High Rate Spinal Cord Stimulation:
Field Shape and Amplitude Sensitivity Exploratory Study
CONTOUR

CLINICAL INVESTIGATION PLAN

[redacted]

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Revision History

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
AA	08Sep2016	[redacted]	All	N/A	Initial Release
AB	26Jan2017	[redacted]	11.1 – Data Collection Schedule	Inserted tests Pain, PSWT, PGIC and Tolerance tests into Bipole search. Removed specification "7 days" in LongTerm FU column	Correct the mistake made in protocol vAA
AB	26Jan2017	[redacted]	11.6	Inserted "outcome reporting"	Clarify the requirements
AB	26Jan2017	[redacted]	11.7	Replaced "at" by "until" in "follow up of subject until the End of study"	Clarify that subject FU is over a period of time as illustrated in Fig 8.1
AC	2May2017	[redacted]	Synopsis and Section 8	Replaced "single" with "multi" and with "up to two" center	Allow for up to 2 centers in study to aid enrollment
AC	2May2017	[redacted]	11.6	Added "when healing period complete"	Specify that wound healing is allowed post-implant prior to Bipole Search Phase
AC	2May2017	[redacted]	Synopsis, 4.5, Fig8.1, 9.2 and 10.2	Specified "at or near the T9/T10 region"	Clarification
AC	2May2017	[redacted]	11.14	Included examples of Unscheduled visit	Clarification to give guidance to the site

2. Protocol Synopsis

High Rate Spinal Cord Stimulation: Field Shape and Amplitude Sensitivity Exploratory Study (CONTOUR Study)	
Study Objective(s)	Explore electrical field shape sensitivity and amplitude sensitivity in sub-perception SCS (anatomically-guided 1kHz stimulation) to obtain initial impressions of effect (i.e. not statistically powered based on a priori information about effect size).
Test Device	Boston Scientific Neuromodulation (BSN) Precision Spectra™ system with tightly spaced percutaneous lead(s)
Control Device	None; each patient will serve as their own control
Study Design	Prospective, postmarket, exploratory, multi-center, randomized, double-blinded (subject, evaluator blinded; programmer un-blinded)
Planned Number of Subjects	Approximately 10 patients to enter randomization phase
Planned Number of Investigational Sites / Countries	Up to two centers (United Kingdom)
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 with 1KHz therapy
[redacted]	[redacted]

High Rate Spinal Cord Stimulation: Field Shape and Amplitude Sensitivity Exploratory Study (CONTOUR Study)	
	[redacted]
Method of Assigning Patients to Treatment	Subjects in whom an effective 1kHz bipole setting is found, will be randomized in an equal distribution to bipole or "Dorsal Horn Modulation" stimulation setting for 15 days, followed by a crossover to the opposite programming method for additional 15 days. Subjects in whom an effective 1kHz bipole setting was not found will continue participation in the study for 3 month follow-up period, under center's standard of care SCS strategy.
Follow-up Schedule	• Screening period (>7 days) • Baseline Visit • Implant visit (standard of care) • Bipole Search Visit (start of bipole search) • Bipole search (approx. 21±7 days) • Randomization Visit (end of bipole search) • Cross-over Visit (21±5 days post Randomization Visit) • Release Visit (21±5 days post Cross-over Visit) • End of study (90±14 days post Release Visit)
Study Duration	The entire study will take approximately 1 year to complete. Each patient will be enrolled for approximately 6 months.
Key Inclusion Criteria	[redacted]

High Rate Spinal Cord Stimulation: Field Shape and Amplitude Sensitivity Exploratory Study (CONTOUR Study)	
	[redacted] Documented average low back pain intensity of at least 6 out of 10 over 7 days during Screening (Numerical Rating Scale) [redacted] [redacted] Stable daily pain-related medication prescription and intake of ≤100mg morphine-equivalents [redacted] Capacity to describe and rate pain intensity, complete study measurements, and use the study device (e.g. patient remote control, charger, paper and electronic diaries) (physician discretion)
Key Exclusion Criteria	[redacted] Presence of pain or psychological condition that in the opinion of the investigator may interfere with the subject's ability to rate their pain and communicate such ratings [redacted] Previous Spinal Cord Stimulation trial or is already implanted with an active implantable device(s) (e.g. pacemaker, drug pump, implantable pulse generator) [redacted]
Statistical Methods	
Primary Statistical Hypothesis	None
Statistical Test Method	Descriptive statistics will be employed in post-hoc analysis
Sample Size Parameters	Sample size not determined in prospective manner

3. Table of Contents

3.1. *Table of Figures*

3.2. *Table of Tables*

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 causes 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), and 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 current stimulates 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 to conventional medical management alone (CMM group) and 52 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, Spinal Cord Stimulation (SCS) has relied on the understanding that to achieve pain relief, dorsal column stimulation-induced paresthesia has to be generated around 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 $\pm$ 0.1 at baseline to 3.3 $\pm$ 0.3 at 24 months ($p < 0.001$), and mean leg pain was reduced from 5.4 $\pm$ 0.4 to 2.3 $\pm$ 0.3 ($p < 0.001$). At 24 months, 60% of implanted patients had a greater than 50% pain relief in back pain.

