Endomagnetics, Inc.

100 Congress, Suite 2000, Austin, Texas, 78701

Magseed Magnetic Marker Localization

A prospective, open label, post marketing study of Magseed and Sentimag in patients undergoing surgical excision of a breast lesion that requires preoperative radiographic localization.

Clinical Investigational Plan Number: US-002

Version 1.2

Date: 30th December 2016

Endomagnetics Limited: 

Signature Quentin Harmer, CTO

30 Dec 2016

Date

CONFIDENTIAL

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INVESTIGATOR'S AGREEMENT

By signing below, I confirm that I have read this Clinical Investigational Plan and agree that it contains all necessary details for conducting the study. I will conduct the study according to the procedures described in the Clinical Investigational Plan.

Principal Investigator's Signature: _____Date:_____

Principal Investigator's Name (Print):_____

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1 CLINICAL STUDY SYNOPSIS

Title	A prospective, open label, post marketing study of Magseed and Sentimag in patients undergoing surgical excision of a breast lesion.
Device intervention	Magseed and Sentimag® by Endomagnetics, Inc.
Study Purpose	The purpose of this post-marketing study is to provide prospective evidence that the Magseed and Sentimag® is effective for lesion localization in patients undergoing surgical excision of a breast lesion and to summarize measures of product safety and performance.
Method of Use	The Endomag Magseed® magnetic marker is intended to be placed percutaneously in the breast under imaging guidance (ultrasound or mammography) to mark temporarily (< 30 days) a lumpectomy site intended for surgical removal. The Magseed® magnetic marker is localized using the Sentimag® handheld probe and surgically removed with the target tissue.
Study Design	This is a post-market, prospective, open label, single arm study of Magseed and Sentimag in patients undergoing surgical excision of a breast lesion. Eligible subjects have breast lesions requiring excision. Subjects will have the Magseed marker deployed under imaging guidance up to thirty days prior to surgery. The Magseed marker will be localized using the Sentimag system during surgery and removed with the lesion. After the lumpectomy procedure, subjects will be evaluated up to 8 weeks post-procedure for safety and patient reported outcomes.
Study Population	Subjects considered for enrollment will be at least 18 years old at the time of consent, and be scheduled for a lumpectomy[1] procedure (which also includes excisional biopsy) of the breast; and meet all other inclusion and exclusion criteria.
Planned Number of Subjects	At least 100 subjects will be enrolled.
Investigational Sites	United States: MD Anderson Cancer Center, Houston, TX.
Study Duration	The expected duration of enrolment is approximately 10 months across all sites with each individual subject's participation lasting 1-8 weeks after enrolment. The total study duration is approximately 12 months.
Primary Objective	To provide evidence that the index lesion and Magseed can be successfully retrieved in the initial excised specimen when Magseed and Sentimag are used as indicated in lumpectomy procedures in patients requiring surgical excision of a breast lesion.
Primary Endpoint	The primary endpoint is the percent retrieval rate of the index lesion and Magseed in the initial excised specimen. This is defined as the number of subjects in whom the index lesion and Magseed are retrieved in the initial excised specimen divided by the total number of subjects undergoing surgery.
Other Endpoints	Safety • Rates of device-related adverse events and device-related serious adverse events Radiological Placement • Radiologist rated ease of marker placement • Success rate of Magseed placement (placement accuracy): <5mm to lesion; 5-10mm to lesion; >10 mm to the target. • Duration of Magseed placement (lesion localization) procedure

[1] The term lumpectomy here refers to the removal of any lesion from the breast and will include partial mastectomy, segmental mastectomy, wide local excision, and excisional biopsy.

	Surgical Localization • Overall re-excision rate • Re-excision rate necessary to remove the Magseed or targeted lesion • Surgeon rated ease of localization during surgery • Duration of lumpectomy procedure Pathology • Pathologist rated ease of marker identification and retrieval.
Inclusion Criteria	• Subjects with a breast lesion requiring image-guided localization prior to excision. • Subjects aged 18 years or more at the time of consent.
Exclusion Criteria	• The subject is pregnant or lactating. • Subject has pacemaker or other implantable device in the chest wall. • Subject has current active infection at the implantation site in the breast (per investigator discretion)
Statistical Test Method for the Primary Hypotheses	Statistical methods are descriptive for this single arm study. Exact 95% confidence intervals will be calculated for the primary endpoint.
Sample Size Calculation for the Primary Endpoint	Sample size for this single arm study has been calculated based on the precision of the confidence interval for the primary endpoint, the proportion of successful retrievals. A sample of 100 patients will provide an exact 95% confidence interval with maximum width ±0.092 providing the proportion of successes is at least 80%. At the anticipated success rate of 90% the confidence interval precision will be ±0.076. Up to 120 patients will be enrolled to ensure excision data for 100 patients.
Sponsor	Endomagnetics, Inc. 100 Congress, Suite 2000 Austin, Texas, 78701

2 ABBREVIATIONS

AE	Adverse Event
BCS	Breast Conserving Surgery
CE	Conformité Européenne
CFR	Code of Federal Regulations
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IRB	Institutional Review Board
HIPAA	Health Insurance Portability and Accountability Act
MDACC	MD Anderson Cancer Center
MRI	Magnetic Resonance Imaging
PAL	Product Accountability Log
RSL	Radioactive Seed Localization
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect
US	United States

3 INTRODUCTION AND BACKGROUND

Breast cancer is the most common cancer among American women, except for skin cancers. About 1 in 8 (12%) women in the US will develop invasive breast cancer during their lifetime.

The American Cancer Society's estimates for breast cancer in the United States for 2016[2] are:

- An estimated 246,660 new cases of invasive breast cancer are expected to be diagnosed in women in the U.S.
- 61,000 new cases of non-invasive (in situ) breast cancer will also be diagnosed
- About 40,450 women are expected to die from breast cancer

Breast cancer is a heterogeneous disease, with great diversity in the site, size and progression of tumors. Some are palpable and discovered by the patient, but many early cancers identified through screening programs are too small to detect by palpation. For these nonpalpable cancers, localization is necessary, to guide surgeons to the target excision site prior to breast conserving surgery (BCS) being performed. With the increased rate of mammographic screening and improved imaging techniques the numbers of nonpalpable breast lesions detected is also increasing. In addition, lesions not yet proven to be cancers by needle biopsy but suspicious may also require localization to guide their excision in order for a definitive diagnosis to be made.

