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Focal Pain Outcomes using Configurations Applied for Lateral Stimulation

FOCAL
A4068
CLINICAL INVESTIGATION PLAN

National Clinical Trial (NCT) Identified Number: NCT04073446

Sponsored By

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Original Release: January 22, 2019

Current Version: February 24, 2021

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					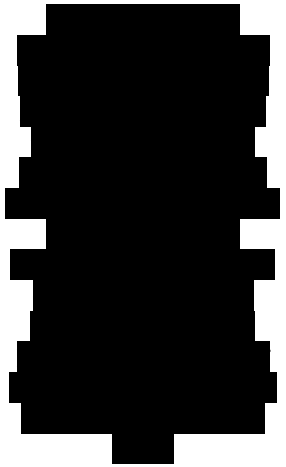	
					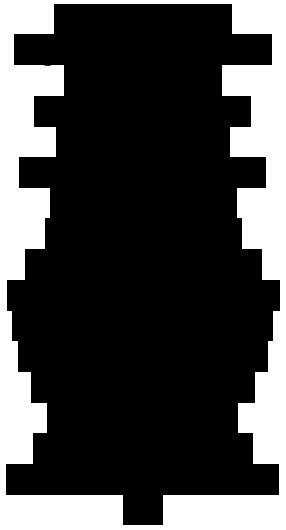	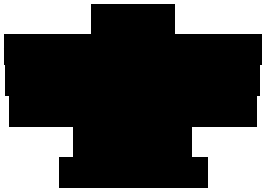

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2 Protocol Synopsis

Focal Pain Outcomes using Configurations Applied for Lateral Stimulation **FOCAL**	
Study Objective(s)	To evaluate Multiple Independent Current Control (MICC) perception and sub-perception based programming at Dorsal Column (DC) targets and Dorsal Root (DR) targets for focal foot, knee, or groin pain relief.
Device/System used in accordance with the Instructions For Use (IFU)	WaveWriter™ Boston Scientific Spinal Cord Stimulation systems.
Control Device applied as Standard of Care and sizes, if applicable	None; each subject will serve as their own control.
Study Design	Multi-center, double blind randomized controlled cross-over (Study design flow chart, see **Error! Reference source not found.**).
Planned Number of Subjects	[redacted]
Planned Number of Sites / Countries	[redacted].
Primary Endpoint	There is no primary endpoint. Collected data will be used to increase the understanding of the therapy, guide product development and help define the best practice for programming patients with focal foot, knee, or groin pain using Spinal Cord Stimulation devices.
Safety parameters	• Rate of device and/or procedure related non-serious adverse events • Rate of device and/or procedure related serious adverse events • Rate of unanticipated adverse device effects
Exploratory Endpoints	[redacted]

[redacted]

Focal Pain Outcomes using Configurations Applied for Lateral Stimulation **FOCAL**	
	[redacted]
Method of Assigning Patients to Treatment	[redacted]

[redacted]

Focal Pain Outcomes using Configurations Applied for Lateral Stimulation **FOCAL**	
	[redacted]
Follow-up Schedule	• Screening/Baseline Visit • Implant (contingent on >80% coverage of pain location in OR) Period 1 (4 ± 1.5 weeks) • Visit 1: Perception based search • Visit 2: Perception based evaluation • Visit 3: Perception based search for opposite lead Washout Period (up to 7 days) Period 2 (4 ± 1.5 weeks) • Call or Optional Visit: Perception based stimulation turn on • Visit 1: Perception based evaluation • Visit 2: Sub-perception based search (Randomized lead implant) Washout period (up to 7 days) Period 3 (6 ± 2 weeks) • Call or Optional Visit: Sub-perception based stimulation turn on • Visit 1: Sub-perception based evaluation • Visit 2: Sub-perception based search for opposite lead Washout period (up to 7 days) Period 4 visit (6 ± 2 weeks) • Call or Optional Visit: Sub-perception based stimulation turn on • Visit 1: Sub-perception based evaluation Long Term Follow up (12 ± 4 weeks) • Visit 1: Initial long-term follow-up visit • Call or Optional Visit: Long term follow-up evaluation • Visit 2: Final long-term follow-up visit = end of study
Study Duration	[redacted]
Participant Duration	[redacted]

Focal Pain Outcomes using Configurations Applied for Lateral Stimulation **FOCAL**	
	[redacted]
Inclusion Criteria	IC1. Average unilateral foot, knee, or groin pain (of neuropathic origin only) intensity of 6 or greater on a 0-10 numerical rating scale at Baseline Visit based on 7-day average NRS score IC2. Subject signed a valid, EC-approved informed consent form (ICF) IC3. Willing and able to comply with all protocol-required procedures and assessments/evaluations IC4. [redacted] IC7. 18 years of age or older when written informed consent is obtained
Exclusion Criteria	EC1. Significant cognitive impairment at Screening that, in the opinion of the Investigator, would reasonably be expected to impair the study candidates to participate in the study EC2. [redacted] EC3. Participating (or intends to participate) in another drug or device clinical trial that may influence the data that will be collected for this study EC4. [redacted]
Multiple Interventions	NA
Statistical Methods	

[redacted]

Focal Pain Outcomes using Configurations Applied for Lateral Stimulation **FOCAL**	
Primary Statistical Hypothesis	None
Statistical Test Method	Analysis of study data will include descriptive statistical methods in post-hoc analysis.
Sample Size Parameters	No power estimates were used to drive sample size calculations.

[redacted]

[redacted]

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3 Table of Contents

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4 Introduction

4.1 Chronic Intractable Pain

Chronic intractable pain is often defined as pain persisting for at least 6 months which has not responded to conservative treatment(s). The pain may be due to current or past nerve injury and can result in significant disability, reduced work productivity, reduced quality of life, and significant cost burden. Early treatments for chronic pain typically include over –the-counter and prescription medications. Later treatments like physical therapy and interventional pain procedures (e.g. intraspinal injections, vertebroplasty, pulsed RF) are attempted, sometimes followed by chronic high dose opioids and back surgery, if indicated. If back surgery is unsuccessful in relieving the chronic pain, the patient can be labeled as having failed back surgery syndrome (FBSS). Spinal cord stimulation is an option in the well-selected patient with chronic low back and/or leg pain. Such pain can lead to a number of co-morbidities, including reduced health-related quality of life, reduced ability to engage in activities of daily living, increased disability, increased emotional depression, and weight gain due to the adoption of a sedentary lifestyle. Chronic low back and/or leg pain is typically categorized as either neuropathic, which involves pathological nerve activity and is commonly characterized by patients as 'shooting' or 'burning'; nociceptive, which involves nerve signals indicating actual or impending tissue damage or inflammation (Grabois et al., 2005); or a varying mixture of neuropathic and nociceptive pain.