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.

A randomized double-blinded comparison of high frequency SCS (HF SCS) and sham stimulation on patient's global impression of change, pain intensity and quality of life in existing SCS patients was conducted and reported by Perruchoud et al. (Perruchoud et al., 2013). Of 33 patients, the proportion of patients responding under HF SCS was 42.4% (14/33) versus 30.3% (10/33) in the sham condition. The mean benefit of HF vs. sham was not statistically significant.

4.4. *Dorsal Horn Modulation (DHM) Technique*

Traditional stimulation fields involve bipoles and tripoles which create localized concentrations of stimulation to evoke activity in the dorsal columns. Dorsal Horn Modulation Technique is a novel stimulation field which is designed to minimize stimulation of the dorsal column fibers and maximize stimulation of nerve fiber terminals that exist in the more lateral aspects of the cord (dorsal horn, dorsal root entry zone). It consists of a strip of cathodes whose individual amplitudes are calibrated according to the measured perception

thresholds from each contact. An algorithm takes the thresholds as inputs and outputs current percentages which are manually programmed.

4.5. *1 kHz Anatomically Targeted Sub-perception SCS*

Similar to the experience with 10kHz SCS (see Van Buyten et al., 2012, Al-Kaisy et al., 2014), 1kHz subperception SCS has been reported to provide pain relief when programming is aimed at maximizing the overlap of pain with paresthesia when run at supraperception amplitudes (data unpublished).

The present study differs in that it targets the same anatomical target as traditional 10kHz SCS, namely the dorsal aspect of the epidural space overlying the region near the T9/T10 intervertebral disc, but using lower stimulation rates, namely 1kHz.

The purpose of this study is to explore field shape sensitivity and amplitude sensitivity in sub-perception SCS (anatomically-guided 1kHz stimulation) to obtain initial impressions of effects.

5. Device Description

The Precision Spectra™ System (Figure 5-1 and Figure 5-2) is an implantable neurostimulator system intended to aid in the management of chronic intractable pain.

The Precision Spectra™ System includes an implantable 32-contact, multi-channel pulse stimulator (IPG) with a rechargeable power source. Periodically, the implant battery is recharged transcutaneously by a Precision™ radiofrequency charging unit. The stimulator can accept up to 4 leads and support a maximum of 32 contacts. The Precision Spectra™ System can be used with any commercially available Boston Scientific SCS leads.

A 32-contact Precision Spectra™ External Trial Stimulator (ETS) is used to provide trial stimulation through the surgically placed leads prior to implantation of the implantable stimulator. The leads are connected to the trial stimulator by means of the Precision Spectra™ OR Cable during the trial period, which may occur intraoperatively (on-the-table trial).

A Clinician Programmer (CP) is provided to facilitate communication with, and programming of, the IPG and ETS. A programming Wand is used to provide a link between the Clinician Programmer and the ETS/IPG.

A hand-held battery operated Precision Spectra™ Remote Control provides the patient with the ability to access basic stimulator functions.

The Precision Spectra™ System uses the standard surgical tools and accessories for facilitating lead insertion and placement.

Figure 5-1: Precision Spectra™ Products and Accessories

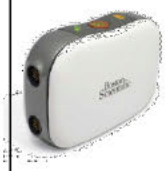
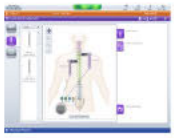
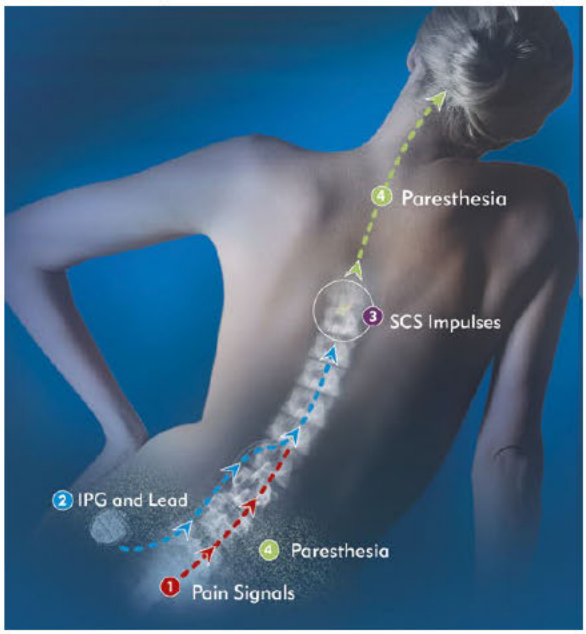
IPG	ETS	OR Cables	Remote Control	Clinician Programmer	Wand
		 2x8 OR Cable  1x16 OR			

Figure 5-2: Implantable Neurostimulator System



The Precision Spectra™ System delivers current-controlled, asymmetrical biphasic charge-balanced electrical pulses to each contact. Patients control the amplitude of stimulation and turn stimulation on or off via a wireless handheld remote control. The available stimulation parameters are as follows: frequency 2 to 1200 Hz, pulse width 20 to 1000 µsec, and amplitude 0-25.5 mA with a 12.7 µC pulse charge limit.

