# Clinical Investigational Plan

Reference:
SJM-CIP-10126

**CRISP**

**"CompaRison of paresthesia mapping to anatomIc midline-based burSt Programming strategies"**

**Clinical Investigation Plan (CIP)**

Sponsor

St. Jude Medical, Inc.
6901 Preston Road
Plano, TX 75024
USA
Tel: 972 309 8000
Fax: 972 309 8150

NCT Number: NCT02986074
Document Date: May 5th, 2016

## PRINICPAL INVESTIGATOR SIGNATURE PAGE

**CRISP**

**"CompaRison of paresthesia mapping to anatomIc midline-based burSt Programming strategies"**

Version A

Reference #: SJM-CIP-10126

I have read and agree to adhere to the clinical investigational plan and all regulatory requirements applicable in conducting this clinical study.

**Principal Investigator**

Printed name: _____

Signature:_____

Date: _____

## Table of Contents

Page

1.0 Synopsis ..... 5
1.1 Study Flow Chart ..... 9
1.2 Study Contacts ..... 9
2.0 Background And Justification For Clinical Study ..... 10
3.0 Risks And Benefits Of The Clinical Study ..... 12
3.1 Description Of Subject Population ..... 12
3.2 Anticipated Clinical Benefits ..... 12
3.3 Anticipated Adverse Events And Adverse Device Effects ..... 12
3.4 Residual Risks Associated With The Device Under Investigation, As Identified In The Risk Analysis Report 13
3.5 Risks Associated With Participation In The Clinical Study ..... 13
3.6 Possible Interactions With Concomitant Medical Treatments And/Or Concurrent Medical Interventions ..... 13
3.7 Steps That Will Be Taken To Control Or Mitigate The Risks ..... 13
3.8 Risk-To-Benefit Rationale ..... 13
3.9 Description Of History Of Modifications Or Recall In Relation To Safety And Clinical Performance For Device Under Investigation ..... 14
4.0 Study Design ..... 14
4.1 Purpose ..... 14
4.2 Study Design And Scope ..... 14
4.3 Objectives ..... 15
4.4 Endpoints ..... 16
4.5 Inclusion And Exclusion Criteria ..... 16
4.6 Subject Population ..... 18
4.7 Informed Consent Process ..... 18
5.0 Device Under Investigation ..... 19
5.1 Device Description ..... 19
5.2 Device Accountability (If Applicable) ..... 20
6.0 Procedures ..... 21
6.1 Study Flow Chart ..... 21
6.2 Procedures ..... 22
6.3 Enrollment Visit ..... 22
6.4 Baseline Visit ..... 23
6.5 Scs Trial Implant ..... 24
6.6 Trial Assessment Visit 1. ..... 25
6.7 Trial Assessment 2 ..... 25
6.8 Scs Implant Procedure ..... 25
6.9 Activation Visit ..... 26
6.10 Scheduled Follow-Ups ..... 26
6.11 Unscheduled Visits ..... 26
6.12 Description Of Activities Performed By Sponsor Representatives ..... 27
6.13 Subject Study Completion ..... 27
6.14 Any Known Or Forseeable Factors That May Compromise The Outcome Of The Clinical Study Or The Interpretation Of The Results ..... 27
6.15 Criteria And Procedures For Subject Withdrawal Or Discontinuation ..... 27
7.0 Compliance To Cip ..... 28
7.1 Statements Of Compliance ..... 28
7.2 Adherence To The Clinical Investigation Plan ..... 29
7.3 Repeated And Serious Non-Compliance ..... 30

8.0 Adverse Event, Adverse Device Effect, Device Deficiency ..... 30
8.1 Definitions ..... 30
8.2 Procedure For Assessing, Recording, And Reporting Adverse Events, Device Deficiencies/Complaints, Adverse Device Effects, Serious Adverse Events, And Serious Adverse Device Effects: ..... 32
8.3 Subject Death ..... 33
9.0 Data Management ..... 33
9.1 Data Management Plan ..... 33
9.2 Document And Data Control ..... 34
10.0 Monitoring ..... 34
11.0 Regulatory Inspections ..... 34
12.0 Statistical Considerations ..... 35
12.1 Statistical Design, Hypotheses, Method And Analytical Procedures ..... 35
12.2 Sample Size ..... 35
12.3 Pass/Fail Criteria To Be Applied To The Results Of The Clinical Study ..... 35
13.0 Document Retention ..... 35
14.0 Amendments To Clinical Investigational Plan ..... 36
15.0 Investigation Suspension Or Termination ..... 36
15.1 Premature Termination Of The Whole Clinical Study Or Of The Clinical Study In One Or More Investigational Sites 36
15.2 Resuming The Study After Temporary Suspension ..... 38
15.3 Study Conclusion ..... 38
16.0 Publication Policy ..... 38
17.0 Bibliography ..... 38
Appendix A: Abbreviations ..... 40
Appendix B: Cip Revision History ..... 41
Appendix C: Declaration Of Helsinki ..... 42
Appendix D: List Of Clinical Investigation Sites And Irb/Ec ..... 43
Appendix E: Sample Informed Consent ..... 44
Appendix F: Case Report Forms ..... 45

## 1.0 SYNOPSIS

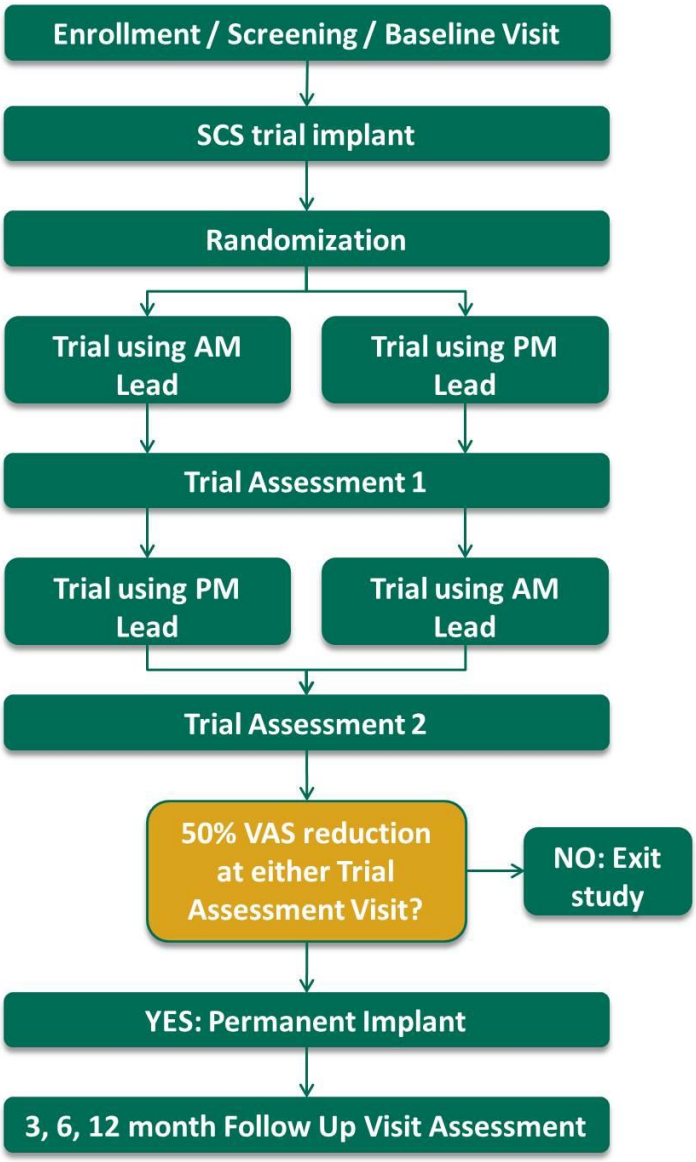
| | |
|---|---|
| Title: | CompaRison of paresthesia mapping to anatomIc midline-based burSt Programming strategies |
| Acronym: | CRISP |
| Purpose: | The primary purpose of this study is to compare the therapeutic efficacy of the conventional, paresthesia mapping-based burst spinal cord stimulation (SCS) implantation strategy to a more novel, anatomic midline-based approach that has the potential to streamline the workflow associated with the SCS treatment continuum. |
| Primary Objective: | • Compare pain relief provided by paresthesia mapping-based burst trial to anatomical midline-based burst trial |
| Secondary Objectives: | • Compare subject preference between the paresthesia mapping-based and anatomical midline-based burst trial<br>• Compare improvements in quality of life and disability between the paresthesia mapping-based burst trial and the anatomical midline-based burst trial<br>• Evaluate pain relief, improvements in quality of life, disability, and subject satisfaction at 3, 6 and 12 months after permanent implant by burst SCS delivered through electrodes positioned using either anatomical midline-based or paresthesia based implantation |
| Primary Endpoint: | • Changes in low back and lower limb pain between baseline and trial assessments |
| Secondary Endpoints: | • Comparison of subject preference between the 2 lead implantation techniques during the SCS trial<br>• Changes in low back and lower limbs pain between baseline and at 3, 6 and 12 months after permanent implant (evaluated using Visual Analog Scale (VAS) assessments)<br>• Changes in quality of life assessed using the EQ-5D questionnaire and in disability assessed using the Oswestry Disability Index (ODI) between baseline, trial assessments and at 3, 6 and 12 months after permanent implant<br>• Evaluate subject satisfaction at 3, 6 and 12 months after permanent implant |
| Design: | This is a prospective, multicenter, double-blinded, feasibility study consisting of two phases: SCS trial and permanent implant follow up.<br><br>After baseline evaluation, subjects will undergo SCS trial using the St. Jude Medical (SJM) Invisible Trial system. During the trial implant, two SCS leads will be implanted, one using the standard paresthesia-based mapping, and the other using the anatomical midline-based technique. Subjects will be blinded and then randomized 1:1 to receive burst SCS using one of the 2 leads (lead placed using paresthesia-based mapping or the anatomical midline) for 2 weeks, and will then receive burst stimulation on the alternate lead for an additional 2 weeks. Therapeutic efficacy for stimulation delivered through each of the 2 leads will be evaluated at the |

