Study to Demonstrate the Value of Paresthesia- Free Fast-Acting Subperception (FAST) and other SCS therapies using WaveWriter™ Spinal Cord Stimulator Systems in the Treatment of Chronic Pain

FAST Study

A4099

CLINICAL INVESTIGATION PLAN

NCT # 04618471

Sponsored By

Boston Scientific Neuromodulation Corporation

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United States of America

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

2. Protocol Synopsis

FAST Study A Study to Demonstrate the Value of Paresthesia-Free Fast-Acting Subperception (FAST) and other SCS therapies using WaveWriter™ Spinal Cord Stimulator Systems in the Treatment of Chronic Pain	
Primary Objective	To evaluate the effectiveness of FAST-SCS (fast-acting paresthesia-free therapy) and additional SCS therapy options in patients with chronic pain using Boston Scientific WaveWriter SCS Systems.
Secondary Objectives	To determine the impact of WaveWriter SCS System on global patient outcomes and objective metrics including quality of life, patient preference, fitness etc.
Indication(s) for Use	The WaveWriter Spinal Cord Stimulator (SCS) System is indicated 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, Complex Regional Pain Syndrome (CRPS) Types I and II, intractable low back pain and leg pain.
Commercial Device/System	BSC WaveWriter™ SCS Systems
Study Design	Prospective, multi-center, single-arm study with an adaptive design
[redacted]	[redacted]
Planned Number of Sites / Countries	Up to 15 sites in the United States.
Safety Parameters	Rates of occurrence of all device hardware, device stimulation and procedure related non-serious adverse events, all serious adverse events, and unanticipated adverse events through the end of the study.

FAST Study **A Study to Demonstrate the Value of Paresthesia-Free Fast-Acting Subperception (FAST) and other SCS therapies using WaveWriter™ Spinal Cord Stimulator Systems in the Treatment of Chronic Pain**	
Primary Endpoint	Proportion of subjects with 50% or greater reduction from Baseline Visit in average targeted* pain intensity at 3 months post-activation, with no increase in baseline average daily opioid medications used to treat pain. *targeted pain is the area of pain intended to be treated by SCS
Secondary Endpoint	The following secondary endpoints will be analyzed. Assessments required for deriving each endpoint are denoted in parentheses. • [redacted] • [redacted]
[redacted]	[redacted]

FAST Study

A Study to Demonstrate the Value of Paresthesia-Free Fast-Acting Subperception (FAST) and other SCS therapies using WaveWriter™ Spinal Cord Stimulator Systems in the Treatment of Chronic Pain

[redacted]

FAST Study **A Study to Demonstrate the Value of Paresthesia-Free Fast-Acting Subperception (FAST) and other SCS therapies using WaveWriter™ Spinal Cord Stimulator Systems in the Treatment of Chronic Pain**	
	• [redacted]
Follow-up Schedule	Study events occur at the following time points: • Screening • Opioid Medication Lock Visit (Up to 35 days following Informed Consent) • Baseline Period (14 days) • Baseline Visit (0 - 7 days post Baseline Period) • Implant Procedures (up to 90 days post Baseline Visit) • Healing Period (14 - 28 days) • Activation Visit (Day 0) • Programming Lock Visit (70 - 7 days post-activation Visit) • 3 Month Visit (90 + 14 days post-activation Visit) • 6-Month Visit (180 ± 30 days post-activation Visit) • 9-Month Visit (270 ± 30 days post-activation Visit)

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	• Year 1 Visit (365 ± 30 days post-activation Visit) • Year 2 Visit (730 ± 30 days post-activation Visit)
[redacted]	[redacted]
[redacted]	[redacted]
Inclusion Criteria	IC1. Chronic pain (predominantly neuropathic) of the trunk and/or limbs for at least 6 months with back pain greater or equal to leg pain. [redacted]

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	[redacted] IC11. 22 years of age or older when written informed consent is obtained [redacted] IC13. Able to independently read and complete all questionnaires and assessments provided in English [redacted] IC15. Subject signed a valid, IRB-approved informed consent form (ICF) provided in English
Exclusion Criteria	[redacted] EC7. Any pain-related diagnosis or medical/psychological condition or external factors that, in the clinician's best judgment, might confound reporting of study outcomes (e.g. pelvic pain, anginal pain, chronic migraine, brain or spinal cord tumor, involved in litigation, workmen's compensation) [redacted]

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[redacted]

