Clinical Protocol

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Protocol Title: NAPS (Non-awake versus Awake Placement of Spinal cord stimulators) Study for the evaluation of awake and non-awake methods of SCS paddle lead placement

Funding Sponsor: St. Jude Medical
6901 Preston Rd.
Plano, TX 75024

Coordinating Investigator: Steven Falowski, MD
St. Luke's Neurosurgical Associates
701 Ostrum St
Suite 302
Bethlehem, PA 18015
Office 484-526-6000
Fax 484-526-9410

Participating Investigators: Ashwini Sharan, MD
Thomas Jefferson University Hospital
Department of Neurosurgery
909 Walnut Street
2nd Floor
Philadelphia, PA 19107

Darren L. Jacobs, DO
Neurosurgery, Geisinger Medical Center
100 N Academy Ave
Danville, PA 17822

James McInerney, MD
Penn State Hershey Neurosurgery
Milton S. Hershey Medical Center
30 Hope Drive, Building B, Suite 1200
P.O. Box 859
Hershey, PA 17033

Approval Signatures:

Investigator _____ **Date** _____

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Confidentiality Statement

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Protocol Summary

Title:	NAPS (Non-Awake versus Awake Placement of Spinal cord stimulators) Study for the evaluation of awake and non-awake methods of SCS paddle lead placement
Study Devices:	Eon Mini™ or Eon™ neurostimulation system with the Penta™ paddle leads or the Lamitrode C-series™ paddle leads.
Objectives:	Determine whether non-awake placement of spinal cord stimulators with electromyography (EMG) neuromonitoring is comparable to awake placement for achieving paresthesia coverage in chronic pain patients. Determine whether non-awake placement reduces procedure time, risk for revision, risk for complications.
Patient Population:	Patients with successful spinal cord stimulator (SCS) trials presenting for permanent implantation of a paddle electrode in the thoracic region
Population Size:	Approximately 50
Structure:	The study is designed as a prospective, multicenter, parallel design, non-randomized, non-blinded, 6-month study.
Method of Assignment:	All patients who comply with the inclusion/exclusion criteria will be enrolled chronologically.
Randomization:	There will be no randomization of the patients. Patients recruited and enrolled at St. Luke's Neurological Associates or Thomas Jefferson University will undergo implantation under general anesthesia with EMG neuromonitoring for testing of the distribution of induced paresthesia ("non-awake"). Patients recruited and enrolled at Geisinger or Milton S. Hershey Medical Centers will undergo implantation of the device in an awake operation with local anesthetic and patient interaction for testing of the distribution of the induced paresthesia ("awake").
Statistical Analysis:	The primary endpoints will be procedure time, rates of adverse events, specifically lead revisions, and patient satisfaction. An additional endpoint will be the proportion of painful regions covered by paresthesia in non-awake compared to awake patients
Adverse Events	All device/procedure-related and all serious adverse events that occur and are volunteered by the patient and solicited by the site staff will be collected.

1. Introduction

Spinal cord stimulation (SCS) is an adjustable, non-destructive, therapy in which an electrical current is applied to the spinal cord for management of neuropathic pain. Leads are placed in the epidural space, which apply electrical stimulation to the spinal cord. It has been used for many years and has proven to be effective in the treatment of chronic, intractable pain including failed back surgery syndrome CRPS, phantom limb pain, cancer pain, peripheral vascular disease, and ischemic limb pain (Burchiel et al., 1996; Cameron, 2004; Kemler, de Vet, Barendse, van den Wildenberg, & van Kleef, 2008; Khan, Raza, & Khan, 2005; Turner, Loeser, Deyo, & Sanders, 2004).

The success of the therapy relies on the ability to create an overlap between the pain areas and the device-induced paresthesia. Lead placement has historically been done under awake conditions, using direct feedback from the patient in order to define adequate paresthesia coverage. The awake operation is performed while the patient is under local anesthesia, which is very stressful for the patient and predisposes them to movement. This can lead to decreased patient satisfaction, equipment migration, undesired stimulation effects, and treatment failure.

Implantation under general anesthesia using electromyography (EMG) responses to determine paresthesia coverage may offer advantages over the awake procedure. This "non-awake" technique is potentially more comfortable for the patient and may carry less risk for revision. Recently, several retrospective studies have found that the non-awake procedure is safe and at least as efficacious in producing adequate paresthesia coverage as the awake procedure (Air, Toczyl, & Mandybur, 2012; Falowski et al., 2011; Shils & Arle, 2012). Falowski et al. found that the non-awake procedure resulted in the same or fewer revisions as the awake procedure. Shils observed a 30 minutes (33%) reduction in procedure time.

These studies are promising, yet there is a need for a prospective study to determine the equivalency or benefit of the non-awake procedure. The purpose of the proposed clinical study is to collect data necessary to demonstrate the safety and efficacy of non-awake implantation of SCS paddle leads compared to the awake procedure. The study is designed to evaluate whether non-awake placement reduces procedure time, complication rates, and/or revision rates while offering comparable paresthesia coverage as the awake procedure.

2. Objectives/Endpoints

2.1. Primary Objective

To demonstrate the safety and efficacy of a non-awake implantation method (EMG neuromonitoring) of a SCS paddle lead as compared to an awake implantation method (with local anesthesia and patient feedback).

2.2. Secondary Objective

To demonstrate that implantation non-awake and awake methods result in comparable paresthesia coverage of painful regions.