4.2 Conventional Spinal Cord Stimulation

SCS is effective for chronic intractable pain associated with a variety of conditions, including, but not limited to: FBSS (Carter et al., 2004, Taylor et al., 2004), complex regional pain syndrome (Sears et al., 2011), low back pain and leg pain (Cameron et al., 2004). Spinal cord stimulation (SCS) is a less invasive treatment option for FBSS but has generally been reserved for patients who have failed multiple, and indeed all possible, repeat operations. With SCS, an implanted pulse generator (IPG) delivers electrical current to electrode(s) implanted in the epidural space. This electrical current causes activation of nerves and can be programmed to direct stimulation to the nerves innervating the painful location, resulting in a reduction of the intensity of that pain (Kumar et al., 2006). Before an SCS system is implanted, a patient often undergoes a screening trial with an electrode that is connected to an external stimulator that the patient wears outside of the body. The results of the screening trial can predict the patient's outcome with an implanted system (Kumar et al., 2006).

In SCS pain relief is realized when the nerves that innervate the painful region(s) are electrically stimulated (North et al., 1990). To increase the chance of success, the electrode contacts are programmed based on the patient feedback about location of the stimulation induced paresthesia in response to various combinations of contact polarities (anodes and cathodes), pulse rate (or frequency), pulse amplitude (or current), and pulse width.

In an international multi-center RCT, Kumar et al (2007) randomized 100 patients: 48 subjects to conventional medical management alone (CMM group) and 52 subjects to SCS plus CMM (SCS group). At 6 months, patients randomized to SCS achieved significantly greater pain relief and improved functional capacity and health-related quality of life compared with patients randomized to CMM. Specifically, twenty four patients in the SCS group (48%) and four

patients in the CMM group (9%) achieved the primary outcome of 50% leg pain relief ($p < 0.001$) at 6 months. This trend continued over the duration of 12 months as reported in Kumar 2007 with the SCS group experiencing improved pain relief, quality of life and functional capacity, as well as greater treatment satisfaction ($p \leq 0.05$). At 24 months (Kumar 2008), 37% of patients in SCS group continued to achieve at least 50% pain relief versus 2% of patients in the CMM group ($p = 0.003$). The results from the PROCESS study provide evidence that SCS is effective and cost effective in relieving chronic neuropathic pain associated with FBSS.

4.3 Sub-perception Electrical Stimulation

Traditionally, SCS has relied on the understanding that to achieve pain relief, dorsal column stimulation-induced paresthesia has to be generated overlying the area of pain in order to successfully treat pain (North et al. 1991). However, recent studies indicate that effective pain relief may be obtained by employing stimulation without paresthesia.

Van Buyten et al. (Van Buyten et al. 2012) reported the outcomes of a prospective, open-label, multicenter European clinical trial that utilized high frequency (up to 10 KHz) which did not produce paresthesia. Of 82 patients, 72 reported a significant improvement in VAS scores after trial and underwent permanent implantation. At six months, 74% of patients had a greater than 50% pain relief in back pain. Al-Kaisy et al. (Al-Kaisy et al., 2014) reported the long term outcomes of this cohort at 24 months – Mean back pain was reduced from 8.4 ± 0.1 at baseline to 3.3 ± 0.3 at 24 months ($p < 0.001$), and mean leg pain was reduced from 5.4 ± 0.4 to 2.3 ± 0.3 ($p < 0.001$). At 24 months, 60% of implanted patients had a greater than 50% pain relief in back pain.

Thomson et al. (Thomson et al., 2018) reported outcomes of a multicenter, double-blind, crossover, randomized controlled trial (PROCO) that investigated the effects of rate on analgesia in kilohertz frequency (1–10 kHz) spinal cord stimulation (SCS). The sweet spot identified at 10 kHz in all patients was tested at 1, 4, 7, and 10 kHz SCS in randomized order (four weeks at each frequency). With appropriate titration of pulse width and amplitude, all frequencies resulted in equivalent pain relief ($p \leq 0.002$). The charge was not constant across all frequencies and 1 kHz stimulation required significantly less charge than higher frequencies.

DeRidder et al. (DeRidder et al 2010) reported the outcomes of a new stimulation paradigm (burst) used in 12 patients without paresthesia induction. During the trial period, an improvement of 5.25 points on VAS for axial pain for burst stimulation ($p < 0.001$) was reported versus a 1.83 points improvement for tonic stimulation. After more than 1 yr. of follow up, significant reduction in VAS scores for axial pain of 3.7 points and for limb pain of 5.15 points was noted with burst stimulation.

4.4 Lateral nerve root stimulation for focal pain

Lateral stimulation, leads placed laterally in the epidural space to target roots has been previously reported (Palmeri et al., 2012 and Sharan et al., 2008). MacDougall et al. has recently published outcomes in an open label, single site, prospective study (MacDougall et al., 2017) using lateral stimulation to target nerve roots. In the patients that recevied laterally implanted leads targeting DNR (dorsal nerve root), there was a VAS score decrease from 7.5 (SD 1.4) to

4.4 (SD 2.6). Forty seven percent of patients with permanent DNR stimulation implants achieved at least 50% pain relief. Dr. Pyles has published outcomes (Pyles et al., 2017) using lateral stimulation to target foot pain. Leads were placed antegrade through the sacral hiatus within a range of L5 - S1. The average decrease in pain was 6.3 across 9 patients. Both standard stimulation parameters and higher rates were tested. At the final follow up, 55.6% of patients were using standard based programs and 44.4% of patients were using higher rates.

4.5 Optimized lateral nerve root stimulation for focal foot, knee, or groin pain

Outcomes reported by Drs. Parrent, MacDougall, and Pyles, have shown lateral stimulation to be effective for targeting focal pain with a single lead implanted on each side. Paddle leads with multiple columns have also been used to target roots (data not published).

The purpose of this study is to explore spatial sensitivity and frequency sensitivity in sub-perception in lateral nerve root stimulation to obtain initial impressions of effects.

5 Device Description (used in accordance with the IFU)

[redacted]

6 Study Objectives and Endpoints

The objective of this study is to evaluate MICC perception and sub-perception based programming at DC and DR targets for focal pain relief. [redacted].

