Study to Evaluate Automated Intensity Management in Patients Undergoing a BSC SCS Temporary Trial:

The AIM Study

A4091

CLINICAL INVESTIGATION PLAN

Sponsored By

Boston Scientific Neuromodulation Corporation
25155 Rye Canyon Loop
Valencia, CA 91355
United States of America

Contact Information

Role	Contact
[redacted]	[redacted]
[redacted]	[redacted]

Original Release: March 9, 2021

Current Version: July 2, 2021

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]

2. Protocol Synopsis

Study to Evaluate Automated Intensity Management in Patients Undergoing a BSC SCS Temporary Trial: **The AIM Study**	
Study Objective(s)	To assess the feasibility of using information extracted from physiologic (e.g. evoked compound action potentials) and electrospinogram (ESG) signals to automatically adjust stimulation intensity in an acute setting in patients undergoing a Spinal Cord Stimulation (SCS) trial.
Planned Indication(s) for Use	The investigational devices are intended as an aid in the management of chronic intractable pain of the trunk and/or limbs in typical chronic pain patients who are candidates for spinal cord stimulation (SCS).

Study Devices	• BSN commercially approved SCS trial systems including External Trial Stimulator (ETS), lead(s)/extensions(s), and operating room (OR) cable(s)/extender(s).
	• Optional commercially-approved wearable Motion Sensor (WitMotion, Inclinometer model HWT905).
	• Investigational Devices:
	  • The Neuromodulation Experiment Testbed (NEXT), whose components include:
	  ○ Sardeen External Neurostimulator (SEN) programmed within Boston Scientific's commercially approved spinal cord stimulation rate, amplitude, and pulse width, and
	  ○ SPARK (Sardeen Programming Application and Research Kit) software tool

Study Design	Prospective, multi-center, non-randomized, exploratory, single-arm study.
Planned Number of Subjects	A maximum of 25 subjects completing the programming visit will be enrolled in this study.

Study to Evaluate Automated Intensity Management in Patients Undergoing a BSC SCS Temporary Trial: The AIM Study	
Planned Number of Investigational Sites / Countries	Up to 5 U.S. sites.
Exploratory Endpoints	Exploratory endpoints include but are not limited to (the study assessment used to derive each endpoint is denoted in parentheses): • Percent change in perception threshold from sitting to standing (*Physiologic Thresholds)*
Method of Assigning Patients to Treatment	Subjects will be considered enrolled into the study at the time of the study-specific informed consent form (ICF) execution.
Follow-up Schedule	Study assessments will be required, as appropriate, at the following scheduled time points: • Screening Visit (up to 14 days prior to Programming Visit) • Programming Visit (Day 0) • Unscheduled Visit(s) (if applicable)
[redacted]	[redacted]
Participant Duration	The study duration for each subject is expected to be approximately 15 days.
Inclusion Criteria	IC1. Study candidate is undergoing a temporary SCS trial of commercially approved BSC neurostimulator system, per local directions for use (DFU). IC2. Subject signed a valid, EC/IRB-approved informed consent form.

Study to Evaluate Automated Intensity Management in Patients Undergoing a BSC SCS Temporary Trial: The AIM Study	
	IC3. Age 18 or above, or above legal age and willing and capable of giving informed consent specific to national law when written informed consent is obtained. IC4. In the clinician best judgment, subject is able to distinguishably describe quality and location of sensation and pain.
Exclusion Criteria	EC1. Subject meets any contraindication in BSC neurostimulation system local DFU. EC2. Investigator-suspected gross lead migration during the SCS trial period which may preclude the study candidate from receiving adequate SCS therapy. EC3. Subject is currently diagnosed with cognitive impairment, or exhibits any characteristic, that in the clinician's best judgement would limit study candidate's ability to assess and report sensation information. EC4. Subject is currently diagnosed with a physical impairment, or exhibits a condition that would limit study candidate's ability to complete study assessments.
Statistical Methods	
Exploratory Statistical Methods	This exploratory study does not include any powered endpoints or sample size calculations. Univariate and multivariable models may be used to determine correlations in effects on recorded physiological signals as amplitude is automatically adjusted.

[redacted]

[redacted]

4. Introduction

4.1. *Background*

4.1.1. Chronic Pain

Chronic pain is a significant world-wide complaint and consumes considerable healthcare resources and heavily impacts quality of social and working life for many. A 2001 European investigation showed that 30% of patients treated in primary care facilities were treated by a physician for a pain complaint, and 37% of those patients (11% of total) suffered from chronic pain (Hasselstrom, Liu-Palmgren, & Rasjo-Wraak, 2002). More recently an epidemiological study conducted in Scotland found the prevalence of chronic pain to be 48%, 8% of which is of neuropathic origin. The authors concluded that chronic pain is more prevalent than what previous studies have suggested (Torrance, Smith, Bennett, & Lee, 2006). In a separate European study done in 2006, 19% of adults surveyed reported suffering from chronic pain (Breivik, Collett, Ventafridda, Cohen, & Gallacher, 2006).

In the 2010 report of the health and status of the nation, Health, the U.S. Center for Disease Control and Prevention reports that over 28% of adults suffer from non-fleeting low-back pain. In patients with low-back pain, approximately half of the patients reported limitation in at least one basic action from the following list: movement difficulty, emotional difficulty, sensory difficulty, cognitive difficulty, self-care limitation, social limitation, or work limitation (National Center for Health Statistics, 2011).

Chronic 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.

4.1.2. Spinal Cord Stimulation

Spinal cord stimulation (SCS) is a treatment option for chronic pain that has generally been reserved for patients who have failed multiple, and sometimes all, conservative chronic pain therapies. With SCS, an implanted pulse generator (IPG) delivers electrical current to a lead(s) implanted in the epidural space at spinal level(s) where access can be obtained neural structures that are implicated in the chronic pain circuits. Electrically stimulating these nerves creates a comfortable tingling sensation, known as paresthesia, that can be directed to the painful location to mask the sensation of pain (Kumar *et al*., 2006).

SCS is effective for neuropathic pain associated with a variety of conditions, including failed back surgery syndrome (FBSS), which is the most common condition associated with chronic pain (Carter *et al*., 2004, Taylor *et al*., 2004). For best pain relief, the paresthesia must be programmed to overlap the regions of pain (North *et al.,* 1990). To achieve overlap, the electrode contacts are programmed based on the patient's feedback to various

combinations of stimulation parameters such as polarities, pulse rate, amplitude, and pulse width.

Two randomized controlled trials (RCTs) have been conducted on the use of SCS to treat patients with FBSS. Each study demonstrated the superiority of SCS compared with the alternative therapy, reoperation in one case (North *et al.*, 2005) and conventional medical management (CMM), including medication, nerve blocks, physical therapy, massage, etc., in the other (Kumar *et al.,* 2007).

In a single-center study, North et al. randomized 50 patients: 24 to SCS and 26 to reoperation. At an average follow-up of 2.9 years, the success rate (at least 50% pain relief and patient satisfaction) was reported to be significantly higher among patients randomized to SCS (9 of 24 patients) than among those randomized to reoperation (3 of 26 patients). Crossover was permitted if a patient's randomized therapy did not provide adequate pain relief, and significantly more patients crossed from reoperation to SCS (14 of 26) than from SCS to reoperation (5 of 24). Six of the reoperation crossovers achieved success with SCS, bringing the success rate to 15 of 38 who received SCS as a final treatment. None of the patients who failed SCS achieved success with reoperation (3 of 31 who received reoperation as a final treatment achieved success).