[2] https://cancerstatisticscenter.cancer.org

3.1 Wire Guided Localization

Traditionally, surgical guidance for nonpalpable lesions involves image-guided insertion of a wire into the breast, with positioning of the wire tip at the centre of the lesion. The surgeon estimates the position of the wire tip and excises a margin of tissue around it. However, this procedure has a number of limitations[3] including:

- Wire localization must be performed on the day of surgery to minimize risk of wire migration or dislodgement, a significant possibility due to the external section of wire left protruding from the breast.
- Same-day appointments demand excellent coordination between radiological and surgical departments to ensure that disruption to procedure scheduling is minimized.
- Wires have also been associated with higher re-operation rates[2,3].
- From the patient perspective, wire placement necessitates a sometimes painful extra procedure on the day of surgery, which can increase stress levels[2].
- The position of the surgical incision can be influenced by the wire placement[4]. This can lead to excessive dissection and suboptimal cosmetic results due to resection of uninvolved breast tissue.

3.2 Radioactive Seed Localization

Radioactive seed localization (RSL) is a newer technique which overcomes some of the limitations of guidewires[5]. A radioactive seed is inserted to mark the lesion prior to surgery, thus eliminating the requirement for radiology appointments on the day of surgery. The seed is detected in the operating room using a handheld gamma probe. With RSL, there is no distraction from external projections of wire, and the surgeon is guided purely by the audible response to the seed using the probe.

Where available, RSL potentially offers improved scheduling and improved surgical outcomes over wires[6]. However, implementing and running an RSL system is challenging because of the stringent regulatory regime for the use of radioactive materials, in particular:

- An on-site nuclear medicine facility is required;
- A total chain of custody of radioactive material at the site (hospital) must be maintained, and loss of a seed can result in closure of the program;
- Regulations govern the safe disposal of radioactive waste[7].

As a result, significant planning, training and administration across multiple departments is required to implement RSL, and this has limited its wider uptake.

3.3 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, for sentinel lymph node identification. A handheld magnetometer is then used to detect the iron oxide in the nodes. A meta-analysis of five studies concluded that the

[3] S.M. Dua et al., The Breast 20 (2011) 246-253
[4] P.J. Lovrics et al., Annals of Surgical Oncology, (2011), 18: 3407-3414
[5] Gray RJ, et al. Randomized prospective evaluation of a novel technique for biopsy or lumpectomy of non-palpable breast lesions: radioactive seed versus wire localization. Ann Surg Oncol 2001;8:711–5.
[6] Gray RJ et al., Radioactive seed localization of nonpalpable breast lesions is better than wire localization, Am Jnl of Surgery, (2004), 188, 377-380
[7] Rao R, et al. Experience with seed localization for nonpalpable breast lesions in a public health care system. Ann Surg Oncol. 2010;17(12):3241–6

magnetic technique is non-inferior to the standard radioisotope & blue dye injections in sentinel node identification[8].

In addition, Ahmed et al. tested localization of cancerous lesions using a magnetic tracer injection[9]. The tracer successfully localized all tumors and resulted in appropriate excisional margins, without excess tissue excision; thus demonstrating the feasibility of magnetic tracer localization of tumors.

3.4 Magseed Magnetic Localization

Magnetic marker localization has similar principles to RSL. However, instead of radioactive seeds, a magnetically responsive marker called Magseed is placed into the breast. The marker 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 marker. The magnetometer produces an audible response and numerical display when held close to the Magseed marker, and can be used by surgeons to locate target excision sites. Magseed is indicated for implantation up to 30 days before surgery.

3.5 Summary of Localization Techniques

The scheduling difficulties and the patient inconvenience encountered in wire guided localization, alongside the logistical and regulatory issues of radioisotope usage, highlight a requirement for further innovation and acquisition of new localization technologies. Magnetic marker localization offers an alternative that can overcome the limitations of these existing technologies. This study will evaluate a magnetic marker called Magseed and its accompanying handheld magnetic probe called Sentimag.

4 DEVICE DESCRIPTION

4.1 Device Name

Sentimag® and Magseed by Endomagnetics, Inc.

4.2 Device Description

The Sentimag® and Magseed intra-operative magnetic sensing system (Figure 1) comprises a magnetic marker, Magseed, and a sensitive handheld magnetometer attached to a base unit, Sentimag®. The magnetometer and magnetic marker have been FDA cleared (K153044) for the following intended use:

The Endomag Magseed Magnetic Marker is intended to be placed percutaneously in the breast to mark temporarily (< 30 days) a lumpectomy site intended for surgical removal. Using imaging guidance (such as ultrasound or radiography) or aided by non-imaging guidance (Endomag Sentimag® System) the Endomag Magseed® Magnetic Marker is located and surgically removed with the target tissue.

The Endomag Sentimag® System is intended for the non-imaging detection and localization of the "Endomag Magseed Magnetic Marker" that has been implanted in a lumpectomy site intended for surgical removal.

The Magseed device is a small (5 x 0.9 mm) metallic magnetic marker that has soft magnetic properties. This means that when exposed to a magnetic field it becomes magnetic. The magnetic signature can then be detected using a magnetometer and probe which gives an audible and visual signal of the strength of response from the marker, and as it is directional, this can accurately guide the user to the site of the magnetic marker. The marker is deployed by a radiologist into the center of the lesion planned for

[8] Teshome M., et al. Use of a Magnetic Tracer for Sentinel Lymph Node Detection in Early-Stage Breast Cancer Patients: A Meta-analysis., Ann Surg Oncol. 2016 May;23(5):1508-14

[9] Ahmed M, et al. Magnetic sentinel node and occult lesion localization in breast cancer (MagSNOLL Trial), Br J Surg. 2015 May;102(6):646-52

excision, a similar technique to that currently used to place a wire into the breast. During surgery, the surgeon uses the Sentimag handheld probe to localize the marker for excision.

There is no radiation exposure from this device, nor are there any special considerations for handling or disposal of Magseed.

Figure 1: Sentimag® and Magseed System Showing Base Unit, Probe, and Magseed Delivery System

4.2.1 Sentimag Magnetic Probe

The Sentimag® Base Unit and handheld probe form an ultrasensitive magnetometer that is designed to detect small amounts of magnetic markers. The detachable hand-held probe is connected to the base unit with a flexible cable. A detachable footswitch is connected to the base unit via a flexible hose (Figure 2).

The sensing of a magnetic marker is indicated by a change in pitch of an audio output from the base unit, enabling the surgeon to move the hand-held probe around the area of the marker, and localize the lesion containing it. A numerical representation of the detected signal level is simultaneously displayed on the

base unit's display. The pitch of the audible tone and the numerical signal increase with closer proximity to the marker.

(a) (b)

(c)

Figure 2: a) Sentimag® Base Unit; b) Sentimag® Probe; c) Sentimag® Footswitch

4.2.2 Magseed Magnetic Marker

The magnetic marker system comprises a magnetic marker (magnetic seed) and an 18 gauge needle delivery system that is used to deliver the marker to the intended deployment location. The ferritic stainless steel marker is magnetically responsive but does not magnetically attract other metallic objects. The product is designed as a single use device that is supplied sterile in an individual sealed tyvek pouch.