The following Safety parameters will be collected in the study:

- Rate of device and/or procedure related non-serious adverse events
- Rate of device and/or procedure related serious adverse events

[redacted]

[redacted]

7 Study Design

*: Randomization

Figure 7-1: FOCAL Main-Study Design Flowchart

[redacted]

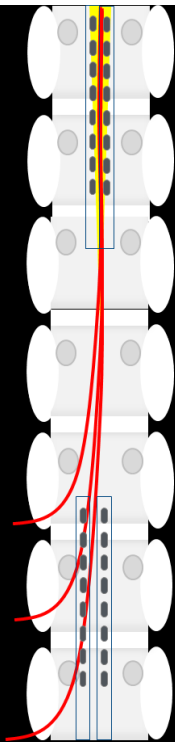
[redacted]

[redacted]

8 Surgical Methodology

Subjects with a history of unilateral neuropathic foot, knee, or groin pain will be enrolled.

[redacted]



[redacted]

[redacted]

9 Study Design

[redacted]

9.2.1 Treatment and Control

This study compares two stimulation implant locations, DC and DR, with both perception based and sub-perception types of stimulation. The cross-over study design allows for comparing these treatments using one of the stimulation types as an active control.

9.3 Justification for the Study Design

[redacted]

[redacted]

10.2 Inclusion Criteria

Subjects who meet all of the following criteria (see Table 10.2-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 10.3) is met.

Table 10.2-1: Inclusion Criteria

Inclusion Criteria	IC1. Average unilateral foot, knee, or groin pain (of neuropathic origin only) intensity of 6 or greater on a 0-10 numerical rating scale at Baseline Visit based on 7-day average NRS score IC2. Subject signed a valid, EC-approved informed consent form (ICF) IC3. Willing and able to comply with all protocol-required procedures and assessments/evaluations IC4. [redacted] IC7. 18 years of age or older when written informed consent is obtained

10.3 Exclusion Criteria

Subjects who meet any one of the following criteria (Table 10.3-1) cannot be included in this study or will be excluded from this clinical study.

Table 10.3-1: Exclusion Criteria

Exclusion Criteria	EC1. Significant cognitive impairment at Screening that, in the opinion of the Investigator, would reasonably be expected to impair the study candidates to participate in the study EC2. [redacted] EC3. Participating (or intends to participate) in another drug or device clinical trial that may influence the data that will be collected for this study EC4. [redacted]

11 Subject Accountability

11.1 Point of Enrollment

A subject will be considered enrolled in this study after he/she signs and dates the informed consent form (ICF). No study-related procedures or assessments can take place until the informed consent form is signed. Patients with a failure to find the Sweet Spot (paresthesia overlap with pain) at neither the DC nor the DR leads during OR testing will be withdrawn from the study. All applicable case report forms (CRFs) up to the point of subject withdrawal and an "End of Study" form must be completed. Additional data may no longer be collected after the point at which a subject has been withdrawn from the study. Data collected up to the point of subject withdrawal may be used and analyzed. These patients will not be count towards the enrollment ceiling.

11.2 Withdrawal

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

Reasons for withdrawal could include but are not limited to:

Physician discretion

- Subject's choice to withdraw consent;
- Subject's failure to meet inclusion or not meet exclusion criteria after enrollment but prior to first study related programming
- Failure to find the Sweet Spot (paresthesia overlap with pain) at neither the DC nor DR leads during OR testing
- Subject is lost to follow-up or
- Subject's death

While study withdrawal is discouraged, subjects may withdraw from the study at any time, with or without reason, and without prejudice to further treatment.

All applicable case report forms (CRFs) up to the point of subject withdrawal and an "End of Study" form must be completed. Any subject deemed "lost to follow-up" should have a minimum of three documented attempts to contact him/her prior to completion of the "End of Study" form.

Additional data may no longer be collected after the point at which a subject has been withdrawn from the study or withdraws consent, for whatever reason. All open adverse events should be closed or documented as unresolved. Data collected up to the point of subject withdrawal may be used and analyzed.

Withdrawn subjects will not be included in the site's overall total for subjects.

11.3 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for 1 of the programming visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required programming visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.

Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

11.4 End-of-Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit shown in the Data Collection Schedule.

The end of the study is defined as completion of the last visit or procedure shown in the Data Collection Schedule in the trial.