North et al. then used data from this study to compare the cost of SCS versus reoperation over a 2.9-year follow-up period and demonstrated that SCS was the least expensive and was dominant in terms of cost-effectiveness and cost-utility (North *et al.,* 2007).

In a separate, international, multi-center RCT, Kumar et al. randomized 100 patients: 48 to CMM and 52 to SCS plus CMM (Kumar *et al.,* 2007). 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. The patients randomized to SCS who actually received SCS (42 of 52) and were followed for 24 months reported significantly improved leg pain relief, functional capacity, and quality of life compared with their pre-treatment status (Kumar *et al.,* 2008). While initial SCS costs were greater than CMM costs, by 6 months post-randomization, health-related quality of life scores were preferentially improved for the SCS group. Thus, the authors inferred that SCS cost-effectiveness studies must examine costs and quality of life data beyond six months to paint an accurate picture (Manca *et al.,* 2008).

The results of these RCTs provide evidence that SCS is effective and cost effective in relieving chronic neuropathic pain associated with FBSS. North et al. also indicate that SCS might provide the best outcome and economic value for patients who are eligible for both SCS and reoperation (North *et al.,* 2007). The results of North's single-center RCT, however, have not been confirmed by a multi-center RCT that reflects the advances in surgical practice and in SCS that might have changed the comparative efficacy of these procedures.

In 2004, FDA approved the Boston Scientific Corporation (BSC) Precision® SCS system as an aid in the management of chronic intractable pain of the trunk and/or limbs. The Precision System received CE mark in 2005 for treatment of chronic intractable pain. The results of a multi-center, non-randomized feasibility study conducted with this system demonstrated more than 50% pain relief through a maximum follow-up of 18 months, but the single-arm design and small number of subjects enrolled limit the strength of the conclusions (Oakley et al., 2007).

4.1.3.Physiologic and Electrospinogram (ESG) Signals

The efficacy of SCS can be putatively explained by the Gate Control Theory, which posits that the activation of dorsal column fibers related to the dermatome of pain results in synaptic activation of inhibitory interneurons in the dorsal horn that, in turn, suppress the activity of nociceptive projection neurons (Shealy, Mortimer et al. 1970). Thus, localizing the effects of SCS to the appropriate dorsal columns is an important element of SCS programming and effective therapy that, without a physiological recording or biomarker indicating dorsal column activation, must be done by communicating with the patient during the programming process to confirm that paresthesias related to dorsal column activation overlap with the site of pain (North, Ewend et al. 1991). However, this process is labor and time intensive, and because this process cannot be easily performed in real time at all times, therapeutic outcomes may be vulnerable to lead migration, patient postural changes, and disease progression, among other factors.

The use of electrophysiological signals such as electrospinogram has become relevant for treating neurological conditions as they contain promising biomarkers (i.e. evoked compound action potentials, ECAPs) for monitoring the effects of SCS and adjust the stimulation parameters in a closed-loop manner. Notably, because ECAPs represent the summation of dorsal column activity generated by SCS, the amplitude of the ECAP from a single stimulation pulse can be used to determine the degree to which SCS activates dorsal columns (Parker, Karantonis et al. 2012), (King, 1997). As well, ECAP amplitude has been demonstrated pre-clinically to include effects of nociceptive projection neuron responses to SCS (Foreman, Beall et al. 1976, Zhang, Janik et al. 2015). As dorsal columns may be somatotopically organized by dermatome along the mediolateral aspect of the dorsal spinal cord (Feirabend, Choufoer et al. 2002), and as ECAPs propagate rostrocaudally and disperse as they propagate orthodromically and antidromically, sensing the ECAP from the spinal cord using electrodes on the SCS lead at specific mediolateral and rostrocaudal displacements from the stimulating electrode(s) may be used to monitor the coverage provided by a given electrode configuration and as a metric and/or flag for stimulation adjustment should postural changes or lead migration alters this coverage.

Understanding the correlation between postural/activity changes as measured per the motion sensor and the ESG from one or more contacts in the SCS leads can help evaluate and compare objectively the performance of algorithms that automatically adjust therapy settings.

It can also allow to discriminate objectively small differences between the same posture repeated multiple times.

4.2. *Study Rationale*

AIM Study is intended to assess the feasibility of using information extracted from physiologic and electrospinogram (ESG) signals to automatically and algorithmically adjust stimulation intensity (e.g. current amplitude) acutely in real-time for patients receiving SCS therapy while undergoing a BSN SCS temporary trial.

Spinal cord stimulation (SCS) devices implanted for the treatment of chronic pain deliver an electromagnetic field into the epidural space that can elicit a physiological response provided the stimulus intensity is high enough. This physiological response to electrical stimulation is the result of the cumulative signals produced by multiple axons recruited and action potentials triggered, leading to an electrical nerve response known as a compound action potential. Electrically evoked compound action potentials (ECAPs) represent the physiological response to the stimulus.

Different postures and body motions may elicit a variable ESG signal profile in relation to stimulation current amplitude delivered. Patients receiving constant current amplitude SCS therapy may perceive different intensity levels of stimulation depending on their activities and movements, and this sensation may at times extend below the perception threshold (PT) or reach discomfort threshold (DT). Adjusting the stimulation current amplitude delivered to the patient according to changes in the recorded ESG signal may therefore produce a more consistently and comfortably perceived therapy.

The AIM Clinical Study will investigate and characterize the algorithms and perceived effects of closed-loop SCS based on sensed ESG signals. Results from this study will be used to guide development and refinement of automated programming algorithms that may be implemented in future Spinal Cord Stimulation (SCS) systems.

This study is a pilot stage study according to ISO/FDIS 14155:2020(E) - Annex I.

5. Device Description

5.1. *Test Device*

Figure 5.1-2 below shows the AIM Study System test device setup compared to a commercial device setup. The AIM Study System uses the Neuromodulation Experiment Testbed (“NEXT System”), which consists of the Sardeen External Neurostimulator (SEN), a modified version of commercially available external trial stimulator by Boston Scientific (Valencia, CA) programmed with the Sardeen Programming Application and Research Kit

(SPARK) software tool, a modified version of commercially available neurostimulation programming software by Boston Scientific (Valencia, CA).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.1.1.Boston Scientific SCS Systems

BSC commercially approved SCS systems are approved by the Food and Drug Administration and have received CE-mark as an aid in the management of chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: failed back surgery syndrome, intractable low back pain and leg pain. Associated conditions and etiologies may be

- radicular pain syndrome,
- radiculopathies resulting in pain secondary to failed back syndrome or herniated disc,
- epidural fibrosis,
- degenerative disc disease (herniated disc pain refractory to conservative and surgical interventions),
- arachnoiditis,
- multiple back surgeries.

These systems include both an External Trial Stimulator (ETS) and an Implantable Pulse Generator (IPG) with their associated components. The ETS are used to perform an initial temporary SCS trial in order to determine a patient's suitability for SCS treatment. If the temporary SCS trial is successful, the IPG is then used for permanent implantation of the SCS system. This study will span the duration of the temporary trial with the use of the ETS and will end upon completion of each subject's study visits, not to exceed 15 days post-Screening Visit. For patients who move forward to a permanent implant, the permanent implant procedure will not be within the scope of this study.