2.3. Primary Variables

- Procedure time
- Number and type of adverse events
- Number of revisions

2.4. Secondary Variables

- Pain mapping and paresthesia coverage

2.5. Additional Data

- Demographics: gender, age, height, weight, ethnicity, marital status
- Pain history: primary diagnosis, pain duration, pain etiology, prior treatments
- Medication usage including rescue medication
- Pain quality as assessed by the Short-Form McGill Pain Questionnaire version 2
- Quality of life as assessed by EuroQol (EQ-5D) generic health index questionnaire
- Patient global impression of satisfaction with device implantation compared to trial system implantation.
- Surgery and device information
- Programming data
- Patient reported perception of pain relief.
- Responder classification for average daily overall pain. Responders are classified as patients with ≥30% or ≥50% reduction in pain.

3. Study Design

3.1. **Design**

This is a post-market, prospective, multicenter, parallel designed, non-randomized, non-blinded, 6-month study. A minimum of 50 patients will be implanted from up to 4 active sites, coordinated by a single lead investigator.

Patients who have had a successful SCS trial and are indicated for permanent implantation will be approached to participate in this study prior to permanent implantation. Patients will be recruited and enrolled by physicians at any one of the involved sites. Each Investigator will only use one method (awake or non-awake) according to his/her typical practice. Patients will receive treatment from their enrolling physician.