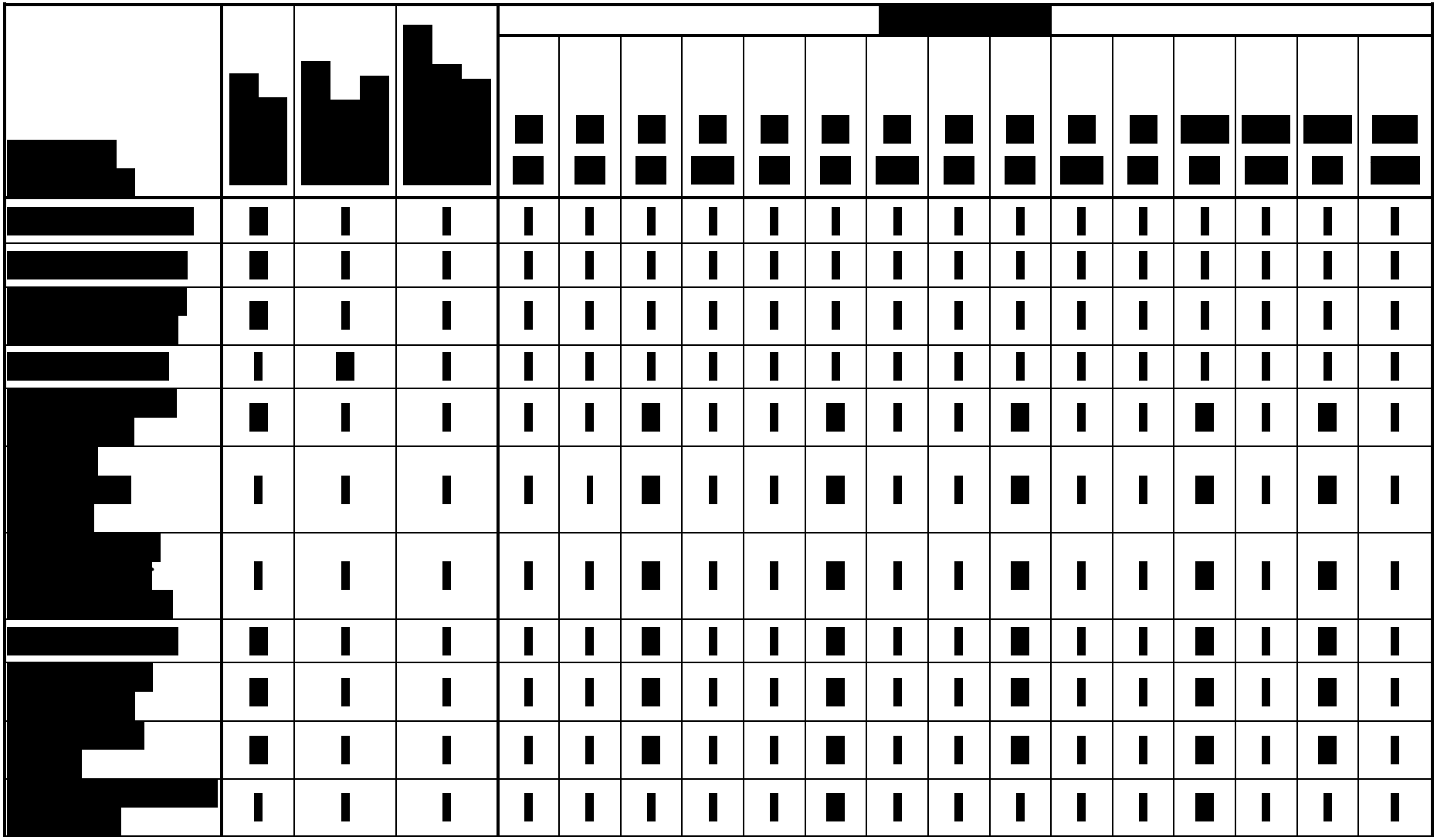
12 Study Methods

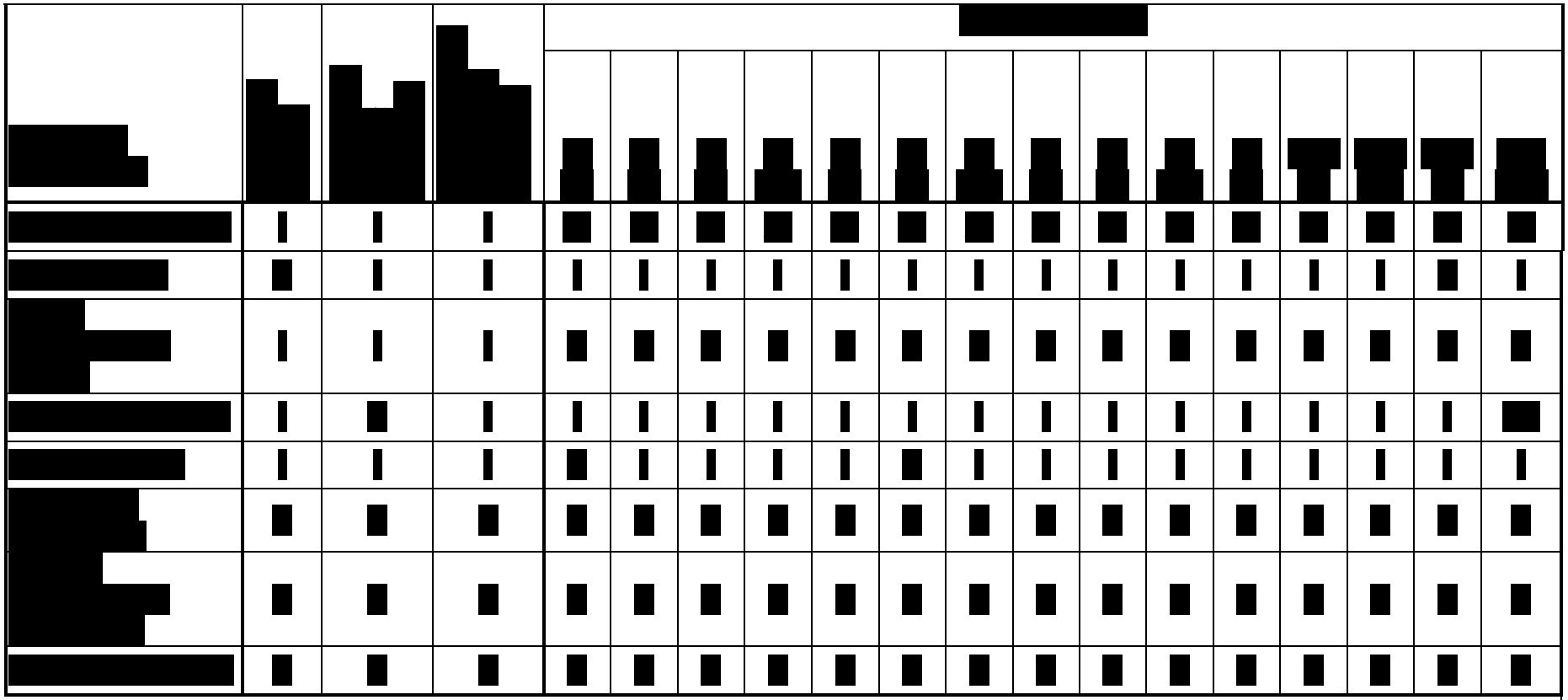
12.1 Data Collection

The data collection schedule is shown in Table 12.1-1 and

Table 12.1-2, as well as described below.