All of the devices used in this study are commercially approved in Europe.

6. Study Objectives

The objective of this study is to explore electrical field shape sensitivity and amplitude sensitivity in sub-perception SCS (anatomically-guided 1kHz stimulation) to obtain initial impressions of effect.

7. Study Endpoints

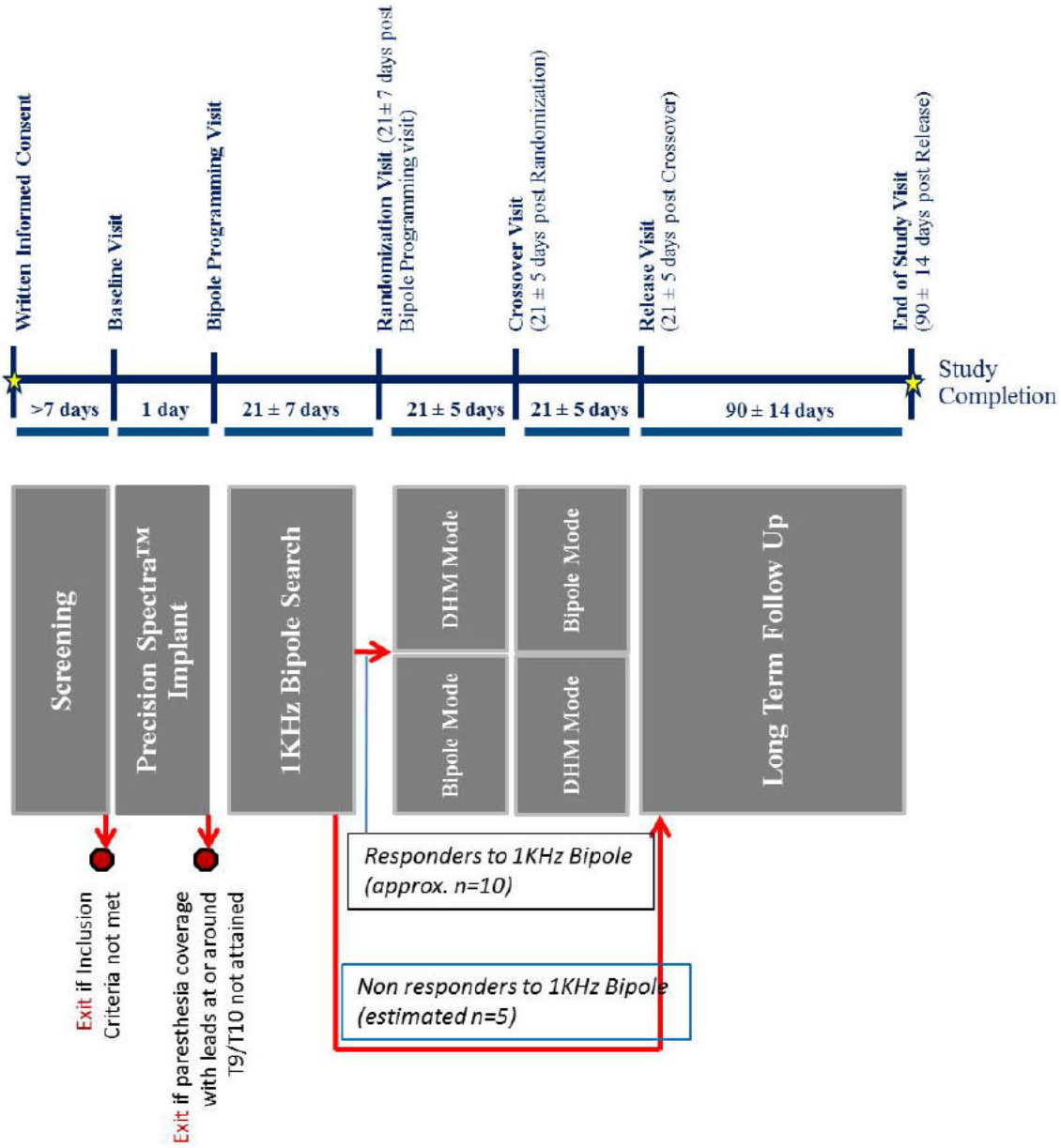
Collected data will be used to increase the understanding of the therapy, guide product development and help define the best practice for programming with 1kHz therapy.

[redacted]

8. Study Design

Prospective, postmarket, exploratory, multi-center, randomized, double-blinded (subject, evaluator blinded; programmer un-blinded) (Figure 8-1)

Figure 8-1: CONTOUR Study Design



8.1. *Scale and Duration*

The study will be conducted at up to two centers in UK. Approximately ten (10) patients will be randomized. Follow-up of each randomized patient will continue for 3 months after the randomization (cross-over) phase. Patients who complete all study measurements will participate in the study approximately 6 months from enrollment to their end of participation. The overall study may require up to one year to complete.

