the device itself but can cause rehospitalisation or require further surgery.

- Bleeding - requiring hospitalisation, transfusion or further surgery;
- Seroma formation – often requiring drainage in the outpatient clinic;
- Skin necrosis – requiring debridement.

Adverse Events requiring reporting:

- Allergy to Magtrace® injection
- Magseed® device not resected from breast during cancer surgery.

Safety Oversight:

The Trial Steering Committee (TSC) 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.

10. Statistics

10.1 Sample Size

- as above within relevant section.

10.2 Randomisation

Patients will be randomised in blocks of ten as surgical pathways may need to change through the study in response to changing COVID requirements of the hospital. The data would still be valid but the groups would need to be matched in size, hence randomising in small blocks. Block size may be increased by the Chief Investigator if it was clear that the surgical site was fixed for a prolonged period.

10.3 Analysis

As above

11. Trial Steering Committee (TSC)

The Trial Steering Committee will consist of;

- Chief Investigator and co-investigators – Mr J. Harvey, Mr S. Leigh, Prof C. Kirwan, Dr C Fullwood
- Research staff conducting the study
- Independent Chairman – Mr Chatterjee
- Statistician – Dr Fullwood
- Endomagnetics - 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 three months to review the primary end-point and to discuss the safety of the Study, and to discuss recruitment.

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.), in line with participant consent.

13. Ethics and Regulatory Approvals, Amendments and Reports.

Before the start of the study, a favourable opinion will be sought from an NHS Research Ethics Committee (REC) for the study and all the supporting documents including the protocol, information sheets, informed consent forms and other relevant documents. The study team will be responsible for the maintenance of a study site file, in which all current and superseded study documents will be retained. Also contained in the site file will be the approval documentation including correspondence with relevant authorities such as the HRA and REC.

The study team are responsible for producing progress reports throughout the study, including an annual progress report (APR) which will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The Chief Investigator will notify the REC of the end of the study, and will submit a final report with the results, including any publications/abstracts, to the REC within 12 months of the end of the study. If the study

is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

During the life of the study, there may be amendments to the study protocol and/or documentation. Substantial amendments will not be implemented until NHS REC review is in place and local approvals have been obtained.

No participants will be enrolled into this research study prior to the study being reviewed by the relevant regulatory authorities and receiving HRA and REC approvals, as well as approval from the R&I office at Manchester University NHS Foundation Trust. All correspondence including amendments with the REC will be retained in the Trial Master File.

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.

The study will be subject to the audit and monitoring regime of Manchester University NHS Foundation Trust in line with applicable MFT SOPs and policies. The study will have, as a minimum, an annual survey sent out for completion by a member of the research team.

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 pseudonymised using a study code that is linked to the recruitment log

All pseudonymised data will be stored on a password protected computer within MFT;

Anonymised data will be transferred to Nexus Clinical Analytics for health economics analysis by Encrypted email.

All data will be kept strictly confidential according to Good Clinical Practice (GCP) Guidelines. All identifiable data will be stored by the Manchester University NHS Foundation Trust in a secure fashion for 10 years after completion of the study in accordance with the ICH GCP. Source data for the trial are the consent form, Case Report forms and patients' medical notes. The trial data and documentation will be archived as per the MFT archiving SOP.

Excel spreadsheets used for the study, including the recruitment log, will be saved under a study folder that will be permissions based as to who can amend and view the data within the study team. Each excel spreadsheet containing patient identifiable data will be password protected. If any changes are made to the excel spreadsheets by the CI, then a new iteration of the excel form will be saved each time any changes are made. These will be named with the date of the update and the name of the team member who made the change and saved. In the properties section of the saved Excel file, the created, accessed and modified dates will all be the date of the update. The file will not be modified in any way after they have been saved. A new iteration will be created for live data. The spreadsheets will be updated and maintained by the research practitioner.

These will be stored on Trust encrypted password protected devices within MFT. Data on the trust servers is backed up continuously and at the end of each day. If data is lost, data will be recovered via the trust IT department back up service for data stored on the share drive.

The final data set will be fully anonymised including removal of study code prior to being transferred to Simon Leigh, Statistician, Nexus Clinical Analytics for health economics analysis by Encrypted email. The final trial data set will be shared with authorised representatives at Manchester University NHS Foundation Trust,members of the Trial Steering Committee and Endomagnetics

15.1 Data Management

The CRF will be developed by the CI and trial steering group (TSC). CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial in accordance with regulatory requirements and for follow-up as required. Completion of CRFs shall be restricted to those personnel approved by the Chief Investigator or designated deputy and recorded on the 'Trial Delegation Log'. All paper forms shall be

filled in using black or blue ballpoint pen. Errors shall be crossed out (but not obliterated by using correction fluid) and the correction inserted, initialled and dated. Corrections should be made legibly and initialled and dated by approved personnel. The reasons for significant changes must be provided. If any data are not available, omissions should be indicated on the case report forms. The NHS Code of Confidentiality will be followed for this study.

16. Publication Policy

The study data will be presented at national and international conferences and published in a peer reviewed journal. The Chief Investigator will have rights to publish the trial data with a fully anonymised data set.