A Clinician Programmer (CP) is provided to facilitate communication with, and programming of the ETS. A hand-held battery-operated remote control provides the patient with the ability to access basic stimulator functions.

5.1.2. The Neuromodulation Experiment Testbed (NEXT) system:

The Neuromodulation Experiment Testbed (NEXT) consists of modified versions of commercially available external trial stimulator (SEN) and commercially available programming software (SPARK). The SPARK software tool provides the user interface and capability for controlling the delivery of electrical stimulation from the SEN via commercially available BSN SCS lead(s) connected to BSN OR cable(s)/extender(s). An electronic device (e.g. laptop) running the SPARK software tool communicates directly with the SEN through either: a. USB optically isolated connection or b. USB with the power supplied from the internal battery or optional external battery, sending stimulation commands to SEN that result in: 1) delivery of electrical stimulation, and 2) receiving and recording sensed data (both from the SCS leads and optionally the wearable motion sensor). A patient-specific model is developed by measuring thresholds and properties extracted from the ESG and/or the optional motion sensor data so that automated stimulation intensity adjustments are designed to only be within comfortable ranges. The SPARK mathematical control algorithms determine the next intensity to program in the SEN using the patient-specific model.

The commercially available motion sensor (WitMotion, Inclinometer model HWT905) connects to the NEXT system via the SEN and is worn by the patient using a commercially available strap/belt.

The Sardeen External Neurostimulator, SPARK software, and motion sensor may only be operated by authorized BSC personnel in a study physician's office under the direction of a study healthcare clinician and will remain under the control of authorized BSC personnel at all times. It may not be sent home with the patient or otherwise dispensed to either the site or the patient.

6. Study Objectives and Endpoints

6.1. *Study Objective*

The objective of the AIM study is to assess the feasibility of using information extracted from physiologic (e.g. evoked compound action potentials) and electrospinogram (ESG) signals to automatically adjust stimulation intensity in an acute setting in patients undergoing a Spinal Cord Stimulation (SCS) trial.

Results from this study will be used to guide development and refinement of automated programming algorithms that may be implemented in future Spinal Cord Stimulation (SCS) systems.

The AIM Study is an exploratory study and no formal endpoints or hypothesis testing are planned in the study. This study is not designed to collect data for a product approval and as such does not have a safety or efficacy endpoint.

6.2. *Study Endpoints*

The AIM Study is an exploratory study and no formal endpoints or hypothesis testing are planned in the study. This study is not designed to collect data for a product approval and as such does not have a safety or efficacy endpoint.

Exploratory endpoints include but are not limited to (the study assessment used to derive each endpoint is denoted in parentheses):

- Percent change in perception threshold from sitting to standing (Physiologic Thresholds)

Additional endpoints will be evaluated post-hoc for data collected in assessments not listed in the predefined clinical endpoints.

7. Study Design

The AIM study is a prospective, multi-center, non-randomized, exploratory, single-arm study. Patients meeting the inclusion/exclusion criteria will be considered for enrollment in the study. Subjects will be considered enrolled after signing the informed consent.

7.1. *Scale and Duration*

This study will be conducted in up to 5 centers and will enroll subjects who are undergoing an SCS trial with a BSC neurostimulation system, per local directions for use (DFU). Up to 25 subjects who complete the Programming Visit will be enrolled. There is no maximum or minimum enrollment for sites participating in the study, but investigators will be asked to communicate with the sponsor regarding screened patients per Section 10.2. The study requires a screening visit and a programming visit. [redacted]

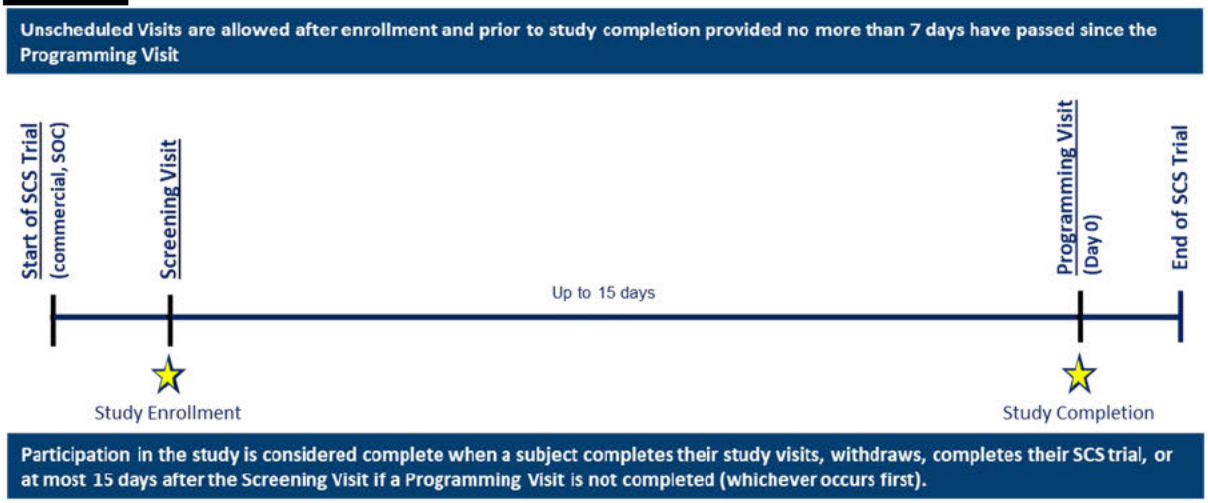


Figure 7.1-1 shows the study design.

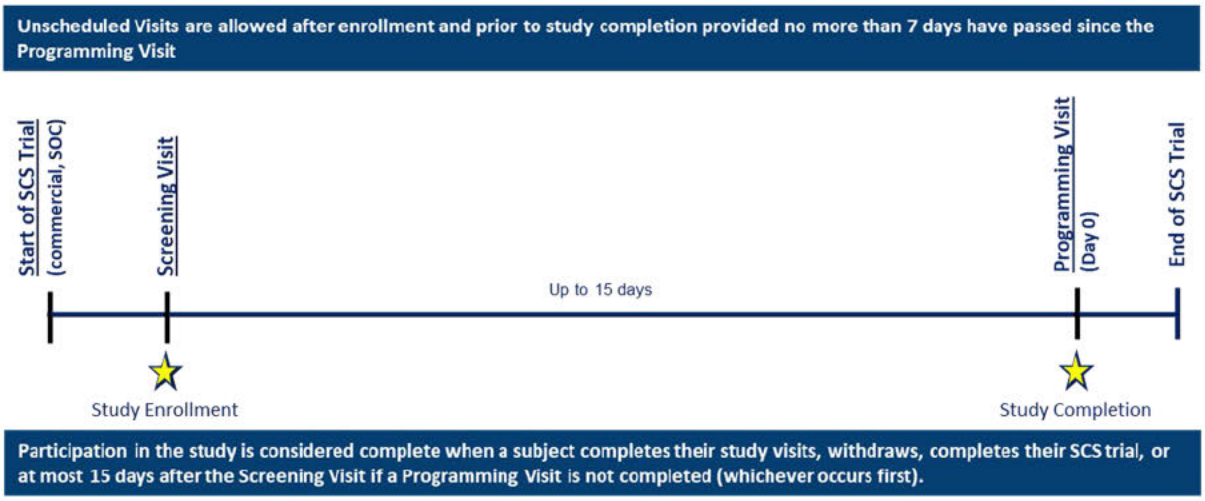


Figure 7.1-1: AIM Study Design

7.2. *Treatment Assignment*

Consecutive eligible patients who consent to participation and have met all of the inclusion and none of the exclusion criteria will be enrolled and assigned a unique subject identifier.