8.2. *Treatment Assignment*

Eligible patients who consent to participation and have met all of the inclusion and none of the exclusion criteria will undergo implant of the system. The subjects would undergo a 2-4 week period of 1 kHz bipole search. Those subjects in whom an effective bipole setting is found, will be randomized 1:1 to bipole stimulation followed by DHM for 15 days each, or DHM followed by bipole stimulation for 15 days each. After the crossover period, the subject enters into a 3 month follow-up period with the best of the two setting. Subjects for whom an effective 1 kHz bipole setting was not found will continue participation in the study for 3 month follow-up period, according to standard-of-care.

8.2.1. Treatment and Control

This study compares two stimulation field types: bipolar vs DHM, both at 1 kHz. The cross-over study design allows for comparing these treatments using one of the stimulation types as an active control.

8.3. *Justification for the Study Design*

The study design is prospective, postmarket, exploratory, multi-center, randomized, double-blinded (subject, evaluator; programmer un-blinded) study to obtain initial impression on the sensitivity to electrical field shape and amplitude in 1kHz anatomically-guided subperception spinal cord stimulation for chronic neuropathic pain treatment. It is exploratory because little is known about the best electric field and amplitudes to optimize subperception SCS. Due to the nature of sub-perception SCS, blinding is possible and will contribute to the strength of the evidence gathered from this study. Randomization will allow for controlling for order effect as previous research in subperception SCS has shown that the order effect can dominate the treatment effect (Perruchoud et al., 2013).

9. Subject Selection

9.1. *Study Population and Eligibility*

The study will include patients until approximately 10 have entered the randomization phase.

Patients will generally be recruited from physician's practice and will be eligible to receive 1 kHz Spinal Cord Stimulation therapy to treat their chronic neuropathic pain condition in the legs and back using the commercially-approved Boston Scientific's Precision Spectra™ System per local DFU.

9.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (Table 9.2-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see 9.3) is met.

Table 9.2-1: Inclusion Criteria

Clinical Inclusion Criteria	[redacted] [redacted] [redacted] Documented average low back pain intensity of at least 6 out of 10 over 7 days during Screening (Numerical Rating Scale) [redacted] [redacted] Stable daily pain-related medication prescription and intake of ≤100mg morphine-equivalents [redacted] Capacity to describe and rate pain intensity, complete study measurements, and use the study device (e.g. patient remote control, charger, paper and electronic diaries) (physician discretion)

Abbreviations: NRS – Numerical Rating Scale

9.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (Table 9.3-1) will be excluded from this clinical study.

Table 9.3-1: Exclusion Criteria

Clinical Exclusion Criteria	[redacted] Presence of pain or psychological condition that in the opinion of the investigator may interfere with the subject's ability to rate their pain and communicate such ratings [redacted] Previous Spinal Cord Stimulation trial or is already implanted with an active implantable device(s) (e.g. pacemaker, drug pump, implantable pulse generator) [redacted]

10. Subject Accountability

10.1. *Point of Enrollment*

A patient 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.

10.2. *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. The subjects who have withdrawn will continue to be followed per center's standard of care.

Reasons for withdrawal could include but are not limited to

- physician discretion
- patient choice to withdraw consent
- patient's failure to meet inclusion or not meet exclusion criteria after enrollment but prior to system implant
- failure to proceed to implantation with a BSC SCS IPG
- failure to be implanted with lead(s) at or near the region overlying the T9/10 intervertebral disc
- failure to achieve adequate pain relief during rescue period that follows the bipole search period
- lost to follow-up or
- death

While study withdrawal is discouraged, patients 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 patient withdrawal and an "End of Study" form must be completed. Any patient 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 patient 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 patient withdrawal may be used for study analysis.

Patients withdrawn prior to randomization will be replaced and will not be included in the site's overall total for randomized patients.

10.3. *Enrollment Controls*

Enrollment will remain open until one of the following events occurs:

- Approximately 10 patients are randomized
- The study is terminated at any time, at the Sponsor's discretion.

Enrollment controls will be implemented per the Enrollment Communication Plan developed for this study.

11. Study Methods

11.1. *Data Collection*

The data collection schedule is shown in Table 11.1-1.