| | |
|---|---|
| | end of the 2-week trial period during trial assessment visits 1 and 2.<br><br>Subjects who underwent a successful trial (≥50% overall pain relief) will then be implanted with a SJM Proclaim™, Prodigy™ or Prodigy MRI™ system. The lead activated will depend on the subject's preference following the trial. It the subject has no preference, the lead placed using the anatomic midline-based technique will be activated. The subject will then be followed for 12 months to assess the long term treatment outcome.<br><br>Subjects who do not experience a ≥50% overall pain relief on either of the 2 leads will exit the study.<br><br>This clinical study will be conducted in up to 3 centers in the EU.<br><br>Approximately 50 subjects will be enrolled in this study.<br><br>Subjects will be followed up for 12 months. |
| Devices used: | • SJM Invisible trial™ system<br>• Proclaim™, Prodigy™ or Prodigy MRI™ Implantable Pulse Generator (IPG)<br>• Clinician Programmer<br>• Patient Programmer<br>• IPG recharger (for Prodigy MRI™ patients) |
| Study Population: | Failed back surgery syndrome (FBSS) subjects with predominant low back pain eligible for a SCS trial will be considered for enrollment in this study. |
| Inclusion/Exclusion Criteria | <u>Inclusion Criteria</u><br>• Subject is able to provide informed consent to participate in the study;<br>• Subject is 18 years of age or older;<br>• Subject has failed to respond to at least 6 months of conventional treatment including pharmacological treatment, physical therapy, epidural injections and/or radiofrequency therapy as per NICE Tag 0159;<br>• FBSS subjects with predominant low back pain;<br>• Subject has a lower back pain intensity of at least 6.0 out of 10.0 on the VAS at baseline;<br>• Subject is on stable pain medications with a total opioid equivalent of 120 mgs a day or less for at least 28 days prior to enrolling in this study, and is willing to stay on those medications with no dose adjustments until activation of the permanently implanted SCS device;<br>• Subject's medical record has been evaluated by the Investigator to ensure that the subject is a good candidate for a neurostimulation system;<br>• Subject is willing to cooperate with the study requirements including compliance with the regimen and completion of all office visits;<br>• Female candidates of child-bearing potential agree to commit to the use of an effective method of contraception (including but not limited to sterilization, barrier devices, oral contraceptives, intrauterine devices |

| | |
|---|---|
| | (IUDs), condoms, rhythm method, or abstinence) for the duration of the study<br><br><u>Exclusion Criteria</u><br>• Subjects with significant scoliosis even if surgically corrected<br>• Subject is currently participating in a clinical investigation that includes an active treatment arm;<br>• Subject has been implanted with or participated in a trial period for a neurostimulation system;<br>• Subject has an infusion pump;<br>• Subject has evidence of an active disruptive psychological or psychiatric disorder as determined as per standard of care;<br>• Subject has a current diagnosis of a coagulation disorder, bleeding diathesis, progressive peripheral vascular disease or uncontrolled diabetes mellitus;<br>• Subject has a current diagnosis of a progressive neurological disease as determined by the Investigator;<br>• Subject is immunocompromised;<br>• Subject 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);<br>• Subject has history of cancer requiring active treatment in the last 12 months;<br>• Subject has an existing medical condition that is likely to require the use of diathermy in the future;<br>• Subject has documented history of allergic response to titanium or silicone;<br>• Subject has a documented history of substance abuse (narcotics, alcohol, etc.) or substance dependency in the 6 months prior to baseline data collection;<br>• Female candidates of child bearing potential that are pregnant (confirmed by positive urine/blood pregnancy test). |
| Data Collection | FBSS subjects with predominant low back pain will be screened as per the inclusion/exclusion criteria, and those who successfully meet these criteria and provide their consent will be considered for enrollment.<br><br>Subjects will undergo a baseline assessment to collect primary and secondary outcome measures prior to the SCS trial. Specifically, assessments will include: pain rating as assessed by the VAS, quality of life as assessed by EQ-5D and disability as assessed by ODI.<br><br>*Trial phase:*<br>Therapeutic efficacy of trial SCS will be evaluated during trial assessment visits 1 and 2 using the VAS, EQ-5D, and ODI. . Pain diaries will be used to record subjects' pain during the trial period. Subject preference for stimulation delivered through either of the 2 leads will also be recorded. Subjects who experienced at least a 50% overall pain reduction at either of the trial assessment visits will be considered for permanent implant. |

| | |
|---|---|
| | *Permanent implant follow up:*<br>Subjects who receive permanent SCS implant will be followed up for 12 months. Assessments, performed at the 3, 6 and 12 month visits, will include: pain rating as assessed by the VAS, quality of life as assessed by EQ-5D, disability as assessed by the ODI, and subject satisfaction. Pain diaries will be used to record subjects pain during the last week before each of the follow up visits. |

## 1.1 STUDY FLOW CHART




**AM lead:** lead implanted using Anatomical Midline-based positioning

**PM lead:** lead implanted using Paresthesia Mapping-based positioning

## 1.2 STUDY CONTACTS

Jeff Kramer
Lalit Venkatesan
Filippo Agnesi

## 2.0 BACKGROUND AND JUSTIFICATION FOR CLINICAL STUDY

Spinal cord stimulation (SCS) is a well-established therapy for the treatment of chronic, intractable pain. In a systematic meta-analysis of the literature, (Taylor *et al.* 2006) reported that SCS reduces pain, improves quality of life, reduces analgesic use, allows some patients to return to work and may also result in significant cost savings over time, while having minimally significant adverse events in patients with neuropathic back and/or leg pain.

Patients receiving conventional tonic SCS (electrical pulses delivered in the 40-60Hz stimulation frequency range) experience paresthesia or a tingling sensation. Burst SCS is a newer paradigm currently approved for use in the European Union and Australia to treat chronic pain conditions. Burst stimulation eliminates or greatly reduces the incidence of paresthesia (Courtney *et al.* 2014), and it entails delivering groups of pulses called burst trains (A) repeated at a burst rate (B); within each burst train, several pulses are issued at an intra-burst rate (C) (See Figure 1). Individual pulses are characterized by a pulse amplitude (D) and pulse width.

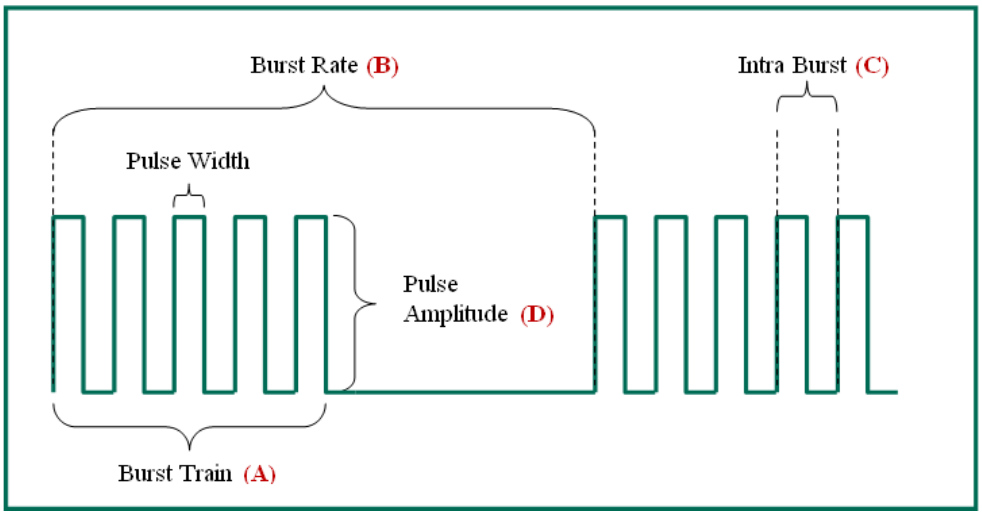



**Figure 1:** Burst Pattern

The current conventional strategy for implanting SCS leads involves physiologically mapping the dermatomal areas encompassing the painful target location using traditional tonic stimulation parameters and adjusting the lead position accordingly. Although effective, this process can prove cumbersome for both the patient and the clinician programmer as different combinations of electrode contacts and polarities have to be tested in order to identify the optimal configuration that maximizes the overlap of the pain and paresthesia regions while minimizing stimulation-induced side effects. While this process can be optimal for tonic SCS, it is unclear if it represents the ideal approach for burst SCS. As burst SCS can be delivered without producing stimulation-induced sensory side effects, the physiological-mapping procedure using tonic stimulation can potentially be eliminated from the workflow.

Of late, anatomical midline-based lead implantations have been performed successfully (Al-Kaisy et al. 2014). Two leads are inserted at the T12 level and tunneled such that the tip of the first lead typically is positioned at the start of the T8 segment while the tip of the second lead is

positioned at the T9 segment. Such an implantation strategy provides coverage extending from T8-T11 (figure 2) and maximizes the number of contacts in the T9-T10 junction. Use of a high frequency stimulation paradigm in two of the contacts in one lead at the T9-T10 junction has resulted in sustained long-term pain relief over a period of 24 months (Al-Kaisy et al. 2014) in 65 chronic pain patients.

