Reference:
SJM-CIP-10125

BOSS

"Burst Optimized Stimulation Study"

Clinical Investigation Plan (CIP)

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PRINICPAL INVESTIGATOR SIGNATURE PAGE

BOSS

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Version A

Reference #: SJM-CIP-10125

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: _____

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1.0 SYNOPSIS

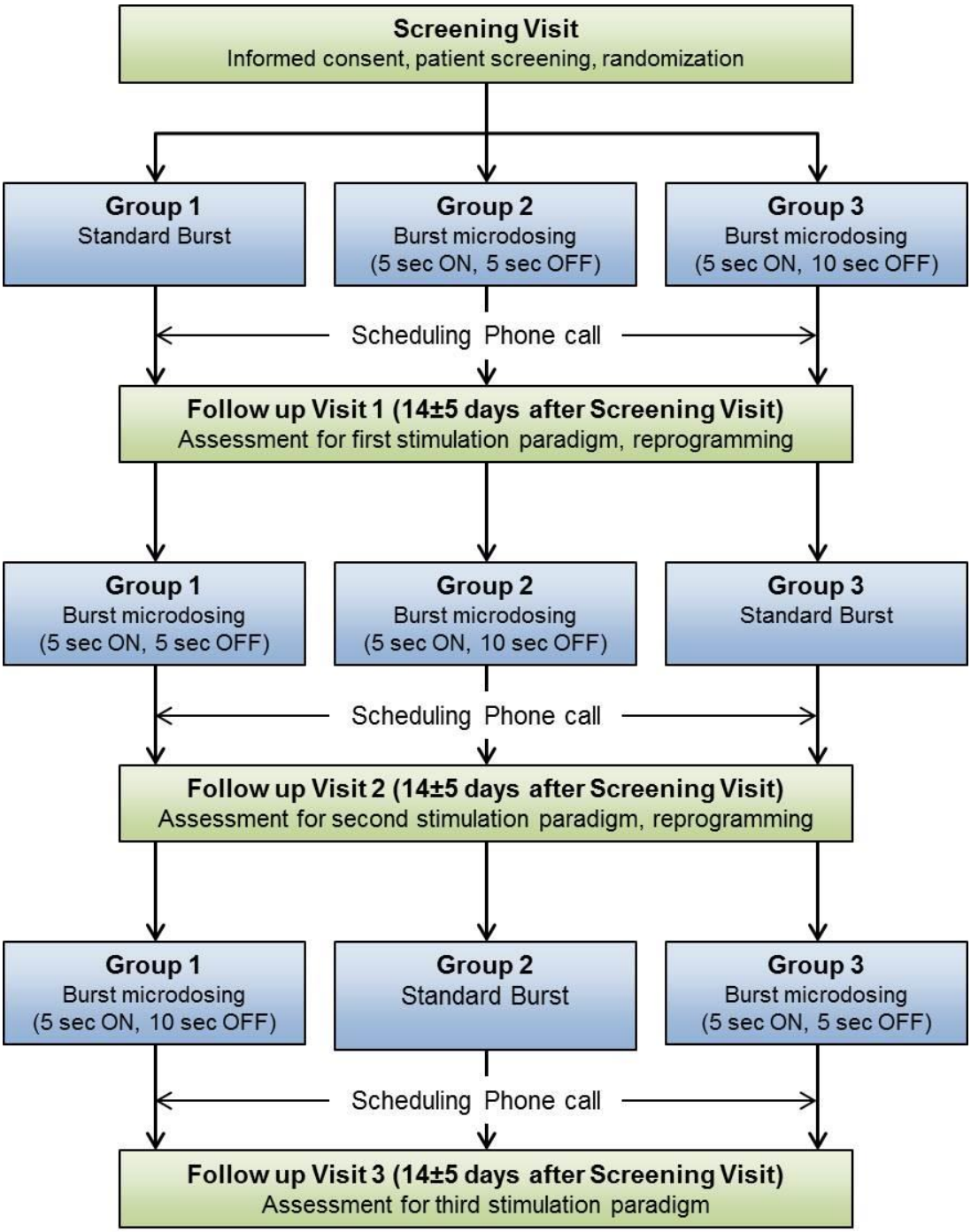
Title:	Burst Optimized Stimulation Study
Acronym:	BOSS
Purpose:	This purpose of this study is to evaluate the therapeutic efficacy of energy efficient burst microdosing stimulation paradigms in patients with chronic pain.
Primary Objectives:	To compare differences in therapeutic efficacy between conventional burst stimulation parameters (Burst train consisting of 5 pulses, Intraburst frequency: 500 Hz, Burst Rate: 40 Hz, Pulse width: 1000 µs) and energy efficient burst microdosing stimulation paradigms listed below: • Standard burst stimulation parameters with 5 seconds of STIM ON, followed by 5 seconds of STIM OFF • Standard burst stimulation parameters with 5 seconds of STIM ON, followed by 10 seconds of STIM OFF
Secondary Objectives:	To compare differences in: • Quality of life • Subject satisfaction • Patient preference • Incidence of adverse events between standard burst stimulation and the two different burst microdosing paradigms.
Primary Endpoints:	• Change in Visual Analog Scale (VAS) between baseline and follow up visits
Secondary Endpoints	Difference in • Quality of life (EQ-5D) • Subject satisfaction • Incidence rate of adverse events between standard burst stimulation and the two different burst microdosing paradigms