EC15. Significant cognitive impairment at Screening that, in the opinion of the Investigator, would reasonably be expected to impair the study candidate's ability to participate in the study

EC16. Participating (or intends to participate) in another drug or device clinical trial that may influence the data that will be collected for this study

[redacted]

EC18. A female who is breastfeeding

EC19. A female of childbearing potential planning to get pregnant during the course of the study or not using adequate contraception

[redacted]

FAST Study **A Study to Demonstrate the Value of Paresthesia-Free Fast-Acting Subperception (FAST) and other SCS therapies using WaveWriter™ Spinal Cord Stimulator Systems in the Treatment of Chronic Pain**	
Statistical Methods	
Primary Statistical Hypothesis	The primary statistical hypothesis in this study is that the proportion of subjects with 50% or greater reduction from Baseline Visit in average daily targeted pain intensity at 3 months is non-inferior to the Objective Performance Criteria (OPC) of 40% H_0: $\pi_{opc} - \pi_t \geq 0.20$ H_1: $\pi_{opc} - \pi_t < 0.20$ Where π_t is the proportion of subjects with 50% or greater reduction from Baseline in average daily targeted pain intensity at 3 months post activation with no increase in baseline average daily pain medications using WaveWriter.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

FAST Study

A Study to Demonstrate the Value of Paresthesia-Free Fast-Acting Subperception (FAST) and other SCS therapies using WaveWriter™ Spinal Cord Stimulator Systems in the Treatment of Chronic Pain

[redacted]

[redacted]

3. Table of Contents

[redacted]

[redacted]

[redacted]

4. Introduction

4.1. *Chronic Intractable Pain*

Chronic intractable pain is often defined as pain persisting for at least 6 months which has not responded to conservative treatment(s). The pain may be due to current or past nerve injury and causes significant disability, reduced work productivity, reduced quality of life, and significant cost burden.

The complexity of chronic pain and the diverse population it affects have resulted in varying results between the various treatment approaches including medications, physical therapy, stimulation etc. Early treatments for chronic pain typically include over the counter and prescription medications. Later treatments like physical therapy and interventional pain procedures (e.g. intraspinal injections, vertebroplasty, pulsed radiofrequency (RF) are attempted, sometimes followed by chronic high dose opioids and back surgery, if indicated. If back surgery is unsuccessful in relieving the chronic pain, the patient can be labeled as having failed back surgery syndrome (FBSS). Spinal cord stimulation (SCS) is an option in well-selected patients with chronic low back and/or leg pain.

4.2. *Spinal Cord Stimulation*

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

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

Traditionally, Spinal Cord Stimulation (SCS) has relied on the understanding that to achieve pain relief, dorsal column stimulation-induced paresthesia has to be generated around the area of pain in order to successfully treat pain (North et al. 1991). However, recent studies indicate that effective pain relief may be obtained by employing stimulation without paresthesia (Van Buyten et al., 2012, De Ridder et al., 2010, Kapural et al 2015, North et al., 2019).

Traditional SCS therapy optimization typically requires face to face interaction with healthcare professionals and ongoing iterations of programming sessions based on patient reported outcomes. Wearable devices, digital solutions, and other recent technology advances allow for more frequent, comprehensive monitoring. Additionally, frequent interaction with patients, while at home or remote, presents an opportunity to provide a treatment approach tailored to each patient using digital solutions.

This study, in addition to patient reported outcomes, will collect objective metrics including quality of life, patient preference, fitness etc. to determine the impact of the WaveWriter Systems in patients with chronic pain.

5. Commercial Device Description (part of Standard of Care)

The WaveWriter™ Spinal Cord Stimulator (SCS) Systems are indicated 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, Complex Regional Pain Syndrome (CRPS) Types I and II, intractable low back pain and leg pain.

The System includes an Implantable Pulse Generator (IPG), External Trial Stimulator (ETS), Remote Control (RC), External Charger, and Clinician's Programmer (CP) and a portfolio of lead options. All tight-spaced lead options are available with the exception of the Artisan paddle, which is not permitted for use in this study. The IPG is rechargeable and is recharged transcutaneously by a charging unit. The System is capable of providing multiple waveforms.

The WaveWriter™ SCS System is approved by the Food and Drug Administration (FDA) and will be used per approved Instructions for Use (IFU) in this study.