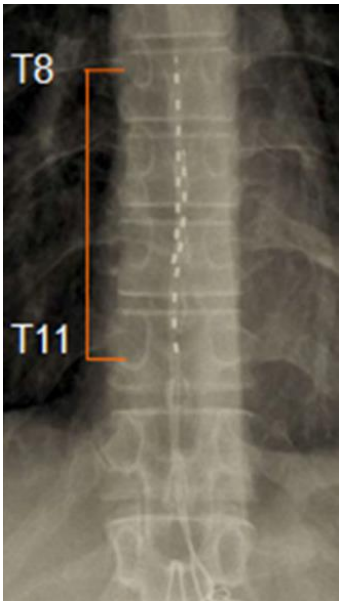



**Figure 2:** X-ray of anatomic midline-based lead implants spanning the T8 to T11 vertebral segments.

The current implantation procedure for burst stimulation involves placement of leads using tonic stimulation based physiological mapping. Anatomical midline-based lead implantation has the potential to reduce the time associated with the surgical procedure, and thus could assist in establishing a more streamlined and time-efficient treatment continuum while using burst SCS. As anatomical midline-based lead implantation does not require patient input, this novel approach will improve patient's comfort, as sedation can be maintained constant throughout the procedure. However, the therapeutic efficacy of burst stimulation delivered through the leads placed using the anatomical midline-based approach is unknown. In this feasibility study, we aim to compare the therapeutic efficacy of the conventional, paresthesia mapping-based burst spinal cord stimulation (SCS) programming strategy to the anatomic midline-based approach while using burst stimulation during a SCS trial. Additionally, the study design also includes a long-term follow up period in order to assess the pain-relief provided by burst stimulation delivered using the lead implant technique preferred by the subject at 3,6 and 12 months following the permanent implant.

## 3.0 RISKS AND BENEFITS OF THE CLINICAL STUDY

Only devices that are currently market approved for treatment of chronic intractable pain of the trunk and limbs will be used during this study. Subjects will be asked to stabilize their medication regimen with no dose adjustments until activation of the permanently implanted SCS device.

### 3.1 DESCRIPTION OF SUBJECT POPULATION

Approximately 50 subjects will be enrolled in the study. The study population consists of failed back surgery syndrome (FBSS) subjects with predominant low back pain eligible for a SCS system trial.

### 3.2 ANTICIPATED CLINICAL BENEFITS

We anticipate that the participants in this study will experience reduction of pain intensity commonly afforded by SCS.

### 3.3 ANTICIPATED ADVERSE EVENTS AND ADVERSE DEVICE EFFECTS

In addition to those risks commonly associated with surgery, the following risks are associated with implanting or using this neurostimulation system for SCS:

| **Anticipated adverse events** |
|---|
| Undesirable changes in stimulation, which may be related to cellular changes in tissue around the electrodes, changes in electrode position, loose electrical connections, or lead failure |
| Lead migration, causing changes in stimulation and/or reduced pain relief |
| Epidural hemorrhage, hematoma, infection, spinal cord compression, or paralysis from placement of a lead in the epidural space |
| Cerebrospinal fluid (CSF) leakage |
| Paralysis, weakness, clumsiness, numbness, or pain below the level of the implant |
| Persistent pain at the electrode or IPG site |
| Seroma (mass or swelling) at the IPG site |
| Infection of the lead extension at the exit zone during trial or infection of the IPG site |
| Allergic or rejection response to implant materials |
| Implant migration or skin erosion around the implant |
| **Anticipated adverse device effects** |
| Battery failure |
| Battery leakage |

These adverse events and adverse device effects are not specific to the study, but related to the approved SCS implant procedure.

### 3.4 RESIDUAL RISKS ASSOCIATED WITH THE DEVICE UNDER INVESTIGATION, AS IDENTIFIED IN THE RISK ANALYSIS REPORT

There are no residual risks associated with the stimulation protocol under investigation.

### 3.5 RISKS ASSOCIATED WITH PARTICIPATION IN THE CLINICAL STUDY

In this study, the position of one lead will be optimized using a paresthesia-based mapping approach ensuring that the subjects will receive adequate paresthesia coverage. The second lead will be positioned using an anatomical midline-based approach. The anatomical midline-based approach is a novel technique and the subjects might not receive adequate pain relief on use of the lead placed using that technique. In that case, activation of the paresthesia mapping-based lead is expected to mitigate the issue and provide the subject with adequate pain relief.

Additionally, both the two leads will be implanted using standard SCS surgical techniques, so we do not foresee any additional risks associated with the participation in this clinical study compared to the SCS treatment continuum.

### 3.6 POSSIBLE INTERACTIONS WITH CONCOMITANT MEDICAL TREATMENTS AND/OR CONCURRENT MEDICAL INTERVENTIONS

There are no possible interactions with concomitant medical treatment and/or concurrent medical intervention beyond those associated with standard medical care using SCS.

### 3.7 STEPS THAT WILL BE TAKEN TO CONTROL OR MITIGATE THE RISKS

This study consists of implantation of leads using two different techniques. The conventional paresthesia mapping-based procedure is currently being utilized in the SCS treatment continuum while using burst stimulation and was shown to be successful in treating chronic pain associated with FBSS (Shu *et al.* 2014, de Vos *et al.* 2015). Recent data shows that the newer anatomic midline-based lead implants deliver adequate pain relief while using high frequency stimulation, but therapeutic efficacy provided by burst stimulation is unknown. During the 2-week trial, the subject might not get adequate pain relief while using burst stimulation delivered using the anatomic midline-based lead. But, the trial's phase involving burst stimulation delivered through the paresthesia mapping-based lead will ensure that the subject undergoes a SCS trial conducted according to standard clinical practice.

### 3.8 RISK-TO-BENEFIT RATIONALE

Subjects participating in this study will incur risks that are no greater in significance when compared to risks associated with standard SCS treatment continuum. The anatomic midline-based lead implantation technique is expected to reduce the time associated with lead implantation surgery, thus reducing the burden on the patients as well as clinicians. The procedure to implant the SCS leads will be shorter than the tonic stimulation based paresthesia mapping procedure. As a result, X-ray radiation exposure may also be reduced. Subjects can also be under conscious sedation for the entire duration of the procedure compared to having to provide input regarding the paresthesia coverage during physiologic mapping based lead implant procedures.

### 3.9 DESCRIPTION OF HISTORY OF MODIFICATIONS OR RECALL IN RELATION TO SAFETY AND CLINICAL PERFORMANCE FOR DEVICE UNDER INVESTIGATION

There have been no modifications or recalls in relation to safety and clinical performance of the devices utilized in this study.

## 4.0 STUDY DESIGN

### 4.1 PURPOSE

The primary purpose of this study is to compare the therapeutic efficacy of the conventional, paresthesia mapping-based burst SCS implant strategy to a more novel, anatomic midline-based approach that has the potential to streamline the workflow associated with the SCS treatment continuum.

### 4.2 STUDY DESIGN AND SCOPE

This study is a prospective, multicenter, single-blinded feasibility study consisting of two phases: SCS trial and permanent implant follow up.

Patients recommended by the Principal Investigator as a candidate and who meet the standard requirements will be approached to participate in this study. Patients that meet the inclusion/exclusion criteria and sign the informed consent will be enrolled in the study and undergo baseline assessment to collect primary and secondary outcome measures prior to the SCS trial. Specifically, assessments will include pain ratings as assessed by visual analog scale (VAS), quality of life as assessed by the EQ-5D and disability as assessed by the Oswestry disability index (ODI).

Subjects will subsequently undergo a SCS trial using the St. Jude Medical (SJM) Invisible Trial system. During the trial implant, two SCS leads will be implanted using standard surgical techniques. One lead will be implanted using paresthesia mapping to maximize the overlap between painful regions and evoked paresthesia according to standard clinical practice. A second lead will be implanted using a novel anatomical midline-based approach. Under fluoroscopic guidance, the lead will be positioned above the anatomical midline such that it extends over the T9-T10 junction.

Subjects will be randomized 1:1 to receive burst stimulation using one of the 2 leads (lead placed using paresthesia mapping or lead placed by anatomic midline-based approach or vice versa), and will be blinded to the randomization order.

The SCS trial will consist of two phases, and will last for a total of 4 weeks.

During the first trial phase, burst SCS will be delivered for two weeks using the first lead in the randomization sequence. After two weeks, subjects will assess the pain level, quality of life and disability associated with stimulation delivered.

Subjects will then cross over to the second trial phase during which burst stimulation will be delivered for an additional two weeks using the second lead in the randomization sequence.

At the end of the second trial phase, subjects will assess pain level, quality of life and disability associated with stimulation delivered using the second lead. Subject preference for stimulation delivered during the two trial phases will also be recorded during this visit.

If the VAS score during either of the two trial assessments is reduced by at least 50% compared to the baseline score, the subject will be considered for permanent SCS implant. Subjects who do not experience a ≥50% overall pain relief on either of the 2 leads will exit the study.

Subjects who underwent a successful trial (≥50% overall pain relief) will then be implanted with a SJM Proclaim™, Prodigy™ or Prodigy MRI™ system. The lead activated will depend on the subject's preference following the trial. It the subject has no preference; the lead placed using the anatomic midline-based technique will be activated. The subject will then be followed for 12 months to assess the long term treatment outcome. Follow up visits will occur at 3, 6 and 12 months after permanent implant. During each of these visits, subjects will rate their pain using the VAS, their quality of life using the EQ-5D, their disability using the ODI.

The total duration of the study is expected to be approximately 2 years.

The clinical study will be conducted in up to 3 centers in the E.U.

#### 4.2.1 Number of subjects required to be included in the study

Approximately 50 subjects will be enrolled in this study. Enrollment will end when 40 subjects will have received permanent SCS implant.

#### 4.2.2 Estimated time needed to enroll this subject population

The study may continue up to 2 year, dependent on the rate of enrollment.

### 4.3 OBJECTIVES

#### 4.3.1 Primary Objective

- Compare pain relief provided by paresthesia mapping-based burst trial to anatomical midline-based burst trial

#### 4.3.2 Secondary Objective

- Compare subject preference between the paresthesia mapping-based anatomical midline-based burst trial
- Compare improvements in quality of life and disability between the paresthesia mapping-based burst trial and the anatomical midline-based burst trial
- Evaluate pain relief, improvements in quality of life, disability, and subject satisfaction at 3, 6 and 12 months after permanent implant by burst SCS delivered through electrodes positioned using anatomical midline-based implantation

## 4.4 ENDPOINTS

### 4.4.1 Primary Endpoint

- Changes in low back and lower limb pain between baseline and SCS trial assessments.

