"PREDICT"

a PRospEctive post market trial of Drg stImulation with the Commercially available axium® neurosTimulator system

Protocol 08-SMI-2012

Spinal Modulation
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Sponsor	**Spinal Modulation** **1135 O'Brien Dr.** **Menlo Park, CA 94025** **USA**

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
AIMDD	Active Implantable Medical Devices Directive
BPI	Brief Pain Inventory
BSI	British Standard Institution
CE mark	Conformité Européenne (In accordance to European Regulations)
CIBG	executive agency of the Dutch Ministry of Health, Welfare and Sport
CRF	Clinical Research Form
CRPS	Complex Regional Pain Syndrome
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
DRG	Dorsal Root Ganglion
EQ-5D	© 1987 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group
EU	European Union
FBSS	Failed Back Surgery Syndrome
FU	Follow Up
GCP	Good Clinical Practice
INS	Implantable NeuroStimulator
IRAS	Integrated Research Application System
ISO	International Organisation for standardisation
OLBPDQ	Oswestry Low Back Pain Disability Questionairy
REC	Research Ethical Committee
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SCS	Spinal Cord Stimulation
Sponsor	The party that commissions the organisation or performance of the research
SPSS	Statistical computer program
TNS	Trial NeuroStimulator
VAS	Visual Analogue Scale

SUMMARY

Rationale: Initial clinical studies have shown that stimulation of the dorsal root ganglion (DRG) can significantly reduce chronic intractable pain. These results have supported the CE marking of the Spinal Modulation Neurostimulator system in the management of chronic pain. As DRG stimulation with the Axium® Neurostimulator System is a new type of Spinal Cord Stimulation (SCS) and to follow the requirements of the AIMDD, Spinal Modulation would like to collect clinical data on this commercially available therapy.

Objective: The purpose of this PRospEctive post market trial of Drg stImulation ("PREDICT") is to evaluate the commercially available Axium® Neurostimulator System in the management of intractable chronic pain in patients that are routinely scheduled to receive a Spinal Modulation Axium® Neurostimulator System.

- Primary Objective: Evaluate reduction in pain (VAS)
- Secondary Objectives: Safety (AE/SAE), Quality of life, Physical functioning, Subject satisfaction and Device performance

Study design: This is a prospective, post market, multi centre, single-arm trial.

Device: Commercially available, CE marked, Axium® Neurostimulator System for the management of chronic intractable pain (CE 567069).

Study population: Up to 125 Males and females at least 18 years of age suffering from chronic neuropathic pain for at least 6 months that are routinely scheduled to receive a commercially available Axium® Neurostimulator System.

Intervention: Under monitored anaesthesia care, subjects will undergo minimally invasive placement of leads in the lateral epidural space of the neural foramen following standard clinical procedures. Subjects having successful trial stimulation will receive the fully-implantable system and will be followed for 24 months. They will be asked to complete several questionnaires at baseline and at follow-up visits.

Follow-up visits: The patients will visit the hospital for the following visits: Baseline, Trial NeuroStimulator (TNS) procedure, End of TNS (if applicable), Implantable NeuroStimulator (INS) procedure, 1 week follow-up (FU), 4 week FU, 3 month FU, 6 month FU, 12 month FU and 24 month FU. If needed the site can contact the patients by phone at 8 weeks FU, 9 months FU, and 18 months FU.

Risks: There are no additional risks for the patients by participating in this prospective post market trial. The implantation of the system is a standard clinical procedure in the hospital and the additional data that will be collected consists only of questionnaires.

1. INTRODUCTION AND RATIONALE

1.1 History

Neuromodulation for the treatment of chronic pain has been used for over a century1. The first use of electricity in the spine for neuromodulation of pain was conducted by Norm Shealy in 19672. The development of spinal cord stimulation (SCS) technology has grown rapidly in the past 40 years and is now used in over 40,000 new patients each year.

1.2 Spinal Neuromodulation

Several recent systematic reviews have provided evidence that this stimulation technology is a safe and, to a lesser extent, effective treatment option for patients suffering from chronic, intractable pain[3-5]. The effective rate of serious complications is quite low[3-5]. The treatment has been found to be successful in approximately 50% of patients that have a successful temporary stimulation trial period[6,7]. In the largest prospective trial published to date, Kumar and colleagues found a significant reduction in leg pain when compared to a conventional medical management control group[6,8]. In a similar manner, Kemler and colleagues found that Spinal Cord Stimulation (SCS) can be effective in the treatment of complex regional pain syndrome (CRPS)[9-11]. Despite varying levels of success in the literature, approximately 50% of patients will not receive adequate pain relief from traditional spinal cord stimulation. This suggests that alternative neuromodulation techniques are needed to improve pain relief in these patients.