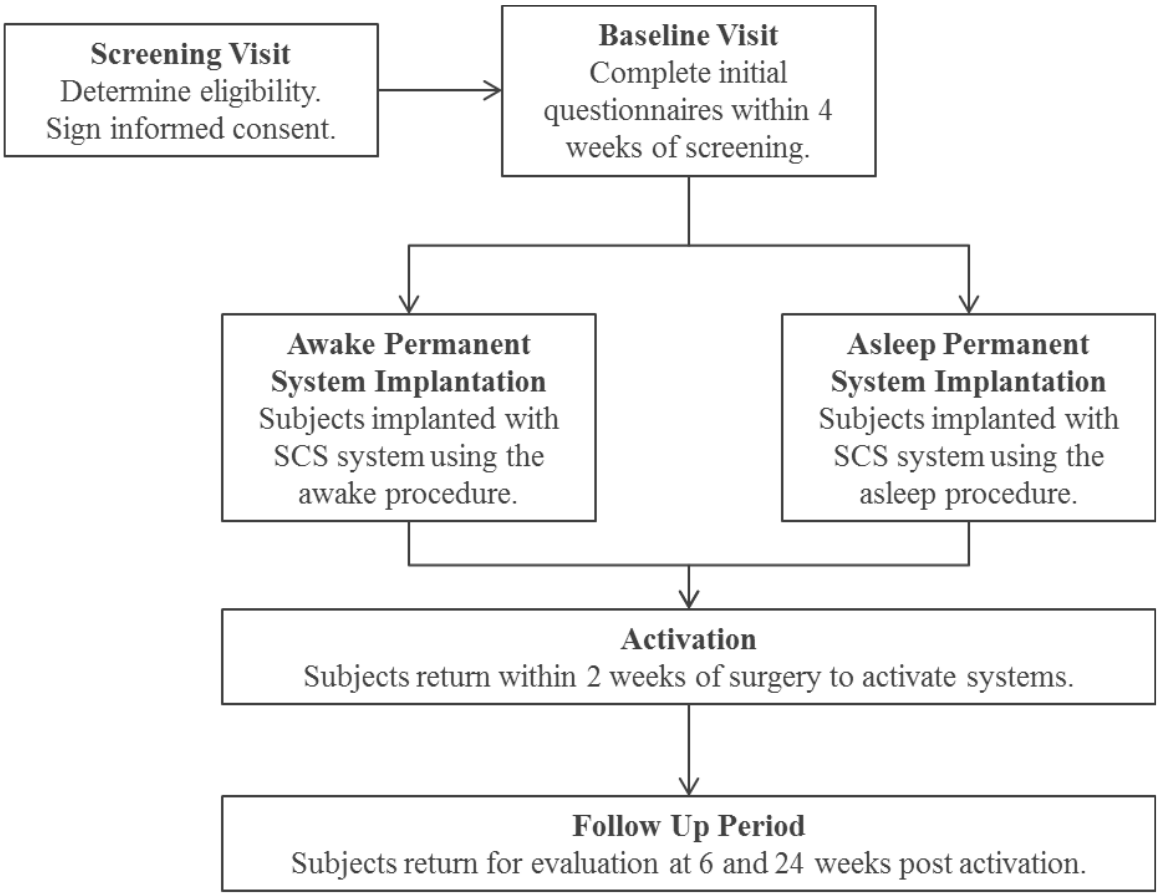

Table 1: Study Schedule

Timing of visit	Activities at visit	Case Report Forms
Screening and Informed Consent *(may be immediately after Trial System Explant)*	Patient evaluated for eligibility Patient signs informed consent Schedule patient for baseline evaluation at treatment site	Enrollment Form Inclusion/Exclusion Criteria Form
Baseline Evaluation *7-28 days after screening*	Patient completes questionnaires Complete history and physical exam Record current medication use Collect patient reported data	Baseline Self Evaluation Form Pain Location Form Pain Evaluation Form SF-MPQ-2 (Pain Quality) EQ-5D (Quality of life) Medication Form
Permanent System Implantation	Permanent system implantation Record any complications Record any changes in medication Discourage activation at discharge Save digital recording or EMG recording if system permits.	Surgery Form Adverse Event Form Programming Form (if programmed at discharge) Medication Form
Initial Programming Visit	Record any complications Record any changes in medication Provide patient with the patient programmer and charging system Record patient's global impression of satisfaction with the implant procedure.	Programming Form Paresthesia Coverage Form Patient Global Impression Form Medication Form
6 weeks *42± 7 days after activation*	Record any complications Record any changes in medication Patient completes questionnaires Modify programming parameters *(if necessary)* Collect patient reported data	Follow-up Visit Form Pain Evaluation Form Pain Location Form Programming Form SF-MPQ-2 (Pain Quality) EQ-5D (Quality of life) Paresthesia Coverage Form Medication Form
24 weeks *168 ± 14 days after activation*	Record any complications Record any changes in medication Patient completes questionnaires Modify programming parameters *(if necessary)* Collect patient reported data	Follow-up Visit Form Pain Evaluation Form Pain Location Form Programming Form SF-MPQ-2 (Pain Quality) EQ-5D (Quality of life) Paresthesia Coverage Form Medication Form
Unscheduled Visit (as needed)	Record any unscheduled visit Record any changes in medication Record any other health care utilized Record any complications	Unscheduled Visit Form Medication Form HCOR Form Adverse Event Form

Timing of visit	Activities at visit	Case Report Forms
	Record programming changes Record paresthesia changes	Product Out of Service Form Programming Form Paresthesia Location Form Additional Surgery Form Exit and Withdrawal form

3.2. **Justification for study given risks/benefit outcome**

Spinal Cord Stimulation is a commercially available neurostimulation therapy available for treatment of chronic intractable pain of the trunk and/or limbs to patients today. Traditionally, SCS leads are placed in the epidural space while the patient is awake and able to give direct feedback in order to ensure adequate paresthesia coverage. Using EMG for lead implantation will allow the patient to be placed under general anesthesia and to be potentially more comfortable than during the awake procedure. The purpose of the proposed clinical study is to collect data necessary to make a direct comparison between the awake procedure and the non-awake procedure using EMG.

The Investigator will review the subject's medical record to ensure that the subject complies with all inclusion/exclusion criteria. The target population consists of subjects indicated for a neurostimulation system. The present study will permit the physician to adhere to their standard of care for continued medication usage or any current treatment methods prior to enrollment.

The risks and benefits are the same for these two lead placement techniques since the implant procedure is the same. No additional adverse events from non-awake placement are anticipated. Considering the severity of chronic pain and its debilitating effect on patients' lives, spinal cord stimulation provides an alternative means of pain reduction with minimal risk for subjects who have exhausted other options.

4. Study Devices

All study devices are in commercial distribution in the United States and Europe as an aid in the management of chronic intractable pain of the trunk and/or limbs. St. Jude Medical (SJM) received FDA approval for the Eon Mini IPG system under the PMA P010032/S32 and Eon IPG system under the PMA P010032/S014. The Lamitrode leads received clearance under K990469 (standard), K053250 (90 and 110cm), K033429 (C-Series), K022222 (S-Series), K063080 (Tripole 8C, 16C, and Exclaim), K090907 (Penta) and K991784 (extensions).

Any SJM market-cleared IPG may be used. Any SJM market-cleared paddle lead may be used. Percutaneous leads may not be used.

The Eon Rechargeable Systems consists of the following components: Model 3716 and 3788, Rechargeable Implanted pulse generator (IPG), Model 3851 Patient Programmer, Programming Wand, Patient Magnet, and Charging System. The Eon Neurostimulation Systems are intended to be used with SJM's leads and extensions and their accessories currently on the market.

5. Patient Selection

5.1. Inclusion Criteria

Patients enrolled in this study must meet the following inclusion criteria:

1. Patient is able to provide informed consent to participate in the study
2. Patient is 18 years of age or older
3. Patient has had a successful trial system and is presenting for permanent implantation of a paddle electrode in thoracic region.
4. Patient is willing to cooperate with the study requirements including compliance with the treatment regimen and completion of all office visits

5.2. Exclusion Criteria

A patient will be excluded from participation in this study if they meet any one of the following criteria:

1. Patient currently participating in a clinical investigation that includes an active treatment arm.
2. Patient has an infusion pump or any implantable neurostimulation device
3. Patient has an existing medical condition that is likely to require repetitive MRI evaluation in the future (i.e. epilepsy, stroke, multiple sclerosis, acoustic neuroma, tumor)
4. Patient has an existing medical condition that is likely to require the use of diathermy in the future
5. Patient is immunocompromised
6. Patient has documented history of allergic response to titanium or silicone
7. Patient has a documented history of substance abuse (narcotics, alcohol, etc.) or substance dependency in the 6 months prior to baseline data collection
8. Female candidates of child bearing potential that are pregnant (confirmed by positive pregnancy test)

6. Patient Assignment to Procedure

Each patient who is willing to participate in the study, signs the informed consent, and complies with the inclusion/exclusion criteria will be enrolled in the study. Patients are considered enrolled in the study from the moment the patient has provided written informed consent. Each patient is enrolled chronologically on a patient enrollment log and given a patient number for the duration of the study.

