Blue Box Study

Study to Characterize the Effects of Programming Spinal Cord Stimulation (SCS) in Patients Undergoing a Boston Scientific (BSC) SCS Temporary Trial

CLINICAL INVESTIGATION PLAN

[redacted]

Sponsored By

Boston Scientific Corporation

Neuromodulation

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[redacted]

Revision History

[redacted]	Release Date	[redacted]
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2. Protocol Synopsis

Blue Box: Study to Characterize the Effects of Programming SCS in Patients Undergoing a BSC SCS Temporary Trial	
Primary Objective	To characterize the effects of programming patterned SCS pulse trains in patients undergoing a Boston Scientific (BSC) SCS temporary trial.
Test Device	• All BSC commercially approved Spinal Cord Stimulation SCS trial systems connected to BSC lead(s) [redacted]
Study Design	Prospective, multi-center, non-randomized, exploratory, single-arm
[redacted]	
[redacted]	Up to 3 sites in the US
[redacted]	

Blue Box: Study to Characterize the Effects of Programming SCS in Patients Undergoing a BSC SCS Temporary Trial	
	[redacted]
Safety Parameters	All device-related and procedure-related adverse events, all serious adverse events and serious adverse device effects will be reported from the time of enrollment until the end of study participation.
Follow-up Schedule	Study assessments will be required, as appropriate, at the following time points: • Screening Visit (up to 14 days prior to Programming Visit) • Programming Visit (Day 0)
Study Duration	Overall study duration is anticipated to take approximately 36 months from first patient enrolled to end of study close out activities.
Key Inclusion Criteria	[redacted] Study candidate is undergoing an SCS trial of BSC neurostimulation system, per local directions for use (DFU). [redacted] Subject signed a valid, IRB-approved informed consent form. Subject is 18 years of age or older when written informed consent is obtained.
Key Exclusion Criteria	[redacted] Subject meets any contraindication in BSC neurostimulation system local DFU. [redacted]

3. Table of Contents

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4. Introduction

4.1. *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.

4.2. *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).

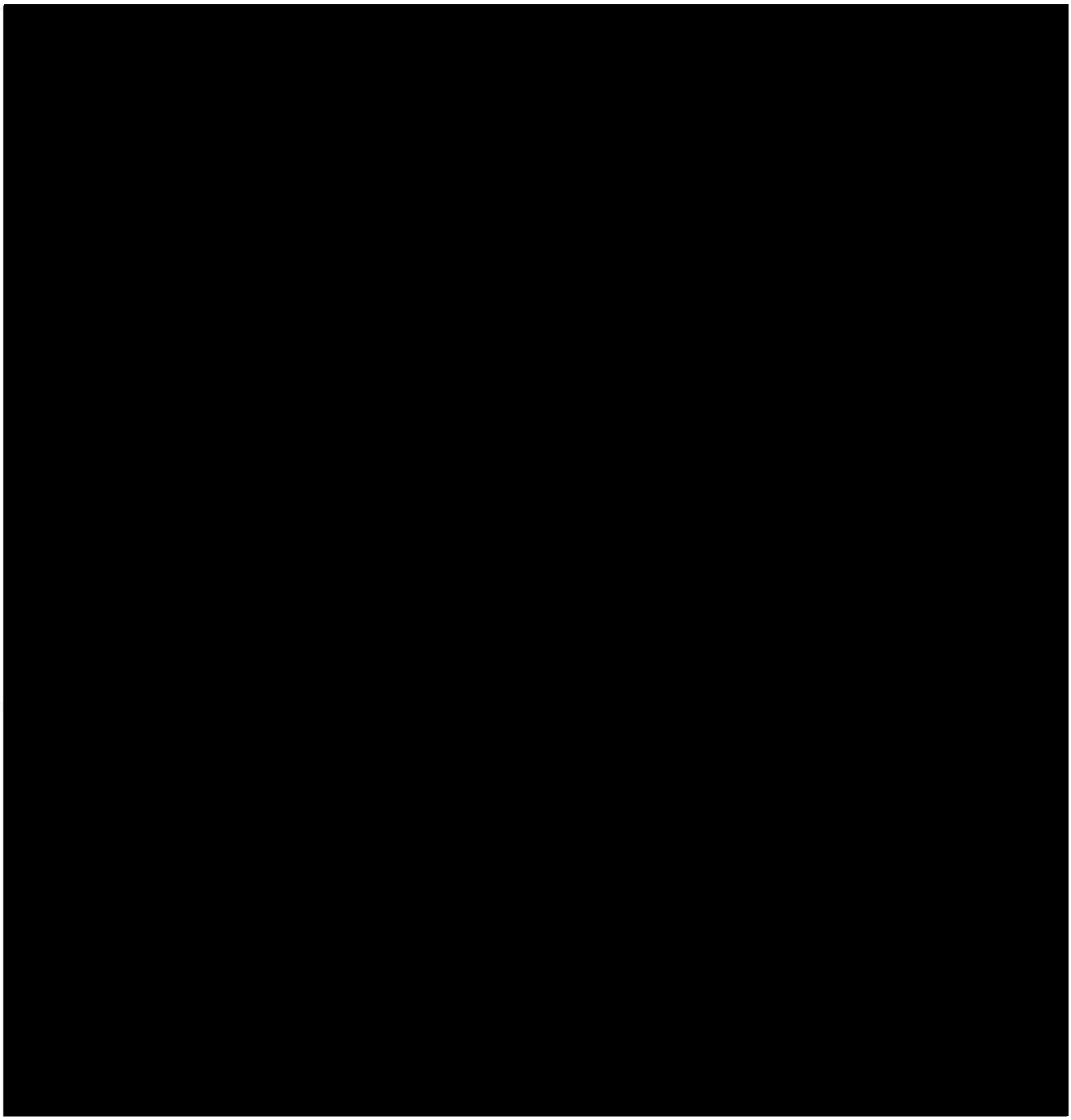
In a separate, international, multi-center RCT, Kumar et al. randomized 100 patients: 48 to CMM and 52 to SCS plus CMM (Kumar *et al.,* 2007). At 6 months, patients randomized to SCS achieved significantly greater pain relief and improved functional capacity and health-related quality of life compared 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).