4.2.3 MR Safety Information

Non-clinical testing has demonstrated that the marker can be scanned safely in an MRI under the following conditions:

- Static magnetic field of 1.5-Tesla (1.5 T) or 3-Tesla (3 T).
- Maximum spatial field gradient of 4,000 G/cm (40 T/m).

- Maximum MR system reported whole body averaged specific absorption rate (SAR) of 4 W/kg (First Level Controlled Operating Mode).

Please see the Magseed Instructions for Use for further MRI information.

Needle delivery system

Seed

(Nominal size: 0.9mm diameter x 5mm)

Figure 3: Magseed magnetic marker needle delivery system and marker

4.3 System Operation

The Magseed magnetic marker is deployed under, either ultrasound or mammography (x-ray) imaging guidance. The needle delivery system and the marker are visible under both these modalities. Magseed is not suitable for MRI guided deployment as the needle delivery system is not MRI compatible. Using the delivery system, the marker is placed percutaneously in the breast up to 30 days prior to surgery.

A post-placement mammogram can be used to confirm that the marker is in the desired position in the breast.

During surgery the marker facilitates magnetic localization of the target lesion using the Sentimag® probe, initially to allow the approximate location to be identified and an incision made, and then post-incision within the surgical site to detect and localize the lesion for excision. For some lesions, the position of the incision can be determined by other means, for example a skin mark.

The Sentimag probe generates an alternating magnetic field that temporarily magnetizes the marker. The magnetic signature generated by the marker is then detected by a sensitive magnetometer in the probe. The unit displays a numerical reading and emits an audible tone that increases in frequency (pitch) with the marker's proximity to the probe.

Once the marker has been localized, it is excised with the lesion.

4.4 Device Intended Use

The Endomag Magseed Magnetic Marker is intended to be placed percutaneously in the breast to mark temporarily (< 30 days) a lumpectomy site intended for surgical removal. Using imaging guidance (such as ultrasound or radiography) or aided by non- imaging guidance (Endomag Sentimag® System) the Endomag Magseed® Magnetic Marker is located and surgically removed with the target tissue.

The Endomag Sentimag® System is intended for the non-imaging detection and localization of the "Endomag Magseed Magnetic Marker" that has been implanted in a lumpectomy site intended for surgical removal.

5 STUDY PURPOSE

The purpose of this post-marketing study is to provide prospective evidence that the Magseed and Sentimag® is effective for lesion localization in patients undergoing surgical excision of a breast lesion and to summarize measures of product safety and performance.

5.1 Study Rationale

The guidewire method for localization of breast lesions has been largely unchanged for thirty years despite a number of drawbacks, including:

- Guidewire placement must happen on the day of surgery to reduce the risk of wire movement and to minimize the risk of infection. This can make scheduling between radiology and surgery departments difficult[10,13].
- Wires can become displaced or transected during surgery, making accurate lesion localization more difficult[10,11].
- The position of the surgical incision can be influenced by the wire placement[10,13].
- The use of guidewires has been associated with high re-excision rates[11,12,13].
- The additional procedure on the same day is stressful for some patients[10].

More recently, the introduction of RSL offers scheduling benefits to surgeons and radiologists and the potential for improved surgical outcomes. However, use of radioactive materials is closely regulated, and in order to set up a seed program, significant multi-disciplinary investment in training and implementation of radioactive materials handling processes is required. This means that in practice, RSL is limited to the larger healthcare institutions where this administrative overhead is more readily justifiable.

The Sentimag and Magseed system overcomes the limitations of guidewires and offers the benefits of RSL without the administrative burden of dealing with nuclear medicine regulations.

This post-marketing study will assess the effectiveness of the Sentimag and Magseed system for breast lesion localization, in particular the % retrieval rate of the index lesion and Magseed in the initial excised specimen.

In addition, other measures of device performance and device safety will be recorded.

As the focus of this study is a new surgical tool, and not a change to the treatment pathway, it is not considered necessary to include a cohort control or to randomize the study. In any case, it would not be possible to mask the radiologists or surgeons who perform the localization procedure due to the packaging and shape differences between the Magseed product and any commercially-approved control product. Therefore, this study will be considered an open-label, single arm study.

6 STUDY DESIGN

The Magseed magnetic marker localization study is a prospective, open label, post marketing study of Magseed and Sentimag in patients undergoing surgical excision of a breast lesion.

The expected duration of enrolment is approximately 10 months with each individual subject's participation lasting 2-8 weeks after enrolment, usually ending at the first post-operative visit. The total study duration is approximately 12 months.

[10] S.M. Dua *et al.*, The Breast 20 (2011) 246-253
[11] M. Ahmed, M. Douek, The Breast 22 (2013) 383-388
[12] P.J. Lovrics et al., Annals of Surgical Oncology, (2011), 18: 3407-3414
[13] L.J. McGhan et al., Annals of Surgical Oncology, (2011), 18: 3096-3101

The study is a non-randomized, open label, post-marketing study. Each eligible subject will have the Magseed marker deployed and subsequently excised with the lesion during the lumpectomy procedure.

7 STUDY PRIMARY OBJECTIVE

To provide evidence that the index lesion and Magseed can be successfully retrieved in the initial excised specimen when Magseed and Sentimag are used as indicated in lumpectomy procedures in patients requiring excision of a breast lesion.

8 STUDY ENDPOINTS

8.1 Primary Endpoint

The primary endpoint is the % retrieval rate of the index lesion and Magseed in the initial excised specimen. This is defined as the number of subjects in whom the index lesion and Magseed are retrieved in the initial excised specimen divided by the total number of subjects undergoing surgery.

8.2 Other Endpoints

Other endpoints to be measured include:

Safety

- Rates of device-related adverse events and device-related serious adverse events

Radiological Placement

- Radiologist rated ease of marker placement
- Success rate of marker placement (placement accuracy): <5mm to lesion; 5-10mm to lesion; >10 mm to the target
- Duration of Magseed placement (lesion localization) procedure

Surgical Localization

- Overall re-excision rate
- Re-excision rate necessary to remove the Magseed or targeted lesion
- Surgeon rated ease of localization during surgery
- Duration of lumpectomy procedure

Pathology

- Pathologist rated ease of marker identification and retrieval in the surgical specimen

9 STUDY POPULATION

9.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be enrolled into the clinical study:

- Subjects with a breast lesion requiring image-guided localization prior to excision.
- Subjects aged 18 years or more at the time of consent.

9.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria cannot be enrolled in the clinical study:

- The subject is pregnant or lactating.
- Subject has pacemaker or other implantable device in the chest wall.
- Subject has current active infection at the implantation site in the breast that may affect the (per investigator discretion)

10 STUDY CONDUCT AND PROCEDURES

The study will be conducted in accordance with the applicable requirements in the US Code of Federal Regulations concerning the protection of human subjects (21 CFR Part 812, 50, 56, and 45 CFR part 46), the guidelines in the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP), and ISO 14155 Clinical investigation of medical devices for human subjects - Good clinical practice.