Design:	This is a prospective, multicenter, randomized, double-blinded crossover study designed to compare conventional burst stimulation parameters to two different burst microdosing paradigms. Subjects previously implanted with any market released St. Jude Medical (SJM) spinal cord stimulator for control of chronic intractable pain associated with a diagnosis of failed back surgery syndrome or neuropathic back and/or leg pain and currently using only burst stimulation parameters for at least 3 months will be considered for inclusion in this study. After signing the informed consent, subjects will be screened. Subjects will be randomized 1:1:1 to one of the three treatment sequences: *Group 1*: • Standard burst • 5 seconds STIM ON, 5 seconds STIM OFF, standard burst parameters • 5 seconds STIM ON, 10 seconds stim OFF, standard burst parameters *Group 2*: • 5 seconds STIM ON, 5 seconds STIM OFF, standard burst parameters • 5 seconds STIM ON, 10 seconds stim OFF, standard burst parameters • Standard burst *Group 3*: • 5 seconds STIM ON, 10 seconds stim OFF, standard burst parameters • Standard burst • 5 seconds STIM ON, 5 seconds STIM OFF, standard burst parameters Subjects will be programmed accordingly and will receive a one-week pain diary to evaluate the pain level during the first stimulation paradigm. After two weeks the subjects will return for the first follow up visit and complete questionnaires and assessments to evaluate pain, quality of life and satisfaction for the first stimulation paradigm. Subsequently subjects will be programmed with the second paradigm according to group assignment and will receive a one-week pain diary. After two weeks, subjects will return for the second follow up visit and complete questionnaires and assessments to evaluate the therapeutic efficacy of the second stimulation paradigm. Subjects will then be programmed with the third stimulation paradigm according to group assignment and receive a one-week pain diary.

	After two weeks, subjects will return for the third follow up visit and complete questionnaires and assessments to evaluate the therapeutic efficacy of the third stimulation paradigm. Subjects will express their preference between the three burst stimulation paradigms, their IPGs will be programmed accordingly and they will exit the study. Primary and secondary assessments will be compared between baseline and the two follow up visits. The total duration of the study is expected to be 6 months. The study will be conducted in a maximum of 4 centers in Europe
Devices used:	Any commercially available SJM neurostimulation system: • Implantable Pulse Generator (IPG) • IPG Charger (in case of a rechargeable IPG) • Clinician Programmer
Study Population	The study population will consist of patients with chronic pain for failed back surgery syndrome or neuropathic back and/or leg pain with an implanted commercially available SJM spinal cord stimulation device and have been using conventional burst stimulation parameters for the past three months (Burst train consisting of 5 pulses, Intraburst frequency: 500 Hz, Burst rate: 40 Hz, Pulse width: 1000 µs). Up to 40 subjects will be enrolled in this study in up to 4 centers. Of these, it is expected that 30 subjects will be successfully screened and complete the study. Patients will be considered for enrollment by the Principal Investigator as a candidate for the study at the study site if they meet the inclusion/exclusion criteria requirements, and agree to participate in the study.
Inclusion/Exclusion Criteria	<u>Inclusion Criteria</u> • Subject has been implanted with a commercially available SJM spinal cord stimulator for controlling chronic intractable pain associated with back and/or leg pain; • Subject has been exclusively using burst stimulation for at least three months; • Subject is 18 years of age or older; • Subject's pain-related medication regimen was stable in the 4 weeks prior to the screening evaluation; • Subject agrees not to add or increase pain-related medication from enrollment through the study duration; • Subject is willing to cooperate with the study requirements including compliance with the regimen and completion of all office visits;

	Exclusion Criteria • Subject is currently participating in a clinical investigation study that includes an active treatment arm; • Subject is currently receiving, applying or considering seeking workers compensation, or is involved in disability litigation; • Subject has a non SJM neuromodulation device
Data Collection	Subsequent to receiving the informed consent, subjects will be screened for inclusion/exclusion criteria. Eligible subjects will be randomized 1:1:1 to one of the treatment groups and be programmed accordingly. Subjects will be provided with a one-week diary to assess the pain relief provided by the first stimulation paradigm. During the first follow up visit, the subjects will evaluate the pain level experienced during standard burst stimulation using the Visual Analog Scale (VAS), the European Quality of Life-5 Dimension (EQ-5D) questionnaire and the subject satisfaction questionnaire. Subjects will be programmed to the second stimulation paradigm and will be provided with a one-week pain diary. During the second follow up visit, subjects will evaluate the efficacy of the second stimulation paradigm using the same assessments used in the first follow up visit. Subjects be programmed with the third stimulation paradigm and will be provided with a one-week pain diary. During the third follow up visit, subjects will evaluate the efficacy of the last stimulation paradigm using the same assessments used in previous follow up visits. Additionally, subjects will be asked to express their preference between the three stimulation paradigms. Occurrence of adverse events will be recorded through the study duration.