6. Study Objectives and Endpoints

6.1. *Primary Objective*

To evaluate the effectiveness of FAST-SCS (fast-acting paresthesia-free therapy) and additional SCS therapy options in patients with chronic pain using Boston Scientific WaveWriter SCS Systems.

[redacted]

6.3. *Primary Endpoint*

The primary endpoint is the proportion of subjects with 50% or greater reduction from the Baseline Visit in average targeted* pain intensity at 3 months post-activation, with no increase in baseline average daily opioid medications used to treat pain.

* targeted pain is the area of pain intended to be treated by SCS

[redacted]

[redacted]

6.6. *Safety Parameters*

Safety parameters include the rates of occurrence of all device hardware, device stimulation and procedure related non-serious adverse events, all serious adverse events, and unanticipated adverse events through the end of the study.

7. Study Design

The post-market study is a prospective, multi-center, single-arm study with an adaptive design. All participants will receive a WaveWriter Spinal Cord Stimulator (SCS) system and followed per the study schedule as shown in study schematic Figure 7.1-1.

[redacted]

[redacted]

8. Subject Selection

[redacted]

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 Table 8.3-1) is met.

Table 8.2-1: Inclusion Criteria

Clinical Inclusion Criteria	IC1. Chronic pain (predominantly neuropathic) of the trunk and/or limbs for at least 6 months with back pain greater or equal to leg pain. [redacted] IC11. 22 years of age or older when written informed consent is obtained [redacted] IC13. Able to independently read and complete all questionnaires and assessments provided in English [redacted] IC15. Subject signed a valid, IRB-approved informed consent form (ICF) provided in English

8.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria cannot be included in this study or will be excluded from this clinical study. No vulnerable populations will be enrolled in this study.

Vulnerable subjects are individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response.

Table 8.3-1 Exclusion Criteria

Clinical Exclusion Criteria	[redacted] EC7. Any pain-related diagnosis or medical/psychological condition or external factors that, in the clinician's best judgment, might confound reporting of study outcomes (e.g. pelvic pain, anginal pain, chronic migraine, brain or spinal cord tumor, involved in litigation, workmen's compensation) [redacted]

	EC15. Significant cognitive impairment at Screening that, in the opinion of the Investigator, would reasonably be expected to impair the study candidate's ability to participate in the study EC16. Participating (or intends to participate) in another drug or device clinical trial that may influence the data that will be collected for this study [redacted] EC18. A female who is breastfeeding EC19. A female of childbearing potential planning to get pregnant during the course of the study or not using adequate contraception [redacted]

9. Subject Accountability

9.1. *Point of Enrollment*

A subject will be considered enrolled in the study when the Informed Consent Form (ICF) is signed. All enrolled and activated subjects will be included in the study analyses.

If device implantation is unsuccessful, the subject will be followed for 2 weeks post implantation attempt to assess for procedure related adverse events.

9.2. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study) 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

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

While study withdrawal is discouraged, subjects may withdraw from the study at any time, with or without reason and without prejudice to further treatment. In all cases of withdrawal or discontinuation, the Investigator will make all reasonable efforts to determine the reason for the subject's withdrawal. Subjects may be discontinued from the study for the various reasons, such as:

- Withdrawal of consent
- A safety concern defined by the Principal Investigator and/or Boston Scientific Neuromodulation (e.g., adverse event)
- Study non-compliance
- Inadequate use of device that may impact study outcomes
- Subject did not meet inclusion criteria or met an exclusion criterion after signing informed consent
- Surgical intervention that affects the Implantable Pulse Generator (IPG) and/or leads
- Lost to follow-up
- Death of the subject

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, at least one of which must be in writing, sent via a traceable method to inform the subject that the device must programmed per standard of care with commercially approved settings.

Data collected up to the point of subject withdrawal, lost to follow-up, or until subject deletes the mobile app and/or ends data transmission may be used for study analysis in accordance with applicable regulations.

Subjects can stop data transmission by deleting the mobile app from their phone.

Withdrawn subjects will be followed per the End of Study Action Plan as described below.

9.3. *Subject Status and Classification*

Subjects who provide written informed consent but do not meet all of the study eligibility criteria will not be implanted or activated. These subjects will be deemed as "enrolled but not activated" and their reason for ineligibility will be documented.

Enrolled subjects who are not activated will not count towards the enrollment cap. Subjects who sign consent, meet all eligibility criteria, undergo permanent implant and are activated cannot be replaced.