Endomag will conduct training of the Sentimag and Magseed with the surgeons and radiologists as part of site initiation. Proctoring is permissible to train additional investigators. All training will be documented.

Required study assessments and procedures are described below. Table 2 presents a schedule of the required assessments and procedures. Information collected during the study procedures will be recorded on the study-specific electronic Case Report Forms (eCRFs).

10.1 Screening

Subjects considered for enrollment will be at least 18 years old at the time of consent, have either a) a diagnosis of breast cancer and be recommended for a lumpectomy procedure, or b) be scheduled for an excisional biopsy of the breast.

All inclusion criteria must be met and no exclusion criteria can be met in order to be enrolled in the study. Enrollment and Baseline (Visit 1)

Prior to any study-specific procedures, the subject's written informed consent and HIPAA authorization will be obtained. A subject will be considered enrolled in the study after granting written informed consent. The informed consent process must be documented in the subject's medical records (Section 15: Informed Consent and Confidentiality). A Subject Identification (ID) Log which captures subject identifiers, for subjects enrolled in the study, will be completed by site personnel and maintained at the site.

Following the informed consent process, a baseline evaluation will be completed. The baseline evaluation will be performed prior to the Magseed placement procedure and will include the following assessments:

- Demographics: age, gender, height, and weight
- Breast history, menopausal status, tumor size, stage, and how detected
- Neo-adjuvant chemotherapy

10.2 Marker Placement Procedure (Visit 2)

All eligible subjects will have the Magseed marker deployed under imaging guidance up to thirty days prior to surgery. All women of child-bearing potential will undergo standard of care pregnancy evaluation prior to the marker deployment. If a single Magseed is placed, the marker will be deployed close to the center of the lesion, and the position of the marker relative to the lesion recorded from the post-placement mammogram. In the beginning of the study (first 20 subjects), only one Magseed will be placed. More than one marker can be deployed to bracket a larger lesion, and the position of the markers relative to the lesion recorded from the post-placement mammogram. In this study, no more than 3 Magseeds are to be placed in one subject.

If more than one Magseed is used, they need to be placed greater than 20mm apart. If the Magseeds are placed less than 20mm apart, they behave as once source spread over a slightly larger area. In this case, the Magseeds can be readily detected, but not easily distinguished apart.

The imaging guidance can be ultrasound or stereotactic mammography. Magseed cannot be deployed under MRI guidance as the Magseed delivery system needle is not MRI compatible.

Radiologist evaluation will include the following assessments:

- Location and depth of lesion
- Number of markers placed
- BI-RADS breast density
- Ease of marker placement

After the procedure, the patient will have a mammogram as per standard of care to confirm marker placement.

10.3 Lumpectomy Procedure And Marker Excision (Visit 3)

The Magseed marker will be localized using the Sentimag system during surgery and planned removal with the lesion per standard procedures.

The Sentimag® probe is not sterile and must be used with a sterile sheath. During the procedure, the surgeon will use the Sentimag® probe to identify the magnetic marker. The location of the surgical incision is made per physician discretion.

Intraoperative X-ray may be used to confirm that the marker is within the excised tissue specimen. The Magseed will be discarded after the pathology assessment is complete.

Figure 4 displays the flow of the lumpectomy procedure.

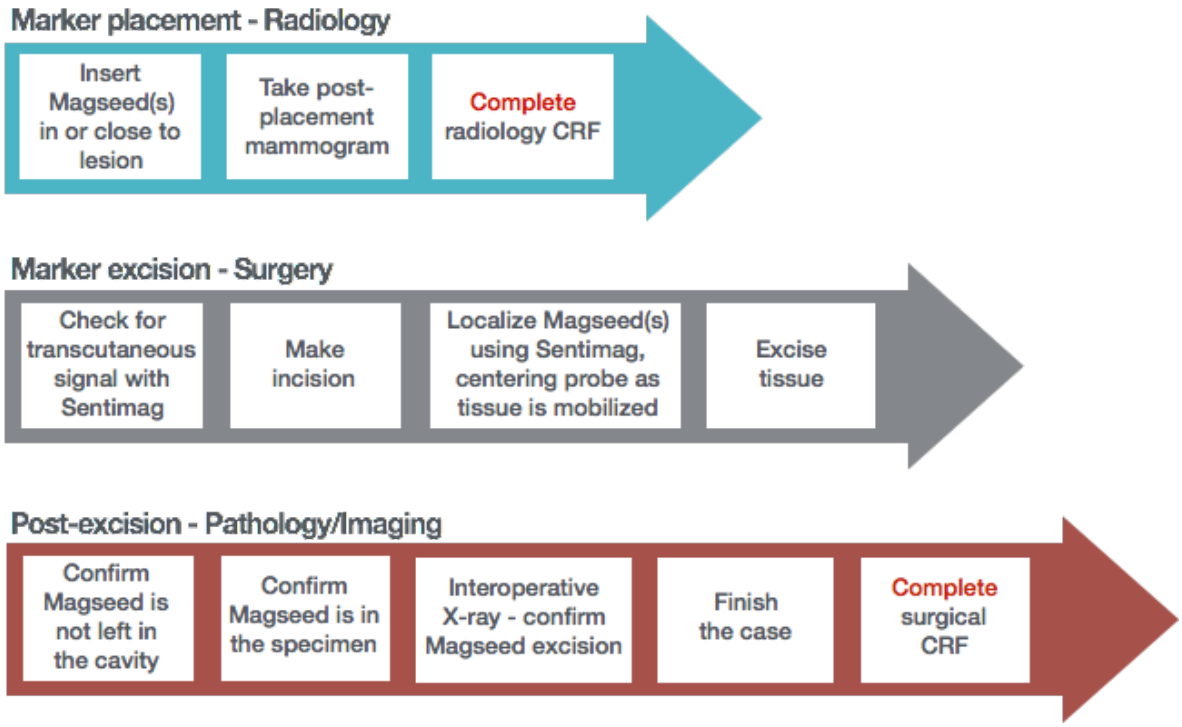

Figure 4: Lumpectomy Procedure Flow

10.4 Post-Operative Visit / Study Completion

The post-procedure evaluation visit should occur up to 8 weeks post-procedure for safety and patient reported outcomes.

Study data collection will include an adverse event assessment, histopathology data and any protocol deviations.

Following collection of the study data, subjects will have completed the study and study completion information will be obtained on the eCRF.

10.5 Pathology Lab

All lumpectomy samples removed will be sent to the site's pathology laboratory for evaluation. A standard of care histopathology report will be obtained. The ease of removal of the magnetic marker will also be recorded.