1.1 STUDY FLOW CHART



1.2 STUDY CONTACTS

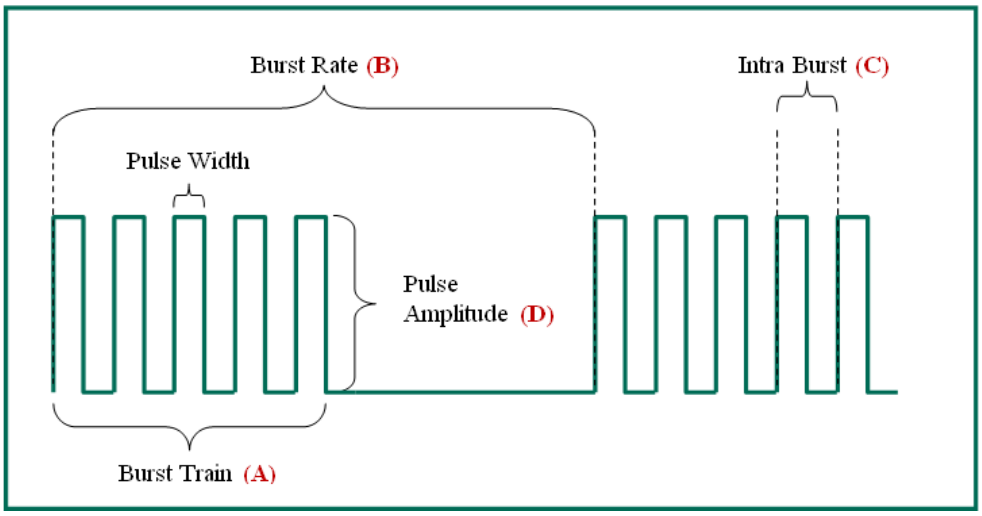
Jeff Kramer
Lalit Venkatesan
Filippo Agnesi

2.0 BACKGROUND AND JUSTIFICATION FOR CLINICAL STUDY

Spinal cord stimulation (SCS) is increasingly being used as an alternative 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 that is 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



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While the efficacy of standard burst stimulation parameters is known (Courtney et al. 2014, DeRidder et al., 2010, 2013), its comparison to more energy efficient settings is unknown.

Burst microdosing consists of delivery of intermittent doses of burst stimulation. Although there is no published information on the therapeutic efficacy of burst microdosing, anecdotal observations lead us to hypothesize its use could result in a similar clinical outcome compared to standard burst stimulation.

Use of these new energy efficient stimulation parameters has the potential to prolong the battery life of a non-rechargeable, primary cell Implantable Pulse Generator (IPG) by approximately

100% or more. It also has the potential to improve patient convenience by decreasing the frequency with which the patient has to recharge a non-primary cell IPG.

In this study, we aim to compare the therapeutic efficacy of standard burst stimulation parameters (Burst train consisting of 5 pulses, Intraburst frequency = 500 Hz, Burst Rate = 40 Hz, Pulse width = 1000 μs) to the following energy efficient burst microdosing stimulation parameters:

- Standard burst stimulation parameters with 5 seconds of STIM ON, followed by 5 seconds of STIM OFF
- Standard burst stimulation parameters with 5 seconds of STIM ON, followed by 10 seconds of STIM OFF

3.0 RISKS AND BENEFITS OF THE CLINICAL STUDY

Subjects enrolled in this study will already have an implanted IPG programmed with burst stimulation as part of their standard pain management. In this study, we propose to evaluate alternative stimulation parameters that will deliver less current compared to the parameters already programmed in the stimulators. The subjects will not be required to discontinue or interrupt any current treatment prior to enrollment. During the study, the subjects will not be allowed access to the patient programmer and therefore will not be able to adjust therapy intensity. There is a possibility that the new stimulation parameters will not provide pain relief that is equivalent to the standard stimulation parameters, but optimal pain relief is expected to return on reuse of standard burst stimulation parameters. Although not expected, it is possible that the new stimulation parameters will instead improve pain relief. Use of these two new energy efficient stimulation parameters has the potential to prolong the battery life of a non-rechargeable, primary cell IPG by approximately 100% to 200%. It also has the potential to improve patient convenience by decreasing the frequency with which the patient has to recharge a non-primary cell IPG.

3.1 DESCRIPTION OF SUBJECT POPULATION

Up to 40 subjects will be enrolled in this study in up to 4 centers. Of these, it is expected that 30 subjects will be successfully screened and complete the study. Subject will be 18 years of age or older. Subjects will already have an implanted SJM spinal cord stimulator for control of chronic intractable pain associated with a diagnosis of failed back surgery syndrome or neuropathic back and/or leg pain. Subjects will be currently using burst stimulation for at least three month as part of their clinical care.

3.2 ANTICIPATED CLINICAL BENEFITS

There are no anticipated clinical benefits over conventional burst spinal cord stimulation. The use of the alternate stimulation paradigms has the potential to prolong the battery life of a non-rechargeable, primary cell IPG by approximately 100% to 200% or to improve patient convenience by decreasing the frequency with which the patient has to recharge a non-primary cell IPG.

3.3 ANTICIPATED ADVERSE EVENTS AND ADVERSE DEVICE EFFECTS

There are no anticipated adverse events and adverse device effects in conjunction with the burst microdosing stimulation parameters. There is a possibility that the new stimulation parameters will not provide pain relief equivalent to the standard stimulation parameters, but optimal pain relief is expected to return on reuse of standard burst stimulation parameters.