7.2.1. Treatment

The study treatment will consist of acute changes to neurostimulation trial therapy for pain programmed according to investigator discretion and within Boston Scientific's currently commercially approved rate, amplitude, pulse width. Automatic stimulation intensity adjustments ("automatic program") will be individualized and are designed to only be within comfortable ranges (as measured by physiologic thresholds).

[redacted]

8. Subject Selection

8.1. *Study Population and Eligibility*

Subjects are established patients in a pain management practice who are eligible to receive an SCS screening trial utilizing a commercially-approved BSC neurostimulation system to treat their pain condition.

8.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see Table 8.2-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 8.3) is met.

Table 8.2-1: Inclusion Criteria

Inclusion Criteria	IC1. Study candidate is undergoing a temporary SCS trial of commercially approved BSC neurostimulator system, per local directions for use (DFU).
	IC2. Subject signed a valid, EC/IRB-approved informed consent form.
	IC3. Age 18 or above, or above legal age and willing and capable of giving informed consent specific to national law when written informed consent is obtained.
	IC4. In the clinician best judgment, subject is able to distinguishably describe quality and location of sensation and pain.

8.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (Table 8.3-1) cannot be included in this study or will be excluded from this clinical study.

Table 8.3-1: Exclusion Criteria

Exclusion Criteria	EC1. Subject meets any contraindication in BSC neurostimulation system local DFU. EC2. Investigator-suspected gross lead migration during the SCS trial period which may preclude the study candidate from receiving adequate SCS therapy. EC3. Subject is currently diagnosed with cognitive impairment, or exhibits any characteristic, that would limit study candidate's ability to assess and report sensation information. EC4. Subject is currently diagnosed with a physical impairment, or exhibits a condition that would limit study candidate's ability to complete study assessments.

9. Subject Accountability

9.1. *Point of Enrollment*

Subjects will be considered enrolled into the study at the time of the study-specific informed consent form (ICF) execution. No study-related procedures or assessments can take place until the informed consent form is signed.

9.2. *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 study device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

A subject is considered lost-to-follow-up after 3 unsuccessful contact attempts have been made to reach the subject (including those who relocate but cannot be transferred to another participating site). Staff at the participating site should make a good faith effort to contact the subject with three documented communication attempts.

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 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.

9.3. *Subject Status and Classification*

A subject is considered enrolled in the AIM study after a signed informed consent form (ICF) has been obtained. Study participation will end for each enrolled subject when (whichever occurs first) they:

- complete their study visits,
- withdraw,
- complete their neurostimulation trial,
- or at most 15 days after the Screening Visit if a Programming Visit is not completed.

All subjects completing the Programming Visit will be counted against the enrollment ceiling for the study.

9.4. *End-of-Study Definition*

A clinical trial is considered completed when participants are no longer being examined or the last participant's last study visit has occurred.

9.5. *End of Study Action Plan*

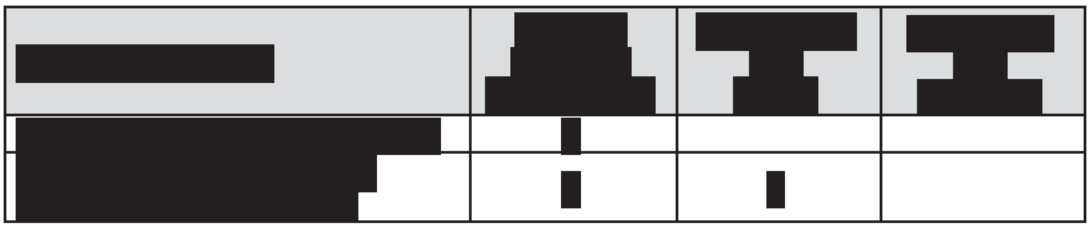
At the completion of the study, subjects will be followed according to standard, routine medical care. If the subject has not completed their neurostimulation trial, the subject may continue to use the external neurostimulator system per the applicable Directions for Use.

9.6. *Enrollment Controls*

All subjects who sign the study-specific Informed Consent Form will be considered enrolled in the study and will count towards the enrollment ceiling. At the time when the study-wide cap of 25 enrolled subjects completing the Programming Visit is reached, further enrollment into the study will cease.

10. Study Methods

[redacted]



[redacted]

10.2. ***Screening***

Investigators will screen eligible patients per the inclusion/exclusion criteria specified in Section 8.2 and 8.3 to determine eligibility for study inclusion.

Screening can begin up to 14 days prior to the Programming Visit. In order to determine eligibility for enrollment into the study, the inclusion and exclusion criteria must be assessed. Those inclusion and exclusion criteria that are part of routine, standard care for spinal cord stimulation may not require informed consent.

10.3. *Informed Consent*

After a patient has been identified as a potential candidate, written Informed Consent must be obtained prior to any study related assessments.

- The context of the study must be fully explained to the patient. The patients must also be given the opportunity to ask questions and have those questions answered to their satisfaction. Study personnel should explain to each potential participant that even if he or she agrees to participate in the study and signs an ICF, further testing might demonstrate that he or she is not eligible for the study.
- Written informed consent must be recorded appropriately by means of the subject's dated signature.
- The consent process must be documented in the subject's medical chart.

No study data may be collected prior to the signing and dating of the informed consent by the subject or their legally authorized representative.

10.4. *Programming Visit – Day 0*

The Programming Visit will occur in the physician's office. The clinician may perform routine clinical care prior to any changes in programming. The study devices may only be operated by authorized BSC personnel in a study physician's office under the direction of a study healthcare clinician. The study devices may not be sent home with the patient or dispensed to the either the site or the patient.

In the event of suspected lead migration or to aid programming the subject's device, optional imaging (anterior-posterior and lateral views recommended) may be performed at the beginning, during, and/or end of the Programming Visit to document lead position.

Prior to any changes in SCS trial programming, the following assessments will be completed:

- [redacted]
- [redacted]
- [redacted]

Upon completion of the above mentioned assessments, subjects will be connected to the AIM Study System with optional motion sensor to perform at least one experiment. More than one experiment may be performed as time allows. Experiments during the Programming Visit are expected to take no longer than approximately 2 – 4 hours and may end at any time the subject requests regardless of time elapsed. Experiments include programming changes to SCS (within Boston Scientific's currently commercially approved spinal cord stimulation parameters [e.g. rate, amplitude, pulse width, etc.]), recording ESG data, creating patient specific models, changes in patient posture (e.g. sitting, standing, lying down, etc.) or activity (e.g. walking, coughing, laughing, etc.), and/or automatic stimulation intensity adjustments (designed to only be within comfortable ranges, as measured by physiologic thresholds for that patient, "automatic programs").

The subject may optionally be asked to complete some or all of the following questionnaires for some or all experiments:

- [redacted]
- [redacted]
- [redacted]

The total number of experiments will depend on the subject's tolerance and time elapsed. The subject will then be disconnected from the AIM Study System and optional motion sensor. Subjects may be asked to return for an Unscheduled Visit to perform additional experiments and will be informed that they may refuse permission without penalty.