5. Device Description

5.1. *System Elements*



The Blue Box Study SCS System setup is similar to others employed in numerous IRB approved studies where an external electrical stimulator was connected acutely to either SCS or deep brain stimulation (DBS) leads, intraoperatively and during stimulation trials, to deliver acute temporal patterns of stimulation to patients (Tan, et al., 2016; Swan, et al., 2016; Swan, et al., 2015; Tan, et

al., 2014; Swan, et al., 2014; Brocker, et al., 2013; Birdno, et al., 2012). The systems used in these studies consist of software on a computer to communicate with an external stimulus generator (via a cable), an isolator to optically isolate the external generator, and a custom interface (passive switch box) to connect the external generator to the lead (via a cable).

5.1.1. Boston Scientific SCS Systems

BSC commercially approved SCS systems are approved by the Food and Drug Administration 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. 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 14 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. Consequently, the IPG and associated components will not be included here.

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.

[redacted]

[redacted]

6. Study Objectives

6.1. *Primary Objective*

To characterize the effects of programming patterned SCS pulse trains in patients undergoing a Boston Scientific (BSC) SCS temporary trial.

[redacted]

8. Study Design

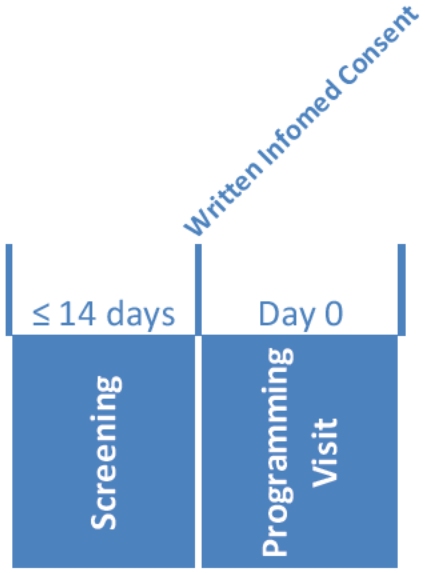
This is a prospective, on-label, multi-center, non-randomized, exploratory, single-arm study.

