A Multi-Center Controlled Study to characterize the real-world outcomes of High Rate Spinal Cord Stimulation therapy using Boston Scientific (BSC) PRECISION Spinal Cord Stimulator System

VELOCITY

CLINICAL INVESTIGATION PLAN

[redacted]

Sponsored By

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Current Version: 09 December 2016, version AB

Revision History

Revision Number	Release Date	Template number and version	Section	Change	Reason for Change
AA	**04 December 2015**	[redacted]	**NA**	**NA as initial release**	**NA**
AB	**09 December 2016**	[redacted]	**All**	**Update of standard protocol text**	**BSC Protocol template update**
			Contact information	**Updated**	**Updated with change**
			All	**Update to Programming Settings**	**Clarified Programming Settings**
			Data Collection Schedule	**Demography and Medical History items from screening to Baseline / Concomitant Medication at Standard of Care visits Optional**	**Corrections**
			All	**Updated References**	**Updates References**
			Section 17.2 Investigator Responsibilities	**Section on Device accountability taken out**	**NA due to the use of commercial device**

2. Protocol Synopsis

VELOCITY **A Multi-Center Controlled Study to characterize the real-world outcomes of High Rate Spinal Cord Stimulation therapy using Boston Scientific (BSC) PRECISION Spinal Cord Stimulator System**	
Primary Objective	To characterize the real-world outcomes of high rate spinal cord stimulation (HR-SCS) therapy as an aid in the management of chronic intractable pain of the trunk, including unilateral or bilateral pain associated with the following: failed back surgery syndrome, intractable low back pain using the Boston Scientific (BSC) PRECISION Spinal Cord Stimulator System with MultiWave Technology.
Planned Indication(s) for Use	The Precision SCS System with MultiWave Technology is indicated as an aid in the management of chronic intractable pain.
Test Parameters	BSC PRECISION SCS System with MultiWave Technology [redacted]
Control Parameters	None: Each subject will serve as their own control.
Study Design	Prospective, multi-center, single-arm study
Planned Number of Subjects	Up to 60 implanted subjects
Planned Number of Centers / Countries	Up to 10 sites / Europe
Primary Endpoint	Low back pain responder rate at 3 months post-activation as compared with Baseline. [redacted]

VELOCITY **A Multi-Center Controlled Study to characterize the real-world outcomes of High Rate Spinal Cord Stimulation therapy using Boston Scientific (BSC) PRECISION Spinal Cord Stimulator System**	
Secondary Endpoints	[redacted]
Exploratory Endpoints	[redacted]

VELOCITY **A Multi-Center Controlled Study to characterize the real-world outcomes of High Rate Spinal Cord Stimulation therapy using Boston Scientific (BSC) PRECISION Spinal Cord Stimulator System**	
	[redacted]
Health Economics Endpoints	[redacted]
Safety Parameters	Rate of occurrence of all device or procedure related adverse events (AEs), SAEs including serious adverse device events (SADEs), unanticipated serious adverse device effects (USADEs) through end of study.
Method of Assigning Patients to Treatment	N/A
Study Schedule	Study events occur at the following time points: • Screening Period (Up to 60 days following Informed Consent) • Baseline Visit (Medication Lock) • SCS Implant procedure (s) • Device Activation Visit (Day 0) • Programming Visit (45 ± 7 days post-Activation Visit) • 3-Month Visit (90 ± 14 days post-Activation Visit) • 6-Month Visit (180 ± 30 days post-Activation Visit) • 12-Month Visit (365 ± 30 days post-Activation Visit).
Study Duration	Overall study duration is anticipated to take approximately 25 months from first patient enrollment to end of study close out activities.

VELOCITY **A Multi-Center Controlled Study to characterize the real-world outcomes of High Rate Spinal Cord Stimulation therapy using Boston Scientific (BSC) PRECISION Spinal Cord Stimulator System**	
Key Inclusion Criteria	[redacted] IC7. [redacted]
Key Exclusion Criteria	[redacted]

VELOCITY **A Multi-Center Controlled Study to characterize the real-world outcomes of High Rate Spinal Cord Stimulation therapy using Boston Scientific (BSC) PRECISION Spinal Cord Stimulator System**	
Statistical Methods	
Primary Statistical Hypothesis	[redacted]
Statistical Test Method	The primary statistical hypothesis will be tested using Fisher's Exact test for a single proportion.
Sample Size Parameters	[redacted]
Interim Analyses	[redacted] • [redacted]

