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NCT Number: NCT02335229
NL Post Surgical
A Post Market Study to Assess the Spinal Modulation Dorsal Root Ganglion Stimulator System in Chronic Post Surgical Pain
Study Document No: 20-SMI-2013
Version 2.0
Date: 24-May-2013

Sponsor

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A Post Market Observational Cohort Study to Assess the Performance of the Spinal Modulation Dorsal Root Ganglion Neurostimulator System for the Management of Chronic Post Surgical Pain

Protocol 20-SMI-2013

Spinal Modulation
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A Post Market Observational Cohort Study to Assess the Performance of the Spinal Modulation Dorsal Root Ganglion Neurostimulator System for the Management of Chronic Post Surgical Pain

Protocol ID	**20-SMI-2013**
Short title	**Performance of the Spinal Modulation DRG Neurostimulator System**
Version	**Version 2.0**
Date	**24 May 2013**
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PROTOCOL SIGNATURE SHEET

Name	Signature	Date
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Principal Investigator: **Professor M.W. Hollmann**		

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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	Case Report 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 Neuro Stimulator
ISO	International Organisation for standardisation
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 Neuro Stimulator
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. Following the requirements of the AIMDD, Spinal Modulation will also collect clinical data on the commercially available Neurostimulator System.

Objective: The purpose of this Post Market Observational Cohort Study is to evaluate the commercially available Spinal Modulation DRG Neurostimulator system, in the management of chronic post-surgical pain, in patients whom are routinely scheduled to receive a Spinal Modulation Neurostimulator system.

Study design: This is a prospective, single-arm, multi -centre, post market observational cohort study to collect data on pain relief, quality of life, physical functioning, subject safety, and subject satisfaction.

Device: Commercially available Spinal Modulation DRG Neurostimulator System for the management of chronic intractable pain (CE 567069).

Study population: Males and females of at least 18 years of age, suffering from chronic post surgical pain for at least 6 months, whom are routinely scheduled to receive a commercially available Spinal Modulation DRG Neurostimulator System.

Intervention: For the post market observational cohort study, the subjects will be asked to complete the standard evaluation questionnaires at baseline. Under monitored anaesthesia care, subjects will undergo minimally invasive placement of leads in the lateral epidural space of the neural foramen, following standard procedures. Subjects who have a successful trial will be implanted with the internal neurostimulator (INS) and will be followed for 24 months. They will be asked to complete questionnaires at the follow-up visits as per standard follow-up neuromodulation care in the Netherlands.

Follow-up visits: The patients will visit the hospital for the following standard follow-up (FU) visits: Baseline, Trial NeuroStimulator procedure, End of Trial, INS implant, 1 week, 1, 3, 6, 12 and 24 months post-operatively. If necessary, the site may contact the patients telephonically at 8 weeks, 9 months and 18 months FU.

Risks: There are no additional risks or burdens to the patients participating in this post market observational cohort study. The implantation of the system and collection of follow up data is a standard procedure in dedicated neuromodulation Pain Clinics in The Netherlands. The data collected consists of standard questionnaires on pain relief, quality of life, physical functioning, subject safety and subject satisfaction.

1 INTRODUCTION AND RATIONALE

History

Neuromodulation for the treatment of chronic pain has been used for over a century[1]. The first use of electricity in the spine for neuromodulation of pain was conducted by Norm Shealy in 1967[2]. 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.

Spinal Neuromodulation

Several recent systematic reviews have provided evidence that stimulation technology is a safe and effective treatment option for patients suffering from chronic, intractable pain[3-5]. The rate of serious complications is relatively low[3-5]. The treatment has been found to be successful in approximately 50% of patients that have a positive 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 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.

Therapy Description

The Spinal Modulation Dorsal Root Ganglion Neuromodulation 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 patients experience sufficient pain relief during this trial stimulation, they will receive an Implantable NeuroStimulatior (INS) system (phase 2).