8.1. *Scale and Duration*

[redacted] The study requires a screening visit and a programming visit. Overall study duration

is planned for approximately 36 months from first patient enrolled to completion of end of study close out activities. Figure 8-1 shows the study design

Figure 8-1: Study Design



8.2. *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.

8.2.1. Treatment

The study treatment will consist of commercially available neurostimulation program settings with any commercially approved Boston Scientific Precision Spectra neurostimulator for pain.

8.3. *Justification for the Study Design*

This is a prospective, on-label, multi-center, non-randomized, exploratory, single-arm study. The endpoints of this study are intended to observe the paresthesia paradigms elicited by programming configurations that are within Boston Scientific's currently commercially approved spinal cord stimulation rate, amplitude, and pulse width. The results of this study will also help Boston Scientific guide the development of next generation programming algorithms.

A prospective study design will ensure that identical procedures are followed for data capture and review.

A multi-center design will minimize the impact on the results due to specific surgical placement and intra-operative techniques as well as to minimize bias that may result from differences in patient selection, regional differences in the patient demographic, and patient management.

This study does not require blinding since there is no treatment comparison based on outcomes and all subjects will be undergoing identical procedures. All end-points are exploratory and the design does not require statistical power.

9. Subject Selection

9.1. *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.

9.2. *Inclusion Criteria*

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

Table 9.2-1: Inclusion Criteria

Clinical Inclusion Criteria	[redacted] Study candidate is undergoing an SCS trial of BSC neurostimulation system, per local directions for use (DFU). [redacted] Subject signed a valid, IRB-approved informed consent form. Subject is 18 years of age or older when written informed consent is obtained.

Abbreviations: BSC - Boston Scientific Corporation, SCS – Spinal Cord Stimulation, DFU - directions for use, IRB - Institutional Review Board

9.3. *Exclusion Criteria*

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

Table 9.3-1: Exclusion Criteria

Clinical Exclusion Criteria	[redacted] Subject meets any contraindication in BSC neurostimulation system local DFU. [redacted]

Abbreviations: BSC - Boston Scientific Corporation, DFU - Directions For Use, SCS – Spinal Cord Stimulation

10. Subject Accountability

10.1. *Point of Enrollment*

The point of enrollment is the time at which a subject signs and dates the valid, IRB/EC-approved informed consent form. No study-related procedures or assessments can take place until the informed consent form is signed.

10.2. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. 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.

Reasons for withdrawal include

- physician discretion,
- subject choice to withdraw consent,
- subject's failure to meet study inclusion or exclusion criteria after enrollment
- lost to follow-up, or
- death

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

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

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

10.3. *Subject Status and Classification*

A subject is considered enrolled after a signed informed consent form (ICF) has been obtained. Study participation will end when each enrolled subject completes their study visits, withdraws, or at most 15 days after the Screening Visit if a Programming Visit is not completed.

10.4. *Enrollment Controls*

At the time when the study-wide cap of 35 enrolled subjects is reached, further enrollment into the study will cease. The sponsor will notify all centers when approximately 30 subjects have been enrolled to alert investigators that enrollment will soon cease. The correspondence may also outline the specific activities to minimize the risk of enrollment after the protocol-specified cap of 10 enrolled subjects has been reached.

10.5. *End-of-Study Action Plan*

Subjects will be followed according to standard, routine medical care.

11. Study Methods

11.1. *Data Collection*

The table below illustrates the data that will be collected during the study visit.

Table 11.1-1: Data Collection Schedule

	Screening (≤ 14 Days prior to Day 0)	Programming Visit (Day 0)
Inclusion/Exclusion Criteria Evaluation	X	
Informed Consent (ICF)	X	
Demographics	X	
Medical History	X	
Adverse Events Assessment	X[1]	X
Imaging		X[2]
Pain Drawing		X
Pain Intensity		X
Programming		X
Paresthesia Drawing		X[3,5]

Stimulation Questionnaire		X[3]
Audio Recording		X[4]

[1] AEs specified in Section 19 must be reported only after signing written informed consent.
[2] Optional.
[3] Complete based on each selected test configuration setting
[4] Optional Audio recording. Subjects will be asked to have their verbal description of the test configuration sensations recorded on audio. Subjects will be informed that they may refuse permission without penalty.
[5] Optional Paresthesia Drawing

11.2. *Screening*

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.