Table 12.1-1: Data Collection Schedule Main-Study





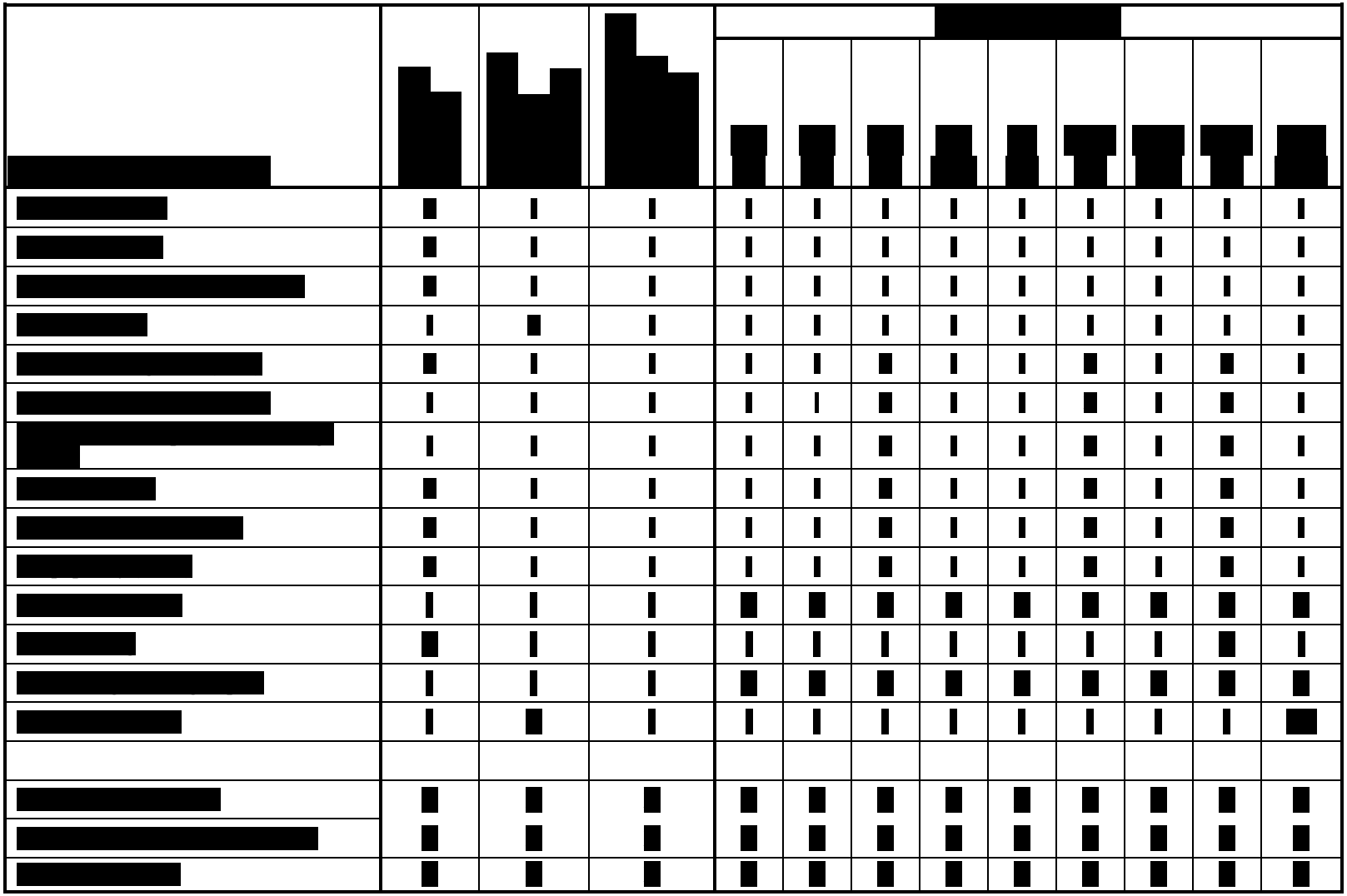
Note: The patient will be filling out a Pain Diary daily throughout the study

**: In the event that Investigator suspects lead migration, per standard of care

#: for all stim combos tested

[redacted]

Table 12.1-2: Data Collection Schedule Sub-study



**: In the event that Investigator suspects lead migration, per standard of care

12.1.1 Pain Diary

The patient will be asked to collect information about their pain on a daily basis with an eDiary. A paper version of the diary will be included as a backup if the eDiary malfunctions or the patient experiences difficulties with the eDiary recordings.

The eDiary is compact wrist-worn electronic diary manufactured by CamNtech Ltd programmed specifically for this study. Data entry is interactive and based on a series of questions and is dated and time stamped. Specific training materials for the use of the eDiary will be provided to each study subject.

Figure 12-1: CamNtech Ltd eDiary

Subjects who meet the applicable inclusion and none of the exclusion criteria will be given an eDiary to capture daily pain intensity assessments two times a day (morning and evening). Activity data will be collected automatically via an accelerometer.

An alarm will sound at these times to ask subjects to report information. If the subject fails to enter the required information, the data for that event will be classified as missing.

12.1.2 EQ-5D 5 Level (EQ-5D-5L)

EQ-5D-5L is comprised of a descriptive system and a visual analogue scale. The descriptive system measures quality of life along five dimensions, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with five levels for each dimension from which subjects are asked to select one.

12.1.3 Numeric Rating Scale (NRS)

NRS will be used to measure the pain intensity, enabling the subject to express the severity of pain by giving it a numerical value from 0 to 10.

12.1.4 Oswestry Disability Index (ODI)

Oswestry Disability Index is a commonly used scale for back pain subjects with a neuropathic pain component. The test is considered the ‘gold standard’ of low back functional outcome tools.

12.1.5 Patient Satisfaction with Treatment (PSWT)

The Patient Satisfaction With Treatment survey will be used at the end of each Period and at end of study.

[redacted]

12.1.6 Patient Global Impression of Change (PGI-C)

PGI-C is a standard seven-point scale used to assess the SCS outcome.

12.1.7 Pittsburgh Sleep Quality Index (PSQI)

PSQI is a self-rated questionnaire assessing sleep quality and disturbances. This questionnaire includes 19 individual items grouped into 7 component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of these 7 scores yields a single global score.

12.1.8 Procedure Information

General information will be collected regarding the SCS procedures performed during the study, including leads used, locations at test/implant and AP fluoroscope image.

12.1.9 Programming Parameters

[redacted]

12.2 Study Candidate Screening

The study clinicians will use the medical record to assess the likelihood that the subject will meet all the inclusion criteria (Table 10.2-1: Inclusion Criteria) and none of the exclusion criteria (Table Table 10.3-1: Exclusion Criteria). Those subjects who are deemed as having a high likelihood of meeting these requirements will be contacted regarding their interest in study participation

12.3 Informed Consent

Written Informed Consent must be obtained for all patients who are potential study candidates. Subjects will be asked to sign the Informed Consent form before any study-specific tests or procedures are performed. The context of the study must be fully explained to the subject in language that is easily understood by the subject. The subjects must also be given the opportunity to ask questions and have those questions answered to their satisfaction. The Informed Consent form is study specific and must be approved by the study Independent Ethics Committee (IEC). Study personnel should explain that even if a subject agrees to participate in the study and signs an ICF, certain diagnostic or screening procedures might demonstrate that the subject is not eligible to continue (see Table 10.2-1: Inclusion Criteria and Table 10.3-1: Exclusion Criteria).

[redacted]

12.3.1 Post-Consent Eligibility Validation

Certain inclusion criteria will be confirmed only after the patient has provided the written informed consent and if they are not met, the subject will be withdrawn from study participation. The withdrawn patients will continue their treatment per center's standard of care.

12.4 Screening/Baseline Period (within 90 days prior to Implant procedure)

Visit type: period at home + office

[redacted]

12.5 Lead + IPG Implant Visit

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12.15 Study Completion

Each subject's participation in the study will be considered complete upon completion of the End of Study Visit or upon subject withdrawal. Upon completing participation in the study subjects will continue to be followed per center's standard of care practice.