### 4.4.2 Secondary Endpoint

- Comparison of subject preference between the 2 lead implantation techniques during the SCS trial
- Changes in low back and lower limbs pain between baseline and at 3, 6 and 12 months after permanent implant (evaluated using Visual Analog Scale (VAS) assessments)
- Changes in quality of life assessed using the EQ-5D questionnaire and in disability assessed using the Oswestry Disability Index (ODI) between baseline, trial assessments and at 3, 6 and 12 months after permanent implant
- Evaluate subject satisfaction at 3, 6 and 12 months after permanent implant

## 4.5 INCLUSION AND EXCLUSION CRITERIA

A subject, who meets all of the inclusion criteria, and none of the exclusion criteria, is eligible to participate in this study.

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) will be accounted for and documented, assigning an identification code linked to their names, alternative identification or contact information.

This log will be kept up to date throughout the clinical study by the principal investigator or his/her authorized designee. To ensure subject privacy and confidentiality of data this log must be maintained throughout the clinical study at the clinical site.

To participate in this clinical subject, the subject must meet all of the following inclusion criteria:

### 4.5.1 Inclusion Criteria

- Subject is able to provide informed consent to participate in the study;
- Subject is 18 years of age or older;
- Subject has failed to respond to at least 6 months of conventional treatment including pharmacological treatment, physical therapy, epidural injections and/or radiofrequency therapy as per NICE Tag 0159;
- FBSS subjects with predominant low back pain;
- Subject has a low back and pain intensity of at least 6.0 out of 10.0 on the VAS at baseline;
- Subject is on stable pain medications with a total opioid equivalent of 120 mgs a day or less for at least 28 days prior to enrolling in this study, and is willing to stay on those medications with no dose adjustments until activation of the permanently implanted SCS device;
- Subject's medical record has been evaluated by the Investigator to ensure that the subject is a good candidate for a neurostimulation system;

- Subject is willing to cooperate with the study requirements including compliance with the regimen and completion of all office visits;
- Female candidates of child-bearing potential agree to commit to the use of an effective method of contraception (including but not limited to sterilization, barrier devices, oral contraceptives, intrauterine devices (IUDs), condoms, rhythm method, or abstinence) for the duration of the study

Subjects are not eligible for clinical study participation if they meet any of the following exclusion criteria:

### 4.5.2 Exclusion Criteria

- Subjects with significant scoliosis even if surgically corrected;
- Subject is currently participating in a clinical investigation that includes an active treatment arm;
- Subject has been implanted with or participated in a trial period for a neurostimulation system;
- Subject has an infusion pump;
- Subject has evidence of an active disruptive psychological or psychiatric disorder as determined as per standard of care;
- Subject has a current diagnosis of a coagulation disorder, bleeding diathesis, progressive peripheral vascular disease or uncontrolled diabetes mellitus;
- Subject has a current diagnosis of a progressive neurological disease as determined by the Investigator;
- Subject is immunocompromised;
- Subject 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);
- Subject has history of cancer requiring active treatment in the last 12 months;
- Subject has an existing medical condition that is likely to require the use of diathermy in the future;
- Subject has documented history of allergic response to titanium or silicone;
- Subject has a documented history of substance abuse (narcotics, alcohol, etc.) or substance dependency in the 6 months prior to baseline data collection;
- Female candidates of child bearing potential that are pregnant (confirmed by positive urine/blood pregnancy test).

## 4.6 SUBJECT POPULATION

The study population consists of FBSS patients with a diagnosis of chronic low back pain accompanied by lower limb pain, and eligible for a SCS trial.

### 4.6.1 Subject Screening

All subjects presenting at the investigational site can be screened by a member of the investigational team previously trained on the CIP and delegated to do so.

Subjects who do not meet the inclusion/exclusion criteria will not be eligible to participate in this study.

Subjects meeting the inclusion/exclusion criteria will be fully informed about the study and asked to participate in the study. In case the subject agrees, a duly signed and dated Patient Informed Consent will be obtained.

### 4.6.2 Point of Enrollment

Subjects are considered enrolled in the study from the moment the subject has provided written Patient Informed Consent, has been screened for inclusion/exclusion criteria and his/her enrollment form has been completed. (Refer to section 4.7 for the Informed Consent Process).

## 4.7 INFORMED CONSENT PROCESS

### 4.7.1 General process

Prior to enrolling in the clinical study and conducting study-specific procedures, all subjects will be consented, as required by applicable regulations and the center's IRB/EC. Informed consent must be obtained from each subject prior to any study related procedures. The consent form must be signed and dated by the subject and by the person obtaining the consent.

The principal investigator or his/her authorized designee will conduct the Informed Consent Process. This process will include a verbal discussion with the subject on all aspects of the clinical study that are relevant to the subject's decision to participate in the clinical study.

The subject shall be provided with the informed consent form that is written in a language that is understandable to the subject and has been approved by the center's IRB/EC. Failure to obtain informed consent from a subject prior to study enrollment should be reported to St. Jude Medical within 5 working days and to the reviewing center's IRB/EC/ consistent with the center's IRB/EC reporting requirements.

## 5.0 DEVICE UNDER INVESTIGATION

### 5.1 DEVICE DESCRIPTION

In this study, the SJM Invisible trial system and the Proclaim™, Prodigy ™ or Prodigy MRI™ neurostimulation system will be used.

Table 1: Description of Proposed Devices

| Device Component | Model/Type | Investigational or Market Released |
|---|---|---|
| SJM Invisible trial external pulse generator (EPG) | 3599 (Base), 3032 (Header) | Released |
| SJM Invisible trial Clinician Programmer | 3870, 3872 | Released |
| SJM Invisible trial Patient Controller | 3871, 3873 | Released |
| SJM Lead extension | 338X | Released |
| SJM Proclaim internal pulse generator (IPG) | 3660, 3662 | Released |
| SJM Prodigy IPG | 3799 | Released |
| SJM Prodigy MRI IPG | 3772 | Released |
| SJM Clinician Programmer App | 3874 | Released |
| SJM Patient Controller App | 3875 | Released |
| SJM Rapid programmer System | 3831,3382 | Released |
| Prodigy MRI Patient programmer | 3855 | Released |
| Prodigy MRI charger | 3730 | Released |
| SJM Octrode™ lead | 318X | Released |
| SJM Cinch™ Lead Anchor | 1194 | Released |
| SJM Swift-Lock™ Anchor | 1192 | Released |

- **SJM Invisible trial™ external pulse generator (EPG):** a 16 channels, software controlled, battery powered, external stimulator that generates the electrical pulses to be used during the trial phase of the study
- **SJM Invisible trial Clinician Programmer:** software compatible with iOS™ App 8.1 or later to be used on iPad mini™; enables the clinician to program the SJM Invisible trial EPG
- **SJM Invisible trial Patient Controller:** software compatible with iOS™ App 8.1 or later to be used on iPad touch™; enables patient-controlled therapy adjustment of the SJM Invisible trial EPG
- **SJM Percutaneous trial lead:** sterile stimulating electrode placed in the epidural space of the spinal cord and connected to the EPG

- **SJM Lead extension:** sterile extension that connects the pulse generator to the stimulating electrode
- **SJM Proclaim™ internal pulse generator (IPG):** a 16 channels, software controlled, battery powered, internal stimulator to be used during the follow up phase of the study that generates the electrical pulses
- **SJM Prodigy IPG:** a 16 channels, software controlled, rechargeable battery powered, internal stimulator to be used during the follow up phase of the study that generates the electrical pulses
- **SJM Prodigy MRI™ IPG:** a 16 channels, software controlled, rechargeable battery powered, internal stimulator to be used during the follow up phase of the study that generates the electrical pulses
- **SJM Clinician Programmer App:** software compatible with iOS™ App 8.3 or later to be used on iPad mini™; enables the clinician to program the Proclaim IPG
- **SJM Patient Controller App: :** software compatible with iOS™ App 8.1 or later to be used on iPad touch™; enables patient-controlled therapy adjustment of the Proclaim IPG
- **SJM Rapid Programmer™ system:** device designed to be used by the clinician to program the Prodigy MRI™ IPG
- **SJM Prodigy MRI™ Patient Programmer:** device designed to enable patient-controlled adjustment of the Prodigy MRI™ IPG
- **SJM Prodigy MRI™ Recharger:** provides the capability to recharge the Prodigy MRI™ battery
- **SJM Octrode™ lead:** sterile stimulating electrode that placed in the epidural space of the spinal cord and connected to the Proclaim IPG
- **SJM Cinch™ Lead Anchor:** securing device designed to reduce lead migration and breakage
- **SJM Swift-Lock™ Anchor:** securing device designed to reduce lead migration and breakage

### 5.2 DEVICE ACCOUNTABILITY (if applicable)

Device accountability is not required in post market studies.