11.3. *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.

11.4. *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. [redacted] may only be operated by authorized BSC personnel in a study physician's office under the direct supervision of a study healthcare professional. [redacted] may 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 to document lead position.

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

- Pain Drawing
- Pain Intensity

The subject will be asked to complete their pain drawing and intensity assessment based on their recollection of pain. Upon completion of the above mentioned assessments, subjects will be programmed to receive multiple test configuration settings using the Blue Box Study SCS System by sponsor's personnel under the direct supervision of a study healthcare professional.

The following assessments will be completed based on each selected test configuration setting:

- Paresthesia Drawing (optional)
- Stimulation Questionnaire
- Audio Recording (optional)

Multiple program settings will be tested and the above assessments completed for each selected configuration. The total number of configurations tested will depend on the subject's tolerance. A minimum of 1 configuration will be tested for each subject.

Following completion of programming, each selected test configuration will be documented in the study records.

11.5. *Study Completion*

Each subject will be followed through the Programming Visit or at most 15 days after the Screening Visit if a Programming Visit is not completed. The study will be completed once all subjects have completed study participation and all site and study close-out activities have been finished.

11.6. *Source Documents*

Where copies of the original source document as well as printouts of original electronic source documents are retained, these shall be signed and dated by a member of the study team with a statement that it is a true reproduction of the original source document. All source documentation will be retained at the study site. Examples of source documents include, but are not limited to the following:

Table 11.6-1: 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
Programming printouts/forms for programming information	Retained at study site
Technical Source Forms	Retained at study site

12. Statistical Considerations

This feasibility study is exploratory in nature and thus no statistical powered end-points are included.

13. Data Management

13.1. *Data Collection, Processing, and Review*

Subject data will be recorded on paper case report forms (CRFs) which will be provided by BSC. The data reported on the CRFs shall be derived from source documents and shall be consistent with these source documents. An exception to this requirement is when data must be recorded directly on the CRF. For example, the questionnaire filled out by the patient describing the details of their pain. Any discrepancies should be explained in writing. Any change or correction made to the clinical data will be dated, initialed and explained, if necessary, and shall not obscure the original entry. A written audit trail shall be maintained which will be made available for review by BSC or its representative.

13.2. *Data Retention*

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

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

13.3. *Study Assessments*

13.3.1. Pain Drawing

Pain areas will be collected on a paper form on which the subject draws their areas of pain. Subjects shall be instructed to complete the drawing as follows:

- Completely fill in all areas of pain, regardless of relative intensity and avoid alternate techniques for marking pain (e.g. circling areas of pain, hash marks, pinpoint markings to indicate lower pain intensity)
- Avoid marking outside the body lines or within the data field box

13.3.2. Pain Intensity

Pain Intensity is a questionnaire assessing the intensity of the subject's different areas of pain. Pain intensity is expressed on a 0 – 10 numerical rating scale (NRS), where 0 indicates "no pain" and 10 indicates "pain as bad as you can imagine".

13.3.3. Paresthesia Drawing

Paresthesia Drawings are an optional assessment that may be collected for a subset of test configurations. Paresthesia coverage will be collected by asking subjects to draw all areas where they currently experiencing any amount of neurostimulation-induced paresthesia.

Subjects shall be instructed to complete the drawing as follows:

- Completely fill in all areas of paresthesia, regardless of relative intensity and avoid alternate techniques for marking paresthesia (e.g. circling areas of paresthesia, hash marks, pinpoint markings to indicate lower paresthesia intensity)
- Avoid marking outside the body lines or within the data field box
- Be aware of the left and right orientation markers on both the front and back images

[redacted]

[redacted]

14. Amendments

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

15. Deviations

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

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

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

Deviations will be classified according to the following definitions:

- Type A - Deviation to protect the life or physical well-being of a patient in an unforeseen emergency.
- Type B - Deviation based on medical judgment.
- Type C - Deviation due to misunderstanding of protocol requirements.
- Type D - Deviation due to a situation that is beyond control.
- Type E - Deviation due to an oversight, error or protocol non-compliance.