12.16 Source Documents

It is preferable that original source documents are maintained, when available. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. Source documentation includes but is not limited to those items noted in Table 12.16-1.

[redacted]

Table 12.16-1: Source Documentation Requirements

Requirement	Disposition
Hospital records or clinical and office charts including the evidence of but not limited to inclusion/exclusion criteria, informed consent, procedures, and assessment of adverse events	Retain at center
Programming Pre- and Post-visit Reports (program settings, impedance measurements, program usage, battery voltage etc)	Retain at center and send copy to Boston Scientific
Lead Fluoro images	Retain at center and send copy to Boston Scientific
Clinical evaluations (e.g.NRS, PSWT, PGIC etc.)	Retain at center
Pain Diary information	Retain at center and send copy to Boston Scientific

13 Statistical Considerations

13.1 Endpoints

13.1.1 Primary Endpoint

Due to the exploratory nature of the study, no prospectively defined, hypothesis driven primary endpoint will be defined.

13.1.1.1 Hypotheses

No formal hypotheses have been defined.

13.1.1.2 Sample Size

The sample size has not been determined in prospective manner.

13.1.1.3 Statistical Methods

Descriptive statistics will be employed

13.1.2 Exploratory Endpoints

A number of exploratory endpoints are included in this study to explore the effect of treatment on additional outcomes. The exploratory endpoints are intended to generate hypotheses for future study. Consequently, no correction for multiple testing will be performed for the exploratory endpoints. All exploratory endpoints will be clearly identified as such in study reports

13.2 General Statistical Methods

13.2.1 Analysis Sets

All endpoints described below may be analyzed on both intent-to-treat and a per-protocol basis.

13.2.2 Control of Systematic Error/Bias

Selection of subjects will be made from the Investigator's usual subject pool. All subjects meeting the inclusion/exclusion criteria and having signed the Informed Consent Form will be eligible for participation in the study. The reasons for exclusion will be indicated.

13.2.3 Number of Subjects per Investigative Site

[redacted]

13.3 Data Analyses

All data analysis will be performed using standard methods and tools, with appropriate validation when needed. Continuous variables will be summarized using descriptive statistics, which includes number of non-missing observations, mean, median, standard deviation, minimum, maximum or 95% confidence interval. For categorical variables, descriptive statistics include frequencies and percentages of categories.

13.3.1 Other Endpoints/Measurements

A number of exploratory endpoints are included in this study to explore the effect of treatment on outcomes. The exploratory endpoints are intended to generate hypotheses for future study. Consequently, no correction for multiple testing will be performed for the exploratory endpoints. Exploratory endpoints will be clearly identified as such in study reports.

13.3.2 Interim Analyses

No formal interim analyses are planned for the purpose of stopping this study early for declaring effectiveness or futility. Handling of drop-outs and missing data will depend on their frequency and the nature of the outcome measure.

13.3.3 Subgroup Analyses

Subgroup analyses will be carried out as needed in this exploratory study.

13.3.4 Justification of Pooling

No analyses to justify pooling of data will be undertaken in this exploratory study.

13.3.5 Multivariable Analyses

No formal covariate analyses are planned.

13.3.6 Other Analyses

No other formal analyses are planned.

[redacted]

14 Data Management

14.1 Data Collection, Processing, and Review

The questionnaires & CRF forms collected on paper will be transmitted from the site via fax, mail or email and stored on the secure server.

Paper and/or electronic diaries will be completed by the subject and original paper diaries (if used) will be returned and stored at the center. Electronic diaries will be downloaded onto a computer at the center to transfer data for later processing.

14.2 Data Retention

The Principal Investigator or his/her designee or Investigational site will maintain all essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements.

The Principal Investigator or his/her designee will take measures to prevent accidental or premature destruction of these documents. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Sites are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

14.3 Core Laboratories

No Core Laboratories will be used in the study.

15 Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor, the reviewing EC, and the regulatory authority if applicable, of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using the corresponding CRF. Sites may also be required to report deviations to the EC, and the regulatory authority, per local guidelines and national/government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including EC & CA notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

The sponsor will not approve protocol waivers.

[redacted]

16 Compliance

16.1 Statement of Compliance

This clinical investigation is financed by the study sponsor. Before the investigational site can be "Authorized to Enroll," the investigational site must enter into a Clinical Study Agreement with the sponsor that details the financing of the study as well as the rights and obligations of the investigational site and the investigator. This study will be conducted in accordance with ISO 14155: Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice ethical principles that have their origins in the Declaration of Helsinki, European Medical Device Regulation and applicable individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the EC and/or regulatory authority has been obtained, if appropriate. Also, the study shall not begin prior to issuance of the site Authorization to Enroll, as provided by the sponsor. Any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.

16.2 Investigator Responsibilities

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan/, the spirit of ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency.
- Report to sponsor, per the protocol requirements, all reportable events.

- Report to the EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential USADE, if required by applicable laws or regulations or this protocol or by the EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Maintain the device accountability records and control of the device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions for use.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the device when it is used/operated by the subject.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.

- All investigators will provide their qualifications and experience to assume responsibility for their delegated tasks through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.

16.2.1 Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training, are competent to perform the tasks they have been delegated and adequate supervision of those to whom tasks are delegated. Where there is a sub-investigator at a site, the sub-investigator should not be delegated the primary supervisory responsibility for the site. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

16.3 Institutional Review Board/ Ethics Committee

The investigational site will obtain the written and dated approval/favorable opinion of the EC for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required.

A copy of the written EC and/or competent authority (CA) approval of the protocol (or permission to conduct the study) and ICF, must be received by the sponsor before recruitment of subjects into the study. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Any amendment to the protocol will require review and approval by the EC before the changes are implemented to the study. All changes to the ICF will be EC approved; a determination will be made regarding whether a new ICF needs to be obtained from participants who provided consent, using a previously approved ICF.

Annual EC approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or EC requirements. Copies of the study reports and the EC continuance of approval must be provided to the sponsor.

16.4 Sponsor Responsibilities

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC and will be kept confidential in accordance with all applicable laws and regulations. Only authorized BSC personnel and/or a BSC representative including, but not limited to Contract Research Organization (CRO), will have access to this information. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

[redacted]

[redacted]

16.5 Insurance

Where required by local/country regulation, proof and type of insurance coverage, by BSC for subjects in the study will be obtained.

17 Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The sponsor will put a plan in place to document the specific monitoring requirements.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

18 Potential Risks and Benefits

18.1 Instructions for Use

Please refer to the Instructions for Use for an overview of anticipated adverseeffects and risks associated with the device(s).