Table 11.1-1: Data Collection Schedule

Procedure/ Assessment	Screening Period (duration >7 days)	Baseline Visit	Implant Procedure (standard of care)	Bipole Search Programming Visit and Period (post implant standard of care)	Randomization Visit (21±7 days post Bipole Search Visit)	Crossover Visit (21±5 days post Randomization Visit)	Release Visit (21±5 days post Crossover Visit)	Randomization Periods 1&2 (duration 21±5 days)	Long Term F/U Period (duration 90 ±14 days)	End of Study Visit (90 ±14 days post Release Visit)	Unscheduled Visit
Informed consent process	X	-	-	-	-	-	-	-	-	-	-
Demographics and Medical History	X	-	-	-	-	-	-	-	-	-	-
Pain Intensity	2x per day AM+PM		-	2x per day AM + PM	-	-	-	2x per day AM + PM	2x per day AM + PM	-	-
Patient Satisfaction with Treatment (PSWT)	-	-	-	1x per day PM	-	-	-	1x per day PM	1x per day PM	-	-
Patient Global Impression of Change (PGIC)	-	-	-	1x per day PM	-	-	-	1x per day PM	1x per day PM	-	-
Tolerance (Sitting/standing/ walking time)	1x per day	-	-	1x per day PM	-	-	-	1x per day PM	1x per day PM	-	-
Disability (ODI)	-	X	-	-	-	X	X	-	-	X	-
Quality of life (EQ5D-5L)	-	X	-	-	-	X	X	-	-	X	-
Sleep quality (PSQI)	-	X	-	-	-	X	X	-	-	X	-
Implant Procedure Form	-	-	X	-	-	-	-	-	-	-	X*
Electrical Mapping	-	-	-	for all stim combos tested	for all stim combos tested	for all stim combos tested	for all stim combos tested	-	-	for all stim combos tested	for all stim combos tested
Pain Drawing		X	-	-	-	-	-	-	-	X	-

Procedure/ Assessment	Screening Period (duration >7 days)	Baseline Visit	Implant Procedure (standard of care)	Bipole Search Programming Visit and Period (post implant standard of care)	Randomization Visit (21±7 days post Bipole Search Visit)	Crossover Visit (21±5 days post Randomization Visit)	Release Visit (21±5 days post Crossover Visit)	Randomization Periods 1&2 (duration 21±5 days)	Long Term F/U Period (duration 90 ±14 days)	End of Study Visit (90 ±14 days post Release Visit)	Unscheduled Visit
Device Programming Report	-	-	-	X	X	X	X	-	-	X	X
Determine Preferred Program	-	-	-	-	-	-	X	-	-	-	-
Lead Fluoro Imaging (per center's standard of care)	-	-	X	-	-	-	-	-	-	-	X**
Randomization	-	-	-	-	X	-	-	-	-	-	-
Adverse event assessment	-	-	X	X	X	X	X	X	X	X	X

Abbreviations: AM – morning, PM - afternoon

* In the event that the unscheduled visit is an additional Device Procedure
** In the event that Investigator suspects lead migration, per standard of care

11.2. *Study Candidate Screening*

Patients will undergo screening during which their eligibility for the study will be determined. The screening will consist of collecting the baseline pain, medication and patient demographic information and determine suitability for SCS treatment.

11.3. *Informed Consent*

Written Informed Consent must be obtained for all patients who are potential study candidates. Patients 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 patient in language that is easily understood by the patient. The patients 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 patient agrees to participate in the study and signs an ICF, certain diagnostic or screening procedures might demonstrate that the patient is not eligible to continue participation (see Section 11.3.1).

11.3.1. Post-Consent Eligibility Validation

Baseline pain scores will be confirmed per inclusion criteria IC3 and IC4 during the screening period (and after patient had provided the written informed consent) and if they are not met, the patient will be withdrawn from study participation. The withdrawn patients will continue their treatment per center's standard of care.

11.4. *Screening Period (duration >7 days within 90 days prior to Implant procedure) ending with Baseline visit*

Visit type: period at home + office

Occurs after the patient has provided a written informed consent. The screening period lasts at least 7 days and should occur no more than 90 days prior to SCS Implant procedure. At the end of the screening period, during the Baseline visit it will be confirmed whether inclusion criteria are met.

Goal: Document pain scores and various quality of life measures to understand baseline pain condition and confirm eligibility of the patient.

11.5. *Implant Procedure (Standard of Care)*

Visit type: office

The SCS lead and system implant procedure will be done per center's standard of care but only those patients whose tight contact leads have contacts at or near the level overlying the T9/T10 intervertebral disc, as documented using standard of care imaging, will continue with

study participation. If this criterion is not satisfied they will be withdrawn and continue their treatment per center's standard of care.

11.6. *Bipole Search Visit (after Implant procedure per center's standard of care when healing period complete, duration 2-4 weeks)*

Visit type: office and home; regular contact with study patient is recommended

Goal: test paresthesia thresholds and distribution for selected programs, ensure that stimulation programs to be tested during bipole search are programmed into the device and study patient understands the use of the system and outcome reporting requirements in order to maximize efficiency of search. Measure the paresthesia thresholds and distribution for the bipole programs to be tested. Multiple programming visits may be done during this period (unscheduled).

11.7. *Randomization Visit (21±7 days post Bipole Search Visit)*

Visit type: office

Goal: collect information from bipole search, determine effective program(s), retest paresthesia thresholds and distribution for selected programs, ensure that stimulation programs to be tested during Randomization Period 1 are programmed into the device and study patient understands the use of the system and requirements in order to ensure appropriate stimulation testing during this period spent at home.

Important: Randomization will only occur for subjects who received adequate therapy from one or more configurations tested since the Bipole Search Visit. For subjects that did not receive adequate therapy, there will be no randomization but subject will be asked to be followed up until the End of Study Visit. Those subjects may be programmed according to site's standard of care.