Rationale

The use of electrical neuromodulation techniques in the successful treatment of various pain conditions is a proven therapy. Research into the role of the DRG in the development and maintenance of chronic pain has led to the development of an electrical neurostimulator system which specifically targets the DRG. This protocol describes a post market observational cohort study to collect the outcome data of the new commercially available Spinal Modulation DRG Neurostimulator System.

This post market observational cohort study is set up to collect prospective data on the performance of the commercially available Spinal Modulation DRG Neurostimulator system in subjects routinely scheduled to receive this system for the management of chronic post-surgical pain.

2 OBJECTIVES

The objective for this multi-centre post market observational cohort study is to assess the performance of the commercially available Spinal Modulation DRG Neurostimulator System in the management of chronic post-surgical pain. The performance will be measured using the following assessments:

Primary Objective:

- Pain relief measured using a Visual Analogue Scale (VAS).

Secondary Objectives:

- Quality of life (EQ-5D)
- Physical functioning (BPI)
- Pain distribution
- Paraesthesia distribution
- Sleep quality
- Subject satisfaction
- Device safety by monitoring
- Device settings and procedural data

3 STUDY DESIGN

This study is a prospective, single-arm, multi-centre post market observational cohort study, designed to assess the clinical effects of the commercially available Spinal Modulation DRG Neurostimulator System, in the management of chronic post-surgical pain. Subjects that are routinely scheduled to receive DRG stimulation will be asked to participate in this observational cohort study. They will be screened based upon the standard inclusion and exclusion criteria for neuromodulation in The Netherlands. Informed Consent will be obtained and they will then be enrolled into the cohort. Baseline parameters will then be measured in subjects using standard questionnaires and according to standard neuromodulation practice.

The study consists of two distinct phases in which the patients are asked to complete questionnaires, corresponding to the two-phase treatment process: 1) Temporary Trial Stimulation, and, 2) Implantable Stimulation (Figure 1).
Subjects will “trial” an external neurostimulator system for a period of time in line with standard hospital practices but no longer than 30 days (phase 1). If subjects experience sufficient pain relief in their primary area of pain, according to current neuromodulation guidelines, they will be eligible to proceed with the second phase of the treatment. If the

eligible subjects agree to move forward into Phase 2, they will undergo another surgical procedure in which the Spinal Modulation implantable Neurostimulator will be implanted. 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 telephonically for a follow-up at 8 weeks, 9 months and 18 months if desired (optional).

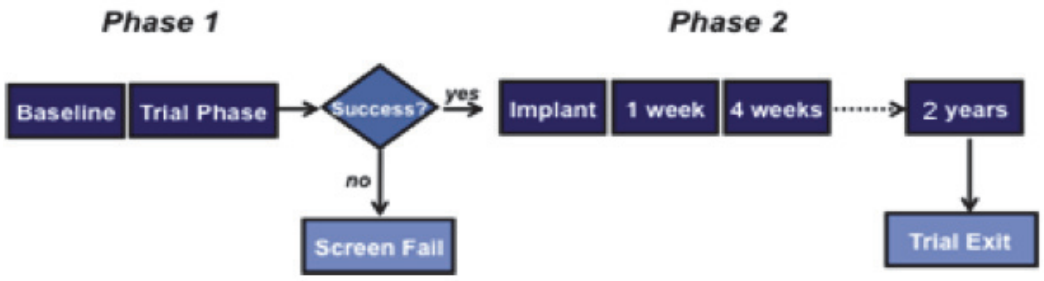

Figure 1. Basic design and follow-up schedule for subjects enrolled into the post-market observational cohort study. Subjects who have consented and been enrolled will undergo a two-phase process for advancement through the cohort. A detailed follow-up scheduled can be found in the *Methods* section.