1.3 Therapy Description

The Axium® Neurostimulator System consists of a two-phase treatment process: 1) a temporary trial phase and 2) a permanent implant phase. The first phase involves implanting stimulation electrodes (or “leads”) into the epidural space, which are connected to an external Trial NeuroStimulator (TNS) to electrically stimulate the Dorsal Root Ganglion (DRG). If the patient experiences sufficient pain relief during this trial stimulation they will progress to receive a fully Implantable NeuroStimulatior (INS) system.

1.4 Rational

Given the success in treating various pain conditions with electrical neuromodulation techniques and the role the Dorsal Root Ganglion (DRG) plays in the development and maintenance of chronic pain, we have developed a neurostimulator system designed for the management of chronic intractable pain by electrically stimulating the DRG.

As DRG stimulation with the Axium® Neurostimulator System is a new type of Spinal Cord Stimulation (SCS) and to follow the requirements of the AIMDD, Spinal Modulation would like to collect clinical data on this commercially available therapy. This multi-centre trial is set up to collect long term prospective data on the performance of the Axium® Neurostimulator system in patients that are routinely scheduled to receive DRG stimulation in the management of chronic intractable pain.

2. OBJECTIVES

The objective for this prospective, multi centre DRG stimulation trial is to assess the performance of the commercially available CE marked Axium® Neurostimulator System in the management of chronic intractable pain.

Primary objectives:

1. Pain relief measured using a Visual Analogue Scale (VAS). The average pain reduction experienced as well as the percentage of subjects with at least a 50% pain reduction will be evaluated.

Secondary Objectives:

3. STUDY DESIGN

This study is a prospective, post market, single-arm, multi centre trial designed to assess the clinical effects of the commercially available Axium® Neurostimulator System in the management of chronic intractable pain. Subjects that are routinely scheduled to receive DRG stimulation will be asked to participate in this trial. They will be screened based upon the inclusion and exclusion criterion, consented with an REC approved Patient Informed Consent Form, and enrolled into the trial. Subjects will then be assessed for baseline measurements.

Patients that are not willing to participate in the trial or that do not fulfill the inclusion criteria, but are, nevertheless, considered to be suitable for neurostimulation will be treated as such under standard of clinical care at the pain clinic.

Subjects will "trial" the therapy with an external Trial NeuroStimulator (TNS), for a maximum of 30 days (Phase 1) depending on standard hospital practice. If subjects obtain sufficient pain relief either overall or in their primary area of pain being treated, they will be eligible to proceed with the second phase of the therapy. If the eligible subjects agree to move forward into Phase 2, they will receive the fully Implantable NeuroStimulator (INS). Subjects will be seen for follow-up at 1 week, 4 weeks, 3 months, 6 months, 12 months and 24 months following implantation (Figure 1). The site can contact the subjects by phone for a follow-up at 8 weeks, 9 months and 18 months (optional).

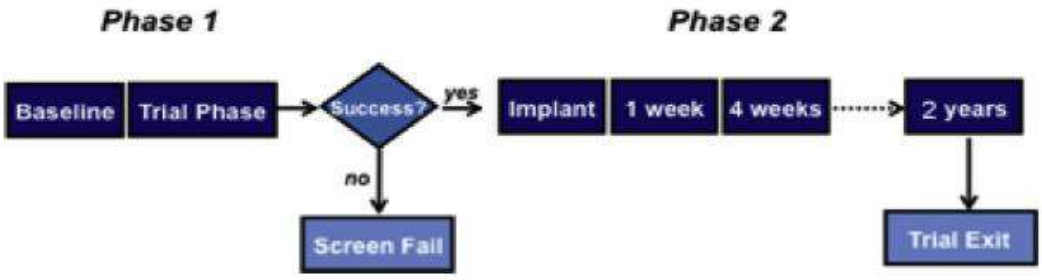

Figure 1. Basic design and follow-up schedule for subjects enrolled into the PREDICT trial. Subjects consented and enrolled will undergo a two-phase process for advancement through the trial. Subjects that do not obtain at sufficient pain relief during Phase 1 will be considered screen failures. A detailed follow-up scheduled can be found in Appendix A.