18.2 Risks associated with Participation in the Clinical Study

During the study the patients will be treated with different types of stimulation. Patients may find certain stimulation parameters to be less effective than others at reducing their pain, and they might experience stimulation-related side effects including, but not limited to, muscle spasm and discomfort, which the physician will address as per standard of care. This study is set up to collect data through questionnaires and diary. To complete these questionnaires, patients may spend additional time at the hospital compared to standard of care. Patients may have an increased number of visits to the doctor’s office compared to standard of care. Patients may find it difficult, uncomfortable or tiresome to complete study visits, the pain diary and/or questionnaires.

Patients who receive the device are subject to the same risks as patients outside of this study who receive the same or other similar commercial devices. However, there are additional risks

related to the implantation of up to 2 electrodes at the lower level of the spine compared with the implantation of the electrodes at the standard level of the spine. In addition, there is also a higher risk related to the number of electrodes implanted in the study (up to 4 electrodes) compared with the number of electrodes implanted as standard of care (2 electrodes only).

The physician will explain to the patients the risks of the implant procedure, use of spinal cord stimulation and the known and significant interactions associated with the WaveWriter™ Technology and other medical procedures. All these are not considered part of the study and are done per standard of care.

18.3 Possible Interactions with Concomitant Medical Treatments, if applicable

No possible interactions have been identified for use of the SCS system concomitant with any specific medications.

Please refer to the Instructions for Use Manual for procedures that should not be used while the SCS system remains implanted.

18.4 Risk Minimization Actions

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

18.5 Anticipated Benefits

The reported benefits of the WaveWriter™ SCS System may include:

- Reduction in the intensity of chronic low back pain
- Reduction in the intensity of chronic leg pain
- Improvement in physical functioning (disability)
- Reduction in pain-related medication use
- Reduction in the occurrence of side-effects of pain-related medications accompanied by reduction in opioid use (e.g. sleep disturbances, constipation, reduction in mental acuity)

18.6 Risk to Benefit Rationale, if applicable

Based on a risk evaluation the potential benefits provided by the WaveWriter™ SCS™ systems to treat chronic intractable pain outweighs residual risks.

19 Safety Reporting

19.1 Reportable Events by investigational site to Boston Scientific

It is the responsibility of the investigator to assess and report to BSC any event which occurs in any of following categories:

- All Adverse Events related to Procedure and/or Device (Hardware and/or Stimulation)
- All Serious Adverse Events regardless of relationship to Procedure, Device Hardware or Stimulation
- All Device Deficiencies
- Unanticipated Serious Adverse Device Effects
- New findings/updates in relation to already reported events

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and/or device deficiency.

Any reportable event, experienced by the study subject after informed consent, whether prior to, during or subsequent to the procedure, must be recorded in the CRF.

Underlying diseases and chronic conditions are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of one (1) specific SAE (see

Table 19.2-1 for AE definitions).

Refer to Instructions for Use for the known risks associated with the device(s).

19.2 Definitions and Classification

Adverse event definitions are provided in

Table 19.2-1. Administrative edits were made on the safety definitions from ISO 14155 and EU 2017/745for clarification purposes.

Table 19.2-1: Definitions and Classification

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the study medical device and whether anticipated or unanticipated.. **NOTE 1**: This includes events related to the study medical device or comparator. **NOTE 2**: This definition includes events related to the procedures involved. **NOTE 3**: For users or other persons, this definition is restricted to events related to the study medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of the study medical device **NOTE 1**: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the study medical device. **NOTE 2**: This definition includes any event resulting from use error from intentional misuse of the study medical device. **NOTE 3**: This includes 'comparator' if the comparator is a medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event that led to any of the following: a) death, b) serious deterioration in the health of the subject, users or other persons as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic diseases, or 3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) Led to foetal distress, foetal death, or a congenital abnormality or birth defect including physical or mental impairment.. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Term	Definition
Ref: ISO 14155 *Ref: MEDDEV 2.7/3*	
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	An inadequacy of a medical device related to its identity, quality, durability, reliability, usability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. **NOTE 2**: This definition includes device deficiencies related to the investigational medical device or the comparator.
The following definitions will be used for defining hospitalization or prolongation of hospitalization for SAE classification purposes:	
Hospitalizations	Hospitalization does not include: • emergency room visit that does not result in in-patient admission Note: although an emergency room visit does not itself meet the definition for hospitalization, it may meet other serious criteria (e.g. medical or surgical intervention to prevent permanent impairment or damage) • elective and pre-planned treatment/surgery for a pre-existing condition that is documented in the subject's record at the time of consent/enrollment

Term	Definition
	• admission for social reasons and/or respite care in the absence of any deterioration in the subject's general condition (e.g. subject is homeless, caregiver relief) • pre-planned, protocol-specified admission related to the clinical study (e.g. procedure required by protocol)
Prolongation of hospitalization	In-patient admission to the hospital that is prolonged beyond the expected standard duration for the condition under treatment. Note: new adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criteria.

19.3 Relationship to Device(s) and/or Study Procedure

The Investigator must assess the relationship of the reportable AE to the device, (device hardware and/or stimulation) and/or study procedure. See criteria in Table 19.3-1.

Table 19.3-1: Criteria for Assessing Relationship of Study Device, Stimulation or Procedure to Adverse Event

Classification	Description
Not Related *Ref: MEDDEV 2.7/3*	Relationship to the device, comparator or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the study device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the study device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Possibly Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the study device or comparator, or the relationship with procedures is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the study device, comparator, or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.

Table 19.3-1: Criteria for Assessing Relationship of Study Device, Stimulation or Procedure to Adverse Event

Classification	Description
Causal Relationship *Ref: MEDDEV 2.7/3*	The serious event is associated with the study device or comparator or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with the study device use/application or procedures; - the event involves a body-site or organ that -the study device or procedures are applied to; -the study device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the study device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

[redacted]

19.4 Investigator Reporting Requirements

The communication requirements for reporting to BSC are as shown in the Table 19.4-1 below.