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

As the alternate stimulation parameters will deliver less current compared to the standard burst stimulation received by the subjects before enrolling in the study, there will not be any additional risk to the subjects beyond those associated with spinal cord stimulation and the potential reduction of therapeutic efficacy during burst microstimulation.

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 spinal cord stimulation.

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

Subjects will be informed concerning the potential risks and benefits associated with participation in the study prior to their enrollment.

3.8 RISK-TO-BENEFIT RATIONALE

The study will use devices currently approved as part of standard pain management care. As the alternate stimulations parameters will deliver less current compared to the standard treatment received by the subjects before enrolling in the study, the only risk entailed by this study is represented by the possibility that the pain relief afforded by the alternative microdosing paradigm might be inferior to the one provided by standard burst stimulation. Sequestering the patient programmer will prevent the subjects from adjusting therapy and can represent an inconvenience to the subjects, but is necessary to ensure blinding of the subjects.

Establishing equivalency between standard burst stimulation and more energy efficient stimulation paradigm could lead to a prolonging battery life up to 200% and/or shorter time for IPG recharging. This will reduce IPG replacement surgeries in primary cell stimulators and increased patient convenience in rechargeable stimulators.

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 purpose of this clinical study is comparing differences in therapeutic efficacy between conventional burst stimulation parameters (Burst train consisting of 5 pulses, Intraburst frequency: 500 Hz, Burst Rate: 40 Hz, Pulse width: 1000 µs) to two energy efficient burst microdosing stimulation paradigms:

- Standard burst stimulation parameters with 5 seconds of STIM ON, followed by 5 seconds of STIM OFF
- Standard burst stimulation parameters with 5 seconds of STIM ON, followed by 10 seconds of STIM OFF

4.2 STUDY DESIGN AND SCOPE

This clinical feasibility study is as a prospective, double-blinded, randomized, crossover, multicenter study designed to compare efficacy of different burst stimulation parameters.

Patients recommended by the Principal Investigator as a candidate and who meet the standard requirements will be approached to participate in this study. The patient will be informed about the study to determine if he/she is interested in participating. After the patient signs the informed consent, he/she will be screened according to the inclusion/exclusion criteria. If the patient meets the study criteria, he/she will continue as a subject in the study, whereas subjects who do not meet the inclusion/exclusion criteria will exit the study. Subjects' patient programmer will be sequestered and subjects will be randomized 1:1:1 to one of the three treatment sequences:

Group 1:

- Standard burst
- 5 seconds STIM ON, 5 seconds STIM OFF, standard burst parameters
- 5 seconds STIM ON, 10 seconds stim OFF, standard burst parameters

Group 2:

- 5 seconds STIM ON, 5 seconds STIM OFF, standard burst parameters
- 5 seconds STIM ON, 10 seconds stim OFF, standard burst parameters
- Standard burst

Group 3:

- 5 seconds STIM ON, 10 seconds stim OFF, standard burst parameters
- Standard burst
- 5 seconds STIM ON, 5 seconds STIM OFF, standard burst parameters

Subject's stimulators will be programmed with the first stimulation paradigm according to the group assignment. Stimulation intensity will gradually be increased until the subject perceives the stimulation to find the Threshold for Perception (TP), and then the intensity will subsequently be reduced to the sub-perception level providing optimal pain relief. Subjects will then receive a one-week pain diary to assess the pain levels during the first assigned stimulation

paradigm. One week after this visit, the subject will be contacted to schedule the first follow up visit and instructed to start recording pain levels on the pain diary.

Two weeks after the screening visit, the subject will visit the clinic for the first follow up assessment. A Visual Analog Scale (VAS) score will be collected to determine pain levels during the first stimulation paradigm; the subject will also fill the EQ-5D and the satisfaction questionnaires administered by a clinician who is blinded to the stimulation paradigm. Subject's stimulators will be programmed with the second stimulation paradigm according to the group assignment. Stimulation intensity will gradually be increased until the subject perceives the stimulation to find the Threshold for Perception (TP), and then the intensity will subsequently be reduced to the sub-perception level providing optimal pain relief. Subjects will return the pain diary and will be provided with a new one for the assessment of the new stimulation paradigm. One week after this visit, the subject will be contacted to schedule the second follow up visit and instructed to start recording pain levels on the pain diary

Two weeks after the first follow up visit, the patient will return for the second follow up visit during which the efficacy of the second stimulation paradigm will be evaluated using the VAS, the EQ-5D and the subject satisfaction assessments administered by a clinician blinded to the stimulation paradigm. Subject's stimulators will be programmed with the third stimulation paradigm according to the group assignment. Stimulation intensity will gradually be increased until the subject perceives the stimulation to find the Threshold for Perception (TP), and then the intensity will subsequently be reduced to the sub-perception level providing optimal pain relief. Subjects will return the pain diary and will be provided with a new one for the assessment of the new stimulation paradigm. One week after this visit, the subject will be contacted to schedule the third follow up visit and instructed to start recording pain levels on the pain diary

Two weeks after the second follow up visit, the subject will return for the third follow up visit where the efficacy of the third stimulation paradigm will be assessed using the VAS, the EQ-5D and the subject satisfaction assessment. Subject will return the last pain diary and will be asked to specify their preference between the three different stimulation paradigms. After all activities are completed, the subject will exit the study.