Protocol Phase 1 – Temporary Trial Neurostimulation

Following consent and entry into the prospective trial, baseline assessments will be taken. Subjects will then have the quadrapolar leads epidurally placed using a percutaneous approach and steered towards the appropriate intraspinal location (see *Physician Implant Manual* for detailed information regarding the procedure).

Protocol Phase 2 – Implantable Stimulation

If a subject obtains sufficient pain relief either overall or in their primary area of pain during the TNS procedure or during the course of the trial phase of the study, the subject will be eligible to continue onto the Implantable Phase of the study. All eligible subjects willing to continue will undergo another surgical procedure to fully-implant the neurostimulator (see *Physician Implant Manual* for detailed information regarding the procedure).

Follow-up

Subjects will be followed for 24 months following implant, returning to the clinic at regular follow-up time points in line with standard clinical care (1 week, 4 weeks, 3 months, 6 months, 12 months and 24 months). Subjects have the option to return to the clinic at unscheduled times to have the device reprogrammed as needed. This can be captured as an interim visit. The site can contact the patients by phone at 8 weeks, 9 months and 18 months (optional).

4. STUDY POPULATION

4.1 Population

[redacted] male and female subjects (minimum age 18 years old) suffering from chronic intractable pain for a minimum of 6 months who are routinely scheduled for DRG stimulation will be recruited [redacted] for inclusion in the trial.

Subjects must meet all of the inclusion and none of the exclusion criteria to be enrolled in the prospective trial. Subjects will read and sign an informed consent prior to undergoing any data collection or trial treatment. Subjects will be recruited from the sites existing patient population and through new patient contacts as normally progresses in standard clinical practice.

4.2 Inclusion criteria

1) Subject is at least 18 years old
2) Subject is able and willing to comply with the follow-up schedule and protocol
3) Chronic, intractable pain for at least 6 months
4) Failed conservative treatments for chronic pain including but not limited to pharmacological therapy, physical therapy and interventional pain procedures for chronic pain
5) Average baseline pain rating of 60 mm on the VAS in the primary region of pain
6) In the opinion of the Investigator, the subject is psychologically appropriate for the implantation for an active implantable medical device
7) Subject is able to provide written informed consent

4.3 Exclusion criteria

1) Female subject of childbearing potential is pregnant/nursing, plans to become pregnant or is unwilling to use approved birth control
2) Escalating or changing pain condition within the past month as evidenced by investigator examination
3) Subject has had corticosteroid therapy at an intended site of stimulation within the past 30 days
4) Subject has had radiofrequency treatment of an intended target DRG within the past 3 months
5) Subject currently has an active implantable device including ICD, pacemaker, spinal cord stimulator or intrathecal drug pump
6) Subject is unable to operate the device
7) Subjects currently has an active infection
8) Subject has, in the opinion of the Investigator, a medical comorbidity that contraindicates placement of an active medical device
9) Subject has participated in another clinical trial within 30 days
10) Subject has a coagulation disorder or uses anticoagulants that, in the opinion of the investigator, precludes participation
11) Subject has been diagnosed with cancer in the past 2 years

4.4 Sample size calculation

[redacted]

5. TREATMENT OF SUBJECTS

5.1 Treatment

The *Physician Implant Manual* provides a detailed description of the implant and surgical technique. Following informed consent and baseline measurements, subjects will begin phase one of a two-phase treatment process. Phase 1 is the Trial Phase and consists of percutaneously implanting neurostimulator leads into the epidural space and attaching them to an external neurostimulator. This system is then “trialed” during the TNS procedure and if needed up to a maximum of 30 days. If the subject experiences sufficient pain relief overall or in their primary area of pain being treated during the trial phase, they will progress to Phase 2, the implantation phase. In this phase, the implanted leads will be connected to a fully implantable neurostimulator. The entire system is then implanted under the skin for the

duration of device use. As a result of the device design, the therapy is fully reversible and can be removed through a similar minor procedure.

5.2 Use of co-intervention

Subjects will be allowed to continue using medication for the treatment of their pain condition. The prescription of medication for pain will be dictated by the Principle Investigators and/or sub-investigator as per standard of care.

6. DESCRIPTION OF THE DEVICE

6.1 Name and description of Axium® Neurostimulator System

On 16 November 2011, BSI granted Spinal Modulation, Inc. CE mark for the Axium® Neurostimulator System for the Management of Chronic Intractable Pain (CE 567069). The system has been registered with the CIBG in the Netherlands on 24 November 2011.