Patients will be enrolled in a 1:1 fashion to the method of surgical implantation, either awake or non-awake. Patients will be treated by the enrolling physician. Patients recruited and enrolled at St. Luke's Neurological Associates or Thomas Jefferson University will undergo implantation under general anesthesia with EMG neuromonitoring for testing of the distribution of induced paresthesia ("non-awake"). Patients recruited and enrolled at Geisinger or Milton S. Hershey Medical Centers will undergo implantation of the device in an awake operation with local anesthetic and patient interaction for testing of the distribution of the induced paresthesia ("awake"). Each treatment arm will enroll a maximum of 30 patients. No blinding is necessary for the purposes of assigned study arm.

7. Methods and Procedures

7.1. Informed Consent

Written informed consent must be obtained from all patients before recruitment into the study. All potential patients must be properly informed as to the purpose of the study and the potential risks and benefits known or that can be reasonably predicted or expected. The Investigator will retain the original copy of the Informed Consent Form signed by the patient and a duplicate will be provided to the patient. Only the consent form approved by the applicable Institutional Review Board (IRB) must be used.

7.2. Screening

The patient is evaluated for eligibility according to the inclusion/exclusion criteria. This evaluation will include a report of medical history, current medication regimen, and completion of questionnaires. At the end of the study visit after the investigator has determined that the patient is eligible for participation, study staff (e.g. study coordinator) collect the following information:

- Enrollment form
- Inclusion/exclusion form

7.3. Randomization

Patients will not be randomized. .

7.4. Baseline Evaluation

Baseline measurements for the patient's back and leg pain symptoms and general well-being will be taken. This evaluation will include a report of medical history, current medication regimen, and completion of questionnaires. Baseline evaluations include the following activities:

- Collection of self-reported patient questionnaires:
  - Baseline self-evaluation form
  - Pain Location form
  - Pain Evaluation form
  - SF-MPQ-2 (Pain Quality)
  - EQ-5D (Quality of Life)
  - Medication Usage form

7.5. Medication Collection

Since certain non-pain medications have the ability to affect pain (e.g. certain antidepressants), we are collecting other medication usage outside of pain management medication. However, medications taken for common cold and allergies will not be recorded.

7.6. SCS Permanent System Implantation Guidelines

This section of the protocol provides a guideline for surgical implantation of the permanent system; however, implantation of the devices is performed at the discretion of the Investigator. The goal of the surgery is to enable coverage of the patient's entire

painful area with stimulation. Patients will be prepped for surgical paddle lead placement via laminectomy or laminotomy according to usual practice at each implanting center, including anesthesia and customary intraoperative monitoring. Initial lead placement is targeted anatomically based on patient-specific painful areas and trial lead experience.

7.6.1. Lead Placement for Awake Arm

Upon approximate lead positioning, the patient is brought to a conscious sedated state while maintaining local anesthetic. Stimulation of the spinal cord through the paddle lead is accomplished with an external pulse generator, while communicating with the patient regarding paresthesia coverage of painful regions. Upon satisfactory coverage, the IPG is implanted per 7.6.3 below.

7.6.2. Lead Placement for Non-awake Arm

The patient is maintained under general anesthesia for the full duration of the implant. Upon approximate lead positioning, bilateral EMG of myotomes overlapping dermatomal regions of pain are monitored. Stimulation is delivered through the lead by an external pulse generator in order to elicit compound muscle action potentials (CMAPs) in the target regions. Lead placement is targeted to have symmetric CMAPs (i.e. physiologic midline) and adequate coverage of the painful regions as described by Falowski et al. (Falowski et al., 2011). Upon satisfactory coverage, the IPG is implanted per 7.6.3 below.

7.6.3. Pulse Generator Placement and Data Collection for Both Arms

The IPG is implanted by making a pocket incision at the desired location, and creating a subcutaneous pocket by blunt dissection. The pocket should be created so that the IPG is parallel to the skin surface. Subcutaneous tunnels are made from the lead incision site(s) to the IPG implantation site, using a tunneling tool. The leads/extension is tunneled to the IPG site. The lead/extension is connected to the IPG, the IPG is placed in the subcutaneous pocket, and all incisions are closed.

Additional guidance on system placement is located in the device manuals distributed with each device.

System implantation visit include recording the following information:

- Device information
- Collection of complications or changes in medication
- Total operating room time
- Skin-to-skin surgical time
- Intraoperative programming time
- Total fluoroscopy used (time and dose)
- Final lead position

7.7. Postoperative Management and Instruction

The physician will provide normal standard of care after implantation of the system, including standard post-operative monitoring. Instructions for wound care and monitoring will be provided to the patient by the implanting physician. Patients will be informed to report any adverse events or changes in medication to study personnel. Patients will be informed not to manipulate the leads after implantation because tissue erosion may occur. The patient will be sent home for a 2-3 week recovery period to let any swelling and/or post-operative pain subside prior to activation of SCS system, unless otherwise

determined by the installing investigator. During this time, the device may not be activated and the patient may not be provided with the Patient Programmer. Prophylactic antibiotic therapy may be instituted at the discretion of the Investigator.

If the leads migrate during the study, the implanting physician will examine the area of implantation. The leads can be repositioned or re-implanted if mutually agreed upon by the physician and the patient. The patient and the implanting physician will make the mutual decision about any possible revision of the device based upon what is medically safe, what is desired by the patient, and what is in the patient's best medical interests.