9.4. *Enrollment Controls*

[redacted]

The study will implement a formal *Enrollment Communication Plan*. The plan will outline the specific activities, as well as the nature and timing of communications to investigators in order to minimize the risk of enrollment beyond the protocol-specified enrollment caps determined by the statistical analysis plan.

9.5. *End-of-Study Action Plan*

When each subject completes the 2-Year Visit or withdraws, the subject exits the study and ends study participation. Subjects may continue to use their system per the applicable Directions for Use and will be followed according to standard of care. Boston Scientific Neuromodulation Corporation will not pay for visits that occur after a subject completes the 2-Year Visit, withdraws or is determined to be lost to follow-up.

If the study is terminated early due to sponsor discretion or due to the discovery of an unexpected, significant, or unacceptable risk/safety concern regardless of how far along the subject has reached in their study follow-up, subjects will be followed according to standard of care. Sites will have 30 days to notify all subjects of study closure.

If device implantation is unsuccessful, the subject will be followed for 2 weeks post implantation attempt to assess for procedure related adverse events. If the device is explanted, the subject will be followed for 2 weeks post explant to assess for related adverse events.

Device related adverse events and/or deficiencies occurring after study participation, withdrawal from the study, or after the specified timeframe following unsuccessful trials, implant failures, and explants, should be reported to BSN Patient Care at: 866-360-4747. Such complications should not be captured as adverse events in the study.

10. Study Methods

10.1. *Data Collection*

The data collection schedule is shown in table below.

10.2. *Study Candidate Screening*

Subjects' eligibility for the study will be assessed based on study Inclusion and Exclusion criteria listed in Sections 8.2 and 8.3, respectively. Subjects who have provided informed consent and who have been determined to not meet all eligibility requirements will be withdrawn.

10.3. *Informed Consent*

Written Informed Consent must be obtained for all patients who are potential study candidates. Study candidates will be asked to sign the Informed Consent form before any study-specific tests or procedures are performed.

- The context of the study must be fully explained to the patient and patients must be given an 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 informed consent form, 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.

Research study candidates in the State of California will also be provided with the California Experimental Patient's Bill of Rights

10.3.1. Screening Period

Subjects undergo screening related procedures to determine eligibility for the study. It will take until permanent implantation is complete to determine all eligibility requirements.

[redacted]

10.4. *Opioid Medication Lock Visit (Up to 35 days following informed consent)*

The Opioid Medication Lock Visit will occur within 35 days following informed consent. However, this visit may occur on the same day as that of the Informed consent as well following completion of consent.

At this visit, the subject's opioid pain medications will be locked, with no increase in type/dose/route/frequency, until the 3-Month post-activation Visit.

At this visit (or during the screening period), the investigator will convert the subject's opioid medication prescriptions from PRN to a fixed dose, as needed.

Subjects will be reminded to continue to use their in-home devices the mobile app., as applicable.

Subjects who are not taking opioid medications are not required to Opioid Medication Lock Visit, and can proceed to their Baseline Visit. Subjects who are not taking opioid medications will maintain this status until the 3-Month post-activation Visit.

10.5. *Baseline Period (14 days)*

The Baseline Period will last for 14 consecutive days following the Opioid Medication Lock Visit. At the end of the Baseline Period, subjects will return to the clinic for their Baseline Visit.

Subjects are to not make any increases to their opioid pain medications during this period.

10.6. *Baseline Visit (0 – 7 days post Baseline Period)*

At the Baseline Visit, subjects will return to the clinic to complete remaining screening requirements. Subjects should bring in their phone with mobile app to this visit. Any adverse since the last study visit will be collected.

[redacted]

Subjects that meet all study criteria will be scheduled for the device implant procedures (trial and permanent implant of the SCS system). If a subject fails to meet eligibility criteria, they will be withdrawn from the study.

10.7. *Implant Procedures (Up to 90 days following the Baseline Visit)*

Subjects will have up to 90 days following the Baseline Visit to receive their WaveWriter System.

Subjects with an unsuccessful implant procedure will be followed for 2 weeks for procedure related adverse events then withdrawn from the study. Acute opioid pain medications may be taken.

10.8. *Healing Period (14 - 28 days following Implant Procedures)*

The subject's device will remain inactivated (device OFF) for 14 to 28 days following the permanent implantation procedure to allow for healing. Acute opioid pain medications may be taken during this period. No additional scheduled assessments will be completed during this period.