Participants will be able to indicate on the consent form if they wish to receive a summary of the study results either by email or in the post.

MFT is the owner off all data sponsored at MFT. This research will be registered on the Clincaltrials.gov clinical trial registry as will a summary of the study results.

17. Insurance / Indemnity

The NHS indemnity scheme will apply to this study to ensure it meets the potential legal liability of the sponsor, equipment, employer and investigators/collaborators for harm to participants arising from the management, design and conduct of the research. No arrangements will be made for the payment of compensation in the unlikely event of harm.

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.

19. REFERENCES

i Sharek D, Zuley ML, Zhang JY, Soran A, Ahrendt GM, Ganott MA. Radioactive seed localisation versus wire localisation for lumpectomies: a comparison of outcomes. AJR AM J Roentgenol. 2015 Apr;204(4):872-7

ii Murphy JO, Moo T-A, King T a, Van Zee KJ, Villegas K a, Stempel M, et al. Radioactive seed localization compared to wire localization in breast-conserving surgery: initial 6-month experience. Ann Surg Oncol [Internet]. 2013;20(13):4121–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23943024

iii Kaul D, Fallenberg E, Diekmann F, Budach V, Maurer M. Dislocability of localization devices for nonpalpable breast lesions: experimental results. Radiol Res Pract [Internet]. 2014;2014:425823. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3964887&tool=pmcentrez&rendertype=abstract

iv Banitalebi H, Skaane P. Migration of the breast biopsy localization wire to the pulmonary hilus. Acta radiologica. 2005. p. 28–31.

[v] Leigh, S, Granby, P, Haycox, A, Mundle, S, Bracken, H, Khedikar, V, Mulik, J, Faragher, B, Easterling, T, Turner, MA, Alfirevic, Z, Winikoff, B, Weeks, AD **(2018)**. Foley catheter vs. oral misoprostol to induce labour among hypertensive women in India: a cost-consequence analysis alongside a clinical trial. *BJOG*, 125, 13:1734-1742.

vi Leigh, S, Grant, A, Murray, N, Faragher, B, Desai, H, Dolan, S, Cabdi, N, Murray, JB, Rejaei, Y, Stewart, S, Edwardson, K, Dean, J, Mehta, B, Yeung, S, Coenen, F, Niessen, LW, Carrol, ED (2019). The cost of diagnostic uncertainty: a prospective economic analysis of febrile children attending an NHS emergency department. *BMC Med*, 17, 1:48.

[vii] Leigh, S, Grant, A, Murray, N, Faragher, B, Desai, H, Dolan, S, Cabdi, N, Murray, JB, Rejaei, Y, Stewart, S, Edwardson, K, Dean, J, Mehta, B, Yeung, S, Coenen, F, Niessen, LW, Carrol, ED (2019). The cost of diagnostic uncertainty: a prospective economic analysis of febrile children attending an NHS emergency department. *BMC Med*, 17, 1:48.

viii Soekhai, V, de Bekker-Grob, EW, Ellis, AR, Vass, CM (2019). Discrete Choice Experiments in Health Economics: Past, Present and Future. Pharmacoeconomics, 37, 2:201-226.

Leigh, S, Ashall-Payne, L, Andrews, T **(2020)**. Barriers and Facilitators to the Adoption of Mobile Health Among Health Care Professionals From the United Kingdom: Discrete Choice Experiment. *JMIR Mhealth Uhealth*, 8, 7:e17704.

Leigh, S, Robinson, J, Yeung, S, Coenen, F, Carrol, ED, Niessen, LW **(2020)**. What matters when managing childhood fever in the emergency department? A discrete-choice experiment comparing the preferences of parents and healthcare professionals in the UK. *Arch. Dis. Child.*, 105, 8:765-771.

Karakatsanis A, C. P. (2016 Jun; 157(2)). The Nordic SentiMag Trial: A Comparison of Super Paramagnetic Iron Oxide (SPIO) Nanoparticles Versus Tc(99) and Patent Blue in the Detection of Sentinel Node (SN) in Patients With Breast Cancer and a Meta-Analysis of Earlier Studies. Breast Cancer Res Treat, 281-94.
Teshome M, W. C. (2016 May, 23(5)). Use of a Magnetic Tracer for Sentinel Lymph Node Detection in Early-Stage breast Cancer Patients: A Meta-analysis. Ann Surg Oncol, 1508-14.

ix Hauber, AB, González, JM, Groothuis-Oudshoorn, CG, Prior, T, Marshall, DA, Cunningham, C, IJzerman, MJ, Bridges, JF (2016). Statistical Methods for the Analysis of Discrete Choice Experiments: A Report of the ISPOR Conjoint Analysis Good Research Practices Task Force. Value Health, 19, 4:300-15.

x Leigh, S, Robinson, J, Yeung, S, Coenen, F, Carrol, ED, Niessen, LW (2020). What matters when managing childhood fever in the emergency department? A discrete-choice experiment comparing the preferences of parents and healthcare professionals in the UK. *Arch. Dis. Child.*, :no page given.
xi Pearmain D, Swanson J, Kroes E, Bradley M. Stated preference techniques: a guide to practice. 2nd ed. Steer Davies Gleave and Hague Consulting Group. 1991