If an infection occurs, standard medical practice suggests that the leads be removed and the patients undergo a standard course of oral antibiotics. Any infection or wound will be given time to heal before any re-implantation is attempted.

If the device is completely explanted from the study patient for any reason and re-implantation is not an option, then the patient will exit the study.

7.8. Device Activation

The permanent system device activation visit will occur approximately 2-3 weeks after permanent system implantation. At this visit, each patient will have their device programmed to comparable individualized programming parameters. All patients will receive a Patient Programmer that will enable him/her to activate the ON and OFF positions and adjust amplitude within the prescribed range.

A map of paresthesia coverage is collected along with final programmed parameters, lead impedance, and device data. Any changes in medications are noted as well.

7.8.1. Programming Parameters

The programming ranges are defined below to use as a guide for consistency in study programming. Ranges are provided due to differences in patient perception. Programming may vary in cases where coverage is difficult to obtain or the patient experiences uncomfortable stimulation.

- Patients will be stimulated at supra-sensory threshold levels using Spinal Cord Stimulation leads (i.e. leads placed in the epidural space). Typical parameter ranges are pulse width of 150-350 μs and frequency of 20-80 Hz. Amplitude will be programmed according to individual patient perception and comfort and to a level that produces paresthesia for the patient.
- Patient Global Impression Form

  Patient satisfaction with permanent implant procedure will be assessed on a 5 point Likert scale. Patients will be asked to rate their satisfaction as very satisfied/ satisfied/ neither satisfied nor dissatisfied/ dissatisfied/ very dissatisfied as compared with their trial implantation procedure.

7.9. Blinding

The study is non-blinded.

7.10. Follow-up Visits

Patients will report to the office at the specified intervals below. Under the guidance of the Investigative team at each visit, SJM field representatives may assist with programming of the patient's device as needed during the course of the study.

Missed visits and visits that occur outside of the specified time windows will be documented as protocol deviations.

7.10.1. 6 Week Visit

Patients will complete additional follow-up visits at 6 weeks for continued monitoring of the safety and efficacy of the therapy. All programming data will be captured on the appropriate case report form.

A map of paresthesia coverage is collected along with programming parameters, lead impedance, and device data. Any changes in medications will be recorded.

Pain metrics to be collected are patient reported pain relief, NRS, and SF-MPQ. Quality of Life (EQ-5D) will also be also assessed.

7.10.2. 24 Week Visit

Patients will complete additional follow-up visits at 24 weeks for continued monitoring of the safety and efficacy of the therapy. All programming data will be captured on the appropriate case report form.

A map of paresthesia coverage is collected along with final programming parameters, lead impedance, and device data. Any changes in medications will be recorded.

Pain metrics to be collected are patient-reported pain relief, NRS, and SF-MPQ. Quality of Life (EQ-5D) will also be assessed.

7.10.3. Unscheduled Visit

An Unscheduled Visit form will be used if a patient makes an unscheduled office visit. The Healthcare Utilization (HCOR) form will be completed for all unscheduled visits.

The primary reason for the visit determines the need for additional information. In the event of a device malfunction, the changes in device will be captured on the Product Out of Service form. In the event of an adverse event, the investigator should complete the Adverse Event form. If the patient needs to be reprogrammed, the Paresthesia Location and Programming forms. If a revision or replacement is required, then the Additional Surgery and Product Out of Service forms will be completed.

7.11. Outcome Measures

7.11.1. Characterization of Procedure Time

Procedure time will be characterized along the following metrics

- Total operating room time (from prep to recovery)
- Skin-to-skin surgery time (from first incision to last suture)
- Programming time (time while delivering test stimulation to address proper lead placement)
- Fluoroscopy time

7.11.2. Adverse Events

Adverse events will be collected according to the section below. Outcomes will be in percentage of patients experiencing events and total number of events, and will be stratified by severity, type, and resolution.

7.11.3. Coverage

As described below, paresthesia coverage of painful regions will be measured by comparing pain maps to paresthesia maps. Adequate coverage of painful regions with paresthesia and avoidance of paresthesia outside of painful regions will be assessed.

7.12. Additional Data

The Study Coordinator or designee will give the patient the questionnaires to complete on his or her own. It is important that the patient understands the meaning of all the words in the questionnaires. The patient should be instructed to ask any questions about the questionnaires if further explanation is needed. Once the patient has completed the questionnaire, the Study Coordinator or designee will review the questionnaire for completeness to verify that all questions have been answered and only one response is chosen for each item.

Short-Form McGill Pain Questionnaire (SF-MPQ-2) (Dworkin et al., 2009)

The Short-Form McGill Pain Questionnaire version 2 (SF-MPQ-2) is a widely used scale used to measure the major symptoms of both neuropathic and non-neuropathic pain. The self-administered questionnaire consists of a set of 22 different pain descriptors. The patient is instructed to indicate how accurately the applicable the descriptor word describes their pain on a scale ranging from 0 ('None') to 10 ('Worst Possible'). The questionnaire takes approximately 5-10 minutes to complete. There are a total of 3 sensory subscales (continuous pain descriptors, intermittent pain descriptors, and predominantly neuropathic pain descriptors) and 1 affective subscale scores. The total SF-MPQ-2 score is the sum of the four subscale scores. Higher scores indicate a higher severity of symptoms.