10.9. *Activation Visit (Day 0)*

At the Activation Visit, subjects' device will be activated. Subjects should bring their phone with mobile app to this visit.

[redacted]

10.10. *Programming Lock Visit (Day 70 - 7 days post-activation Visit)*

At the Programming Lock Visit, subjects will return to the clinic to have their programs locked. Any protocol required adverse events since the last study visit will be collected.

No further changes to the subject's programs (for e.g. electrode configuration) will be

[redacted]

10.11. *3-Month Visit (90 + 14 days post-activation Visit)*

During the 3-Month Visit, subjects will return to the clinic for study evaluations and programming. Any protocol required adverse events since their last study visit will be collected.

[redacted]

- [redacted]

10.12. *6-Month Visit (180 ± 30 days post-activation Visit)*

During the 6-Month Visit, subjects will return to the clinic for study evaluations and programming. Any protocol required adverse events since their last study visit will be collected.

[redacted]

[redacted]

10.13. *9-Month Visit (270 ± 30 days post-activation Visit)*

During the 9-Month Visit, subjects will return to the clinic for study evaluations and programming. Any protocol required adverse events since their last study visit will be collected.

[redacted]

- Subjects should be reminded to continue to use their in-home devices including [redacted]

10.14. *Year 1 and Year 2 Visit (365 ± 30 days post-activation Visit and 730 ± 30 days post-activation Visit))*

During the 1 and 2 Year Visits, subjects will return to the clinic for study evaluations and programming. Any protocol required adverse events since their last study visit will be collected.

[redacted]

[redacted]

The 2 Year Visit is the End of Study Visit and End of Study Action Plan (ESAP) will be followed as described in Section 9.5.

10.15. *Unscheduled Visit*

Subjects may have as many unscheduled visits as required for device-related in-office or procedure visits (e.g., optimization of programming during the programming period) or for evaluation of possible adverse events and if applicable, re-positioning, replacement or explant of a device component. Unscheduled visit information will be captured, as applicable.

10.15.1. Revision or Replacement of Leads, Extensions and/or IPGs

During the study, it is possible that leads may be placed incorrectly, migrate, or malfunction and require repositioning or replacement. It is also possible that the extensions or splitters or IPG may be uncomfortable or malfunction and may require repositioning or replacement. The decision to reposition or replace any device component will be made by the investigator and only if the subject agrees. Subjects not agreeing to a recommended lead revision will be withdrawn from the study but will be included in the intent-to-treat and safety analyses. Subjects agreeing to revision will continue study and will be followed according to the original study schedule. Effectiveness data from these subjects will be included in the intent to treat analysis. Lead revisions/replacements for correcting for migration and/or malfunction must be performed as soon as is reasonably possible following determination of the need for revision/replacement.
The investigator should notify Boston Scientific prior to any study procedures. Any replacements or revisions performed during the study should be recorded in the EDC system, including information about the procedure, device, and/or adverse event if applicable. Information on assessing revisions or replacements of leads, extensions or IPGs as adverse events is described in Safety Reporting Section.

[redacted]

[redacted]

10.17. *Study Completion*

All activated subjects permanently implanted will be followed through completion of the 2-Year Visit or study withdrawal. The End of Study Action Plan defines the actions to be taken when the subject reaches the end of their study participation.

10.18. *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 10.18-1.

Table 10.18-1: 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, exams, SCS System procedure(s) and devices used, evaluations,	Retained at investigational site

[redacted]

Table 10.18-1: Source Documentation Requirements

Requirement	Disposition
health economic assessments, laboratory results, medications, assessment of adverse events.	
Assessments and questionnaires	Retained at investigational site and/or electronic data collection platform/EDC
Programming information	Retained at investigational site and/or electronic data collection platform/EDC
Imaging films/prints documenting lead(s) location	Retained at investigational site

11. Statistical Considerations

11.1. *Endpoints*

11.1.1. Primary Endpoint

The primary endpoint for this study is the proportion of subjects with 50% or greater reduction from Baseline Visit in average targeted pain intensity at 3 months post-activation with no increase in baseline average opioid medications used to treat pain.

[redacted]

11.1.1.1. Hypotheses

The primary statistical hypothesis in this study is that the proportion of subjects with 50% or greater reduction from Baseline Visit in average daily targeted pain intensity at 3 months post-activation is non inferior, compared to an Objective Performance Criteria (OPC) of 40%.