Any unscheduled visits that occur within the study, and the reason for the visit will be documented. Stimulation related adverse events will be recorded throughout a subject's participation in the study.

The duration of each subject participation is expected to be between 6 and 8 weeks; the duration for the study is expected to be 6 months.

The clinical study will be conducted at a maximum of four centers in the European Union (EU).

An envelope-based system will be used for identifying which group the subject has been assigned. St. Jude Medical will provide sealed envelopes containing the site number and subject ID/sequence number. Inside the envelope, the randomization assignment will be identified along with the site number and subject ID/sequence number.

4.2.1 Number of subjects required to be included in the study

Up to 40 subjects will be enrolled in this study. Of these, it is expected that 30 subjects will be successfully screened and complete the study. Patients who fail screening will not participate in the study.

4.2.2 Estimated time needed to enroll this subject population

Up to 40 subjects will be enrolled in this study. Of these, it is expected that 30 subjects will be successfully screened and complete the study. Patients who fail screening will not participate in the study.

4.3 OBJECTIVES

4.3.1 Primary Objective

To compare differences in therapeutic efficacy between conventional burst stimulation parameters (Burst train consisting of 5 pulses, Intraburst frequency: 500 Hz, Burst Rate: 40 Hz, Pulse width: 1000 µs) and energy efficient burst microdosing stimulation paradigms listed below:

- Standard burst stimulation parameters with 5 seconds of STIM ON, followed by 5 seconds of STIM OFF
- Standard burst stimulation parameters with 5 seconds of STIM ON, followed by 10 seconds of STIM

4.3.2 Secondary Objective

To compare subjects' differences in quality of life, subjects' satisfaction, subjects' preference and incidence rate of adverse events between different stimulation paradigms.

4.4 ENDPOINTS

4.4.1 Primary Endpoint

Changes in Visual Analog Scale (VAS) scores between baseline and follow up visits

4.4.2 Secondary Endpoint

Difference in:

- Quality of Life (EQ-5D)
- Subject satisfaction
- Subject preference
- Incidence rate of adverse events

between standard burst stimulation and the two burst microdosing paradigms.

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 in an enrollment log, assigning an identification code linked to their names, alternative identification or contact information.

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

4.5.1 Inclusion Criteria

- Subject has been implanted with a commercially available SJM spinal cord stimulator for control of chronic intractable back and/or leg pain
- Subject has been exclusively using burst stimulation for at least three months
- Subject is 18 years of age or older
- Subject's pain-related medication regimen was stable in the 4 weeks prior to the screening evaluation
- Subject agrees not to add or increase pain-related medication from activation through the 24 week follow-up visit
- Subject is willing to cooperate with the study requirements including compliance with the regimen and completion of all office visits

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

4.5.2 Exclusion Criteria

- Subject is currently participating in a clinical investigational study that includes an active treatment arm
- Subject is currently receiving, applying or considering seeking workers compensation, or is involved in disability litigation
- Subject has a non SJM neuromodulation device

4.6 SUBJECT POPULATION

The study population will consist of patients with chronic pain for failed back surgery syndrome or neuropathic back and/or leg pain with an implanted commercially available SJM spinal cord stimulation device and have been using conventional burst stimulation parameters for the past three months as part of their clinical care.

4.6.1 Subject Screening

Patients who are recommended by the Investigator as a candidate for the study will be fully informed about the study and asked to participate in the study. In case the patient agrees, a duly signed and dated Patient Informed Consent will be obtained. Subjects will then 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.

4.6.2 Point of Enrollment

Subjects are considered enrolled in the study from the moment the subject has provided written Patient Informed Consent. (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 Ethic Committee (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 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 EC consistent with the center's EC reporting requirements.

5.0 DEVICE UNDER INVESTIGATION AND CONTROL/COMPARATORS (IF APPLICABLE)

5.1 DEVICE DESCRIPTION

Subjects with SJM commercially available spinal cord stimulation devices capable of delivering burst stimulation will be considered for participation in this study
The spinal cord stimulator system consists of the following components:

- Implantable Pulse Generator (IPG) - a software controlled, battery powered stimulator that generates the electrical pulses
- Lead - sterile stimulating electrode that is placed in the epidural space of the spinal cord
- Extensions - The IPG connects to the implanted extensions, which in turn connects to the leads
- IPG Charger - External power source that allows for recharging of the IPG internal battery (only for rechargeable IPG models)
- Clinician Programmer - Electronic device that communicates wirelessly with the IPG and allow the clinician to alter stimulation parameters and program different stimulation patterns

The device components used in the study should be manufactured by St Jude Medical Inc, commercially available, and should already be part of the pain management continuum of the subjects before study enrollment (i.e. the study will be performed on subjects that already have an implanted SCS system). Any SJM commercially available IPG capable of delivering burst stimulation, SCS lead and extension can be used in this study.

Further description of each component of a SCS system to be used in this study can be found below.