Deviations will be classified according to the following definitions:

- Major PD is a protocol deviation that directly or potentially disrupts the study progress (i.e., the study design, study data and results can be compromised), OR a protocol deviation that compromises the rights, safety and welfare of study participants.
- Minor PD is a protocol deviation that does not disrupt study progress (i.e., the study design, study data and results will not be compromised), AND does not compromise the rights, safety and welfare of study participants.

16. Device/Equipment Accountability

This study will not dispense the investigational devices to either the site or the patient. Investigational devices will be securely maintained, controlled, and used only in this clinical study by authorized BSC personnel. Investigational devices will not be shipped but instead will be hand carried by authorized BSC personnel to the site. Use of investigational devices will occur only in-office under the direction of a clinician. The use of the investigational devices will be documented on the CRF. Investigational devices are physically stored in a securely maintained, controlled location with access limited to authorized BSC personnel.

17. Compliance

17.1. *Statement of Compliance*

This study will be conducted in accordance with ISO 14155: Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice; 21 CFR Part 812, 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.

17.2. *Investigator Responsibilities*

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the investigational plan/protocol, 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 Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.

- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency.
- Report to sponsor, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by the national regulations or this protocol or by the IRB/EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- 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/directions for use.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB/EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the investigational device when it is used/operated by the subject.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.

- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

17.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training and adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

17.3. *Institutional Review Board/ Ethics Committee*

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

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

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

17.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC. Only authorized BSC personnel or a BSC representative including but not limited to Contract Research Organization (CRO) will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this study will be without identifiable reference to specific subject name.

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

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

17.4.1. Role of Boston Scientific Representatives

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

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

- Interrogating the device or programming device parameters to investigator-requested settings as well as operating equipment
- Performing lead diagnostic testing using a programmer to obtain thresholds and impedance measurements
- Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel
- Assisting with the collection of study data
- Entering technical data on technical source forms
- Print out programming reports directly from the clinician programmer and provide original to clinical site as source documentation
- Provide technical expertise/support to subjects during office visits and/or during teleconference calls/electronic communications with the principal investigator or their delegated site staff and the subject.

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

- Observing testing or medical procedures to provide information relevant to protocol compliance
- Reviewing collected data and study documentation for completeness and accuracy

[redacted]

- Programming device parameters to preset test configuration configurations.

Boston Scientific personnel will not do the following.

- Practice medicine

- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of the investigator or their designee
- Independently collect critical study data (defined as primary or secondary endpoint data)

17.5. *Insurance*

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

18. Monitoring

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

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

19. Potential Risks and Benefits

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.

19.1. *Anticipated Adverse Events*

The following anticipated adverse events (AE) have been identified.

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
- Death
- 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

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
- 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
- Infection ranging from cellulitis or subcutaneous abscess to epidural abscess or sepsis
- 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
- Pain, including post-operative pain, pain at IPG site, or worsening of original pain

- Pneumothorax, pneumocephalus, or injury to other tissues during surgery
- 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
- 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

19.2. *Anticipated Adverse Device Effect*

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, (i.e., pain, pressure, numbness, uncomfortable paresthesia)

Common:

- Overstimulation of tissue, 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 Blue Box 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
- Stimulation-related symptoms in other body systems, e.g. changes to urinary function, persistent penile erection

19.3. *Risks associated with the Study Devices*

[redacted]

If the subject's pain had improved while a test configuration is turned on during the study Programming Visit, there is a risk that some or all of this improvement may be lost when the test configuration is stopped.

The study device has no other incremental risks beyond other similar market-available external Spinal Cord Stimulation products.

19.4. *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.

19.5. *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).

19.6. *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 both the Multichannel Stimulus Generator System and Modified OMG are 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.

[redacted]

- Safety review processes by Boston Scientific
- Monitoring visits as needed

19.7. *Anticipated Benefits*

The reported benefit of the implementation of the Blue Box 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

19.8. *Risk to Benefit Rationale*

The risk evaluation for the study determined that all hazards attributed to the Blue Box 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 Blue Box 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 Blue Box Study SCS System is acceptable for use in a clinical setting.

19.9. *Warnings and Precautions*

To avoid possible complications, be sure to review warnings and precautions section of the directions for use manuals.