Pain Evaluation Form

Patients will be provided with a questionnaire to complete at follow-up visits. Patients will evaluate their pain relief from the device and rate their current, average, worst, and least pain.

EuroQol (EQ-5D) generic health index questionnaire (Hurst, Kind, & Ruta, 1997)

EQ-5D is a standardized instrument for measuring health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profiles and single index value for health status. The EQ-5D has standard layout for the five-dimensional (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) descriptive system for recording an individual's current EQ-5D self-reported health state. Each of the five dimensions will be answered by one of five responses of increasing severity (no problems/slight problems/moderate problems/severe problems/unable or extreme) within a particular EQ-5D dimension.

Pain Location Form

The Pain Location Form includes a map of the body that is labeled with different numbered regions. The patient is instructed to shade in or place an X in the area the patient is feeling pain.

Paresthesia Coverage Form

The Paresthesia Coverage Form includes a map of the body that is labeled with different numbered regions. The patient is instructed to shade in or place an X the area the patient is feeling stimulation/paresthesia. Patients will also indicate which area(s) of pain relief has given them the greatest improvement over their daily activities. This form looks similar to the Pain Location Form so it should be made clear to the patient that one is for pain and one is for paresthesia.

8. Adverse Events (AEs)

Adverse events are solicited at every study visit throughout the duration of the study. Adverse events will also be solicited at any unscheduled visits that occur.

8.1. AE Definitions

An ADVERSE EVENT is "Any change, undesired, noxious or pathological in a patient or patient illustrated by signs, symptoms and /or laboratory changes that occur during a clinical study, whether or not considered drug/treatment related."

A SERIOUS ADVERSE EVENT (SAE) is where the event is/causes:

- Life threatening or fatal
- Requires hospitalization ≥ 24 hours or prolongs an existing hospitalization
- The patient to be disabled
- Congenital anomaly or birth defect

A NON-SERIOUS ADVERSE EVENT is an event other than one described above.

A DEVICE-RELATED ADVERSE EVENT is an event where the Investigator feels that the device (i.e. IPG, lead, external device) contributed in any way to the adverse event occurring.

A PROCEDURE-RELATED ADVERSE EVENT is one that the Investigator feels that the implant procedure (i.e. permanent or revision) contributed in any way to the adverse event occurring within 30 days post-procedure.

As defined in 21 CFR §812.3 an UNANTICIPATED ADVERSE DEVICE EFFECT (UADE) is "any serious adverse 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 was not previously identified in nature, severity, or degree of incidence in the 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 patients." An adverse device event that is not listed in Section 8.4 or included in the labeling for the device could potentially be classified as a UADE. If an UADE occurs, the investigator must notify St. Jude Medical Technical Services immediately, but no later than 10 working days after the investigator first learns of the effect, or in accordance with IRB policies.

A LIFE-THREATENING ADVERSE EVENT is one that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse event as it occurred, i.e., it does not include an event that, had it occurred in a more severe form, might have caused death.

DISABILITY is defined as a substantial disruption of a person's ability to conduct normal life functions, as assessed by the patient and the Investigator.

A TREATMENT EMERGENT ADVERSE EVENT includes an event that was not present during the Baseline Evaluation and that occurred or worsened during treatment.

8.2. AE Recording

All device and/or procedure-related Adverse Events volunteered by the patients or elicited by the Investigator must be recorded on the AE forms provided. All serious AEs must be recorded whether or not considered device or procedure- related.

8.3. Reporting AEs

Throughout the course of the proposed study, all device and/or procedure-related adverse events will be recorded and monitored by the Investigator(s) at each participating site. Additionally, any serious adverse events observed by the investigator or reported by the patients, whether or not ascribed to the device or procedure will be recorded. Non-device/procedure-related adverse events including but not limited to common cold, other bodily pain (such as dental or neck pain) or elective outpatient surgery with hospitalization less than 24 hours will not be recorded.

Only adverse events that occur during or after system implantation will be collected. Every effort will be made to remain alert to possible adverse experiences and unexpected findings. If adverse experiences occur, the first concern will be the safety of the patient and appropriate medical intervention will be made.

Individual reports of device and/or procedure-related adverse events and all serious adverse events should be documented and reported appropriately on the adverse event case report form. An investigator shall submit to the IRB a report of any unanticipated adverse effect (UADE) occurring during the investigation as soon as possible, in accordance with IRB policies.

The Investigator must report all SAEs (e.g. unanticipated death or serious injury require hospitalization greater than 24 hours) to the IRB as soon as possible, in accordance with IRB policies. This notification can occur by email, telephone, or fax and the site will forward the completed AE form as soon as it is available.

The Investigator must also promptly report the resolution to all reported serious, unanticipated, or device/procedure-related AEs. Non-serious adverse events should be reported at the next routine contact.

All AEs shall also be reported to SJM and reviewed on a monthly basis. All SAEs will be submitted to the FDA by SJM immediately upon receipt. All AEs will be reviewed on a quarterly basis by SJM per their own standard operating procedures.

8.4. Anticipated Adverse Events and Complications

Complications and anticipated adverse effects associated with SCS implantation include but are not limited to:

- Stimulation at high outputs may cause unpleasant sensations or motor

disturbances, including involuntary movement. If either occurs, turn off your IPG immediately.