Protocol Phase 1 – Temporary Trial Neurostimulation

Following consent and entry into the post market observational cohort study, baseline parameters will be measured by means of the standard evaluation questionnaires used in The Netherlands

Protocol Phase 2 – Implantable Stimulation and Follow Up

If subjects experience sufficient pain relief in their primary area of pain during the TNS procedure or during the course of the trial phase, they will be eligible for INS implantation. Subjects will be followed for 24 months following implant, returning to the clinic at regular follow-up intervals (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 or for other reasons. This can be captured as an interim visit. The site may contact the patients by phone at 8 weeks, 9 months and 18 months for follow-up (optional).

4 STUDY POPULATION

4.1 Population

30 male and female subjects, (minimum age 18 years old) suffering from chronic post-surgical pain, for a minimum of 6 months, whom are routinely scheduled for a DRG stimulation will be recruited by the study site and Investigators for inclusion in the cohort.

Subjects must meet all of the inclusion and none of the exclusion criteria to be enrolled in the post market observational cohort study. Subjects will read and sign an informed consent prior to the treatment. Subjects will be recruited from the site's 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 post surgical 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) Minimum baseline pain rating of 60 mm on the VAS in the primary region of pain
6) Subject is able to provide written informed consent
7) Pain medication dosage has been stable for at least 30 days
8) Patient has been included for implantation according to standard criteria from the Dutch Neuromodulation Society

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 with indwelling devices that may pose an increased risk of infection

8) Subjects currently has an active infection
9) Subject has participated in another clinical investigation 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.
12) Patient has no other exclusion criteria according to standard criteria from the Dutch Neuromodulation Society

4.4 Sample size calculation

As this is a post market observational cohort study, no sample size calculations are necessary. We aim to enrol 30 subjects in this cohort.

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 connecting them to an external neurostimulator. This system is then “trialed” for a period of time not to exceed 30 days. If the subject achieves sufficient pain relief in their primary area of pain according to Dutch Neuromodulation criteria during the trial phase, they will progress to Phase 2, the implantation phase. In this phase, the implanted leads will be connected to an implantable neurostimulator. The entire system is implanted under the skin for the duration of device use. The therapy is fully reversible and the leads and device can be removed through a similar procedure.

5.2 Use of co-intervention

Subjects may continue using medication for the treatment of their pain condition. The prescription of medication for pain will be dictated by the Pain Specialist according to standard care.

6 Description of the Device

6.1 Name and description of Neurostimulator System

The Spinal Modulation Neurostimulator System consists of the following components:

- Trial Neurostimulator
- Implantable Neurostimulator
- Trial Lead Kit
- Implant Lead Kit
- Connector Cable Kit
- Tunneling Tool Kit
- Clinical Programmer
- Patient Programmer
- Auxillary 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.

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

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 packaging of the components. The general risks associated with the Spinal Modulation DRG 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
- Swelling
- 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 Spinal Modulation DRG Neurostimulator System and already have experience in the use of the commercially available products.

6.4 Devices

The devices that will be used in the post market observational cohort study are commercially available products and will be bought and paid for according to the standard hospital system. Serial and lot numbers 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 measurements will be performed. Table 1 in appendix A gives a detailed description of the measurements per follow-up.

- Pain relief (VAS)
- Quality of life (EQ-5D)
- Physical functioning (BPI)
- Pain distribution
- Paresthesia Distribution
- Sleep quality
- Subject satisfaction
- Device safety
- Device settings and procedural information

7.2 Randomisation, blinding and treatment allocation

As this is an observational study, no randomisation or blinding will occur. All subjects will be receiving the Spinal Modulation DRG Neurostimulator System and data will be collected at each follow-up time point.

7.3 Study procedures

During the post market observational cohort study, 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 post-surgical pain for at least 6 months will be screened for possible entry into the post market observational cohort study. 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 post market observational cohort study will be explained to all subjects and subjects will provide informed consent prior to any data collection for the study. Subjects will be allowed to discuss their participation in the cohort 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.

Trial Stimulation Lead Implant Procedure

Following collection of baseline measurements, subjects will begin Phase 1 of the two-step treatment process.