20. Safety Reporting

20.1. *Reportable Events by investigational site to Boston Scientific*

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

- All Serious Adverse Events
- All Investigational Device Deficiencies
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- New findings/updates in relation to already reported events
- All Device Related Adverse Events evaluated by an investigator as clinically significant
- All Study Procedure Related Adverse Events evaluated by an investigator as clinically significant

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

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

Any AE event required by the protocol, experienced by the study subject after informed consent and once considered enrolled in the study (as defined in study subject classification section), whether during or subsequent to the procedure, must be recorded in the CRF.

Underlying diseases are not reported as AEs unless there is an increase in severity of frequency during the course of the investigation. Death should not be recorded as an AE, but should only be reflected as an outcome of ONE (1) specific SAE (see Table 20.2-1 for AE definitions).

Refer to Section 18 for the known risks associated with the study devices.

20.2. *Definitions and Classification*

Adverse event definitions are provided in Table 20.1. Administrative edits were made to combine definitions from ISO 14155-2011 and MEDDEV 2.7/3 (2015).

Table 20.1: Adverse Event Definitions

Term	Definition

Adverse Event (AE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 (2015)*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This includes events related to the investigational medical device or comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Adverse event related to the use of an investigational medical device • NOTE 1: This definition includes any adverse event resulting from insufficient or inadequate 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.
Serious Adverse Event (SAE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	Adverse event that: • Led to death, • Led to serious deterioration in the health of the subject, that either resulted in: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient or prolonged hospitalization of existing hospitalization, or o medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **NOTE 1**: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	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 14155-2011 Ref: MEDDEV 2.7/3 (2015)	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. NOTE 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	A device deficiency is any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, misuse or use errors, and inadequate labeling.
Abbreviations: EC=Ethics Committee; IRB=Institutional Review Board	

NOTES:

1. For the purposes of this study, hospitalization is defined as any in-patient admission.
2. Hospitalizations occurring for the purpose of performing a planned procedure as per routine care such as implant procedures are not to be reported as a SAE. However, complications or adverse events that occur during the planned procedure should be reported as (S)AEs if they meet the protocol specified definitions.
3. Elective/planned hospitalization(s) need not be reported as an SAE. However, complications or adverse events that occur during an elective/planned hospitalization, should be reported as (S)AEs if they meet the protocol specified definitions.
4. In the event of subject death during the conduct of the study, efforts should be made to perform an autopsy.
5. Sensations or side effects that occur during the programming session should not be reported as AEs. However, sensations or side effects that persist or occur after the completion of the programming will be reported as AEs.
6. 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.
7. 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.
8. 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. Device/lead migration should be documented in the *Device Deficiency* CRF.
9. 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.

20.3. *Relationship to Study Device(s)*

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

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

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

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

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

20.4. *Investigator Reporting Requirements*

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

All device-related 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 20.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline pre-market studies*** (MEDDEV 2.7/3 (2015): CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)	**Communication Timeline post-market studies**** (MEDDEV 2.12/2 rev.2 (2012): GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Unanticipated Adverse Device Effect /	Complete applicable CRF page(s) with all available new and	• Within 1 business day of first becoming aware of the event.	• Within 1 business day of first becoming

Table 20.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline pre-market studies*** (MEDDEV 2.7/3 (2015): CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)	**Communication Timeline post-market studies**** (MEDDEV 2.12/2 rev.2 (2012): GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Unanticipated Serious Adverse Device Effect	updated information and fax to 661-949-4592 or email to BSNClinicalSafety@bsci.com	• Reporting required through the end of the study participation	aware of the event. • Terminating at the end of the study
Serious Adverse Event	Complete applicable CRF page(s) with all available new and updated information and fax to 661-949-4592 or email to BSNClinicalSafety@bsci.com	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study participation	• Within 10 business days after becoming aware of the event or as per local/regional regulations. • For Austria: within 2 business days of first becoming aware of the event. • Reporting required through the end of study
	Provide all relevant source documentation (unidentified) for reported event upon request of the sponsor	• At request of sponsor	• When documentation is available
Serious Adverse Device Effects	Complete applicable CRF page(s) with all available new and updated information and fax to 661-949-4592 or email to BSNClinicalSafety@bsci.com	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study participation	• Within 2 business days of first becoming aware of the event or as per local/regional regulations. • Reporting required