Table 2: Schedule of Study Procedures

Procedure/ assessment	Screening / enrollment	Visit 1 Baseline / medical history	Visit 2 Marker placement procedure	Visit 3 Lumpectomy and marker excision	Visit 4 Post-procedure evaluation (up to 8 weeks)	Unscheduled visit
Inclusion / exclusion criteria	X					
Informed consent	X					
Demographics, medical / surgical history		X				
Pregnancy test[1]			X			
Marker placement			X			
Lumpectomy and marker excision				X		
Excised tissue sent for histological analysis & pathology evaluation				X		
Lumpectomy results				X	X	
Adverse event assessment		X	X	X	X	X
Device deficiency assessment			X	X		
Study completion					X	

[1] To be obtained prior to procedure for females of childbearing potential.

10.6 Subject Completion, Withdrawal Or Death

10.6.1 Subject Completion

A subject's participation in the study is considered complete when all study requirements, including completion of the follow-up visit and assessments, have been met. After all assessments have been completed at the Post-Operative Visit (Visit 4), subject completion information will be captured on the Post-Operative Visit eCRF.

10.6.2 Withdrawal or Death

Subjects have the right to withdraw from the study at any time and for any reason. If a subject chooses to voluntarily withdraw after being enrolled (e.g. signing the informed consent), data that were collected prior

to the subject's withdrawal from the study will be analyzed. The Principal Investigator has the right to discontinue a subject's participation in the study in the event of an underlying illness, adverse event or protocol violation. All subject withdrawals will be documented on the Subject Exit eCRF. Withdrawn subjects will not be replaced.

For subject's who expire during their participation in the study, an Adverse Event eCRF may be completed in addition to a Subject Exit eCRF. Copies of the death record, death certificate and/or autopsy report (if performed) are requested to be sent to Endomagnetics as soon as they become available.

10.6.3 Lost to Follow-Up

For subjects that appear to be lost to follow-up, the site coordinator must document in the medical records at least three attempts to contact the subject. The coordinator must use at least two methods (phone, e-mail, certified mail, personal visit) and one contact must be made using certified mail to the subject's last known address. All lost-to-follow-ups will be documented on the Subject Exit eCRF.

11 ADVERSE EVENTS

11.1 Adverse Event Overview And Reporting

Adverse event definitions are provided in Section 11.2. Administrative edits were made to combine definitions from ISO 14155-2011.

In this study, only the following AEs must be reported and recorded in the eCRF:

- Device-related AEs experienced by the study subject from the time of study enrollment through to study subject exit; and
- Device-related SAEs experienced by the study subject from the time of study enrollment through to study subject exit.

The following SAEs do not need to be reported or recorded in the eCRF:

- Anticipated SAEs, see section 11.2.1, that are related to the index procedure; and

Death should not be recorded as an AE, but should only be reflected as an outcome of a specific SAE.

Adverse event reports will include a description including the suspected diagnosis, signs and symptoms, actions taken and the clinical outcome for the subject. The Investigator must provide his/her medical judgment of the following:

- Whether the event is an unanticipated adverse device effect (UADE);
- Whether the event is serious (SAE); and
- The relationship of the event to the study device.

In the case of serious (SAE) or unanticipated adverse device effect (UADE), or those deemed to be related to the study device, de-identified copies of medical record documentation (e.g. procedure notes, discharge summary, relevant progress notes, imaging or lab studies) will be sent to Endomagnetics with the AE eCRF to describe the treatment, resolution and outcome of the adverse event.

All AE notification for SAEs and UADEs will be sent to Endomagnetics within 3 business days of discovery of the event by site personnel. All AE eCRFs must be reviewed and signed by the Investigator. It is the Investigator's responsibility to inform the IRB of adverse events as required by the IRB's procedure.

11.2 Definitions

Adverse Event (AE)	An adverse event is defined as any untoward medical occurrence, unintended disease or injury experienced by a subject during this trial regardless of its relationship to the trial product.
Serious Adverse Event (SAE)	An adverse event is considered serious if it meets at least one of the following criteria: a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in • a life-threatening illness or injury, or • a permanent impairment of a body structure or a body function, or • in-patient or prolonged hospitalization, or • medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect *NOTE*: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.
Unanticipated Adverse Device Effect (UADE)	An Unanticipated Adverse Device Effect (UADE) is any adverse device effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death that is not previously identified in nature, severity, or degree of incidence in this Investigational Plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

11.2.1 Anticipated Adverse Events

Adverse events that are anticipated to occur during this clinical trial are believed to be similar to those associated with undergoing the same lumpectomy or excisional biopsy (the index procedure) and those associated with implantation of material similar to Magseed, or have been identified by Endomagnetics as part of their risk assessment. Anticipated AEs are tabulated below.

Table 3: List of Anticipated Adverse Events

Adverse events associated with lumpectomy or breast conserving surgery	Ecchymyosis / Bruising Cellulitis Respiratory Disorder Rash Pain Nausea Allergic Reactions (Anaphylaxis) Seroma	Erythema Superficial eschar Hypotension Cellulitis Ecchymyosis / Bruising Skin Ischemia Infection
Adverse events associated with implantation of similar materials	Hematoma Hemorrhage Infection Adjacent tissue injury	Pain Allergic reaction Foreign body reactions (e.g. granulomas)

11.2.2 Device-related Adverse Event

An adverse event is considered to be device-related when, in the judgment of the Investigator, the clinical event has a reasonable time sequence associated with use of the trial device or control and is unlikely to be attributed to concurrent disease or other procedures or medications, or it is reasonable to believe that the device directly caused or contributed to the adverse event.

11.3 Adverse Event Relatedness

Adverse events will be determined by the Investigator as to their relatedness to the study device using the following classifications:

- **Not related:** An adverse event for which sufficient information exists to indicate that there is no causal connection between the event and the trial device. The adverse event is due to and readily explained by the subject's underlying disease state or the index procedure or is due to concomitant medication or therapy not related to the use of the study device.
- **Definitely related:** The adverse event has a strong causal relationship to the trial device. The adverse event follows a strong temporal relationship to the use of the study device, follows a known response pattern to the study device, and cannot be reasonably explained by known characteristics of the subject's clinical state, the index procedure or other therapies.
- **Undetermined relationship:** Sufficient information is not available to determine the event's causality.

11.4 Medical Monitor

An additional Medical Monitor, is not required for this study as the study device is FDA approved and being used within its label indication.

11.5 Device Deficiencies And Observations

A device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. All device deficiencies and observations of the Sentimag and Magseed are required to be documented on a Device Deficiency eCRF. In the event of the product not performing to specifications, the product shall be returned to the Sponsor for analysis. Analysis of the product will be provided to the investigational site from which the product performance issue was reported.