SJM Implantable pulse generator
The IPG is a 16 channel, multi-programmable system designed to be connected to a lead arrangement containing either 4 or 8 electrodes. It is powered by a hermetically sealed battery within a titanium case and uses microelectronic circuitry to generate constant current electrical stimulation. The battery can be a primary cell or a rechargeable lithium ion battery. Stimulation programs can be delivered as either single stimulation or MultiStim™ programs depending on the subject's needs.

SJM Leads
Leads consist in arrays or grids of platinum-iridium electrodes encased in a silicone sheath. Any commercially available SCS SJM lead may be used in the study.

SJM Extensions
Extensions are designed to connect the lead to the IPG. One end of the extension is designed to receive the proximal end of the lead, and the opposite end of the extension is designed for insertion and connection with the IPG. Any commercially available SCS SJM lead may be used in the study.

SJM IPG Recharger
The IPG Charging System provides the capability to recharge the IPG battery while stimulation is either on or off. The charging system has several main parts: AC line cord, AC power supply, power cable, and charger antenna. The charger transmits RF energy through the antenna to the IPG battery to recharge it. Only subjects with implanted rechargeable IPGs will use IPG rechargers.

SJM Clinician Programmer

The Clinician Programmer system is a programming component of the SCS system and is intended to provide a rapid and efficient means of programming. It is designed to be used by clinicians for the purpose of collection/transfer of stimulation parameters and noninvasive control of programmer function. The Clinician Programmer system uses a touch screen to program the stimulator to the required waveforms and electrode configurations and to log the information derived.

5.2 DEVICE ACCOUNTABILITY (if applicable)

Devices used in this study are market released and implanted in the patients prior to enrollment. So device accountability is not required.