## 6.0 PROCEDURES

### 6.1 STUDY FLOW CHART

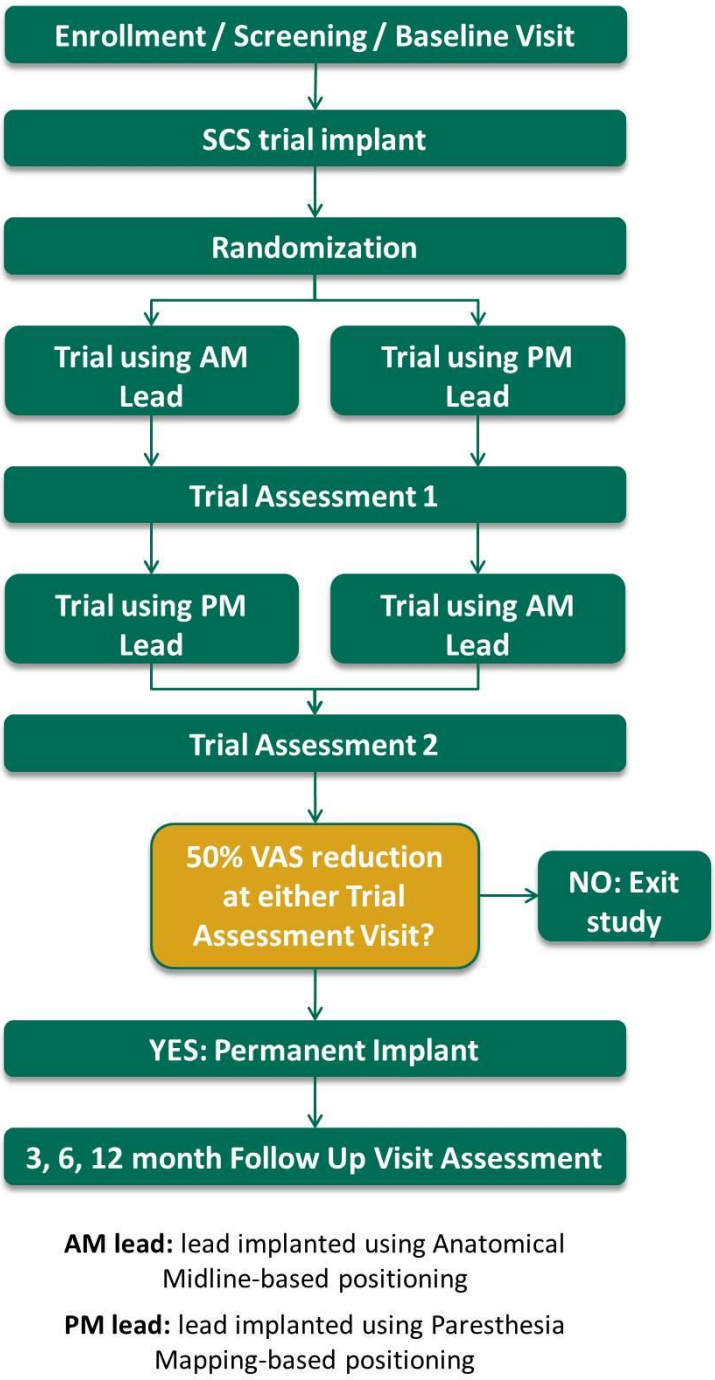



**Figure 3:** Flow Chart

## 6.2 PROCEDURES

The clinical study will be conducted in accordance with the CIP. All parties participating in the conduct of the clinical study will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

The clinical study will not commence until St. Jude Medical receives written approval from the IRB/EC and relevant regulatory authorities and all required documents have been collected from the site(s).

Table 1: List of all study specific activities/procedures

| Visit / Study Activity | Enrollment | Baseline Screening | SCS Trial | Trial Assessment 1 | Trial assessment 2 | SCS Implant procedure | Activation | Follow up Visits* |
|---|---|---|---|---|---|---|---|---|
| Informed Consent Process | X | | | | | | | |
| Inclusion/Exclusion Criteria Screening | X | | | | | | | |
| VAS assessment | | X | | X | X | | | X |
| EQ-5D questionnaire | | X | | X | X | | | X |
| ODI questionnaire | | X | | X | X | | | X |
| Provide pain diary | | | X | X | | | X | X |
| Collect pain diary | | | | X | X | | | X |
| | | | | | | | | |
| Subject Preference questionnaire | | | | | X | | | |
| Trial leads implant | | | X | | | | | |
| EPG programming | | | X | X | | | | |
| Permanent implant | | | | | | X | | |
| IPG Programming | | | | | | | X | |
| Subject Satisfaction questionnaire | | | | | | | | X |

* Follow up visit assessments will be performed after activation visit at weeks 12 (84±7 days), 26 (182±7 days), and 52 (365±7 days).

## 6.3 ENROLLMENT VISIT

The following enrollment activities are performed after the subject has been screened and must occur before any study procedure/visit.

- The principal or delegated study personnel are responsible for screening all potential subjects to determine subject eligibility for the study

- Record enrollment information (name of the study, date of consent and Inclusion/exclusion information) in the hospital records and complete and submit the Enrollment form in a timely manner (recommended within 5 days)
- Notification of enrollment to the sponsor will take place only when the sponsor receives the enrollment form

NOTE: As soon as the subject signs the Patient Informed Consent, adverse events need to be reported according to the guidelines mentioned in section 8.

If a subject does not meet all inclusion criteria or meets any of the exclusion criteria, the subject cannot participate in the study and cannot be enrolled.

In case the subject was already consented to participate in the study, but does not meet inclusion/exclusion criteria, the following actions will be taken.

If study procedure/device implant has not occurred:

- Document enrollment information (name of the study, date of consent and inclusion/exclusion) in the hospital records; complete the Enrollment and Withdrawal Forms. The form must be authorized / approved by the principal or delegated investigator.
  - Inform the subject about the withdrawal.
  - The EC/IRB and CA should be notified appropriately about any deviations with regards to obtaining the informed consent.

If study procedure/device implant has occurred:

- Document enrollment information (name of the study, date of consent and inclusion/exclusion) in the hospital records; complete the Enrollment and Withdrawal Forms. The form must be authorized / approved by the principal or delegated investigator.
  - Complete study deviation for inclusion/exclusion not met
  - The EC/IRB and CA should be notified appropriately about any deviations with regards to obtaining the informed consent.

The following activities and assessments will be performed during enrollment:

| Timing of visit | Activities at visit | Case Report Form |
|---|---|---|
| Enrollment | • Subject signs informed consent<br>• Subject is screened for inclusion/exclusion criteria<br>• Subject is enrolled | • Inclusion/Exclusion Form<br>• Enrollment Form |

### 6.4 BASELINE VISIT

Baseline screening of subjects can occur at the same visit of enrollment after the informed consent has been obtained. Subjects will be screened according to inclusion/exclusion criteria. Subjects will perform assessment of pain levels (VAS), quality of life (EQ-5D) and disability (ODI).

Subjects will be provided with a pain diary, instructed to fill it daily and return it at the SCS trial implant visit.

The following activities and assessments will be performed during baseline visit:

| Timing of visit | Activities at visit | Case Report Form |
|---|---|---|
| Baseline | • Subject assessments of current pain levels, quality of life and disability | • VAS Form<br>• EQ-5D Form<br>• ODI Form |

### 6.5 SCS TRIAL IMPLANT

During the trial implant, two SCS leads will be implanted using standard surgical techniques. One lead will be implanted using paresthesia mapping to maximize the overlap between painful regions and evoked paresthesia according to standard clinical practice. A second lead will be implanted using a novel anatomical midline-based placement. Under fluoroscopic guidance the lead will be positioned above the anatomical midline such that it extends over the T9-T10 junction. No tonic stimulation based paresthesia mapping will be performed to implant this lead. Leads will be connected to the EPG such that channels 1-8 will provide stimulation through the paresthesia mapping-based lead and channels 9-16 to the anatomical midline-based lead.

Subjects will be randomized 1:1 to either lead sequence (paresthesia lead first followed by anatomical lead or vice versa). Only stimulation programs using the lead selected by the randomization will be programmed in the EPG. When programming stimulation delivered with the lead implanted using the paresthesia-based placement, paresthesia mapping will be used to define the optimal contacts to activate. When programming stimulation delivered with the lead implanted using the anatomical-midline placement, a generalized bipolar stimulation approach will be used.

During the programming sessions, burst stimulation amplitude will be slowly increased up to the point where the subject feels any stimulation induced sensation (paresthesia, warmth, heaviness, cramping); this intensity value will constitute the Threshold for Perception (TP). Intensity will be then set at 60% of TP and the subject will be asked to move around, walk and cough. If sensations are still experienced, amplitude will be reduced in 0.05 mA steps until no sensations are experienced during the aforementioned activities. This intensity level will be used to define the target intensity and the stimulator will be programmed to allow the subjects to increase stimulation intensity up to 80% of TP. Subjects will be instructed to increase stimulation intensity slowly (by one click every two hours) if they are not experiencing pain relief. Similarly, intensity should be reduced slowly if they are experiencing increased pain, uncomfortable stimulation, heaviness or any other side effects.

Subjects will be provided with a pain diary, instructed to fill it daily and return it at the trial assessment visit 1.

The following activities and assessments will be performed during SCS trial:

| Timing of visit | Activities at visit | Case Report Form |
|---|---|---|
| SCS Trial | • SCS lead implant<br>• EPG programming<br>• Collect stimulation parameters<br>• Provide pain diary | • Surgery Form<br>• Randomization Form<br>• Programming Parameters Form<br>• VAS Pain Diary Form |

### 6.6 TRIAL ASSESSMENT 1

Two weeks after the start of the trial subject will assess therapeutic efficacy of the stimulation delivered using the lead assigned by randomization. Subjects will rate their level of pain using the VAS assessment, their quality of life using the EQ-5D questionnaire and their disability level using the ODI questionnaire.
Before any change is made, stimulation parameters used in the previous two weeks will be collected. Subsequently, subjects will cross over to stimulation delivered using the second lead. EPG stimulation programs used in the previous 2 weeks will be deleted and new stimulation programs will be programmed using the procedure detailed in the section 6.5.

Subjects will return the pain diary, be provided with a new one, instructed to fill it daily and return it at the trial assessment visit 2.