End of TNS Trial Phase

At the end of the Trial Phase, pain relief will be assessed to determine whether a subject should receive an INS implant. The duration of the trial will be at the investigators discretion and in line with current clinical practice. This may be done in the theatre during the TNS procedure or after an extended trial period but should be no longer than 30 days.

INS Implant Procedure

Eligible subjects willing to continue with the implant will undergo surgery to implant the internal neurostimulator (INS). If the subdural leads are 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.

Regular Follow-ups

Subjects will be followed according to the standard follow-up schedule for 24-months following implant at regular intervals: 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 contact the subjects telephonically for evaluations at 8-weeks, 9-months and 18 months post-implant.

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

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 Spinal Modulation DRG Neurostimulator System. They will be monitored by their physician in accordance with standard medical procedures.

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

During the course of the cohort, 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 Spinal Modulation Neurostimulator System becomes dysfunctional or requires adjustment following implantation, the patient will come to the site for analysis of the problem (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 study at any time for any reason without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.5 Replacement of individual subjects after withdrawal

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

7.6 Follow-up of subjects withdrawn from treatment

Any patient leaving the study will receive standard follow-up care in accordance with the criteria of the Dutch Neuromodulation Society.

7.7 Premature termination of the study

The Post Market Observational Cohort Study will be terminated prematurely if the Investigators 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 local laws and regulations

All AEs and SAEs will be reported according to the applicable local laws and regulations for CE marked products

8.2 Adverse and serious adverse events

Adverse events are defined as any undesirable experience occurring in a subject during the study, whether or not considered to be related to the Spinal Modulation DRG Neurostimulator System. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

Adverse events related to the commercially available Spinal Modulation DRG Neuromodulation System will be reported to Spinal Modulation representatives and handled according to the Spinal Modulation internal vigilance regulations for CE marked products.

Clinical study staff will start assessing subjects for adverse events (AEs) once the Informed Consent form has been signed and at each visit thereafter. They will be instructed to request AE information in a nonspecific, non-suggestive manner. Investigators will report all AEs regardless of causality.

Serious Adverse Events (SAE):

A serious adverse event is any untoward medical occurrence or effect that:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event in the cohort likely to affect the safety of the other study subjects, such as an unexpected outcome of an adverse reaction, major safety finding from a newly completed animal study, etc.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

For the purposes of this study the following events will not be reported as serious adverse events due to the nature of the treatment.

- Prolonged hospitalization as a result of a revision procedure, which is allowed in the protocol.
- Hospitalization as a result of or in conjunction with treatment that is part of the subject's conventional medical management.

All SAEs must be reported within 24 hours of the investigational site's knowledge of the occurrence by entering the required information into the appropriate CRF.

The following SAE information will be provided as available:

- Patient ID;
- SAE term, onset date, severity, and causal relationship;
- Basic demographic information (e.g., age, gender, etc.);
- The outcome(s) attributable to the event (death, life-threatening, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect or other important medical event(s));
- A summary of relevant test results, pertinent laboratory data, and any other relevant medical history;

- Date study device was implanted;
- Supplemental information may include, but may not be limited to, the following records: laboratory results, progress notes, admission and emergency room notes, discharge summaries, autopsy reports, death certificates, etc.

The Investigator will report all SAEs in accordance with the regulatory reporting requirements. Documentation will be provided to the sponsor.