Each experiment and associated data, as outlined in the **Table 10.1-1: Data Collection Schedule**, will be documented in the study records.

10.1. *Unscheduled Visit*

Unscheduled visits may be made after enrollment and prior to study completion provided no more than 7 days have passed since the Programming Visit. Each unscheduled visit should be documented with the reason for the visit stated. Data should be collected according to Table 10.1-1: Data Collection Schedule.

If the Unscheduled Visit reason includes performing additional experiments, subjects will be connected to the AIM Study System with optional motion sensor to perform at least one experiment. More than one experiment may be performed as time allows. Experiments during the Unscheduled Visit are expected to take no longer than approximately 2 – 4 hours and may end at any time the subject requests regardless of time elapsed. Experiments include programming changes to SCS (within Boston Scientific's currently commercially approved spinal cord stimulation parameters [e.g. rate, amplitude, pulse width, etc.]), recording ESG data, creating patient specific models, changes in patient posture (e.g. sitting, standing, lying down, etc.) or activity (e.g. walking, coughing, laughing, etc.), and/or automatic stimulation intensity adjustments (designed to only be within comfortable ranges, as measured by physiologic thresholds for that patient).

The subject may optionally be asked to complete some or all of the following questionnaires for some or all experiments:

- [redacted]
- [redacted]
- [redacted]

The total number of experiments will depend on the subject's tolerance and time elapsed. The subject will then be disconnected from the AIM Study System and optional motion sensor.

Each experiment and associated data, as outlined in the **Table 10.1-1: Data Collection Schedule**, will be documented in the study records.

10.2. *Study Completion*

Each subject will be followed until (whichever occurs first) they:

- complete their study visits,
- withdraw,
- complete their neurostimulation trial,
- or at most 15 days after the Screening Visit if a Programming Visit is not completed.

If a subject returns for an Unscheduled Visit, their participation in the study is complete once the Unscheduled Visit is complete and the subject exits the study. If the subject is not asked to return for an Unscheduled Visit, once the subject completes the Programming Visit, their participation in the study is complete and the subject exits the study. A withdrawal of the subject also completes his/her participation in the study. The study will be completed once all subjects have completed study participation and all site and study close-out activities have been finished.

10.3. *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 10.8-1.

Table 10.3-1: Source Documentation Requirements

Requirement	Disposition
Hospital records and/or clinical and office charts including the evidence of but not limited to inclusion/exclusion criteria, informed consent, procedures, laboratory results, medications, assessment of adverse events, health resource utilization information	Retained at study site
Assessments and Questionnaires	Retained at study site and/or retained at sponsor site
Imaging films/prints (if applicable)	Retained at study site
NEXT System data (e.g. study stimulation, electrospinogram, and optional motion sensor data)	Retained at study site and/or retained at sponsor site
Programming printouts/forms for programming information	Retained at study site
Technical Source Forms	Retained at study site
SCS Data	Retained at study site and/or retained at sponsor site

11. Statistical Considerations

This exploratory study does not include any powered endpoints or sample size calculations. Univariate and multivariable models may be used to assess automated therapy adjustments.

12. Data Management

12.1. *Data Collection, Processing, and Review*

Subject data will be recorded on paper case report forms (CRFs), which will be transmitted from the site to Boston Scientific electronically and stored on the secure server of Boston Scientific.

12.2. *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.

[redacted]

12.4. *Study Assessments*

12.4.1. Adverse Events

Adverse event evaluation will be conducted to identify adverse events occurring during the study and classify them in regard to seriousness, relationship to the procedure and/or device, action taken and outcome. Safety events will be reported as specified in the Safety Reporting Section.

12.4.2. Demography

Demographic information will include date of birth, gender, and race/ethnicity.

12.4.3. Device Deficiency Evaluation

Device Deficiency evaluation will be conducted to identify deficiencies occurring during the study and device type and action taken. Safety events will be reported as specified in the Safety Reporting Section.

[redacted]

[redacted]

12.4.5. End of Study

End of Study form will collect the date the subject completed participation in the study and the reason (i.e. completed study, withdrawal, etc.).

[redacted]

12.4.7. Medical History

Medical history will include medical and procedural history relating to pain management, onset of chronic pain, etc.

[redacted]

[redacted]

13. 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, 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 CRF. Sites may also be required to report deviations to the IRB/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 IRB/EC/regulatory authority/FDA notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

The sponsor will not approve protocol waivers.

[redacted]

15. Compliance

15.1. *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 21 CFR part 56, part 50, part 54 and part 812 or 813, European Medical Device Regulation, EN ISO 14155: Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice; ; Japan Medical Device GCP etc.) 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 IRB/EC and/or regulatory authority has been obtained, if appropriate. Any additional requirements imposed by the IRB/EC or regulatory authority shall be followed, 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 IRB/EC or regulatory authority shall be followed, if appropriate.

15.2. *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 the Investigator Brochure Signature Page and 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 reportable events.
- 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 applicable laws or 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.

- As applicable, 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 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.

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.

15.2.1. 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.

15.3. *Institutional Review Board/ Ethics Committee*

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

A copy of the written IRB/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 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.

Any amendment to the protocol will require review and approval by the IRB/EC before the changes are implemented to the study. All changes to the ICF will be IRB/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 IRB/EC approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IRB/EC requirements. Copies of the study reports and the IRB/EC continuance of approval must be provided to the sponsor.

15.4. *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. 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.

17. Potential Risks and Benefits

The terms describing the estimated risk occurrences are:

- "Very Common" (occur in ≥50% of patients)
- "Common" (occur in ≥20% to <50% of patients)

- "Less Common" (occur in ≥5% to <20% of patients)
- "Uncommon" (occur in ≥2% to <5% of patients)
- "Rare" (in <2% of patients)

The estimated rates apply to typical use of SCS and likely overestimate risk occurrence given the brief time of the study intervention.

17.1. *Anticipated Adverse Events*

The following anticipated adverse events (AE) have been identified for this study:

Unknown:

- The subject may find it difficult, uncomfortable, or tiresome to complete study measurements and questionnaires. The rate of this occurring in study participants is unknown.

Less Common:

- Infection such as cellulitis or subcutaneous abscess
- Pain

Uncommon:

- Swelling
- Worsened back pain

Rare:

- Abnormal healing or failure to heal
- Allergic, immune, or inflammatory response or reaction to medication or surgical materials
- Death
- Deep vein thrombosis/thrombophlebitis
- Depression due to unmet expectations of treatment
- Headache
- Infection that is severe or life-threatening, such as epidural abscess, meningitis or sepsis
- Nerve injury, which can result in symptoms such as tingling, numbness, pain, loss of bladder or bowel control, weakness, or paralysis
- Pulmonary embolism
- Radiation exposure (harm from this is rare)

The adverse events summarized below are anticipated during use of SCS beyond the programming procedures that are the primary focus of this study. The risks listed include those associated with the trial procedure and the presence of the SCS device system within the body. Potential risks not already identified may exist.