Table 20.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline pre-market studies* (MEDDEV 2.7/3 (2015): CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)	Communication Timeline post-market studies** (MEDDEV 2.12/2 rev.2 (2012): GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
			through the end of the study
	Provide all relevant source documentation (unidentified) for reported event	• When documentation is available	• When documentation is available
Investigational Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Investigational Devices only: Complete applicable CRF page(s) with all available new and updated information and fax to 661-949-4592 or email to BSNClinicalSafety@bsci.com	• Within 3 calendar days of first becoming aware of the event. • Reporting of investigational device deficiencies required through the end of the study participation	• Within 2 business days of first becoming aware of the event. Reporting required through the end of the study
Adverse Event including Adverse Device Effects	Complete AE CRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner (e.g. Recommend within 10 business days) after becoming aware of the information • Reporting required through end of the study participation	• In a timely manner (e.g. recommend within 30 business days) after becoming aware of the information • Reporting required through end of study

Table 20.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline pre-market studies* (MEDDEV 2.7/3 (2015): CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)	Communication Timeline post-market studies** (MEDDEV 2.12/2 rev.2 (2012): GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)

Abbreviations: AE=adverse event; CRF=case report form; IDE=Investigational Device Exemption; UADE=unanticipated adverse device effect

* 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.

**Please note that post-market studies are clinical studies where the medical devices used in the study bear the regulatory approval and are used for the same approved indications.

20.5. *Boston Scientific Device Deficiencies*

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.

All commercially available BSN device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) 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.

20.6. *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.

BSC shall notify all participating Chinese study centers if SAEs/SADEs occur which imply a possible increase in the anticipated risk of the procedure or use of the device or if the occurrence of certain SAEs/SADEs demands changes to the protocol or the conduct of the study in order to further minimize the unanticipated risks.

21. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from all subjects or their legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority body, as applicable. The ICF must be approved by BSC, the center'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 center's IRB/EC. Any modification requires approval 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 center 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. The original signed ICF will be retained by the center and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory body according to their requirements (e.g., FDA requirement is within 5 working days of learning of

such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB/EC), as appropriate.

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. Boston Scientific approval is required if changes to the revised ICF are requested by the center's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

Study personnel should explain that even if a subject agrees to participate in the study and sign an Informed Consent form, additional screening may demonstrate that the subject is not a suitable candidate for the study.

A Screening/Enrollment Log should be maintained to document select information about candidates who fail to meet the entry criteria.

22. Committees

22.1. *Safety Monitoring Process*

To promote early detection of safety issues, the Boston Scientific Neuromodulation medical monitor and safety medical director will provide evaluations of safety events. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. This is expedited through BSC's Global Safety Office, which is responsible for coordinating the collection of information for the subject dossier from the centers. During regularly scheduled monitoring visits, clinical research monitors will support the dynamic reporting process through their review of source document information.

23. Suspension or Termination

23.1. *Premature Termination of the Study*

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

23.1.1. Criteria for Premature Termination of the Study

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

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

- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development of the device.

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

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

23.3. *Requirements for Documentation and Subject Follow-up*

In the event of premature study termination, a written statement as to why the premature termination has occurred will be provided to all participating centers by Boston Scientific. The IRB/EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

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

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

The investigator must return all documents and investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

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

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled for a period beyond 6 months after center initiation, or if the center has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of investigator participation, all study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/EC and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the center will continue to be followed. The Principal Investigator at the center must make provision for these follow-up visits unless BSC notifies the investigational site otherwise.

24. Publication Policy

In accordance with the Corporate Policy on the Conduct of Human Subject Research, 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 Corporation may adhere 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 may be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

25. Reimbursement and Compensation for Subjects

25.1. *Subject Reimbursement*

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

25.2. *Compensation for Subject's Health Injury*

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

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27. Abbreviations and Definitions

Abbreviations and definitions are shown in Table 27-1

Table 27-1: 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
CRF	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
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.
[redacted]	
MRI	Magnetic resonance imaging
OMG	Observational Mechanical Gateway
OR	Operating room (e.g. OR cable)
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
[redacted]	

Abbreviation/Acronym/Term	Term/Definition
UADE	Unanticipated adverse device effects: 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.