The Spinal Modulation Axium® Neurostimulator System consists of the following components:

- Trial NeuroStimulator (TNS)
- Implantable NeuroStimulator (INS)
- Trial Lead Kit
- Implant Lead Kit
- Connector Cable Kit
- Tunnelling Tool Kit
- Clinical Programmer
- Patient Programmer
- Auxiliary Magnet Kit
- Programmer Charger Kit
- Programmer Carrying case
- Lead Accessories Kit
- 22 cm Small Curve Delivery Sheath Kit
- 22 cm Big Curve Delivery Sheath Kit
- Lead Extension Kit

A detailed description of the components can be found in the physician implant manual.

Briefly, the Axium® Neurostimulator System is a fully implantable medical device designed to aid in the management of intractable chronic pain. The device, which is surgically placed in a similar fashion to other approved spinal cord stimulator systems, produces controlled electrical stimulation to spinal neural tissue. A minimally invasive procedure, similar to that used by other approved spinal cord stimulator systems is used to place the device in the body. Also similar to approved spinal cord stimulator systems, individuals first undergo a trial phase in which they can test the effects of the stimulation. If they wish to continue with the therapy they will receive a fully implantable system. The implantable system is reversible in that it can be explanted at any time.

6.2 Summary of known and potential risks and benefits

A summary of the known and potential risks and benefits can be found in the accompanying manuals that are included in the package of the components. The general risks associated with the Axium® Neurostimulator System are similar to those associated with other currently approved Spinal Cord Stimulator systems. Possible risks to the subjects include both device and procedural based risks. The most common side effects and risks are:

- Pain (where the needle is to be inserted)
- Pain caused by understimulation due to lead migration
- Pain over the implantable neurostimulator site (only applicable in Phase 2)
- Escalating pain
- Bleeding (where the needle has been inserted)
- Headache
- Infection
- Localized collection of serous (clear) fluid at injection site
- Discomfort during the treatment
- Allergic or rejection response to implant materials
- Constant pain at the lead site
- Stimulation of the chest wall
- Lead migration (movement) and/or local skin breakage
- Weakness
- Clumsiness
- Numbness
- Temporary muscle activation

Very rare risks and side effects include:

- Cerebral Spinal Fluid (CSF) leakage
- Tissue damage
- Nerve damage
- Spinal cord compression
- Paralysis
- Hematoma
- Seroma
- Sensory loss
- Skin erosion around the INS or leads
- Battery failure and/or battery leakage
- Lead breakage requiring replacement of the lead
- Hardware malfunction requiring replacement of the neurostimulator
- Pain from a non-injurious stimulus to the skin (allodynia)
- An exaggerated sense of pain (hyperesthesia)

6.3 Device utilization

A detailed description of device utilization can be found in the Physican Implant Manual. All investigators involved in the study have been trained on the use of the Axium® Neurostimulator System.

6.4 Devices

The devices that will be used in the prospective trial have CE mark, are commercially available products and will be bought and paid for according to the standard hospital system. A label of the products used will be added to the patient files to document and identify the devices.

7. METHODS

7.1 Assessments

During the scheduled follow-ups the following assessments will be performed. Table 1 in appendix A gives a detailed description of the assessments per follow-up.

- Pain relief (VAS)
- [redacted]

7.2 Randomisation, blinding and treatment allocation

As this is a single-arm study, no randomisation or blinding will occur.

7.3 Study procedures

During the prospective trial, data will be collected on Case Report Forms (CRFs). A copy of the CRFs will be provided for review.

Subject Screening and baseline

Subjects presenting with chronic pain for at least 6 months will be screened for possible entry into the prospective trial. Subjects will be screened according to the Inclusion/Exclusion criteria and only subjects meeting all Inclusion criteria and none of the Exclusion criteria will be enrolled. The prospective trial will be explained to all subjects and subjects will provide informed consent with an REC-approved Informed Consent Form prior to any data collection. Subjects will be allowed to discuss their participation in the trial with the study physician, clinical staff, family, friends and personal or external physician.

Following subject screening and acquisition of Informed Consent, subjects will undergo a baseline assessment to collect clinical data prior to lead implantation and stimulation. Baseline pain scores (VAS) will be evaluated using the average score from a 4 day pain dairy completed by subjects before their trial procedure. Women of child bearing potential will take an HCG-based pregnancy test to confirm that they are not pregnant prior to entry into the trial.