11.8. *Randomization Period 1 (duration of 21±5 days)*

Visit type: home; regular contact with study patient is recommended

Goal: offer study patient opportunity to test, for each given stimulation program, a number of different amplitudes, each over a duration of several days, and report the outcomes.

11.9. *Crossover Visit (21±5 days post Randomization Visit)*

Visit type: office

Goal: This is the crossover visit. The purpose is to collect information from Randomization Period 1, determine effective amplitude(s) and program(s), retest paresthesia thresholds and distribution for selected programs, ensure that stimulation programs to be tested during Randomization Period 2 are programmed into the device and study patient understands the use of the system and requirements in order to ensure appropriate stimulation testing during this period spent at home.

11.10. *Randomization Period 2 (duration 21±5 days)*

Visit type: home; regular contact with study patient is recommended

Goal: offer study patient opportunity to test, for each given stimulation program, a number of different amplitudes, each over a duration of several days and report the outcomes

11.11. *Release Visit (21±5 days post Crossover Visit)*

Visit type: office

Goal: collect information from Randomization Period 2, determine effective amplitude(s) and program(s), retest paresthesia thresholds and distribution for selected programs, ensure that stimulation programs to be tested during Long term Follow up are programmed into the device and study patient understands the use of the system and requirements in order to ensure appropriate stimulation testing during this period spent at home.

11.12. *Long Term Follow-up Period (duration approximately 90 days)*

Visit type: home; regular contact with study patient is recommended

Goal: Subject will be encouraged to keep their preferred program. Further therapy optimizations are allowed in this period (physician discretion). Multiple programming visits may be done during this period (unscheduled).

11.13. *End of Study Visit (90±14 days weeks post Release Visit for subjects who completed crossover phase or 90±14 days post Bipole Search Phase for subjects who did not respond to 1kHz Bipole Search)*

Visit type: office

Goal: collect information on the outcome and various quality of life measures during Long-term Follow-up and conclude study patient's participation in the study.

11.14. *Unscheduled Visit*

An unscheduled visit is any visit that occurs during patient's participation in the study that is not aforementioned.

Visit type: office

Goal: There are many reasons for an unscheduled visit, which include (but not limited to) loss of therapy, suspected lead migration, need for additional reprogramming, need for addressing a complaint or potential adverse event. Information will be collected from the previous period as well as the reason for the unscheduled visit, retest paresthesia thresholds and distribution for selected programs, and to plan and explain patient's continuation in the study. If imaging is required per standard of care to address suspected lead migration, it may be performed at an unscheduled visit.

11.15. *Study Completion*

Each patient's participation in the study will be considered complete upon completion of the End of Study Visit or upon patient withdrawal.

Upon completing participation in the study patients will continue to be followed per center's standard of care practice.

11.16. *Source Documents*

Table 11.16-1 summarizes all source data requirements for this protocol. Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the investigational site team with a statement that it is a true reproduction of the original source document.

Table 11.16-1: 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
Clinical evaluations (eg. questionnaires, drawings)	Retain at center
Programming Pre and Post-visit Reports (program settings, impedance measurements, program usage, battery voltage etc)	Retain at center
Lead Fluoro Images (if done per center's standard of care)	Retain at center
Diary data	Retain at center

12. Statistical Considerations

12.1. *Endpoints*

12.1.1. Primary Endpoint

Due to the exploratory nature of the study no prospectively defined, formal statistical methods will be employed.

12.1.2. Hypotheses

No formal hypotheses have been defined.

12.1.3. Sample Size

The sample size has not been determined in prospective manner.

12.1.4. Statistical Methods

Descriptive statistics will be employed in post-hoc analysis

[redacted]

12.2. *General Statistical Methods*

12.2.1. Analysis Sets

All exploratory endpoints will be analyzed on both intent-to-treat and a per-protocol basis. Full definitions of the analysis set will be provided in the Statistical Analysis Plan.

12.2.2. Control of Systematic Error/Bias

Selection of patients will be made from the Investigator's usual patient load. All patients meeting the inclusion/exclusion criteria and having signed the Informed Consent Form will be eligible for participation in the study. The reasons for exclusion, for subjects who sign an informed consent form but are not implanted, will be indicated. Patients who reach Randomization Visit will be randomly allocated into the two arms of the Crossover Phase of the study, minimizing the systematic error.

12.2.3. Number of Subjects per Investigative Site

There is only one investigative site which will enroll all subjects.

12.3. *Data Analyses*

All data analysis will be performed using standard methods and tools, with appropriate validation when needed.

12.3.1. 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. Data Management

13.1. *Data Collection, Processing, and Review*

The questionnaires/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.

13.2. *Data Retention*

The Principal Investigator or his/her designee or Investigational site will maintain, at the investigative site, all essential study documents and source documentation that support the data collected on the study subjects in compliance with ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other country/regional/local regulations.