H_0: $\pi_{opc} - \pi_t \geq 0.20$

H_1: $\pi_{opc} - \pi_t < 0.20$

Where π_t is the proportion of subjects with 50% or greater reduction from Baseline in average daily targeted pain intensity at 3 months post-activation with no increase in baseline average daily opioid pain medications, π_{opc} is the responder rate of an OPC based on Kumar paper (Kumar 2008). The study's non-inferiority margin is 0.20.

[redacted]

66

11.1.1.3. Statistical Methods

The 95% confidence interval of $\pi_{opc} - \pi_t$ will be computed. The study will be considered a success if, using the Intent-To-Treat (ITT) analysis, the upper bound of the two-sided 95% confidence interval for the difference is less than 0.20.

For the primary endpoint, statistical testing will be performed to determine if the targeted pain responder rate is non inferior to the OPC of this study with a margin of 0.2.

The statistical test will be a Fisher's Exact test for a single proportion.

[redacted]

11.2. *General Statistical Methods*

11.2.1. Analysis Sets

- **Intent-to-Treat (ITT) Population**: All subjects who receive the study device and are activated, regardless of the treatment received.
- **Per Protocol (PP) Population**: All subjects who receive the study device, with no major protocol deviations.
- **Safety Population**: All subjects who sign the IRB-approved written Informed Consent form

11.2.2. Control of Systematic Error/Bias

Selection of patients will be made from the Investigator's usual patient load. All patients meeting the inclusion/exclusion criteria and having signed the Informed Consent Form will be eligible for participation in the study. The reasons for exclusion, for subjects who sign an informed consent form but are not implanted, will be indicated in EDC. Boston Scientific will report to the ethic committee any evidence of fraud, including deliberate tampering with the selection of subjects.

[redacted]

11.2.4. Data Analyses

All statistical analyses will be done using the SAS System software, version 8.2 or later (Copyright © 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved). Additional details on these analyses can be found in the Statistical

[redacted]

[redacted]

12. Data Management

12.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by Medidata EDC System. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor or its representative. The associated Rave software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data

previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the Medidata EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

[redacted]

12.1.1. Electronic Questionnaires

Questionnaires in electronic form may be collected directly using an electronic data collection platform at the clinical site (e.g. iPad). After completion by the subject or a clinician, data from the electronic questionnaires are transmitted directly into the EDC system.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12.3. *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]

[redacted]d.

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 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.

Subject non-compliance related to at-home activities, including but not limited to, the mobile app will not be reported as deviations due to the exploratory nature of the data being collected.

All other 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 EDC system. Sites may also be required to report deviations to the IRB, 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 IRB notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

The sponsor will not approve protocol waivers.

14. Compliance

14.1. *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 50 and 56, ISO EN 14155: Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice, the relevant parts of the ICH Guidelines for Good Clinical Practices, ethical principles that have their origins in the Declaration of Helsinki, and applicable individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB has been obtained, if appropriate. Also, the study shall not begin at a site prior to issuance of the site Authorization to Enroll, as provided by the sponsor. Any additional requirements imposed by the IRB or regulatory authority shall be followed, if appropriate.

14.2. *Investigator Responsibilities*

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation

plan/, the spirit of ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB, 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 Investigational Plan/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 clinical investigation.
- Report protocol deviations to the sponsor, IRB and/or regulatory authorities, as required by the protocol, IRB guidelines, and/or national/regulatory regulations.
- 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 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, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- 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 when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB requirements.

- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the device when it is used/operated by the subject.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study and make the necessary arrangements for emergency treatment.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- 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 study is appropriately performed and documented, where applicable.

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.

14.2.1. 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, ensuring individuals are competent to perform the tasks they have been delegated and have 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.

14.3. *Institutional Review Board*

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

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

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

14.4. *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]

15. 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.

16. Potential Risks and Benefits

16.1. *Instructions for Use*

Please refer to the Instructions for Use for an overview of anticipated adverse (device) effects, and risks associated to the commercial device(s).

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

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

16.3. *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.

The following medical treatments should not be used while the SCS system remains implanted.

Magnetic Resonance Imaging (MRI) for WaveWriter System only. The subject should not be exposed to full-body MRI. Exposure may result in dislodgement of the Stimulator or lead(s), heating of the Stimulator, damage to the Stimulator electronics and/or voltage induction through the leads or Stimulator which can cause an uncomfortable or "jolting" sensation.