The following activities and assessments will be performed during end of anatomical lead trial visit:

| Timing of visit | Activities at visit | Case Report Form |
|---|---|---|
| Trial Assessment 1 | • Subject assessments of current pain levels, quality of life and disability<br>• Collect stimulation parameters<br>• EPG programming<br>• Collect pain diary<br>• Provide pain diary | • VAS Form<br>• EQ-5D<br>• ODI<br>• Programming Parameters Form<br>• VAS Pain Diary Form |

### 6.7 TRIAL ASSESSMENT 2

At the end of the trial, subject will assess therapeutic efficiency of the stimulation delivered in the previous two weeks. Subjects will rate their level of pain using the VAS assessment, their quality of life using the EQ-5D questionnaire, their disability level using the ODI questionnaire and their preference. If the improvement in VAS obtained at either of the two trial assessment visits is ≥50% of the baseline score, SCS trial will be considered successful and subjects will be considered for permanent IPG implant. Otherwise the subject will exit the study.

The following activities and assessments will be performed during end of anatomical lead trial visit:

| Timing of visit | Activities at visit | Case Report Form |
|---|---|---|
| Trial Assessment 2 | • Subject assessments of current pain level, quality of life and disability<br>• Collect stimulation parameters<br>• Record subject preference between stimulation delivered using the 2 leads<br>• Collect pain diary | • VAS Form<br>• EQ-5D<br>• ODI<br>• Subject Preference Form<br>• VAS Pain Diary Form |

### 6.8 SCS IMPLANT PROCEDURE

IPG will be implanted using standard surgical techniques.

The following activities and assessments will be performed during SCS implant:

| Timing of visit | Activities at visit | Case Report Form |
|---|---|---|
| SCS Implant | • IPG implant | • Surgery Form |

### 6.9 ACTIVATION VISIT

The lead activated will depend on the subject's preference following the trial. It the subject has no preference, the lead placed using the anatomic midline-based technique will be activated. Stimulation intensity will be programmed with the same method used in the SCS trial implant visit.

Subjects will be provided a pain diary and instructed to complete it on the last week before the first follow up visit.

The following activities and assessments will be performed during activation visit.

| Timing of visit | Activities at visit | Case Report Form |
|---|---|---|
| Activation | • IPG programming<br>• Provide pain diary | • Programming Parameters form |

### 6.10 SCHEDULED FOLLOW-UPS

Subjects will be followed up for 12 months. During each visit, the subjects will rate their level of pain using the VAS assessment, their quality of life using the EQ-5D questionnaire and their disability level using the ODI questionnaire. Stimulation parameters used will be collected before any change (if necessary) is made.

Subjects will return the pain diary, be provided a new one and instructed to complete it on the last week before the following follow up visit.

The following activities and assessments will be performed during follow up visits.

| Timing of visit | Activities at visit | Case Report Form |
|---|---|---|
| Follow up | • Subject assess current pain levels, quality of life and disability<br>• Collect stimulation parameters<br>• Collect pain diary<br>• Provide pain diary | • VAS Form<br>• EQ-5D Form<br>• ODI Form<br>• Programming Parameters Form<br>• VAS Pain Diary Form<br>• Subject Satisfaction Form |

### 6.11 UNSCHEDULED VISITS

An Unscheduled Visit is defined as any visit where an active study subject returns to the participating study site for medical care outside of a specified study visit. Unscheduled visits may include subjects returning to the office for an adverse event.
The visit should be documented by completing the Unscheduled Visit Form and any other applicable forms (Adverse Event, Deviation, Death and/or Withdrawal Form).

## 6.12 DESCRIPTION OF ACTIVITIES PERFORMED BY SPONSOR REPRESENTATIVES

Trained sponsor personnel may perform certain activities to ensure compliance to the clinical investigational plan and may provide technical expertise.

Sponsor personnel may:
- Provide technical support to the Investigators during trial

Sponsor personnel will not:
- Perform the informed consent process
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of a health care practitioner
- Independently collect clinical investigational data

## 6.13 SUBJECT STUDY COMPLETION

When the subject's participation in the clinical study has been completed the subject will return to the medical care as per physician's recommendation.

## 6.14 ANY KNOWN OR FORSEEABLE FACTORS THAT MAY COMPROMISE THE OUTCOME OF THE CLINICAL STUDY OR THE INTERPRETATION OF THE RESULTS

All foreseeable factors that may compromise the outcome have been taken into account by clinical study design and well-defined subject selection criteria.

Patient recruitment and retention will be monitored throughout the study and include (but are not limited to) the following activities: evaluation of the site and investigators, training of site personnel, developing site support materials, providing patient visit calendars.

## 6.15 CRITERIA AND PROCEDURES FOR SUBJECT WITHDRAWAL OR DISCONTINUATION

Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled and withdrawal from the study will not jeopardize their future medical care or relationship with the investigator. Subjects will be asked to specify the reason for the termination, but have the right not to answer.

The investigator may decide to withdraw a subject from the study at any time with reasonable rationale. The subject's future care will not be influenced by a decision, voluntary or otherwise, to withdraw from the study. All reasonable efforts should be made to retain the subject in the clinical study until completion of the study.

Reasons for subject's withdrawal include, but are not limited to:

- Subject refuses to continue participating in the study
- Subject does not meet the inclusion/exclusion criteria and does not require additional follow-up for safety reasons.
- Subject is deceased (cause must be documented)
- Subject's non-compliance
- Subject's participation is terminated by the PI or investigator, although the subject consented, since participation is no longer medically appropriate

- Subject is 'lost to follow up': Subject does not adhere to the scheduled follow up visits but has not explicitly requested to be withdrawn from the clinical study. (This does not apply to missed visits). Site personnel should at all times make all reasonable efforts to locate and communicate with the subject in order to achieve subject compliance to the scheduled follow up visits:
  1. A subject will be considered 'Lost to Follow Up' after a minimum of 2 phone calls of a physician or delegate at the investigational site to the subject or contact. These 2 phone calls need to be documented in the subject's hospital records.
  2. If these attempts are unsuccessful, a letter should be sent to the subject's last known address or general practitioner (GP) and a copy of this letter should be maintained in the subject's hospital records.

Note: If a subject misses one or more of the scheduled follow up visits (inclusive of the assigned visit windows), this will be considered as a missed visit. The subject may therefore still return for subsequent visits and will not be excluded from the study.

If a subject withdraws from the clinical study, the site will record the subject's reasons for withdrawal, on a Withdrawal CRF.

When subject withdrawal from the clinical study is due to an adverse event the subject will be followed until resolution of that adverse event or determination that the subject's condition is stable. The status of the subject's condition should be documented at the time of withdrawal.

The subject should be seen for a final study visit. At this final study visit, the subject will undergo the following evaluations:

- Identify and describe required evaluations or other procedures

## 7.0 COMPLIANCE TO CIP

### 7.1 STATEMENTS OF COMPLIANCE

The study will be performed in accordance with the most current versions of the World Medical Association (WMA) Declaration of Helsinki, ISO14155 and any regional and/or national regulations and will be compliant to this International Standard and any regional and national regulations, as appropriate.

The investigator will not start enrolling subjects or requesting informed consent from any subject prior to obtaining IRB/EC approval and Competent Authority approval, if applicable, and authorization from the sponsor in writing for the study.

In case additional requirements are imposed by the IRB/EC or Competent Authority, those requirements will be followed, if appropriate. If any action is taken by an IRB/EC, and regulatory requirements with respect to the study, that information will be forwarded to St. Jude Medical.

As sponsor, St. Jude Medical has taken up general liability insurance in accordance with the requirements of the applicable local laws. Appropriate country representative will be utilized to understand the requirements for the type of insurance that will be provided for subjects, such information will be incorporated into the informed consent, as applicable

If required, additional subject coverage or a study specific insurance will be provided by the Sponsor as well.

## 7.2 ADHERENCE TO THE CLINICAL INVESTIGATION PLAN

A deviation is defined as an event where the clinical investigator, site personnel, sponsor or sponsor representative did not conduct the clinical study according to the Clinical Investigational Plan, IRB/EC requirements or the Investigator Agreement. The investigator is not allowed to deviate from the CIP, except as specified under emergency circumstances.

In some cases, failure to comply with the CIP may be considered failure to protect the rights, safety and well-being of subjects, since the non-compliance exposes subjects to unreasonable risks. For example, failure to adhere to the inclusion/exclusion criteria: these criteria are specifically defined by the Sponsor to exclude subjects for whom the device is not beneficial and the use involves unreasonable risks. This may be considered failure to protect the rights, safety and well-being of the enrolled subject. Similarly, failure to perform safety assessments intended to detect adverse events may be considered failure to protect the rights, safety and well-being of the enrolled subject. Investigators should seek minimization of such risks by adhering to the CIP.

Simultaneously, in the event that adhering to the CIP might expose the subject to unreasonable risks, the investigator is also required to protect the rights, safety and well-being of the subject by intentionally deviating from the requirements of the CIP, so that subjects are not exposed to unreasonable risks.

It is the responsibility of the investigator to provide adequate medical care to a subject enrolled in a study.

Regulations require that the PI maintain accurate, complete, and current records, including documents showing the date of and reason for every deviation from the Clinical Investigational Plan. Relevant information for each deviation will be documented on a Deviation Case Report Form. The site will submit the CRF to St. Jude Medical.

Regulations require Investigators obtain approval from St. Jude Medical and the IRB/EC [as required] before initiating changes in or deviations from the protocol, except when necessary to protect the life or physical well-being of a subject in an emergency. Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the EC. Such deviations shall be documented and reported to the sponsor and the EC as soon as possible, but no later than 5 working days.

Prior approval must be requested when the PI anticipates, contemplates, or makes a conscious decision to depart from the CIP, except when unforeseen circumstances are beyond the investigator's control (e.g. a subject who fails to attend a scheduled follow-up visit, a subject is too ill to perform a CIP-required test, etc.). All deviations, including those beyond the investigator's control, must be reported on a CRF.