The Principal Investigator or his/her designee will take measures to ensure that these essential documents are not accidentally damaged or destroyed. 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. Amendments

If a protocol revision is necessary which affects the rights, safety or welfare of the subject or scientific integrity of the data, an amendment is required. Appropriate approvals (e.g., IRB/EC/FDA/CA) of the revised protocol must be obtained prior to implementation.

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 and the reviewing IRB/EC 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 paper CRF. Sites may

also be required to report deviations to the IRB/EC, per local guidelines and government regulations.

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

16. Device/Equipment Accountability

The study will use only the commercially available Boston Scientific's Precision Spectra™ Spinal Cord Stimulation System. No investigational equipment will be used as test equipment. No device tracking/accountability is required.

17. Compliance

17.1. *Statement of Compliance*

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, and pertinent 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. Any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.

17.2. *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, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/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.
- Prior to beginning the study, sign Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- 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 SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by the national regulations or this protocol or by the IRB/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/directions 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 IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/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 investigational 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.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

17.2.1. 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 and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

17.3. *Institutional Review Board/ Ethics Committee*

Prior to gaining Approval-to-Enroll status, the investigational site will provide to the sponsor documentation verifying that their IRB/EC is registered or that registration has been submitted to the appropriate agency, as applicable according to national/regulatory requirements.

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

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

17.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC. Only authorized BSC personnel or a BSC representative including, but not limited to Contract Research Organization (CRO) will have access to these confidential records. 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. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

Boston Scientific will keep subjects' identifiable health information confidential in accordance with all applicable laws and regulations. Boston Scientific may use subjects' health information to conduct this research, as well as for additional purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products or procedures, and other business purposes. 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.

17.4.1. Role of Boston Scientific Representatives

Boston Scientific personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during implant, testing required by the protocol, and follow-ups. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices (including programmers, analyzers, and other support equipment).

At the request of the investigator and while under investigator supervision, BSC personnel may operate equipment during implant or follow-up, assist with the conduct of testing specified in the protocol, and interact with the subject to accomplish requested activities. Typical tasks may include the following.

- Interrogating the device or programming device parameters to investigator-requested settings as well as operating investigational equipment
- Performing lead diagnostic testing or determining sensation thresholds and impedance measurements
- Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel
- Assisting with the collection of study data from programmers, and other equipment
- Entering technical data on technical source form as long as the responsible investigator verifies and signs the completed worksheet
- Print out programming reports directly from the clinician programmer and provide original to clinical site as source documentation
- Provide technical expertise/support to subjects during office visits and/or during teleconference calls/electronic communications with the principal investigator or their delegated site staff and the subject.
- Programming and maintaining electronic diaries including programming diaries, downloading data from diaries, and instructing subjects on the use of diaries and troubleshooting diaries.

In addition, BSC personnel may perform certain activities to ensure study quality. These activities may include the following.

- Observing testing or medical procedures to provide information relevant to protocol compliance

- Reviewing collected data and study documentation for completeness and accuracy

Boston Scientific personnel will not do the following:

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of the investigator
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

17.5. *Insurance*

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

18. 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 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.

19. Potential Risks and Benefits

19.1. *Anticipated Adverse Events*

All potential Anticipated Adverse Events as specified in the Precision Spectra™ SCS system's Directions for Use (DFU) are also applicable to study subjects.

19.2. *Anticipated Adverse Device Effects*

All potential Anticipated Adverse Device Effects as specified in the Precision Spectra™ SCS system's Directions for Use (DFU) are applicable to study subjects.

19.3. *Risks Associated with the Study Device(s)*

All potential risks associated with the Study Devices as specified in the Precision Spectra™ SCS system's Directions for Use (DFU) are applicable to study subjects.

19.4. *Risks associated with Participation in the Clinical Study*

The subject might find it difficult, uncomfortable, or tiresome to complete study visits, diary, and/or questionnaires.

19.5. *Possible Interactions with Concomitant Medical Treatments*

Refer to the Directions for Use Manual for a list of procedures that may cause interaction with the Precision Spectra™ SCS system.

19.6. *Risk Minimization Actions*

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.

19.7. *Anticipated Benefits*

There are no anticipated benefits for subjects participating in the study. However, the knowledge learned from this study may benefit future patients receiving SCS.

19.8. *Risk to Benefit Rationale*

The potential benefits of participating in the study can outweigh the risks associated with study participation in appropriately selected subjects. While subjects might find it difficult, uncomfortable, or tiresome to complete study visits, the diary, and/or questionnaires they may benefit from the therapy provided and the monitoring of their outcomes as required by the study protocol.

20. Safety Reporting

20.1. *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 Investigational Device Deficiencies
- All Serious Adverse Device Effects
- New findings/updates in relation to already reported events
- All Device Related Adverse Events
- All Study Procedure Related Adverse 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 AE event required by the protocol, experienced by the study subject after informed consent and once considered enrolled in the study (as defined in study subject classification section), whether during or subsequent to the procedure, must be recorded in the CRF.

Underlying diseases are not reported as AEs unless there is an increase in severity of 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 20.2-1) for AE definitions).