For each AE or SAE the following information will be recorded on the appropriate CRF:

- Name of event: The Investigator should use standard medical terminology that clearly describes the pathophysiology of the event and identifies the body system affected.
- Onset date: Date that the AE was first experienced at the reported severity and frequency.
- Resolution date: Date that the AE was last experienced or was completely resolved. In the case of an AE that changes in severity or frequency, the resolution of the AE is the date it was last experienced at the previously reported severity.
- Severity: All AEs will be graded according to the following:
    - Mild, easily tolerated by the subject, causing minimal discomfort and not interfering with every day activities;
    - Moderate, sufficiently discomforting to interfere with normal every day activities;
    - Severe, prevents normal, everyday activities; Life threatening, places the subject in immediate risk of death
- Relationship to study device: All AEs will have a study device causality assessment performed at the time of reporting the event to document the Investigator's perception of causality. As stated in the ISO standards, adverse events classified as device-related should involve one of the following:
    - Insufficient or inadequate instructions for use
    - Deployment of the device
    - Implantation of the device
    - Operation of the device
    - Malfunction of the device
    - Misuse of the device

If the Investigator feels the AE is related to the implant procedure and related or possibly related to the device, he/she should assign causality to either “Related to the Device” or “Possibly related to the Device.”

Unexpected Adverse Device Event (UADE)

Unexpected adverse reactions are adverse events, of which the nature, or severity, is not consistent with the applicable product information (e.g. *IFU*).

UADEs will be reported to regulatory authorities as is outlined and required by law. Expedited reporting will occur in the timeframes that regulatory authority deems appropriate.

8.3 Follow-up of adverse events

All adverse events determined to be device related will be followed until they have abated, or until a stable situation has been reached. All AEs determined to not be device related with be followed through the end of the study. All SAEs, regardless of the relationship to the device will be followed until resolution or stabilization unless the subject is lost to follow-up. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

8.4 Data Safety Monitoring Board (DSMB)

We will not have a DSMB for this study.

9 STATISTICAL ANALYSIS

9.1 Descriptive statistics

Descriptive statistics will be used to evaluate the means and standard deviations of data collected as well as to compute the changes in the outcomes compared to baseline.

9.2 Analysis

Univariate, multivariate and covariate statistical analyses will be conducted as appropriate to statistically tests for both primary and secondary outcomes. Statistical analyses will be conducted utilizing SAS and/or SPSS statistical software. *Post-hoc* power analyses will also accompany the omnibus testing and *post-hoc* analyses determining differences

between baseline and treatment means. All levels of significance will be deemed to occur at $p<0.05$.

10 ETHICAL CONSIDERATIONS

10.1 Regulation statement

The current Post Market Cohort will adhere to the ethical principles of the Declaration of Helsinki (2008) and will use the Medical Research Involving Human Subjects Act (WMO), 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 ethics committee has confirmed that the Medical Research involving Human Subjects Act (WMO) does not apply to this Post Market Observational Cohort Study and that an official approval of this study is not required. Potential subjects will be identified from the investigator's patient population and will be informed about the purpose, nature, and duration of the cohort. 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 to read the consent form and have the study procedures and alternative therapies discussed prior to signing the Informed Consent form.. 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 cohort 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 be part of future device designs that may benefit subjects who suffer from chronic intractable pain.

There are no additional risks to participation in this post market observational cohort study. The implantation of the system is a standard procedure in the hospital and the data that is collected consists of standard questionnaires regarding pain relief, quality of life and subject satisfaction that are normally measured according to the criteria of the Dutch Neuromodulation Society.

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 applicable regulatory requirements

10.4 Compensation for injury

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

10.5 Compensation

Subjects that participate in the cohort will be compensated for additional travel expenses which would not have been incurred had they not been part of this study. 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 cohort. 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 cohort. Information regarding 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 cohort 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.

Data storage will reside at both the clinical research site, any contract agent acting on behalf of the sponsor, and at the Sponsor Company, Spinal Modulation. Sites will retain data collected during the post market observational cohort study for a minimum of 5 years. The sponsor will retain the data per Company Standard Operating Procedures.

11.2 Amendments

Amendments are changes made to the post market observational cohort study after confirmation by the METC that the Medical Research Involving Human Subjects Act (WMO) does not apply to this study. The METC will be notified of all substantial amendments to the protocol that will influence the WMO applicability. The METC will not be notified of non-substantial amendments.

11.3 Annual progress report

The sponsor/investigator will not submit a summary of the progress of the cohort to the METC as this is not a regulatory requirement.