To obtain approval, the Principal Investigator may call or email and discuss the potential deviation with St. Jude Medical or designee prior to initiating any changes.

All deviations must be reported to appropriate regulatory authorities in specified timelines (if appropriate).

Investigators or the designee must notify St. Jude Medical, Inc. as soon as possible and complete the Deviation CRF.

The Investigator is required to adhere to local regulatory requirements for reporting deviations to IRB/EC.

### 7.3 REPEATED AND SERIOUS NON-COMPLIANCE

In the event of repeated non-compliance or a one-time serious non-compliance, as determined by the Sponsor, a Clinical Research Associate or clinical representative will attempt to secure compliance by one or more of the following actions:

- Visiting the investigator
- Contacting the investigator by telephone
- Contacting the investigator in writing
- Retraining of the investigator

If an investigator is found to be repeatedly non-compliant with the signed agreement, the CIP or any other conditions of the clinical study, the Sponsor will either secure compliance or, at its sole discretion, terminate the investigator's participation in the clinical study.

## 8.0 ADVERSE EVENT, ADVERSE DEVICE EFFECT, DEVICE DEFICIENCY

### 8.1 DEFINITIONS

#### 8.1.1 Medical device

Any instrument, apparatus, implement, machine, appliance, implant, software, material or other similar or related article

- Intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of
  - Diagnosis, prevention, monitoring, treatments or alleviation of disease,
  - Diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury,
  - Investigation, replacement, modification, or support of the anatomy or of a physiological process,
  - Supporting or sustaining life,
  - Control of conception,
  - Disinfection of medical devices and
- Which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means

#### 8.1.2 Adverse Event (AE)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device under study.

This definition includes events related to the investigational medical device or the comparator.
This definition includes events related to the procedures involved.

### 8.1.3 Serious Adverse Event (SAE)

An adverse event that led to:

- Death
- A serious deterioration in the health of the subject, that either resulted in:
  - A life-threatening illness or injury OR
  - A permanent impairment to a body structure or a body function OR
  - An in-patient or prolonged hospitalization OR
  - A medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body OR
  - A malignant tumor
- Fetal distress, fetal death or a congenital abnormality or birth defect

A planned hospitalization for a pre-existing condition, or a procedure required by the CIP is not considered a serious adverse event.

### 8.1.4 Adverse Device Effect (ADE)

An adverse event related to the use of an investigational medical device.

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

This definition includes any event resulting from the use error or from intentional misuse of the investigational medical device.

### 8.1.5 Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

1. **Unanticipated Serious Adverse Device Effect (USADE) [applicable to studies following ISO 14155]**

A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

2. **UADE [applicable to investigational studies following FDA regulations]**

As defined in 21 CFR §812.3, unanticipated adverse device effects (UADE) are defined as 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 clinical investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

If an unanticipated adverse device effect occurs, the investigator must notify St. Jude Medical and the IRB/MEC immediately, but no later than 10 working days of the investigator's knowledge of the event, as required by 21 CFR §812.150. St. Jude Medical will take any steps necessary to investigate the event, and will be responsible for notifying FDA and all other participating IRBs/MECs and investigators.

3. **Anticipated Serious Adverse Device Effect (ASADE)**

A serious adverse device effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

## 8.2 PROCEDURE FOR ASSESSING, RECORDING, AND REPORTING ADVERSE EVENTS, DEVICE DEFICIENCIES/COMPLAINTS, ADVERSE DEVICE EFFECTS, SERIOUS ADVERSE EVENTS, AND SERIOUS ADVERSE DEVICE EFFECTS:

Safety surveillance within this study and the safety reporting both performed by the investigator, starts as soon as the subject is enrolled in this study (date of signature of the informed consent). The safety surveillance and the safety reporting will continue until the last investigational visit has been performed, the subject is deceased, the subject/investigator concludes his participation into the study or the subject/investigator withdraws the subject from the study, except as otherwise specified in the CIP.

All adverse event data including deaths and device deficiency data (if applicable) will be collected throughout the clinical study and will be reported to the Sponsor on a dedicated case report form. The Investigator will record all adverse events and device deficiencies on the appropriate case report forms.

Records relating to the subject's subsequent medical course must be maintained and submitted (as applicable) to the Sponsor until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained. Adverse events will be monitored until they are adequately resolved. The status of the subject's condition should be documented at each visit.

The investigator will report the event to the IRB/EC per their reporting requirements.

Reportable events to sponsor are considered:

- All Adverse Device Effects
- All Serious Adverse Events (whether or not the event is considered device or procedure related and regardless the randomization group)

All above events will be reported to the Sponsor, as soon as possible, but no later than 72 hours of first learning of the event.

The Sponsor will ensure that all events and device deficiencies are reported to the relevant authorities as per regulations.

Adverse events needs to be reported using the adverse events CRF specifying date of the adverse event, treatment, resolution, assessment of both the seriousness and the relationship to the investigational device, type of treatment and status of the adverse event.

Additional information may be requested, when required, by the Sponsor in order to support the reporting of AEs to regulatory authorities.

The investigator must notify the IRB/EC, if appropriate, in accordance with national and local laws and regulations, of the AEs reported to the Sponsor.

All adverse events will be reported as per applicable regulatory requirements.

### 8.3 SUBJECT DEATH

#### 8.3.1 Procedure for recording and reporting subject death

All subject deaths are to be documented and reported to the sponsor within 72 hours after becoming aware of the event.

In event of subject's death a death and a withdrawal form should be completed. Deaths should be classified according to primary cause (cardiac, non-cardiac, unknown) and relationship to the protocol and or device. Adverse event form should be completed if appropriate.

## 9.0 DATA MANAGEMENT

Overall, the Sponsor will be responsible for the data handling.

The sponsor and/or its affiliates will be responsible for compiling and submitting all required reports to governmental agencies.

Data will be analyzed by the Sponsor and may be transferred to the Sponsor's locations outside of Europe and/or any other worldwide regulatory authority in support of a market-approval application.

St. Jude Medical respects and protects personally identifiable information that we collect or maintain. As part of our commitment, St. Jude Medical is certified to the U.S. - European Union Framework and U.S. – Swiss Safe Harbor Framework Agreements regarding human resources and subject clinical trial personal information. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data. Confidentiality of data will be observed by all parties involved at all times throughout the clinical study. All data will be secured against unauthorized access.

The following documents will be produced and maintained as part of this study:

- Informed consent form
- CRFs

The Principal Investigator or institution will provide direct access to source data during and after the clinical study for monitoring, audits, IRB/EC review and regulatory authority inspections. As required, the Principal Investigator or institution will obtain permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical study.

### 9.1 DATA MANAGEMENT PLAN

A detailed Data Management Plan will be established to ensure consistency of the data. This document will include procedures used for data review, database cleaning, and issuing and resolving data queries. If appropriate, the DMP may be updated throughout the study duration. All revisions will be tracked and document controlled.

CRF data will be captured in a validated electronic database management system hosted by St. Jude Medical.

All CRF received data for the study will be entered by trained and qualified St. Jude Medical personnel. An electronic audit trail will be used to track any subsequent changes of the entered data.

## 9.2 DOCUMENT AND DATA CONTROL

### 9.2.1 Traceability of documents and data

The investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the sponsor on the CRFs and in all required reports.

### 9.2.2 Recording data

Source documents will be created and maintained by the investigational site team throughout the clinical study.

The data reported on the CRFs will be derived from, and be consistent with, these source documents, and any discrepancies will be explained in writing.

The following data can be recorded directly in the CRFs:

- Pain VAS scores
- EQ-5D scores
- ODI scores

The CRFs will be signed and dated by the authorized site personnel. Any change or correction to data reported on a paper CRF will be dated, initialed and explained if necessary, and will not obscure the original entry.

## 10.0 MONITORING

It is the responsibility of St. Jude Medical as the sponsor of the study to ensure the study is conducted, recorded, and reported according to the approved protocol, subsequent amendment(s), applicable regulations, and guidance documents. Monitoring will be conducted according to the St. Jude Medical Clinical Monitoring standard operating procedure.

Prior to beginning the study, St. Jude Medical will contact the investigator or designee to discuss the study and data requirements. A St. Jude Medical monitor will periodically review the subject records and associated source documents.

The investigator shall make subject and study records available to the clinical monitor for monitoring.

## 11.0 REGULATORY INSPECTIONS

The investigator and/or delegate should contact St. Jude Medical immediately upon notification of a governmental agency inspection at the site. A clinical monitor or designee will assist the investigator and/or delegate in preparing for the audit.

An investigator who has authority to grant access will permit authorized governmental agency employees, at reasonable times and in reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are used or where records or results are kept).

An investigator, or any person acting on behalf of such a person with respect to the study, will permit authorized governmental agency employees, at reasonable times and in reasonable manner, to inspect and copy all records relating to the study.

An investigator will permit authorized governmental agency employees to inspect and copy records that identify subjects, upon notice that governmental agency has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator, to the Sponsor or IRB/EC have not been submitted or are incomplete, inaccurate, false or misleading.

## 12.0 STATISTICAL CONSIDERATIONS

### 12.1 STATISTICAL DESIGN, HYPOTHESES, METHOD AND ANALYTICAL PROCEDURES

VAS scores, EQ-5D scores and ODI scores will be tested for statistical differences using a repeated measures ANOVA .

### 12.2 SAMPLE SIZE

Approximately 50 patients will be enrolled in this study. Based on clinical experience atleast 80% of the subjects are expected to have a successful trial and be implanted with permanent IPGs. Enrollment will be discontinued after 40 subjects have received a permanent implant. This study is a feasibility trial; the sample power cannot be calculated because the effect size is not known. The sample size was selected to obtain early evidence and estimates of the effect size.

### 12.3 PASS/FAIL CRITERIA TO BE APPLIED TO THE RESULTS OF THE CLINICAL STUDY

The trial will be considered successful if significant pain relief can be obtained using burst stimulation in leads implanted using anatomical midline-based lead positioning.