12 DEVIATIONS TO THE INVESTIGATIONAL PLAN

An Investigator must not make any changes or deviate from the protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 3 business days after the emergency occurred.

All deviations from the investigational plan will be reported on the eCRF. Investigators must also adhere to local IRB reporting requirements for reporting of deviations.

Deviations will be reviewed throughout the study. If necessary, corrective and preventive actions will be initiated by the sponsor.

13 DATA HANDLING AND RECORD KEEPING

13.1 Case Report Forms

The study will be performed using a secure, validated, 21 CFR Part 11 compliant Electronic Data Capture (EDC) system. The Investigator and study site staff will receive training and support on the use of the EDC system. All eCRF data are to be completed by the Investigator, study coordinator or other designated and trained site personnel. The Investigator is required to review and approve all subject data in the EDC system to agree the data are true and accurate.

Data management activities and processes are detailed in the Data Management Plan.

13.2 Source Documents

Investigators are required to maintain records of each study subject's medical history and study-related procedures. The information in the study subject's medical records must substantiate data collected on the eCRF. All study-related procedures must be documented and the study site personnel trained and delegated to conduct the study-related activity must sign and date the source document.

Shadow charts are not appropriate or adequate for source documentation. Source data includes all information, original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents, which may include, for example: clinic charts, hospital records, laboratory notes, copies or transcriptions certified after verification as being accurate and complete, x-rays, histology reports.

All source documents uploaded into the EDC system will be de-identified prior to upload.

13.3 Records Retention

All study records, including source documents that support the eCRFs for each subject must be retained in the files of the responsible Investigator for a minimum of two years following study closure.

If the responsible Investigator retires, relocates or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Endomagnetics must be notified in writing of the name and address of the individual obtaining custody of the records.

14 MONITORING AND OVERSIGHT

This study will be monitored in accordance with applicable sections of 21 CFR Part 812, 50, 56, HIPAA and the guidelines in the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP).

Endomagnetics or its representatives will conduct all monitoring activities. Monitors selected for the study will be qualified and trained. All Monitor Training Records will be maintained by Endomagnetics.

Safety data will be 100% source verified. A minimum of 25% of other data will be source verified. Monitoring activities and processes are detailed in the Monitoring Plan.

14.1 Direct Access To Source Data / Documents

The Investigator will provide the Monitor with direct access to source documents (e.g. electronic medical records) to substantiate data recorded on the eCRFs. In addition, the Investigator will upload de-identified source documentation into the EDC system for monitoring purposes. The Investigator will also permit audits and inspections by the IRB, Sponsor or Sponsor's representatives, government regulatory bodies and compliance and quality assurance groups.

14.2 Informed Consent And Confidentiality

This study will be conducted in compliance to 21 CFR 50 and HIPAA for the protection of subject rights and data confidentiality. Prior to the conduct of any study-specific procedures, potential subjects will receive a full explanation of the study, including risks and benefits by qualified site personnel. The subjects will be given adequate time to review the IRB-approved Informed Consent / HIPAA Form and have all of their questions answered to their satisfaction. If the subject makes the decision to participate in the clinical study, the Form will then be signed. The original Form will be placed in the subject's medical record; a copy will be given to the subject for his / her records. The informed consent process will be documented in the subject's medical record.

De-identified data may be shared with Federal agencies that require reporting of clinical study data (such as the FDA, National Cancer Institute [NCI], and OHRP), authorized representatives of Endomagnetics, Inc. and foreign government authorities that review medical devices.

14.3 Product Accountability

The Sentimag® units will be provided to the investigational site by Endomagnetics. Shipping records will be maintained by Endomagnetics detailing the lot, model and serial number of each device and the date of shipment to the site. The site will maintain a product accountability log (PAL) to track the Sentimag units. The Magseeds will be purchased / provided by the investigational sites and will not be tracked on the PAL. Study product(s) which appear to not be functioning within product specification will be returned to Endomagnetics and recorded on the PAL.

14.4 Investigator And Investigative Site Selection

Investigators will be qualified using predetermined criteria to ensure they have the experience and expertise to perform breast conserving surgery procedures with the study products and to conduct human clinical research with adherence to applicable federal regulations. Sites will be required to demonstrate that they have qualified clinicians and research staff to ensure proper study conduct, including the safeguarding of subject rights, safety and welfare.

Investigators must agree to conduct the study in accordance with the Investigational Plan, Clinical Trial Agreement/Investigator Agreement, the US Code of Federal Regulations (21 CFR Part 812, 50, 56) and the guidelines in the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP). Investigators and Investigational sites will be qualified and selected based on investigator qualification, related therapeutic experience, adequate and available facility and research staff, and subject availability.

Investigators and investigative sites selected to be responsible for conducting the clinical trial are listed below. Investigator and/or investigative sites may be revised if changes occur.

Table 4: List of Investigators / Investigative Sites

Investigator / Investigative Site	Contact Information
Kelly Hunt, MD University of Texas MD Anderson Cancer Center	Department of Breast Surgical Oncology 1400 Pressler Street, Unit 1484 Houston, TX 77030-4008 khunt@mdanderson.org
Elizabeth Mittendorf, MD, PhD University of Texas MD Anderson Cancer Center	Department of Breast Surgical Oncology 1400 Pressler Street, Unit 1484 Houston, TX 77030-4008 eamitten@mdanderson.org
Marion Scoggins, MD University of Texas MD Anderson Cancer Center	Department of Diagnostic Radiology 1515 Holcombe Blvd. Unit 1350 Houston, TX 77030
Aysegul Sahin, MD University of Texas MD Anderson Cancer Center	Department of Pathology 1515 Holcombe Blvd. Unit 1350 Houston, TX 77030

14.5 Investigator Agreement

A study-specific Clinical Trial Agreement/Investigator Agreement will be provided by the Sponsor for signature and must be executed prior to the Investigator's enrollment of subjects. This document will signify the Investigator's agreement to comply with this Investigational Plan as well as all pertinent regulations and laws.

14.6 Investigational Site Training

All site personnel will be trained prior to performing or being delegated to conduct study-specific activities. Endomag will conduct training of the Sentimag and Magseed with the surgeons and radiologists as part of site initiation. Proctoring is permissible to train additional investigators. The site staff responsible for completing the eCRFs will be instructed on the proper procedure for completing the forms and ensuring that all data are collected. They will be trained by members of the Sponsor's clinical staff or nominated representatives. All site personnel (Investigator(s) and site staff) will be instructed on the protocol, including all follow-up requirements, adverse event reporting, trial product handling and accountability, good clinical practices, HIPAA regulations, regulatory requirements and instructions for obtaining consent. All site personnel involved in investigational product use will also be trained on product use. In addition, Investigator Responsibilities (Section 17.4) training will be conducted with the responsible Investigator. All training will be documented.