Table 19.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline post-market studies*** (MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Unanticipated Serious Adverse Device Effect	Complete AE CRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event for applicable study*.. • Terminating at the end of the study. *Applicable study= post market interventional study non-standard of care
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon request of sponsor
Serious Adverse Event	Complete AE CRF page with all available new and updated information.	• Within 10 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon request of sponsor
Serious Adverse Device Effects*	Complete AE CRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon request of sponsor

[redacted]

Event Classification	**Communication Method**	**Communication Timeline post-market studies*** (MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete Device Deficiency Form with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event. Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor
Adverse Device Effects*	Complete AE CRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner(e.g. recommend within 30 business days) after becoming aware of the information • Reporting required through the end of study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor

*includes events related to device (hardware and/or stimulation) and/or procedure

The investigator must report Adverse Device Effects, Serious Adverse Events (regardless of relationship to device (hardware and/or stimulation) and/or procedure), Unanticipated Serious Adverse Device Effects, and Device Deficiencies for each subject from the time of Information Consent through the end of study participation.

The Investigator must assess the potential relationship of all adverse events to the study device and/or to study procedures.

- Adverse events must be assessed according to their relationship to one of the following categories:
    - Study Device Related AEs: AEs that can reasonably (i.e. Unlikely, Possibly, Probably and Causally Related) be attributed to a study device hardware and/or stimulation
        - **Device Hardware-Related AEs:** AEs that can reasonably (i.e. Unlikely, Possibly, Probably and Causally Related) be attributed to the mere physical presence of the device or to deficiency of the device (i.e., an allergic response to device materials).

- **Stimulation-Related AEs:** AEs that can reasonably (i.e. Unlikely, Possibly, Probably and Causally Related) be attributed to the effects of stimulation. A relationship to stimulation may be determined by demonstrating a predictable response to the alternating between stimulation-on and stimulation-off settings. However, a relationship to stimulation may also be reported without demonstrating a predictable response to the alternating between the stimulation-on and stimulation-off settings if in the opinion of the Investigator the AE is potentially related to stimulation.

- **Procedure Related AEs:** AEs that can reasonably (i.e. Unlikely, Possibly, Probably and Causally Related) be attributed to a study protocol required procedure.

19.5 Boston Scientific Device Deficiencies

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record. In addition, a Device Deficiency paper CRF should be completed.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are not adverse events. However, an adverse event that results from a device failure or malfunction would be recorded as an adverse event on the appropriate CRF.

Any Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.

19.6 Reporting to Regulatory Authorities ECs / Investigators

BSC is responsible for reporting adverse event information to all participating Principal Investigators and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the EC, and regulatory authorities of UADE and SAE as required by local/regional regulations.

20 Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any study devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO), and approved by the site's EC, or central EC, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative site's EC. Any modification requires acceptance from BSC prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the site in obtaining a written consent translation. Translated consent forms must also have EC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative sign, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the site and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory authority according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. EC), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the EC. The new version of the ICF must be approved by the EC. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's EC. The EC will determine the subject population to be re-consented.

21 Committees

21.1 Safety Monitoring Process

The BSC personnel from the Medical Safety and Safety Trial Operation group review safety data as it is reported by the sites throughout the duration of the study. During scheduled monitoring activities, clinical research monitors further support this review through their review of source documents and other data information. The BSC Neuromodulation Medical Safety group and Safety Trial Operations team include health care providers with expertise in Neurology and Neuromodulation with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

22 Suspension or Termination

22.1 Premature Termination of the Study

Boston Scientific reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or business reasons and reasons related to protection of subjects. Investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

22.1.1 Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following:

-
- Suspicion of an unacceptable risk, including serious health threat. In this case, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed.
- Instructions by the IRB/EC/REB or regulatory authorities to suspend or terminate the clinical investigation.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development/marketing of the device.

22.2 Termination of Study Participation by the Investigator or Withdrawal of EC Approval

Any investigator, or associated EC, or regulatory authority may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

22.3 Requirements for Documentation and Subject Follow-up

In the event of premature study termination, a written statement as to why the premature termination has occurred will be provided to all participating sites by Boston Scientific. The

EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an EC terminates participation in the study, participating investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The Principal Investigator or his/her designee must return all study-related documents and devices, if supplied by Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

22.4 Criteria for Suspending/Terminating a Study Site

Boston Scientific reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled for a period beyond 3 months after site initiation, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of site participation, all devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The EC and regulatory authorities, as applicable, will be notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

23.Study Registration and Results

23.1 Study Registration

To comply with applicable laws and regulations, the study will be registered on a publicly accessible database.

23.2 Clinical Investigation Report

Study results will be made available in accordance with the legal requirements and the recognized ethical principles, in accordance with the Boston Scientific Policy. A Clinical Investigation Report will be made available to all investigators, IRB/EC/REB and regulatory authorities, as applicable in accordance with the Boston Scientific Policy and local requirements. As applicable an abbreviated Clinical Investigation Report will be made available on a publicly accessible database.

23.3 Publication Policy

BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.
- The data, analytic methods, and study materials for this clinical trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (https://www.bostonscientific.com).

24. Reimbursement and Compensation for Subjects

24.1 Subject Reimbursement

Travel and other expenses incurred by subjects as a result of participation in the study will be reimbursed in accordance with pertinent country laws and regulations and per the study site's regulations.

24.2 [redacted]

[redacted]

[redacted]

26. Abbreviations and Definitions

26.1 Abbreviations

Abbreviations are shown in Table 0-1.

[redacted]

Table 0-1: Abbreviations

Abbreviation/Acronym	Term
AE	Adverse Event
BSC	Boston Scientific Corporation
BSN	Boston Scientific Neuromodulation
CA	Competent Authority
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
DC	Dorsal Column
DR	Dorsal Root
EC	Ethics Committee
ETS	External Trial Stimulator
FBSS	Failed Back Surgery Syndrome
FDA	Food and Drug Administration
HCP	Health Care Personnel
ICF	Informed Consent Form
ICH	International Committee on Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IFU	Instructions For Use
IPG	Implantable Pulse Generator
ISO	International Standards Organization
MEDDEV	Medical Device Directives
MICC	Multiple Independent Current Control
NRS	Numeric Rating Scale
ODI	Oswestry Disability Index
PGIC	Patient Global Impression of Change
PSWT	Patient Satisfaction With Treatment
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SCS	Spinal Cord Stimulation
VAS	Visual Analog Scale

[redacted]

26.2 Definitions

Terms are defined in Table 0-1.

Table 0-1: Definitions

Term	Definition
Electrical Mapping	A series of measurements of stimulation sensory thresholds, stimulation induced paresthesia drawings which are intended to assist in determining the clinically optimal stimulation parameters for perception and subperception SCS
Enrollment	A patient is considered to be enrolled as a research subject in the study after informed consent is obtained.
Source Data	All information in original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation. Note 1 to entry: This includes source data initially recorded in an electronic format.
Source Document	Original or certified copy of printed, optical or electronic document containing source data.
Subject	Patient who is enrolled to participate in the study, study participant