- Undesirable changes in stimulation may occur over time. These changes may be related to cellular changes in tissue around the electrodes, changes in electrode position, loose electrical connections, and/or lead failure.
- Stimulation may occur in unwanted places, such as the radicular (nerve root) chest wall area
- A lead can move and result in changes in stimulation and/or a reduction in pain relief
- Placement of a lead in the epidural space may cause epidural hemorrhage, hematoma, infection, spinal cord compression, and/or paralysis
- Cerebrospinal fluid (CSF) leakage is possible
- Paralysis, weakness, clumsiness, numbness, and/or pain below the level of the implant can occur
- Persistent pain may occur at the electrode or IPG site
- Seroma (mass or swelling) may occur at the IPG site
- Implant materials may cause an allergic or rejection response
- The implant can move, or skin can erode from around it
- Battery failure and/or battery leakage is possible

IPG Complications

Changes in stimulation parameters may occur due to the failure of, or changes in, components over time, which results in:

- Understimulation
- Return of underlying symptoms
- Overstimulation
- Premature battery depletion, and
- The need to explant the device

8.5. AE Classification

The Investigator will classify each adverse event. If the adverse event is serious or the Investigator feels that the device contributed in any way to the adverse event, the Investigator must report the event to the IRB.

8.5.1. Severity Rating

The Investigator will use the following definitions to assess the severity of the adverse event to the device/procedure:

A MILD adverse event is an event that causes awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs and symptoms are transient.

A MODERATE adverse event is an event that causes discomfort severe enough to cause interference with usual activities; persistent or requiring treatment.

A SEVERE adverse event is an event severe enough that causes an inability to perform normal, daily activities; persistent or requiring treatment.

8.5.2. Relationship to Device/Procedure

An adverse event where the causal relationship to the device and/or procedure has been classified as *possibly*, *probably*, or *definitely*, the relationship must meet the NIH definition for relatedness of an adverse event to an intervention as follows:

- *Possibly* Device/Procedure-Related: (must meet at least 2 criteria)
  1) Has a reasonable temporal relationship to intervention,
  2) Could not readily have been produced by the patient's clinical state,
  3) Could not readily have been due to environment or other interventions,
  4) Follows a known pattern of response to intervention.
- *Probably* Device/Procedure -Related: (must meet at least 3 criteria)
  1) Has reasonable temporal relationship to intervention,
  2) Could not readily have been produced by the patient's clinical state or have been due to environmental or other interventions,
  3) Follows a known pattern of response to intervention,
  4) Disappears or decreases with reduction in dose or cessation of intervention.
- *Definitely* Device/Procedure -Related: (must meet all 4 criteria)
  1) Has a reasonable temporal relationship to intervention,
  2) Could not readily have been produced by the patient's clinical state or have been due to environmental or other interventions,
  3) Follows a known pattern of response to intervention,
  4) Disappears or decreases with reduction in dose or cessation of interventional and recurs with re-exposure.

9. Data Review and Database Management

9.1. Site Monitoring

Before study initiation at any sub-sites, the sponsor-investigator, or designee, will review the protocol and CRFs with the investigators and their staff, and protocol training will be documented

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

SJM will monitor all sites according to their own internal standard operating procedures.

No information in source documents about the identity of the patients will be disclosed.

9.2. Data Collection

Designated investigator staff must enter the information required by the protocol onto the paper CRFs, and copies of the patient questionnaires will be sent to SJM. SJM will send a

monthly enrollment and CRF report to all investigators.

9.3. Database Management and Quality Control

Data from the patient questionnaires and CRFs will be reviewed by SJM following their own internal standard operating procedures.

Errors or omissions on paper CRFs will generate queries that will be returned to the investigational site for resolution. Quality control audits will be completed by SJM as needed, and prior to finalizing data.

SJM will send an updated database of all data on a quarterly basis unless the enrollment accelerates, in which case, SJM will send an updated database with the monthly enrollment/CRF report.

10. Data Analysis

10.1. Statistical Plan

The study design for this investigation is a post-market, prospective, multicenter, parallel design, non-blinded study with primary analysis at 24 weeks. The primary objective in this study is to demonstrate the effectiveness and safety of the non-awake procedure compared to the awake procedure.

10.2. Sample Size Justification

Recent, retrospective studies of single center experience with the two procedures suggests the following complication and repositioning rates and procedure time (Falowski et al., 2011; Shils & Arle, 2012):;

Table 2: Outcome rates for sample size calculation

	Non-awake	Awake
Revisions for device failure	15%	30%
Lead repositioning for efficacy	1%	15%
Infection rate	4.5%	6.0%
Procedure time	60 minutes	90 minutes

Simulations based on these results indicated that the sample size required to reject the null hypothesis at the 5% significance level is a minimum of 50 patients, who will be enrolled 1:1 between the two procedures. Note that because neither procedure is currently considered the “gold standard”, and given the primary research objective of assessing safety and efficacy, it was determined that the sample size calculation should not be based on a formal hypothesis of non-inferiority with a pre-determined non-inferiority margin.

Sample Size Adjustments - Patients have already been approved for a permanent system implant, thus a screen failure rate of 0% is assumed. The objective of the study is to study the implant procedures, eliminating the need to account for non-responders to treatment.

10.3. Primary Analysis

10.3.1. Procedure Time

Hypothesis:

The non-awake method is faster than the awake method.