- Abnormal healing or failure to heal
- Additional surgical procedure such as explant, revision, or re-implantation of the leads, extensions, or IPG, or revision of the IPG pocket

- Allergic, immune, or inflammatory response or reaction to surgical materials or medication, or the presence of the device or its materials
- Burns, including due to charger misuse
- Death
- Deep vein thrombosis/thrombophlebitis
- Discomfort, which can include minor tenderness, uncomfortable awareness of the device, or anxiety
- Dural tear with or without Cerebrospinal Fluid leak
- Error during implantation of device, e.g. faulty connection of extension to IPG, which can lead to additional surgery
- Headache
- Hematoma ranging from minor bruising to hematoma of a serious type e.g. an epidural hematoma resulting in paralysis
- Hemorrhage requiring transfusion
- Inability to change stimulation, e.g. the remote control stops working
- Infection ranging from cellulitis or subcutaneous abscess to that is severe or life-threatening, such as epidural abscess, meningitis or sepsis
- Minor bruising
- Muscle spasms
- Musculoskeletal stiffness
- Nausea, including associated with anesthesia
- Nerve injury, which can result in symptoms such as unintentional tingling, numbness, pain, loss of bowel or bladder control, sexual dysfunction, weakness, or temporary or permanent paralysis
- Pain, including post-operative pain, pain at IPG site, or worsening of original pain
- Pneumothorax, pneumocephalus, or injury to other tissues during surgery
- Post-operative pain and swelling
- Pulmonary embolism
- Radiation exposure
- Respiratory arrest, e.g. apnea spell during surgical procedure
- Risks associated with any type of surgery, e.g. exposure to biohazardous materials
- Seizure
- Skin erosion over the device
- Stimulation-related symptoms in other body systems, e.g. changes to urinary function, priapism
- Swelling, including seroma at the IPG site or other locations
- Tissue damage at implant site from exposure to MRI
- Undesirable sensations at target stimulation areas, which may include pain, pressure, numbness, or uncomfortable paresthesia
- Weight gain or loss

17.2. *Anticipated Adverse Device Effects*

The anticipated adverse device effects (ADEs) known to be associated with SCS device programming as described in this study design are summarized below. Potential risks not already identified may exist.

Very Common

- Stimulation in target or non-target areas, which may produce undesirable sensations[1], (i.e., pain, pressure, numbness, uncomfortable paresthesia)

Common:

- Overstimulation of tissue[2], which can include feeling sensations such as jolts or shocks, and potential injuries arising from this causing distraction or loss of muscle control, e.g. fall

Less Common

- Inadequate stimulation resulting in increased pain, which may, for example, be due to a system malfunction, poor electrode positioning, or interference from other electromagnetic devices
- Infection, such as cellulitis or subcutaneous abscess

Uncommon

- Discomfort, which can include minor tenderness, uncomfortable awareness of the device, or anxiety

Rare

- Depression due to unmet expectations of treatment
- Electrical shock, e.g. from misuse of the AIM Study SCS System plug-in to the wall outlet
- Headache
- Inability to change stimulation
- Muscle spasms
- Musculoskeletal stiffness
- Nausea
- Nerve injury, which can result in symptoms such as unintentional tingling, numbness, pain, loss of bowel or bladder control, sexual dysfunction, weakness, or temporary or permanent paralysis
- Seizure

[1] Stimulation-induced undesirable sensations that are temporary (e.g. resolve when study stimulation is turned off) will not be considered adverse events

[2] Overstimulation of tissue that does not result in an injury and that is temporary will not be considered adverse events

- Stimulation-related symptoms in other body systems, e.g. changes to urinary function, persistent penile erection

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

There are no known incremental risks associated with the study device above those of market-available products.

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

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

If additional radiographic imaging is performed per study recommendation, the subject will have additional radiation exposure. However, clinical harm from the typical amount of radiation exposure is extremely rare.

17.5. *Possible Interactions with Concomitant Medical Treatments*

No possible interactions have been identified for use of the SCS system concomitant with any specific medications. However, there may be some risk that is unknown.

Medical treatments that should not be used while the SCS lead remains implanted are listed in the BSC directions for use for the applicable commercially approved lead(s).

17.6. *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.

All efforts will be made to minimize the aforementioned potential risks using the following approaches:

- Selection of Investigators (anesthesiologists and neurosurgeons) who are experienced and skilled in the treatment of subjects as per BSC's site selection and qualification procedures
- Clearly defined inclusion and exclusion criteria that ensure only appropriate subjects are enrolled
- Ensuring that treatment and follow-up of subjects is consistent with current medical practice
- Ensuring that the NEXT System is only operated during the study Programming Visit by authorized BSC personnel in a study physician's office under the direct supervision of a study healthcare professional.

- Ensuring that the NEXT System is not sent home with the patient or dispensed to the either the site or the patient.
- Safety review processes by Boston Scientific
- Monitoring visits as needed

17.7. *Anticipated Benefits*

The reported benefit of the implementation of the AIM Study SCS System into future commercially available SCS may include:

- Reduction in the intensity of chronic low back pain
- Reduction in the intensity of chronic leg pain
- Reduction in overall pain (low back and/or leg pain)
- Improvement in physical functioning (disability)
- Improvement in sleep
- Improvement in quality of life
- Reduction in pain-related medication use

17.8. *Risk to Benefit Rationale*

The risk evaluation for the study determined that all hazards attributed to the AIM Study SCS System and overall remaining residual risks after implementations of the required mitigations have been evaluated. Based on the risk evaluation results, the potential future benefit provided by the AIM Study SCS System to treat chronic intractable pain of the trunk and limbs outweighs the remaining residual risk. As the overall residual risk meets BSN's criteria, the AIM Study SCS System is acceptable for use in a clinical setting.

18. Safety Reporting

18.1. *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 Serious Adverse Events related to the Study Device (Investigational Device)
- All Serious Adverse Events, related to the Procedure
- All Stimulation Related Adverse Events
- All Device Deficiencies
- Unanticipated Adverse Device Effects/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 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 prior to, during or subsequent to the procedure, must be recorded in the eCRF.

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 Section 18 for the known risks associated with the study device(s).

18.2. *Definitions and Classification*

Adverse event definitions are provided in Table 19.2-1. Administrative edits were made on the safety definitions from the applicable regulations and guidance including (but not limited to) 21 CFR Part 812, ISO 14155 and EU MDR 2017/745/MDCG 2020-10/-1 Guidance on Safety Reporting in Clinical Investigations for clarification purposes.

Table 18.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) **Ref: ISO 14155** **Ref: MDCG 2020-10/1**	**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 investigational medical device and whether anticipated or unanticipated.** **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: MDCG 2020-10/1**	**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 from intentional misuse of the investigational medical device.** **NOTE 3: This includes 'comparator' if the comparator is a medical device.**
Serious Adverse Event (SAE) **Ref: ISO 14155** **Ref: MDCG 2020-10/1**	**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) 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) **Ref: ISO 14155** **Ref: MDCG 2020-10/1**	**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: MDCG 2020-10/1**	**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: MDCG 2020-10/1**	**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 • 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.

NOTES:

1. In the event of subject death during the conduct of the study, efforts should be made to perform an autopsy.
2. Sensations or side effects that occur during the programming session should not be reported as AEs. However, unwelcome sensations or side effects that persist or occur after the completion of the programming will be reported as AEs. Additionally, if the temporary neurostimulation-induced sensation(s) precipitated an AE, the AE should be reported in the Adverse Event CRF.
3. Lack of efficacy/decreased therapeutic response will not be collected as AEs. Also, return of the patient's pain symptoms to their Baseline level does not meet the criteria for an AE.
4. Clinically significant worsening of the pattern of intensity or distribution of Baseline pain symptoms or other sequelae as a result of lack of efficacy/decreased therapeutic response should be reported as an AE.
5. Device/lead migration will not be collected as an AE. However, if the device/lead migration precipitated an AE, the AE should be reported in the *Adverse Event* CRF.
6. Device deficiencies, failures, malfunctions, and product nonconformities should not be reported as adverse events. However, if an adverse event resulted from a device failure or malfunction, that specific event would be recorded on the *Adverse Event* CRF. Device deficiencies, failures, malfunctions, and product non-conformities should be documented in the *Device Deficiency* CRF.