Trial Stimulation Lead Implant Procedure

Following collection of baseline measurements, subjects will begin Phase 1 of the two-step treatment process. Phase 1 is the Trial Phase and consists of percutaneously implanting quadrapolar neurostimulator leads into the epidural space. The techniques used in implanting the Spinal Modulation Neurostimulator System are consistent with standard of care practices used by other approved spinal cord stimulator systems. The *Physician Implant Manual* provides a detailed description of the implant and surgical technique. Perioperative programming will be performed to verify proper lead placement.

End of Trial Phase

At the end of the Trial Phase, pain relief will be assessed to determine whether a subject should receive an INS implant. This may be done in the theatre during the TNS procedure or after an extended trial period of no more than 30 days based upon the type of pain, the location of the pain, and the standard procedures at the hospital.

INS Implant Procedure

Eligible subjects willing to continue with the implant will undergo surgery to insert the fully implantable neurostimulator (INS). If the epidural leads were removed during the trial period, new leads will also be implanted at this time (see *Physician Implant Manual* for detailed information regarding the procedure). Each subject will receive a hand-held Patient Programmer that can be used to adjust stimulation amplitude as needed throughout the study duration.

Post-implant programming to adjust stimulation settings will occur either immediately after the surgery or the day following implantation.

Regular Follow-ups

Subjects will be followed according to the follow-up schedule for 24-months following implant at regular intervals according to standard clinical practice: 1-week (±5 days), 4 weeks (±1 week), 3 month (±2 weeks), 6 month (±2 weeks), 12 months (±2 weeks) and 24 months (±2 weeks). The given time-windows are advisable and therefore visits outside the time windows will not be seen as a protocol deviation. If desired, the Investigators may call the subjects for evaluation at 8-weeks, 9-months and 18 months post-implant.

Prior to completing the required assessments, the subject will have his/her stimulator reprogrammed if needed.

24-month follow-up (Study Exit)

The study will end 24 months following INS implantation. At this visit, the regular follow-up assessments as outlined in appendix A will be acquired and a trial exit form will be completed

Following completion of the study, subjects will continue to use the Axium® Neurostimulator System. They will be monitored by their physician as needed in accordance with standard clinical practice.

Interim Programming/Revision/Replacement/Explant (if necessary)

During the course of the trial, subjects will have the option to return to the study site at any time to have their neurostimulator re-programmed to achieve maximal benefit. If any part of the Axium® Neurostimulator System becomes dysfunctional or requires adjustment following implantation, it is up to the investigator to perform an interim visit. In appendix A, the assessments are listed for an interim visit and a revision (if applicable).

7.4 Withdrawal of individual subjects

Subjects can leave the trial at any time for any reason without any consequences. The investigator can decide to withdraw a subject from the trial for urgent medical reasons.

7.5 Replacement of individual subjects after withdrawal

Subjects that are withdrawn during the trial will not be replaced.

7.6 Follow-up of subjects withdrawn from treatment

Subjects will continue to receive normal, standard clinical care by the study physician.

7.7 Premature termination of the study

The Prospective Trial will be terminated prematurely if the Investigators or REC feel there is a risk to the subjects enrolled. Subject safety will continue to be monitored by the Investigators for the duration of the device.

8. SAFETY REPORTING

8.1 Applicable laws and regulations

For the reporting of events in this study, we will follow applicable international standards and guidance documents for CE marked products (AIMDD, MEDDEV 2.12/2 rev2 and MEDDEV 2.12-1 rev 8), the applicable local laws and regulations, and the SMI internal operating procedures on complaint reporting (OP #058), whichever is the most stringent.
In this regard we will only report device related AE/SAEs and any unanticipated SAE's.

Additionally, all reported events will be reviewed internally at Spinal Modulation Inc. according to the criteria for incidents to be reported by manufacturers to competent authorities, as defined in section 5.1.1 in the MEDDDEV 2.12-1 Rev 8.

8.2 Definitions

We will use the ISO14155:2011 as reference for the definitions of events.

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

Serious Adverse Event (SAE):

Any AE that led to:

- death
- 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 body function, or
  - in-patient or prolonged hospitalisation, or
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or body function
- foetal distress, foetal death or a congenital abnormality or birth defect

Planned hospitalization for a pre-existing condition, prolonged hospitalization as a result of a revision procedure, which is allowed in the protocol or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

Unanticipated:

An event which by nature, incidence, severity or outcome has not been identified in section 6.2 of this protocol.

8.3 Reporting timelines

All reportable events shall be documented in a timely manner throughout the trial by entering the required information into the appropriate CRF, provided to the site by the sponsor. The completed AE and/or SAEs CRF can be sent to the assigned person within Spinal Modulation (carin@spinalmodulation.com).