6.0 PROCEDURES

6.1 STUDY FLOW CHART

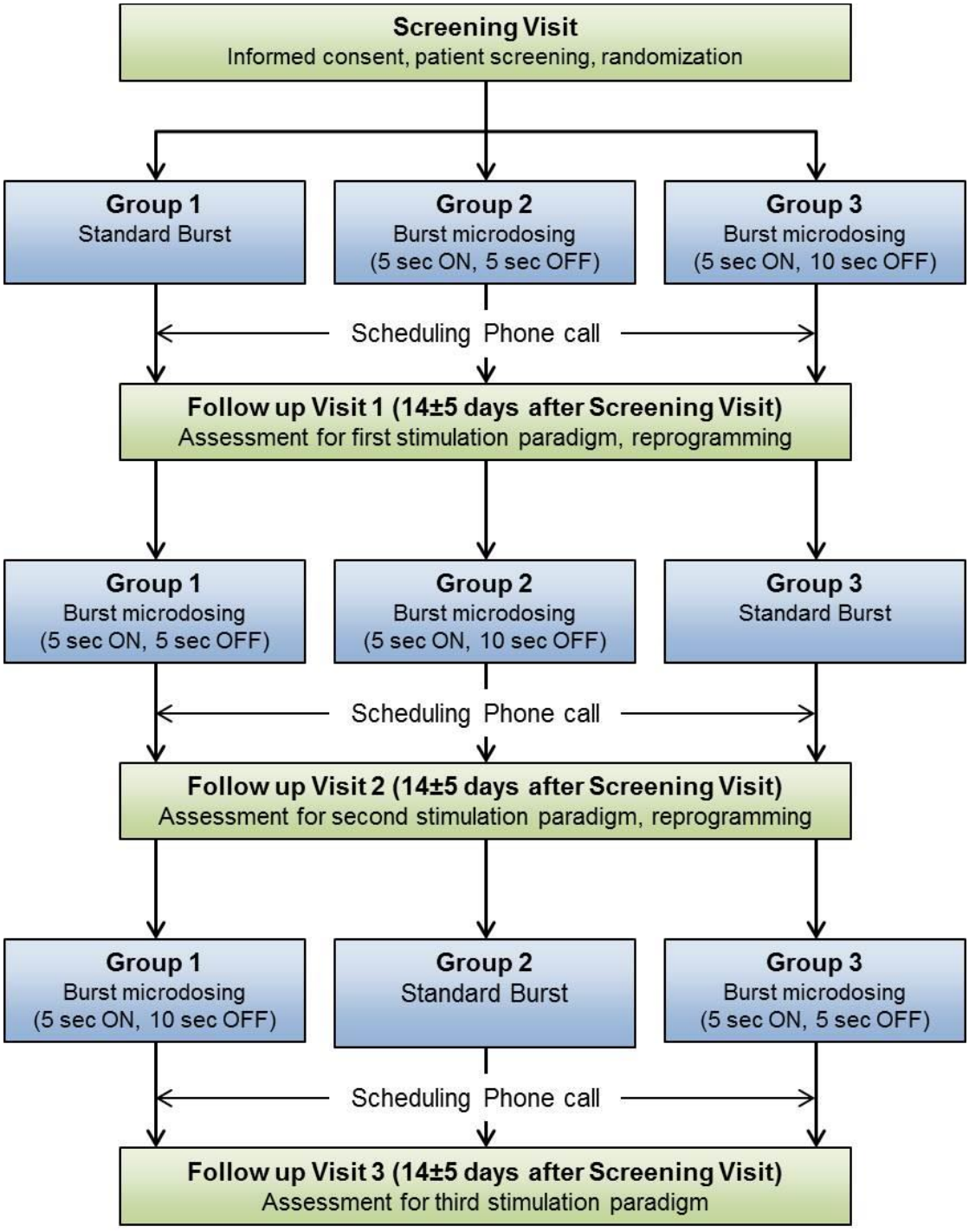

Figure 2: Flow Chart of the study

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 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	Screening	Follow up visit 1	Follow up visit 2	Follow up visit 3
Informed Consent	X			
Inclusion/Exclusion Criteria Screening	X			
Randomization	X			
Sequester patient programmer	X			
Return patient programmer				X
Provide pain diary	X	X	X	
Collect pain diary		X	X	X
VAS assessment		X	X	X
EQ-5D questionnaire		X	X	X
Subject satisfaction questionnaire		X	X	X
Collect programming parameter printouts		X	X	X
Stimulation reprogramming	X	X	X	
Document patient preference				X
Program preferred stimulation paradigm				X

Table 2: Visits Timeline

Visit	Screening	Follow up visit 1	Follow up visit 2	Follow up visit 3
Timing	At enrollment	14±5 days after screening visit	14±5 days after follow up visit 1	14±5 days after follow up visit 2

6.3 SCREENING VISIT

Enrollment of subjects will occur at the investigational sites subsequent to obtaining the EC and site-specific (if needed) approvals. Patients recommended by the Principal Investigator at the study site as a candidate and who meet the standard requirements will be approached to participate in this study. The patient will be informed about the study to determine if he/she is interested in participating. Patients who are interested in participating will first sign the informed consent form. Once the patient signs the informed consent form, they become a subject in the study.

Enrollment activities must be performed before any other study procedure/visit. Enrollment information (name of the study, date of consent) should be recorded in the clinic records, and the Enrollment form should be completed and submitted 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.

In case the subject was consented, but does not meet inclusion/exclusion criteria, the following actions will be taken:
If additional study procedures have not occurred:

- Document enrollment information (name of the study, date of consent) and inclusion/exclusion information in the clinic and/or study records; complete the Enrollment Form and all forms for the Screening visit. The forms must be authorized / approved by the principal or delegated investigator.
- The EC should be notified appropriately about any deviations with regards to obtaining the informed consent.

If additional study procedures have occurred:

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

If the subject meets the inclusion/exclusion criteria, the patient programmer will be sequestered and the subjects will be provided a one-week pain diary. Subjects will be randomized to one of the three treatment groups and their stimulator will be programmed with the first stimulation paradigm according to the group assignment. Stimulation intensity will gradually be increased until the subject perceives the stimulation to find the Threshold for Perception (TP), and then the intensity will subsequently be reduced to the sub-perception level providing optimal pain relief. Subjects will then receive a one-week pain diary to assess the pain levels during the first assigned stimulation paradigm. One week after this visit, the subject will be contacted to schedule the first follow up visit and instructed to start recording pain levels on the pain diary.

NOTE: As soon as the subject signs the Patient Informed Consent, adverse events need to be reported according to the guidelines mentioned in section 8.2.

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

Timing of visit	Activities at visit	Case Report Form
Screening	• Subject signs informed consent • Subject is screened for inclusion/exclusion criteria • Sequester Patient Programmer • Provide pain diary • Randomization • Program IPG with first stimulation paradigm according to group assignment	• Enrollment Form • Inclusion/Exclusion Form • Randomization Parameters Form

6.4 FOLLOW UP VISIT 1

During the baseline visit, the investigator will collect the pain diary provided at the screening visit and record the current stimulation parameters in the parameters form. The subject will rate the pain during the first stimulation paradigm using the VAS, the EQ-5D and the satisfaction questionnaires administered by a clinician blinded to the stimulation paradigm. Subject's stimulators will be programmed with the second stimulation paradigm according to the group assignment. Stimulation intensity will gradually be increased until the subject perceives the stimulation to find the Threshold for Perception (TP), and then the intensity will subsequently be reduced to the sub-perception level providing optimal pain relief. Subjects will be provided with a new pain diary for the assessment of the new stimulation paradigm. One week after this visit, the subject will be contacted to schedule the second follow up visit and instructed to start recording pain levels on the pain diary

The following activities and assessments will be performed during the first follow up visit.

Timing of visit	Activities at visit	Case Report Form
Follow up 1	• Collect pain diary • Programming parameters printout • Subject fills out pain assessment and quality of life questionnaires • Provide pain diary • Program IPG with second stimulation paradigm according to group assignment	• VAS Form • EQ-5D Form • User Satisfaction Form • Parameters Form

6.5 FOLLOW UP VISIT 2

During the second follow up visit, the investigator will collect the pain diary provided at the first follow up visit and record the current stimulation parameters in the parameters form. The subject will rate the pain during the first burst microdosing stimulation paradigm using the VAS, the EQ-5D and the satisfaction questionnaires administered by a clinician blinded to the stimulation paradigm. Subject's stimulators will be programmed with the third stimulation paradigm according to the group assignment. Stimulation intensity will gradually be increased until the subject perceives the stimulation to find the Threshold for Perception (TP), and then the intensity will subsequently be reduced to the sub-perception level providing optimal pain relief. Subjects will be provided with a new pain diary for the assessment of the new stimulation paradigm. One week after this visit, the subject will be contacted to schedule the third follow up visit and instructed to start recording pain levels on the pain diary