Note: MRI may be performed in subjects as applicable, if conditions set in the MRI Guidelines manuals are met accordingly. Refer to those manuals for guidance before proceeding with any MRI.

Diathermy. SCS subjects should not have any form of diathermy either as treatment for a medical condition or as part of a surgical procedure. The high energy and heat generated by diathermy can be transferred through the stimulator system, causing tissue damage at the lead site and, possibly, severe injury or death. The Stimulator, whether it is turned on or off, may be damaged.

Implanted Stimulation Devices. Spinal cord stimulators may interfere with the operation of implanted sensing stimulators such as pacemakers or cardioverter defibrillators. The effects of implanted stimulation devices on neurostimulators are unknown.

Medical Devices/Therapies. The following medical therapies or procedures may turn stimulation off or may cause permanent damage to the Stimulator, particularly if used in close proximity to the device:

- Lithotripsy
- Electrocautery (See "Instructions for the Physician" in the Information for the Prescriber Manual)
- External defibrillation

- Radiation therapy
- Ultrasonic scanning
- High-output ultrasound

16.4. *Risk Minimization Actions*

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

16.5. *Anticipated Benefits*

The reported benefits may include:

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

16.6. *Risk to Benefit Rationale, if applicable*

The risk evaluation for the WaveWriter SCS System determined that all hazards attributed to the WaveWriter SCS System and overall remaining residual risks after implementations of the required mitigations have been evaluated. Based on the risk evaluation results, the benefit provided by the WaveWriter 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 WaveWriter SCS System is acceptable for use in a clinical setting.

17. Safety Reporting

17.1. *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 Device Deficiencies
- Unanticipated Adverse Device Effects
- New findings/updates in relation to already reported events
- Device-hardware, device-stimulation, and procedure related non-serious adverse events

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

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

Any AE reportable event, experienced by the study subject after informed consent a, 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 17.2-1 for AE definitions).

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

17.2. *Definitions and Classification*

Adverse event definitions are provided in Table 17.2-1. Administrative edits were made on the safety definitions from applicable regulation 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. Definitions are aligned with EU 2017/745 and MEDDEV 2.7/3.

Table 17.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1EU*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the study medical device and whether anticipated or unanticipated.

Table 17.2-1: Safety Definitions

Term	Definition
	NOTE 1: This includes events related to the study medical device or comparator. **NOTE 2**: This definition includes events related to the procedures involved. **NOTE 3**: For users or other persons, this definition is restricted to events related to the study medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1EU*	Adverse event related to the use of the study medical device **NOTE 1**: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the study medical device. **NOTE 2**: This definition includes any event resulting from use error or intentional abnormal use of the study medical device. **NOTE 3**: This includes 'comparator' if the comparator is a medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: 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.

Table 17.2-1: Safety Definitions

Term	Definition
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1MEDDEV 2.7/3*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.
Serious Health Threat *Ref: ISO 14155*	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. **NOTE 1**: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.
Device Deficiency *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	An inadequacy of the study medical device related to its identity, quality, durability, reliability, 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 device under study 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, undesired sensations or side effects caused by the final programming parameters (including active contact, pulse width, frequency, and amplitude) that persist or occur after the completion of the programming should be reported as AEs.
3. Lack of efficacy/decreased therapeutic response should not be reported as AEs. Clinical sequelae, other than pain, that occur as a result of lack of efficacy/decreased therapeutic response should be reported as AEs
4. Clinically significant worsening of the pattern of intensity or distribution of Baseline pain symptoms should be reported as an AE.
5. Device deficiencies, including, but not limited to device/lead migrations, which are not associated with an adverse clinical outcome should only be reported as device deficiencies. However, if a device deficiency precipitates an AE, the AE should be reported in the Adverse Event eCRF and the device deficiency should be documented in the Device Deficiency eCRF.
6. If device implantation is unsuccessful, the subject will be followed for 2 weeks post implantation attempt to assess for procedure related adverse events. If the device is explanted, the subject will be followed for 2 weeks post explant to assess for related adverse events.

17.3. *Relationship to Study Device(s) and /or study Procedure*

The Investigator must assess the relationship of the reportable AE to the study device-hardware, device-stimulation and/or study procedure. See criteria in Table 17.3-1:

Table 17.3-1: Criteria for Assessing Relationship of Study Device Hardware, Device Stimulation or Procedure to Adverse Event

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

Causal Relationship *Ref: MDCG 2020-10/1*	The serious event is associated with the study 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 the study device use/application or procedures; - the event involves a body-site or organ that -the study device or procedures are applied to; -the study device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the study device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

17.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown below.