18.3. *Relationship to Study Device(s) (Investigational Devices) and/or Study Procedure*

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

Table 18.3-1: Criteria for Assessing Relationship of Study Device(s) (Investigational Devices) or Procedure to Adverse Event

Classification	Description
Not Related *Ref: MDCG 2020-10/1*	Relationship to the device, comparator or procedures can be excluded when: - the event has no temporal relationship with the use of the investigational device or the procedures related to the use of the investigational device; - 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 that cannot 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; - 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: MDCG 2020-10/1*	The relationship with the use of the investigational 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: MDCG 2020-10/1*	The relationship with the use of the investigational device or comparator, or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause.

Table 18.3-1: Criteria for Assessing Relationship of Study Device(s) (Investigational Devices) or Procedure to Adverse Event

Classification	Description
Causal Relationship *Ref: MDCG 2020-10/1*	The serious event is associated with the investigational 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 investigational device use/application or procedures; - the event involves a body-site or organ that -the investigational device or procedures are applied to;-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 adverse event.

18.4. *Investigator Reporting Requirements*

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

All device-related (hardware and stimulation) and procedure-related adverse events, serious adverse events and serious adverse device effects will be reported from the time of enrollment until the end of study participation.

Table 18.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline pre-market studies (21 CFR Part 812, /MDCG 2020-10/1)

Table 18.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline pre-market studies** (21 CFR Part 812, /MDCG 2020-10/1)
Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor.
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Immediately but not later than 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, as requested by sponsor.	• Upon request of sponsor
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Immediately but not later than 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.
Device Deficiencies (including but not limited to malfunctions, use errors and inadequacy in information supplied by the manufacturer, including labeling) Note: Any Device Deficiency that might have led to a serious adverse event if appropriate action had not been taken,intervention had not occurred , circumstances had been less fortunate is considered a reportable event.	Complete applicable CRF pages with all available new and updated information and email to AIM-safety@bsci.com	• Immediately but not later than 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

Table 18.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline pre-market studies** (21 CFR Part 812, /MDCG 2020-10/1)
Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• Adverse Device Effects (or other key events of interest): In a timely manner but not later than 10 business days after becoming aware of the information • Adverse Events: In a timely manner but recommend within 10 business days after becoming aware of the information • Reporting required through end of study • Upon request of sponsor
	Provide all relevant source documentation (de-identified/pseudonymized) for reported event, as requested by sponsor.	

* Please note that pre-market studies are clinical studies with investigational devices or with medical devices that bear the regulatory approval and are not being used for the same approved indications.

18.5. *Boston Scientific Device Deficiencies*

Device deficiencies are not adverse events. However, an adverse event that results from a device deficiency would be recorded as an adverse event on the appropriate eCRF.

All investigational device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and labeling errors) should be documented and reported to BSC. If possible, the investigational device(s) should be returned to BSC for analysis. Instructions for returning the investigational device(s) will be provided. 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.

The following device deficiencies are to be reported for the AIM study:

- Device deficiencies related to the usage of the Sardeen External Neurostimulator (SEN)
- Device deficiencies related to the SCS Commercial Lead connected to the Sardeen External Neurostimulator (SEN)
- Device deficiencies related to the clinician programmer using the Sardeen Programming Application and Research Kit (SPARK) software tool
- Device deficiencies related to USB connection or optically-isolated USB connection

All commercially available BSN device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) other than above should be reported through the commercial complaint reporting process to the BSC Patient Care Center at (866) 360-4747, ext. 2 or BSN.ComplaintCallCenter@bsci.com.

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.

And, 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.

18.6. *Reporting to Regulatory Authorities / IRBs / ECs/ Investigators*

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

The Principal Investigator is responsible for informing the IRB/EC, and regulatory authorities of unanticipated adverse device effects (UADE) and SAE as required by local/regional regulations.

18.7. *Subject Death Reporting*

A subject death during the study should be reported to Boston Scientific as soon as possible and, in any event, within three calendar days of site notification. The site's IRB/EC must be notified of any deaths in accordance with that site's IRB/EC policies and procedures. Notification of death should include a detailed narrative (death letter) that provides detailed information describing the circumstances surrounding the death. A death narrative in the local language is acceptable, if accompanied by a translation in English. The details listed below should be addressed in the death narrative, in order for BSC to understand the circumstance surrounding the death:

- Date and time of death
- Place death occurred
- Immediate cause of death
- Rhythm at the time of death, if known (include any available documentation)
- Whether the death was related to the clinical investigation, procedure, or patient condition
- Whether or not the death was witnessed
- Any other circumstances surrounding the death
- Approximate time interval from the initiating event to death (temporal course)- items to consider include, but are not limited to: information regarding last time subject was seen by investigator, last office visit, etc.µ
- Investigator or sub investigator signature and date

Also submit the following documentation:
If the patient expired in the hospital:

- A copy of the medical records for that admission (e.g., H & P, consults, test results, operative reports, and/or progress notes from the hospital chart)
- Death certificate (if available)
- Autopsy report (if applicable)

If the patient expired outside of the hospital (e.g., home):

- A copy of the most recent clinic visit (if not already submitted to Boston Scientific)
- Death certificate (if available)

19. 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, 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 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. IRB/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 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.

20. Committees

20.1. *Safety Monitoring Process*

The BSC personnel from the Medical Safety and Safety Trial Operation Teams-review safety data as 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 Medical Safety and Safety Trial Operations team include a physician with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

21. 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 IRBs/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 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 of the device.

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

Any investigator, or associated IRB/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 IRBs/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 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/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.

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 6 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. 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 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 may 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/).

[redacted]

25. Bibliography

Copies of publications are not provided to sites and/or IRBs/ECs unless requested.

1. Birdno, M. J., Kuncel, A. M., Dorval, A. D., Turner, D. A., Gross, R. E., & Grill, W. M. (2012, January). *Stimulus features underlying reduced tremor suppression with temporally patterned deep brain stimulation*. J Neurophysiol., 107(1), 364-383.
2. Breivik, H., Collett, B., Ventafridda, V., Cohen., R., and Gallacher, D. *Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment*. European Journal of Pain. 2006; 10(4):287-333.
3. Brocker, D. T., Swan, B. D., A, T. D., Gross, R. E., Tatter, S. B., Koop, M. M., et al. (2013, January). *Improved efficacy of temporally non-regular deep brain stimulation in Parkinson's disease.* Exp Neurol., 239, 60-67.

4. Carter, M.L., *Spinal cord stimulation in chronic pain: a review of the evidence.* Anaesth Intensive Care, 2004. **32**(1): p. 11-21.

5. Hasselströma, J., Liu-Palmgrenb, J., and Rasjö-Wrååkc, G. *Prevalence of pain in general practice.* European Journal of Pain. 2002;6(5):375-385.