11.4 End of study report

The Investigator will not provide a final report to the METC and other regulatory bodies, as this is not a regulatory requirement .

11.5 Public disclosure and publication policy

Per national guidelines (where applicable) and medical journal editorial board guidelines, the post market observational cohort study will be registered with a public clinical trial registry. The results will be published. Publication of the data collected during this cohort will be in accordance with clinical trial agreements. The Institution and the Principal Investigators involved in the cohort have the right to publish the methods, results of, and conclusions from, the cohort, subject to this clause and in accordance with copyright law. Each Discloser must ensure that it gives notice of any proposed publication drafted by it and/or other personnel involved in the conduct of the cohort to the Sponsor at least 30 days before any forwarding to a party that is not bound by the confidentiality obligations. The Sponsor may, within that 30-day period do any one or more of the following; Provide comments on the proposed publication to the relevant Discloser, in which case the Discloser must consider such comments but will not be bound to follow them; Request delay of publication for no more than 90 days to allow the Sponsor to file patent applications or take other measures to preserve its proprietary rights, in which case the Institution must abide by that request; In case there are differences in interpretation of the research results, both the vision of the Discloser and the sponsor need to be mentioned. Request that the Discloser remove specified Confidential Information (other than the results of the Study) from the publication, in which case the Institution must remove such specified Confidential Information as is reasonably required to protect the Intellectual Property of the Sponsor.

If the Discloser has not received any comments from the Sponsor on the proposed publication within 30 days of giving notice to the Sponsor, the Discloser may proceed to make the publication.

Where the Sponsor intends to publish the method, results, or conclusions from the cohort, any person named as an author on that publication or otherwise noted as the Principal Investigator or an investigator of the cohort; in the publication, will be given a reasonable opportunity to review the publication and request the removal of his or her name from the publication and the Sponsor shall comply with any such request.

In all publications the Sponsor's support of the cohort shall be acknowledged.

The Sponsor may publish a summary of the cohort results and conclusions on the Sponsor's on-line Clinical Trial Register before or after publication by another method.

The Sponsor may freely use, copy, and disseminate any manuscript following its publication in a journal without further obligation to the Disclosers.

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Appendix A: Table 1

Follow-up Schedule Post Market Cohort 20-SMI-2013

CRF #	Assessment	Baseline	TNS Procedure/Programming	End of TNS Trial	INS Implant/Programming	1-week F/U	4-week F/U	2-month F/U	3-month F/U	6-month F/U	9-month F/U	12-month F/U	18-month F/U	24-month F/U	Interim Visit	Revision
	Informed Consent Form	X														
CRF - 1	Inclusion / Exclusion Criteria	X														
CRF - 2	Medical History	X														
CRF - 5	Medication Utilization	X										X		X		
CRF - 6	Pain Distribution	X		X		X	X		X	X		X		X	X	
CRF - 7	Pain Measurement	X		X		X	X		X	X		X		X	X	
CRF - 8	HRQoL	X					X		X	X		X		X	X	
CRF - 9	Functional Assessment	X					X		X	X		X		X	X	
CRF - 10	Psychological Disposition	X					X		X	X		X		X	X	
CRF - 11	Procedural Evaluation		X		X											X
CRF - 15	Paresthesia Mapping			X		X	X		X	X		X		X		
CRF - 16	Programming				X	X	X		X	X		X		X		X
CRF - 33	Sleep Quality	X							X	X		X		X		
CRF - 19	Subject Satisfaction			X		X	X	X	X	X	X	X	X	X		
CRF - 17	AE Reporting	+	+	+	+	+	+		+	+		+		+	+	+
CRF - 18	SAE Reporting	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CRF - 25	Protocol Deviation	+	+	+	+	+	+		+	+		+		+	+	+
CRF - 14	Revision															X
CRF - 21	Trial Exit			+										X	+	+

Required = X
Only if needed = +