Spinal Modulation will forward all reported SAEs to the Chief Investigator for review, as required in section 8.2 of the “after Ethical review-guidance for Sponsors and Investigators”.

8.4 Follow-up of adverse events

All reported events will be followed until they have abated, or until a stable situation has been reached, unless the subject is lost to follow-up.

8.5 Independent Safety Officer

The (S)AE data will be evaluated by an independent safety officer.

9. STATISTICAL ANALYSIS

9.1 Descriptive statistics

[redacted]

9.2 Analysis

[redacted]

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The current prospective Trial will adhere to the ethical principles of the Declaration of Helsinki (2008) and will use the ISO 14155-2011, the MEDDEV 2.12/2 rev 2, as well as standards set forth in GCP/ICH guidelines according to US 21 CFR, Part 50 as guidelines.

10.2 Recruitment and consent

All proposed subjects will be recruited for this study once the Research Ethical committee has approved the prospective trial. Potential subjects will be identified from the investigator's patient population already selected for DRG stimulation and will be informed about the purpose, nature, and duration of the trial. Interested volunteer subjects will then have the protocol, the treatment, the follow-up regimen, and the risks and benefits fully explained to them by the investigator. The potential subject will be given as much time as needed (minimum 24 hours) to read the consent form and have the study procedures and alternative therapies discussed prior to signing the Informed Consent form. Subjects will not be asked to sign the Informed Consent form until the study has been fully-approved by the institution's REC and the Sponsor has received and reviewed the specific REC-approved Informed Consent form to be used by the site. An example of the Informed Consent form and patient information letter is provided. The consent form must be read by the subject, the subject's questions answered, and the form signed by the subject before treatment can be performed. All subjects will receive copies of their signed informed consent documents.

10.3 Benefits and risks assessment

The benefits of this trial could enable improved treatment of chronic, intractable pain, while the potential risks are similar to currently-used spinal cord stimulation systems which are generally minor. Feedback from this study will help inform future device designs that may benefit subjects who suffer from chronic intractable pain.

There are no additional risks with participation in this prospective trial. The implantation of the system is a standard clinical procedure in the hospital and the additional data that will be collected consists of assessments on pain relief, quality of life and subject satisfaction in the form of questionnaires.

Careful monitoring of subjects will ensure that any potential side-effects or adverse events are noticed and treated as quickly as possible. Reporting of adverse events will adhere to local regulatory requirements

10.4 Compensation for injury

The sponsor/investigator has liability insurance. This liability insurance provides cover for damage to subjects through injury or death caused by the use of the device. As this trial represents no risk to the subject (see section 10.3), no additional trial insurance is deemed necessary.

10.5 Compensation

Subjects that participate in the trial will be compensated for travel expenses in association with their participation in the trial. Subjects will not be provided compensation above and beyond reasonable travel expenses.

11. ADMINISTRATIVE ASPECTS AND PUBLICATION

11.1 Handling and storage of data and documents

The Sponsor and their designated representatives will make every reasonable effort to protect the confidentiality of the subjects participating in the trial. Except as required by law, subjects will not be identified by name, social security number, address, telephone number, or any other direct personal identifier. A unique identification code will be assigned to each subject participating in this trial. Information about the code will be kept in a secure location. All subject data will be stored in locked offices. All electronic data will be password-protected on computers stored in locked offices. Access to subject information will be limited to study personnel only. Any data, including photographs, videos, and interviews with the subject that may be published in abstracts, scientific journals, marketing material or presented at medical meetings will reference a unique subject code and will not reveal the subject's identity without the express approval of the subject. Subjects will be asked for approval at the start of the trial as part of the patient informed consent. It is possible that subject personal health records may be disclosed to other agencies such as regulatory bodies as per country regulations.

[redacted]

11.2 Amendments

Amendments are changes made to the prospective trial after approval by the accredited REC. The REC will be notified of all substantial amendments to the protocol. The REC will not be notified of non-substantial amendments.

11.3 Annual progress report

[redacted]

11.4 End of study report

[redacted]

11.5 Public disclosure and publication policy

Per national guidelines (where applicable) and medical journal editorial board guidelines, the prospective trial will be registered with a public clinical trial registry. Publication of the data collected during this trial will be in accordance with clinical trial agreements. The Institution and the principal Investigators involved in the trial have the right to publish the methods, results of, and conclusions from, the trial, subject to this clause and in accordance with copyright law. [redacted]

[redacted]

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