The following activities and assessments will be performed during the second follow up visit:

Timing of visit	Activities at visit	Case Report Form
Follow up 2	• Collect pain diary • Programming parameters printout • Subject fills out pain assessment and quality of life questionnaires • Provide pain diary • Program IPG with third stimulation	• VAS Form • EQ-5D Form • User Satisfaction Form • Parameters Form

	paradigm according to group assignment	

6.6 FOLLOW UP VISIT 3

During the Third follow up visit, the investigator will collect the pain diary provided during the second follow up visit and record current stimulation parameters in the parameters form. The subject will evaluate the pain relief and their quality of life provided by the third stimulation paradigm using the VAS, EQ-5D questionnaires respectively. Subjects will also express preference between the three stimulation paradigms. The investigator will program the subject with the stimulation paradigm of choice and will return the patient programmer. The subject will then exit the study.

6.7 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).

6.8 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

6.9 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.

6.10 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.

6.11 CRITERIA AND PROCEDURES FOR SUBJECT WITHDRAWAL OR DISCONTINUATION

Each subject should remain in the study until completion of the required follow up period; however, a subject's participation in the study may be discontinued at any time. Should this occur, the reason for discontinuation must be documented in the withdrawal form.

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. If subject misses a visit, the subject will be asked to fill the one week pain diary again and the latest pain diary will be used for analysis. 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.

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 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 EC or Competent Authority, those requirements will be followed, if appropriate. If any action is taken by an 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, 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 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.

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).

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 medical device under study.

This definition includes events related to the medical device.

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 a 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 medical device.

This definition includes any event resulting from the use error or from intentional misuse of the 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 will be collected throughout the clinical study and will be reported to the Sponsor on a dedicated case report form or through the EDC system. 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 EC per their reporting requirements.

Reportable events to sponsor are considered:

- All Adverse Device Effects
- All Serious Adverse Events

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.

There are no additional anticipated adverse events associated with the use of devices utilized in this study that are different than those currently identified for the commercially available neurostimulation systems.

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 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.

9.0 DATA MANAGEMENT

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

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.

During the study Clinical Report Forms will be produced to record primary and secondary outcome measures. All the clinical report forms (including informed consent, inclusion/exclusion criteria, user satisfaction and randomization) will be translated in the language used in each of the countries where the study sites will be located.

The Principal Investigator or institution will provide direct access to source data during and after the clinical study for monitoring, audits, 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

Data are captured on paper CRFs which are verified and signed by the Principal Investigator or his/her designee. Paper CRFs will be electronically sent to SJM and then 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
- Subjects satisfaction
- Subject preference

- Stimulation parameters

The CRFs will be signed and dated by the authorized site personnel. Any corrections should be made by scoring through the original value with a single line and writing the new value next to the original entry with the authorized personnel initialing and dating the new entry. Only the authorized personnel may amend or otherwise alter any data documented onto the CRF. In addition, any changes must be made on all copies of the document so that there is no difference between copies. If the reason for the correction is not obvious then, when appropriate, a brief explanation of the reason for the correction should be made. Correction fluids should never be used on any document. Before forwarding copies of completed CRFs to SJM, the Investigator/Appointed Staff Members should review their completeness, accuracy and legibility. The Investigator must always retain a copy of all completed CRFs in their file.

For CRFs that have been submitted to the Sponsor, no corrections or alterations are to be made on the CRF. Any correction, alteration, or clarification must be documented on a Data Clarification Form (DCF) and signed by the Investigator or designated staff.

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.

On-site monitoring may occur at the discretion of the sponsor. If on-site monitoring is utilized, a St. Jude Medical monitor will review the subject records and associated source documents on-site. The investigator shall make subject and study records available to the clinical monitor for monitoring.

Centralized monitoring will occur through routine internal data review. This monitoring is designed to identify missing and inconsistent data, data outliers, and potential protocol deviations that may be indicative of site non-compliance.

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 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

During baseline visit subjects will be randomized 1:1:1 to one of the three treatment sequences. An envelope-based system will be used for identifying which group the subject has been assigned. St. Jude Medical will provide sealed envelopes containing the site number and subject ID/sequence number. Inside the envelope, the randomization assignment will be identified along with the site number and subject ID/sequence number.

During reprogramming the subjects will not be made aware of what paradigm is currently being programmed. Pain questionnaires (VAS, EQ-5D, satisfaction and stimulation preference) will be administered by a clinician blinded to the currently programmed stimulation paradigm.

Scores from the subject's questionnaires as well as subject satisfaction will be compared between follow up visits using a repeated measure ANOVA under the hypothesis of equivalence between standard and burst microdosing stimulation paradigms.

12.2 SAMPLE SIZE

Considering the short time required for assessing the outcomes in each subject, we do not expect any drop-out. We will enroll up to 40 subjects, of these 30 are expected to be successfully screened and complete the study. Patients who fail screening will not participate in the study. 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.

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.

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 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.

17.0 BIBLIOGRAPHY

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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
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMEA	Europe, Middle East, Africa
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
IUD	Intrauterine Devices
MP	Monitoring Plan
NA	Not Applicable
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
TP	Threshold for sensory perception
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	02 Mar 2016	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 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 H: CASE REPORT FORMS

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