## 13.0 DOCUMENT RETENTION

The principal investigator (PI) will maintain all clinical study documents from prior, during and (as specified) after the clinical study on file at the site for a minimum of 15 years after the termination of this study, or longer as per local laws, or when it is no longer needed to support a marketing application, whichever is later.

The PI must contact the sponsor prior to destroying or archiving off-site any records and reports pertaining to this study to ensure that they no longer need to be retained on-site.

All original subject files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the site, the investigator will notify the sponsor.

All data and documents will be made available on request of the relevant authorities in case of an audit.

The sponsor will archive and retain all essential clinical study documents from prior, during and (as specified) after the clinical study as per requirements.

These documents must be retained by the investigational site for a period of 2 years after clinical study conclusion and made available for monitoring or auditing by St. Jude Medical's representative or representatives of the FDA and other applicable regulatory agencies. The Principal Investigator must ensure the availability of source documents from which the information on the case report forms was derived.

## 14.0 AMENDMENTS TO CLINICAL INVESTIGATIONAL PLAN

Study related documents such as, the Investigator Brochure (IB), Report of Prior Investigations (RPI) CIP, CRFs, Informed Consent form and other subject information, or other clinical study documents will be amended as needed throughout the clinical study, and a justification statement will be included with each amended section of a document. Proposed amendments to the CIP will be agreed upon between the Sponsor and the coordinating investigator (if applicable).

The amendments to the CIP and the subject's Informed Consent will be notified to, or approved by, the IRB/EC and regulatory authorities, if required. The version number and date of amendments will be documented.

The amendment will identify the changes made, the reason for the changes and if it is mandatory or optional to implement the amendment.

Any amendment affecting the subject requires that the subject be informed of the changes and a new consent be signed and dated by the investigator at the subject's next follow up.

Changes to, or formal clarifications of, the CIP will be documented in writing and provided to the investigators. This information will be incorporated when an amendment occurs.

## 15.0 INVESTIGATION SUSPENSION OR TERMINATION

### 15.1 PREMATURE TERMINATION OF THE WHOLE CLINICAL STUDY OR OF THE CLINICAL STUDY IN ONE OR MORE INVESTIGATIONAL SITES

The Sponsor reserves the right to stop the study at any stage, with appropriate written notice to the investigator.

Possible reasons for early termination of the study by the sponsor, either at local, national or international level, may include, but are not limited to:

- The device / therapy fails to perform as intended
- Occurrence of USADE which cannot be prevented in future cases
- Sponsor's decision
- Recommendation from DSMB to Steering committee and Sponsor
- Request from Regulatory bodies
- Request of Ethics Committee(s)

- Concern for subject safety and welfare
- Failure to secure subject Informed Consent prior to any investigational activity
- Failure to report unanticipated adverse device effects within 72 hours to St. Jude Medical and the EC
- Repeated non-compliance with this CIP or the Clinical Trial Agreement
- Inability to successfully implement this CIP
- Violation of the Declaration of Helsinki 2008 (refer to Appendix C)
- Violation of applicable national or local laws and regulations
- Falsification of data, or any other breach of ethics or scientific principles
- Loss of or unaccounted use of investigational device inventory

The study will be terminated according to applicable regulations.

The investigator may also discontinue participation in the clinical study with appropriate written notice to the Sponsor.

Should either of these events occur, the investigator will return all documents to the sponsor; provide a written statement as to why the premature termination has taken place and notify the IRB/EC and/or the Competent Authority (if applicable). Follow-up for all enrolled subjects will be as per CIP requirements.

A Principal Investigator, IRB/EC or regulatory authority may suspend or prematurely terminate participation in a clinical study at the investigational sites for which they are responsible.

If suspicion of an unacceptable risk to subjects arises during the clinical study or when so instructed by the IRB/EC or regulatory authority, St. Jude Medical may suspend the clinical study as appropriate while the risk is assessed. St. Jude Medical will terminate the clinical study if an unacceptable risk is confirmed.

St. Jude Medical will consider terminating or suspending the participation of a particular investigational site or investigator in the clinical study if monitoring or auditing identifies serious or repeated deviations on the part of an investigator.

If suspension or premature termination occurs, the terminating party will justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The Principal Investigator and St. Jude Medical will keep each other informed of any communication received from IRB/EC or regulatory authority.

If for any reason St. Jude Medical suspends or prematurely terminates the study at an individual investigational site, St. Jude Medical will inform the responsible regulatory authority, as appropriate, and ensure that the IRB/EC are notified, either by the Principal Investigator or by St. Jude Medical. If the suspension or premature termination was in the interest of safety, St. Jude Medical will inform all other Principal Investigators.

If suspension or premature termination occurs, St. Jude Medical will remain responsible for providing resources to fulfill the obligations from the CIP and existing agreements for following up the subjects enrolled in the clinical study, and the Principal Investigator or authorized designee will promptly inform the enrolled subjects at his/her investigational site, if appropriate.

### 15.2 RESUMING THE STUDY AFTER TEMPORARY SUSPENSION

When St. Jude Medical concludes an analysis of the reasons for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, St. Jude Medical will inform the Principal Investigators, IRB/EC, or regulatory authority, where appropriate, of the rationale, providing them with the relevant data supporting this decision.

Concurrence will be obtained before the clinical study resumes from the IRB/EC or regulatory authority where appropriate.

If subjects have been informed of the suspension, the Principal Investigator or authorized designee will inform them of the reasons for resumption.

### 15.3 STUDY CONCLUSION

The study will be concluded when:

- All sites are closed AND
- The Final report generated by St. Jude Medical has been provided to sites or St. Jude Medical has provided formal documentation of study closure

## 16.0 PUBLICATION POLICY

The results of the clinical study may be submitted for publication.

A 'Publication Agreement' will be signed between the Principal Investigator and the Sponsor either as a separate Publication Agreement or within the Clinical Trial Agreement.

For more information on publication guidelines, please refer to the International Committee of Medical Journal Editors (ICMJE) on www.icmje.org.

## 17.0 BIBLIOGRAPHY

Al-Kaisy A, Van Buyten JP, Smet I, Palmisani S, Pang D, Smith T. Sustained effectiveness of 10 kHz high-frequency spinal cord stimulation for patients with chronic, low back pain: 24-month results of a prospective multicenter study. Pain Med. 2014 Mar;15(3):347-54.

Courtney P, Espinet A, Mitchell B, Russo M, Muir A, Verrills P, Davis K. Improved Pain Relief With Burst Spinal Cord Stimulation for Two Weeks in Patients Using Tonic Stimulation: Results From a Small Clinical Study. Neuromodulation. 2015 Jul;18(5):361-6.

de Vos CC, Bom MJ, Vanneste S, Lenders MW, de Ridder D. Burst spinal cord stimulation evaluated in patients with failed back surgery syndrome and painful diabetic neuropathy. Neuromodulation. 2014 Feb;17(2):152-9.

Schu S, Slotty PJ, Bara G, von Knop M, Edgar D, Vesper J. A prospective, randomised, double-blind, placebo-controlled study to examine the effectiveness of burst spinal cord stimulation patterns for the treatment of failed back surgery syndrome. Neuromodulation. 2014 Jul;17(5):443-50.

Taylor RS. Spinal cord stimulation in complex regional pain syndrome and refractory neuropathic back and leg pain/failed back surgery syndrome: results of a systematic review and meta-analysis. J Pain Symptom Manage. 2006 Apr;31(4 Suppl):S13-9. Review

## APPENDIX A: ABBREVIATIONS

Select or add abbreviations used

| Abbreviation | Term |
|---|---|
| ADE | Adverse Device Effect |
| AE | Adverse Event |
| ASADE | Anticipated Serious Adverse Device Effect |
| CA | Competent Authority |
| CCI | Clinical Coordination Investigator |
| CEC | Clinical Events Committee |
| CIP | Clinical Investigational Plan |
| CRF | Case Report Form |
| CPRB | Clinical Project Review Board |
| DD | Device Deficiency |
| DMP | Data Management Plan |
| DSMB | Data Safety Monitoring Board |
| EC | Ethics Committee |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| EMEA | Europe, Middle East, Africa |
| EPG | External Pulse Generator |
| EQ-5D | European Quality of life questionnaire 5 dimensions |
| GP | General Practitioner |
| IB | Investigator Brochure |
| ICMJE | International Committee of Medical Journal Editors |
| IPG | Implantable Pulse Generator |
| IRB | Institutional Review Board |
| ISB | Investigator Site Binder |
| ISO | International Organization for Standardization |
| MP | Monitoring Plan |
| NA | Not Applicable |
| ODI | Oswestry Disability Index |
| PI | Principal Investigator |
| POA | Power of Attorney |
| RDC | Remote Data Capture |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SC | Steering Committee |
| SCS | Spinal Cord Stimulation |
| SJM | St. Jude Medical |
| USADE | Unanticipated Serious Adverse Device Effect |
| VAS | Visual analog scale |
| WMA | World Medical Association |

## APPENDIX B: CIP REVISION HISTORY

| Revision History | | | | |
|---|---|---|---|---|
| Amendment Number | Version | Date | Rationale | Details |
| Not Applicable | VA | ddMMMyyyy | First release of CIP | NA |
| | | | | |
| | | | | |

## Appendix C: DECLARATION OF HELSINKI

The most current version of the document will be followed.

**Appendix D: LIST OF CLINICAL INVESTIGATION SITES AND IRB/EC**

A list of Clinical Investigational sites and IRB/EC will be kept under a separate cover and is available upon request.

**Appendix E: SAMPLE INFORMED CONSENT**

Study specific informed consent will be kept under a separate cover and is available upon request

**Appendix F: CASE REPORT FORMS**

Case report forms will be kept under a separate cover and are available upon request.