15 STATISTICAL CONSIDERATIONS

15.1 Primary Endpoint

The primary endpoint is the % retrieval rate of the index lesion and Magseed in the initial excised specimen. This is defined as the number of subjects in whom the Magseed is localized and the index lesion and Magseed are retrieved in the initial excised specimen, divided by the total number of subjects undergoing surgery for excision of a breast lesion following placement of Magseed in the lesion.

15.2 Sample Size Determination

Sample size for this single arm study has been calculated based on the precision of the confidence interval for the primary endpoint, the proportion of successful retrievals. A sample of 100 patients with excision data will provide an exact 95% confidence interval[14] with maximum width ±0.092 providing the proportion of successes is at least 80%. At the anticipated success rate of 90% the confidence interval precision will be ±0.076. Up to 120 patients will be enrolled to ensure excision data for 100 patients.

15.3 Statistical Methods

Statistical analysis is the responsibility of the sponsor's designated statistician. A full statistical analysis plan will be written prior to any data analysis.

15.3.1 Analysis Sets

All subjects who undergo the lumpectomy with Magseed excision procedure as part of the study will be included in all analyses of safety. Specific endpoints related to Magseed placement and excision will be based on the total number of subjects undergoing the procedure.

15.3.2 Control of Systematic Error/Bias

Selection of subjects will be made from the Investigator's usual subject load. All subjects meeting the inclusion/exclusion criteria and having signed the ICF will be eligible to enroll in the trial. Consecutively eligible subjects should be enrolled into the study to minimize selection bias.

15.4 Data Analyses

15.4.1 Demographic and Baseline Characteristics

Baseline data will be summarized using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency tables for discrete variables.

15.4.2 Other Endpoints

Procedural data will be summarized using descriptive statistics for continuous measures and frequency tables or proportions for discrete variables. Endpoints will be summarized using proportions for rates or binary outcomes while continuous data will be summarized by presenting means, medians, standard deviations, sample sizes, minimums, and maximums. Point estimates will be provided for rates and mean values along with 95% confidence intervals. Rates of serious adverse events (SAEs) will be reported by relationship to device and severity, and rates of adverse events related to the device will be reported. Any unanticipated adverse device effects (UADEs) will be listed and summarized as appropriate.

No formal tests of hypotheses are proposed for the other endpoints.

15.4.3 Interim Analyses

There are no formal interim analyses planned in this observational study. Ongoing data summaries may be performed at any time.

15.4.4 Subgroup Analyses

No subgroup analyses are planned.

15.4.5 Missing Data Management

The products being evaluated in this study are designed to help physicians localize lesions during surgery for breast cancer or excision of other breast lesions. All required information can be obtained during the

[14] Calculated based on exact confidence intervals using Clopper-Pearson method as expected proportion is high.

lumpectomy procedure and missing data for the primary endpoint are not expected to be a concern nor affect the scientific soundness of this study.

If there are missing data (i.e. data for Magseed has not been recorded or has been lost), a sensitivity analysis will be carried out for the primary endpoint. Both the worst case and the best case proportions will be calculated. For the worst case analysis, subjects with missing data will be assumed to have no magnetic marker detected and retrieved. For the best case analysis, subjects with missing data for will be assumed to have a magnetic marker detected and retrieved. No other imputations for missing data are planned.

15.4.6 Changes to Planned Analyses

Changes to the planned statistical analysis methods are not expected, however, any changes to the planned statistical analysis methods made prior to analysis will be documented in an amended Statistical Analysis Plan. Changes to the planned analysis methods after analyzing the data will be documented in the clinical study report along with a reason for the deviation from plan.

16 RISK ANALYSIS

16.1 Potential Risks

Subjects participating in this study are subject to the same risks shared by all subjects with the underlying medical diagnosis and lumpectomy surgery procedure.

Please refer to the Sentimag and Magseed Instructions for Use (IFU) for warnings and contraindications for the devices. There are no specific additional risks to the subject over and above the risk mentioned in this section related to participation in the study.

16.1.1 Risk Minimization Actions

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying Sponsor with all pertinent information required by this protocol.

16.2 Potential Benefits

All subjects participating in this study may benefit from the use of Magseed and Sentimag for localizing a lesion.

The Sentimag®, used in conjunction with Magseed, assists the surgeon in the localization of the target lesion. This technique avoids the need for the use of guidewires and the drawbacks of this technique for patients: wire placement can be painful; the additional procedure on the day of surgery can be stressful[15]; and there is a risk of wire migration[16]. In centers where RSL is used, Magseed offers the benefit of reduced exposure to radiation.

16.3 Risk to Benefit Rationale

16.3.1 Risks associated with the procedure/implant

Subjects enrolled in this post-market clinical study are subject to the same risks shared by all subjects undergoing a routine procedure with a Magseed, implanted guidewire or radioactive seed. Please refer to the instructions for use (IFU) for the list of risks.

[15] S.M. Dua et al., The Breast 20 (2011) 246-253
[16] P.J. Lovrics et al., Annals of Surgical Oncology, (2011), 18: 3407-3414

16.3.2 Risks associated with the study device

There are no additional risks to the study subjects over and above the risks of routine implant of the Magseed, as noted above.

16.3.3 Risks associated with participation in the clinical study

There are no additional risks to the study subjects over and above the risks mentioned in Section 16.3.1 related to participation in the clinical study.

16.3.4 Potential benefits with participation in the clinical study

As patients will not have a wire or radioactive seed placed, there may be a benefit in terms of improved scheduling convenience for the patient. The data collected in this study may provide information to improve future care or management of subjects undergoing standard Magseed implantation procedures in the future.

16.3.5 Risk Minimization

Risks can be minimized through adherence to the guidelines for subject selection, close monitoring of the subject's physiologic status during study testing and by promptly supplying Sponsor with all pertinent information required by this study protocol.

16.3.6 Risk to Benefit Rationale

Subjects enrolled in the Magseed Magnetic Marker Localization Clinical Study will not be exposed to additional risks as compared to those subjects who are routinely implanted with the Magseed not enrolled in the study. Standard procedures will be conducted during the implant and follow-up of study subjects, just as they are for subjects not enrolled in this clinical study.

Subjects enrolled in this post-market clinical study are subject to the same risks shared by all subjects undergoing a routine procedure with a Magseed, implanted guidewire or radioactive seed. There are no additional risks to the study subjects over and above the risks of routine implant of the Magseed, as noted above.

17 STUDY ADMINISTRATION

17.1 Institutional Review Board Approval

The study will not be initiated before the protocol, informed consent and any applicable subject information forms have been reviewed and approved by the IRB. A copy of all IRB approval letters and correspondence must be maintained in the investigational site study file as well as copies provided to the Sponsor.