Refer to Section 19 for the known risks associated with the study device(s).

20.2. *Definitions and Classification*

Adverse event definitions are provided in Table 20.2-1. Administrative edits were made on the definition of serious adverse event from ISO 14155 and MEDDEV 2.7/3 for clarification purposes.

Table 20.2-1: Safety Definitions

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, whether or not related to the investigational medical device. NOTE 1: This includes events related to the investigational 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 investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of an investigational 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 investigational medical device. NOTE 2: This definition includes any event resulting from use error or intentional abnormal use of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Note: This definition meets the reporting objectives and requirements of ISO 14155 and MEDDEV 2.7/3. Adverse event that: • Led to death, • Led to serious deterioration in the health of the subject as defined by either: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient hospitalization or prolongation of existing hospitalization , or

Term	Definition
	○ medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **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) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
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 version of the risk analysis report. **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 analysis report.
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	A inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

20.3. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the AE to the study device hardware, device stimulation or procedure. See criteria in Table 20.3-1.

Table 20.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Not Related	Relationship to the device 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 investigational 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;

Classification	Description
	- 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 investigational 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.
Unlikely Related	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related	The relationship with the use of the investigational device 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	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Causal Relationship	The serious event is associated with the investigational device 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 investigational device use/application or procedures; - the event involves a body-site or organ that o the investigational device or procedures are applied to; o the investigational 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 investigational 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.

20.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 20.4-1.

Table 20.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline post-market studies*** (MEDDEV 2.12/2: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Serious Adverse Device Effects	Complete AE paper CRF page with all available new and updated information.	• Within 2 business 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 (unidentified) for reported event	• When documentation is available
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational 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 2 business days of first becoming aware of the event. Reporting required through the end of the study
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 the study

Abbreviations: AE=adverse event; CRF=case report form.
* Please note that post-market studies are clinical studies where the medical devices used in the study bear the regulatory approval and are used for the same approved indications.

NOTE: Potential unscheduled hospitalizations performed strictly to optimize SCS programming without any concurrent adverse event do not need to be reported as an Adverse Event/Serious Adverse Event. Such unscheduled visits should be documented in the medical records and the Unscheduled Case Report Form.

20.5. *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.

20.6. *Reporting to Regulatory Authorities / IRBs / 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 IRB/EC, and regulatory authorities of UADE and SAE as required by local/regional regulations.

21. 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 investigational 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 body, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO), and approved by the site's IRB/EC, or central IRB, 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 IRB/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 IRB/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 signs, 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 body 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. IRB/EC), as appropriate.

Study personnel should explain that even if a subject agrees to participate in the study and signs an Informed Consent form, the screening period evaluations may demonstrate that the subject is not a suitable candidate for the study, in which case the subject will be withdrawn.

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 IRB/EC. The new version of the ICF must be approved by the IRB/EC. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

22. Committees

22.1. *Safety Monitoring Process*

To promote early detection of safety issues, the Medical Director will provide evaluations of safety events. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. During regularly scheduled monitoring activities, clinical research monitors will support the dynamic reporting process through their review of source document and other data information.

23. Suspension or Termination

23.1. *Premature Termination of the Study*

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

23.1.1 Criteria for Premature Termination of the Study

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

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- 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 of the device.

23.2. *Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC Approval*

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

23.3. *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 IRB/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 IRB or EC terminates participation in the study, participating investigators, associated IRBs/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 investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

23.4. *Criteria for Suspending/Terminating a Study Site*

Boston Scientific Corporation 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 study 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 IRB/EC and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the site will continue to be followed per standard of care.

24. 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 Corporation 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.

25. Reimbursement and Compensation for Subjects

25.1. *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.

25.2. *Compensation for Subject's Health Injury*

Boston Scientific Corporation will purchase an insurance policy to cover the cost of potential health injury for study subjects, and if required by applicable law.

26. Bibliography

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27. Abbreviations and Definitions

27.1. *Abbreviations*

Abbreviations are shown in Table 27.1-1.

Table 27.1-1: 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
DFU	Directions for Use
DHM	Dorsal Horn Modulation
EC	Ethics Committee
ETS	External Trial Stimulator
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
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
ISO	International Standards Organization
MEDDEV	Medical Device Directives
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SCS	Spinal Cord Stimulation

27.2. *Definitions*

Terms are defined in Table 27.2-1.

Table 27.2-1: Definitions

Term	Definition
Bipole	A stimulation combination commonly used in Spinal Cord Stimulation therapy that consists of one positive and one negative contact
Dorsal Horn Modulation (DHM)	Stimulation technique designed to provide uniform electrical field over a region of the spinal cord to promote modulation of the neural elements of the dorsal horn, preferential to the dorsal column nerve fibers (according to computer modeling)

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 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.
Source Document	Printed, optical or electronic document containing source data. Examples: Hospital records, laboratory notes, device accountability records, photographic negatives, radiographs, records kept at the investigation site, at the laboratories and at the medico-technical departments involved in the clinical investigation.

Abbreviations are defined in Table 27.1-1.