6. Kumar, K., G. Hunter, and D. Demeria, *Spinal cord stimulation in treatment of chronic benign pain: challenges in treatment planning and present status, a 22-year experience.* Neurosurgery, 2006. **58**(3): p. 481-96; discussion 481-96.

7. Kumar, K., et al., *Spinal cord stimulation versus conventional medical management for neuropathic pain: a multicentre randomised controlled trial in patients with failed back surgery syndrome.* Pain, 2007. **132**(1-2): p. 179-88.

8. Kumar, K., et al., *The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation.* Neurosurgery, 2008. **63**(4): p. 762-70; discussion 770.

9. Manca, A., et al., *Quality of life, resource consumption and costs of spinal cord stimulation versus conventional medical management in neuropathic pain patients with failed back surgery syndrome (PROCESS trial).* Eur J Pain, 2008. **12**(8): p. 1047-58.

10. National Center for Health Statistics. Health, United States, 2010: With Special Feature on Death and Dying. Hyattsville, Maryland. 2011.Carter ML. Spinal cord stimulation in chronic pain: a review of the evidence. Anaesth Intensive Care. 2004;32: 11-21.

11. North, R.B., *Spinal cord stimulation for intractable pain: long-term follow-up.* J Spinal Disord, 1990. **3**(4): p. 356-61.

12. North, R.B., et al., *Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: a randomized, controlled trial.* Neurosurgery, 2005. **56**(1): p. 98-106; discussion 106-7.

13. North, R.B., et al., *Spinal cord stimulation versus reoperation for failed back surgery syndrome: a cost effectiveness and cost utility analysis based on a randomized, controlled trial.* Neurosurgery, 2007. **61**(2): p. 361-8; discussion 368-9.

14. Oakley, J., Prager, JP, Stamatos, J, Foster AM, *A new spinal cord stimulation system effectively relieves chronic, intractable pain: a multicenter prospective clinical study.* Neuromodulation, 2007. **10**(3): p. 262-278.

15. 15. Shealy, CN, Mortimer, JT, Hagfors, NR. Dorsal column electroanalgesia. J Neurosurg, 1970 May;32(5):560-4. North, R., Ewend, M, Lawton, M, Piantadosi, S, Spinal cord stimulation for chronic, intractable pain: superiority of "multi-channel" devices. Pain, 1991 Feb;44(2):119-130.

16. Parker, J, Karantonis, D, Single, P, Obradovic, M, Cousins, M, Compound action potentials recorded in the human spinal cord during neurostimulation for pain relief, Pain, 2012 Mar;153(3):593-601.

17. Feirabend, H , Choufoer, H, Ploeger, S, Holsheimer, J, van Gool, JD, Morphometry of human superficial dorsal and dorsolateral column fibres: significance to spinal cord stimulation, Brain, 2002 May;125(Pt 5):1137-49.

18. Swan, B. D., Brocker, D. T., Hilliard, J. D., Tatter, S. B., Gross, R. E., Turner, D. A., et al. (2016, Feb). *Short pauses in thalamic deep brain stimulation promote tremor and neuronal bursting*. Clin Neurophysiol, **127**(2), 1551-1559.

19. Swan, B. D., Brocker, D. T., Hilliard, J. D., Tatter, S. B., Gross, R. E., Turner, D. A., et al. (2015, Jan-Feb). *Measurement of evoked potentials during thalamic deep brain stimulation.* Brain Stimul, **8**(1), 42-56.

20. Swan, B. D., Grill, W. M., & Turner, D. A. *Investigation of Deep Brain Stimulation Mechanisms During Implantable Pulse Generator Replacement Surgery*. Neuromodulation, 2014. **17**: p. 419-424.

21. Tan, D. W., Schiefer, M. A., Keith, M. W., Anderson, J. R., Tyler, J., & Tyler, D. J. *A neural interface provides long-term stable natural touch perception*. Sci Transl Med, 2014 Oct 8. **6**(257):257ra138.

22. Tan, D., Tyler, D., Sweet, J., & Miller, J. *Intensity Modulation: A Novel Approach to Percept Control in Spinal Cord Stimulation*. Neuromodulation, 2016. **19**(3), 254-259.

23. Taylor, R.S., et al., *The cost effectiveness of spinal cord stimulation in the treatment of pain: a systematic review of the literature.* J Pain Symptom Manage, 2004. **27**(4): p. 370-8.

24. Torrance, N., Smith, BH, and Lee, AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. Journal of Pain. 2006; 7(4):281-9.

26. Abbreviations and Definitions

Abbreviations and definitions are shown in Table 24.2-1.

Table 24.2-1: Abbreviations and Definitions

Abbreviation/Acronym/Term	Term/Definition
AE	Adverse event: 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.
ADE	Adverse device effects: AE related to the use of an investigational medical device
AP	Anterior-posterior
BSC	Boston Scientific Corporation
BSN	Boston Scientific Neuromodulation
CA	Competent Authority
CE	Clinical Exclusion Criteria
CI	Clinical Inclusion Criteria
CP	Clinician Programmer: laptop computer running BSC software used to program an external trial stimulator (ETS) or implantable pulse generator
CMM	Common medical management
eCRF	Case Report Form
DBS	Deep Brain Stimulation
DFU	Directions for use
DT	Discomfort Threshold
Enrollment	A patient will be considered enrolled in the study at the point of providing written informed consent
ESG	Electrospinogram
ETS	External Trial Stimulator
FDA	Food and Drug Administration
FBSS	Failed Back Surgery Syndrome
GCP	Good Clinical Practices
HCP	Healthcare personnel
ICF	Patient Information and Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	International committee of medical journal editors
EC	Ethics Committee
IPG	Implantable pulse generator
IRB	Institutional Review Board
Lead	Implantable device that delivers stimulation from an IPG or ETS to the target tissue (e.g. dorsal column stimulation leads in the dorsal epidural space). For this study, only subjects with permanently implanted SCS surgical leads will be enrolled.
MCT	Maximum Comfortable Threshold
MRI	Magnetic resonance imaging
NEXT	Neuromodulation Experiment Testbed (NEXT) which consists of the Sardeen External Neurostimulator (SEN) programmed with the Sardeen Programming Application and Research Kit (SPARK) software tool
OR	Operating room (e.g. OR cable)
PPTS	Patient preferred trial settings
PT	Perception Threshold
Programming	The process of turning on and adjusting the stimulation parameters (amplitude, pulse width, rate, polarity) on an ETS or IPG. For this study, only subjects with an ETS will be enrolled.
RCT	Randomized Controlled Trial
SAE	Serious adverse event: AE that led to death, serious deterioration in the health of the subject or led to fetal distress, death or congenital abnormality.
SADE	Serious adverse device effects: Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
SCS	Spinal Cord Stimulation

SEN	Sardeen External Neurostimulator
SPARK	Sardeen Programming Application and Research Kit software run on laptop computer running used to program the Sardeen External Neurostimulator (SEN) configure recording settings, and manage data collection and storage from the SEN and wearable motion sensor.
Stimulator	External 4 Channel Stimulus Generator, STG4004-16mA, Multi Channel Systems MCS GmbH

Abbreviation/Acronym/Term	**Term/Definition**
Source data Ref: ISO 14155	All information in original records, certified copies of 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 Ref: ISO 14155	Original or certified copy of printed, optical or electronic document containing source data.

[redacted]