17.2 Amendments To The Investigational Plan

During the course of this investigation it may become necessary to amend the protocol, informed consent, CRFs or study subject materials. Such amendments will be made by the Sponsor and presented to the IRB for review and/or approval prior to implementation.

17.3 Early Termination Or Suspension Of Study

The Sponsor of this trial has the sole responsibility for any decision to suspend or terminate this study. Notice of any decision to suspend or terminate the trial will be immediately forwarded by express delivery to the Investigators, IRBs and independent study monitors (if any).

The Sponsor retains the right to suspend or terminate the participation of a study Investigator for non-compliance to this Investigational Plan, the Clinical Trial Agreement/Investigator Agreement, inability to successfully implement this Investigational Plan, falsification of data, or any other breech of federal regulations, ethics or scientific principles.

An Investigator may terminate his participation in the study for due cause with prior notification to the Sponsor. The Investigator will also notify his/her IRB of study termination. In the event of study termination by the Investigator, he/she is still obligated to continue to follow all study subjects as prescribed by this Investigational Plan and to adhere to all other Investigational Plan requirements, including data collection, adverse event notification and to allow monitoring visits by the Study Monitor.

17.4 Investigator Responsibilities

Participating Investigators are responsible for ensuring the rights, safety and welfare of study subjects. Investigators are required to accept the following responsibilities according to 21 CFR 812 (where applicable) and ICH GCP Guidelines:

- Ensure that the investigation is conducted according to the Clinical Trial Agreement/Investigator Agreement.
- Protect the rights, safety, and welfare of subjects.
- Obtain informed consent from each subject.
- Retain specific records and issue specific reports.
- Assure that the IRB is provided information for initial and continuing review of the study.
- Ensure that all work and services described within this protocol are conducted in accordance with the highest standards of medical practice and Good Clinical Practice.
- Ensure that all associated clinical and support staff members conduct the study in accordance with the protocol and amendments.
- Ensure that complete and accurate study data is collected and submitted to the Sponsor.
- Ensure that the study regulatory binder, and study files containing CRFs, consent information, source documentation, records of adverse events and their resolution and all other relevant subject information are complete and up to date.

17.5 Investigator Records

The Investigator is responsible for maintaining adequate records to fully document study activities, which include:

- The Instructions for Use, signed protocol, and amendments;
- Fully executed Clinical Trial Agreement/Investigator Agreement;
- Signed and dated informed consents per institutional policy;
- Signed, dated, and completed CRFs, and documentation of CRF corrections;
- Notification of SAEs, UADEs and related reports;
- All study devices dispensing and accountability logs;
- Shipping records of study devices and study-related materials;
- Dated and documented IRB protocol approvals, and all correspondence between Investigator and IRB;
- Curriculum vitae and current medical licenses for all Investigators and;

- Source documents.

17.6 Investigator Reports

Reports that are the Investigator's responsibility to generate are listed in Table 5. If applicable laws, regulations or IRB requirements mandate stricter reporting requirements than those listed, the more strict requirements must be adhered to.

Table 5: Investigator Reporting Responsibilities

Report	Submitted to	Description
Unanticipated Adverse Device Effects (UADE)	Sponsor & IRB	The Investigator's report on any unanticipated adverse device effect must be submitted as soon as possible but no later than 3 business days after the Investigator first learns of the effect.
Serious Adverse Events (SAE)	Sponsor (and to IRB, if required)	The Investigator's report on all serious adverse events must be submitted within 3 business days after the Investigator first learns of the event.
Withdrawal of IRB approval	Sponsor	The Investigator must report a withdrawal of the reviewing IRB approval within 5 working days.
Progress Report	Sponsor & IRB	The Investigator must submit a progress report on an annual basis if the study lasts longer than one year.
Deviations from Investigational Plan (CFR 812.150	Sponsor & IRB	The Investigator must submit a notification must be made within 5 working days of the occurrence of an emergency deviation (made to protect the life or physical well-being of a subject).
Emergency Use	Sponsor, IRB, Regulatory authority	If the deviation affects scientific soundness of the study or the rights, safety, or welfare of the subject (and is not an emergency), the Investigator must obtain prior approval from Endomagnetics, the reviewing IRB, and FDA or applicable Regulatory Authorities (when required).
Other	Sponsor	Any other deviations
Failure to obtain Informed Consent	Sponsor & IRB	The Investigator must submit a notification within 5 working days after device use.
Final Report	Sponsor & IRB	The Investigator must submit this report within 3 months after termination or completion of the investigation.

17.7 Sponsor Records

The Sponsor or its delegate, is required to maintain the following records:

- Investigational Plan and all amendments.
- Blank sets of each version of eCRFs and Consent Forms.
- Signed Clinical Trial Agreement/Investigator Agreements.
- Institutional Review Board approval letters, including a copy of the approved consent form(s).
- All correspondence relating to this study between the Sponsor, its delegates and the investigational site, Institutional Review Board, Study Monitor and FDA.
- CVs for all study personnel.
- Site personnel signatures and responsibility lists.
- Trial device inventory log including: date, quantity, and lot numbers of product shipped and received

17.8 Sponsor Reports

The Sponsor (or delegate CRO) is required to prepare and submit the following reports:

Table 6: Sponsor Reporting Responsibilities

Report	Submit to	Description
Unanticipated Adverse Device Effects (UADE)	IRB, Investigators, FDA where applicable	Endomagnetics will report on any unanticipated adverse device effect evaluation within 10 working days after receiving notice of the effect.
Withdrawal of IRB approval	IRB, Investigators	Notification, when appropriate, will be made within 5 working days after Endomagnetics receives notice of withdrawal of IRB approval.
Recall and Trial Product Disposition	IRB, Investigators	Notification will be made within 30 working days of Endomagnetic's request that an Investigator return, repair or otherwise dispose of any products. Such notification will state why the request was made.
Final Report	IRB, Investigators	Notification will be made within 30 working days of the completion or termination of the investigation. A final report will be submitted within three months after study completion or termination.

17.9 Publication Policy

Publication of clinical data from this trial will be in accordance with the Clinical Trial Agreements and Publication Strategy. Publication of all data will also conform to standards set forth in peer-reviewed journals. Specifically, this trial will be registered in a clinical registry, www.clinicaltrials.gov, in order to conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

18 STUDY SPONSOR CONTACTS

Study Manager: Quentin Harmer
Endomagnetics Ltd
Jeffreys Building
Cowley Road
Cambridge, UK
CB4 0WS

APPENDIX A: INFORMED CONSENT TEMPLATE

See attachment

APPENDIX B: CASE REPORT FORMS

See attachments

APPENDIX C: CLINICAL TRIAL AGREEMENT/INVESTIGATOR AGREEMENT TEMPLATE

See attachment