Table 17.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline post-market studies*** (*EU MDR 2017/745, MDCG 2020-10/1* MEDDEV 2.12/2: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Unanticipated 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.	• Within 10 days after becoming aware of the event or as per local/regional regulations. • Reporting required through end of the study.

Event Classification	Communication Method	Communication Timeline post-market studies* (*EU MDR 2017/745, MDCG 2020-10/1* MEDDEV 2.12/2: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event if requested by safety.	• When documentation is available
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon request of sponsor
Device Deficiencies (including but not limited to malfunctions, use errors, and inadequacy in information supplied by the manufacturer, including labelling) Note: Any Device Deficiency that might have led to a serious adverse event if appropriate action had not been taken or intervention had not occurred circumstances had been less fortunate is considered a reportable event.	Complete Device Deficiency eCRF with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event. Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event if requested by safety.	• At request of sponsor
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.	• In a timely manner but not later than 30 business days after becoming aware of the information • Reporting of Adverse events which are device hardware, device stimulation and procedure related will be required through the end of the study.
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event if requested by safety.	

17.5. *Device Deficiencies*

Device deficiencies will be documented and reported to BSC. If possible, the device(s) under study should be returned to BSC for analysis. Instructions for returning the device(s) will be provided to study sites. Device deficiencies should also be documented in the subject's source records.

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.

17.6. *Reporting to Regulatory Authorities / IRBs / Investigators*

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

The Principal Investigator is responsible for informing the IR and regulatory authorities of UADEs and SAEs as required by local/regional regulations.

18. Informed Consent

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

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO), and approved by the site's IRB, 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. 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. 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 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 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), 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 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. The new version of the ICF must be approved by the IRB. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB. The IRB will determine the subject population to be re-consented.

19. Committees

19.1. *Safety Monitoring Process*

The BSC personnel from the BSC Medical Safety group review safety data as soon as it is reported, by the sites throughout the duration of the study. During scheduled monitoring activities, clinical research monitors further support this review of source document and other data information. The BSC Medical Safety group includes a physician with the necessary therapeutic and subject matter expertise to evaluate the events outlined above.

[redacted]

20. Suspension or Termination

20.1 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, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

20.1.1 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 or regulatory authorities to suspend or terminate the clinical investigation.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development/marketing of the device.

20.2 Termination of Study Participation by the Investigator or Withdrawal of IRB Approval

Any investigator, or associated IRB 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, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

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

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

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

20.4 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 or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

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

21. Study Registration and Results

21.1. *Study Registration*

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

21.2. *Clinical Investigation Report*

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

21.3. *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/).

22. Bibliography

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23. Abbreviations and Definitions

23.1. *Abbreviations*

Abbreviations are shown in **Error! Reference source not found.**.

Table 23.1-1: Abbreviations

Abbreviation/Acronym	Term
ADE	Adverse device effect
AE	Adverse event
BSC	Boston Scientific Corporation
BSN	Boston Scientific Neuromodulation
CGI-C	Clinical Global Impression of Change
CFR	Code of Federal Regulations
CRPS	Complex Regional Pain Syndrome
CP	Clinician programmer
CRF	Case report form
CRO	Contract research organization
eCRF	Electronic case report form
ESAP	End of study action plan
FAST	Fast Acting Subperception
FBSS	Failed back surgery syndrome
FDA	Food and Drug Administration
GCP	Good clinical practice
HCP	Health care personnel
ICF	Informed consent form
ICH	International Conference on Harmonisation
IPG	Implantable pulse generator
IRB	Institutional review board
ISO	International Organization for Standardization
IFU	Instructions for Use
Mg	Milligram
MRI	Magnetic Resonance Imaging
NRS	Numerical rating scale
ODI	Oswestry Disability Index
PGI-C	Patient Global Impression of Change
PPR	Percent pain relief
SADE	Serious adverse device effect
SAE	Serious adverse event
SCS	Spinal cord stimulation
SF-36v2	Short Form 36 Health Survey ver 2
TSQM-9m	Treatment Satisfaction Questionnaire for Medication - modified
UADE	Unanticipated adverse device effect
VRS	Verbal rating scale

23.2. *Definitions*

Detailed definitions or descriptions are provided in applicable sections of the protocol.