Metrics:

Skin-to-skin surgical time

Intraoperative programming time

Total fluoroscopy used (time and dose)

Statistical Tests:

Test for normality (such as Jarque-Bera)

Unpaired, two-sided Student's t-tests (normally distributed continuous data) or Mann-Whitney rank sums test (skewed continuous data)

Significance at $\alpha < 0.05$, with no adjustment for the multiple comparisons

10.3.2. Number of adverse events

Hypothesis:

The non-awake is comparable to the awake method in the number of adverse events.

Metrics:

Rate of adverse events (percentage of patients with an adverse event)

Statistical Tests:

Chi-square or Fisher's exact test as appropriate based on the number of adverse events

Significance at $\alpha < 0.05$, with no adjustment for the multiple comparisons

10.3.3. Procedure Time

Hypothesis:

The non-awake is comparable to the awake method in the number of revisions

Metrics:

Rate of revisions (percentage of patients with a revision)

Statistical Tests:

Chi-square or Fisher's exact test as appropriate based on the number of adverse events

Significance at $\alpha < 0.05$, with no adjustment for the multiple comparisons.

10.4. Secondary Analysis

10.4.1. Paresthesia coverage

Hypothesis:

The non-awake is comparable to the awake method in the proportion of the painful regions covered by paresthesia

Metrics:

Paresthesia overlap percentage

Extraneous paresthesia percentage

The regions marked on the Pain Location Form and Paresthesia Coverage form will be categorized as overlapping, uncovered pain, excess paresthesia, or none (see Table 3; Alo, Yland, Redko, Feler, & Naumann, 1999).

$$paresthesia\ overlap\ percentage = \frac{N_O}{N_U+N_O} \cdot 100$$

$$extraneous\ paresthesia\ percentage = \frac{N_E}{N_O+N_E} \cdot 100$$

Statistical Tests:

Test for normality (such as Jarque-Bera)

Unpaired, two-sided Student's t-tests (normally distributed continuous data) or Mann-Whitney rank sums test (skewed continuous data)

Significance at $\alpha < 0.05$, with no adjustment for the multiple comparisons

		Paresthesia Coverage Form	
		Marked	**Unmarked**
Pain Location Form	**Marked**	Overlap N_O	Uncovered N_U
	Blank	Excess N_E	None N_N

Table 3: Pain-Paresthesia Comparison Categories

10.5. Additional Analysis

Summary statistics will be calculated for additional data. Post-hoc analysis may be done based on findings.

10.6. Data Sets

All patients who complete the 6 week follow-up appointment and questionnaires will be included in the analysis.

Patients with missing baseline values will be excluded from the analysis. Missing data pertaining to adverse events will not be imputed.

11. Withdrawal of Patients from Study

Withdrawal is defined as a patient's termination of participation from a clinical study. Patients may be discontinued from the study at any time. The reason for discontinuation will be recorded

on the Exit and Withdrawal form. Discontinued patients may not be replaced in the study. Prior to discontinuing a patient, every effort should be made to contact the patient in an effort either to get the patient back into compliance with the protocol, or to obtain as much follow-up data as possible. Reasons for discontinuation include, but are not necessarily limited to:

- Voluntary withdrawal by the patient;
- Patient is Lost to Follow-up: Patient will be considered "lost to follow-up" after a minimum of 2 documented phone calls by personnel at the investigational center to the patient or emergency contact and a certified letter was sent to the last known address.
- Investigator may discontinue the patient's participation in the study for reasons including but not limited to: patient noncompliance, surgical revision not appropriate, unwillingness or inability to cooperate with study requirements (therapy regimen, follow-up visits, etc.).

12. Modification of Protocol

Any amendments to this protocol must be prepared by the Coordinating Investigator and approved by the appropriate regulatory agencies and the local authority (IRB) before implementation by the Investigator.

13. Discontinuation of Study

The Clinical Coordinating Investigator reserves the right to discontinue any study at any time for administrative reasons, such as but not limited to, a decision to discontinue further clinical Investigations with the devices, improper conduct of the study by the Investigator, inability to obtain the number of patients required by the protocol, etc.

If the study is prematurely terminated or suspended, it is the responsibility of the investigator to promptly inform the patients and assure appropriate therapy and follow-up. The Investigator must also adhere to local IRB requirements and reporting of study termination or discontinuation.

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15. Appendix A: Case Report Form Matrix

Case Report Form	Screening	Baseline	Perm Implant Surgery	Initial Programming	6 Weeks	24 Weeks	Unscheduled Visits
Enrollment	x						
Inclusion/Exclusion	x						
Baseline Self Evaluation		x					
Pain Location		x			x	x	
Pain Evaluation		x			x	x	
Medication		x	x	x	x	x	x
SF-MPQ-2		x			x	x	
EQ-5D 5L		x			x	x	
Surgery			x				
Programming				x	x	x	x
Paresthesia Coverage				x	x	x	x
Patient Global Impression				x			
Follow-Up Visit				x	x	x	x
Unscheduled Visit							x
HCOR form							x
Deviation	TO BE COMPLETED AS NEEDED						
Additional Surgery							
Product Out of Service							
Adverse Event							
Exit and Withdrawal							

16. Appendix B: Patient Questionnaires

The following questionnaires will be completed by the patient:

- Baseline Self Evaluation Form
- Patient Global Impression Form
- SF-MPQ-2
- Pain Evaluation Form

[IN FINAL PDF VERSION APPEND CRF PDFs]