3. Table of Contents

3.1. *Table of Figures*

3.2. *Table of Tables*

4. Introduction

4.1. *Chronic Intractable Pain*

Chronic intractable pain is often defined as pain persisting for at least 6 months which has not responded to conservative treatment(s). The pain may be due to current or past nerve injury and causes significant disability, reduced work productivity, reduced quality of life, and significant cost burden. Early treatments for chronic pain typically include over the counter and prescription medications. Later treatments like physical therapy and interventional pain procedures (e.g. intraspinal injections, vertebroplasty, pulsed RF) are attempted, sometimes followed by chronic high dose opioids and back surgery, if indicated. If back surgery is unsuccessful in relieving the chronic pain, the patient can be labeled as having failed back surgery syndrome (FBSS). Spinal cord stimulation is an option in the well-selected patient with chronic low back and/or leg pain.

4.2. *Conventional Spinal Cord Stimulation*

SCS is effective for chronic intractable pain associated with a variety of conditions, including, but not limited to, FBSS (Carter et al., 2004, Taylor et al., 2004), complex regional pain syndrome (Sears et al., 2011), and low back pain and leg pain (Cameron et al., 2004). Spinal cord stimulation (SCS) is a less invasive treatment option for FBSS but has generally been reserved for patients who have failed multiple, and indeed all possible, repeat operations.

With SCS, an implanted pulse generator (IPG) delivers electrical current to electrode(s) implanted in the epidural space. This current stimulates nerves and can be programmed to direct stimulation to the nerves innervating the painful location, resulting in a reduction of the intensity of that pain (Kumar et al., 2006). Before an SCS system is implanted, a patient often undergoes a screening trial with an electrode that is connected to an external stimulator that the patient wears outside of the body. The results of the screening trial can predict the patient's outcome with an implanted system (Kumar et al., 2006).

In SCS pain relief is realized when the nerves that innervate the painful region(s) are electrically stimulated (North et al., 1990). To increase the chance of success, the electrode contacts are programmed based on the patient feedback to various combinations of contact polarities (anodes and cathodes), pulse rate (or frequency), pulse amplitude (or current), and pulse width. Several studies have demonstrated significantly greater pain relief and improved functional capacity and health-related quality of life in patients with SCS (Kumar et al 2007, Kumar et al 2008)

In 2004, the FDA approved the Boston Scientific Corporation (BSC) PRECISION™ Spinal Cord Stimulator (SCS) System as the first rechargeable system for treatment of chronic intractable pain of the trunk and limbs. The results of a multi-center, non-randomized study conducted with this system demonstrated more than 50% pain relief through a maximum

follow-up of 18 months, but the single-arm design and small number of subjects enrolled limit the strength of the conclusions (Oakley et al., 2007).

4.3. *High Frequency Electrical Stimulation*

Spinal cord stimulation as a treatment for chronic pain has been utilized since the 1960s. Stimulation is delivered on a pulsatile basis, with frequencies of pulse delivery typically programmed between 2 and 1200 Hz (1Hz = 1 pulse per second). High frequency (HF) electrical neurostimulation (generally referring to stimulation using >1200 Hz) has been studied by physiologists since the late 20th century (Geddes, 1984). Neurostimulation frequencies in those ranges have been employed in various biomedical applications, including muscle strengthening (Ward et al., 2001; Ward 2009), bladder dysfunction (Jezernik et al., 2002), cochlear stimulation (House and Berliner, 1986; Zhang et al., 2005; Mueller et al., 2011), obesity (Camilleri et al., 2008), and chronic pain (Smet et al., 2011 a&b; Van Buyten et al., 2011). Stimulation of first order sensory nerves may exhibit a similar mechanism of action to spinal cord stimulation and therefore may provide an insight into the safety of spinal cord stimulation.

4.3.1. HF Stimulation for Pain

High-Frequency (up to 10 kHz) spinal cord stimulation has also been evaluated in chronic pain patients. Nevro Corporation's Senza™ System (Menlo Park, CA) delivers electrical stimulation at higher rates than conventional SCS devices (Smet et al., 2011 a&b; Van Buyten et al., 2011). Data from previous European clinical studies suggest that Nevro's therapy may be effective in treating leg and back pain and other challenging types of chronic pain that often do not respond to conventional spinal cord stimulation (Smet et al., 2011 a&b; Van Buyten et al., 2011).

These data also indicate significant and sustained pain reduction in patients with chronic back and leg pain. This study reported that 87% of their patients had predominant back pain, and 80% had pain following prior one or more back surgeries. Study results showed that, following treatment with the Senza™ System, average back pain VAS scores dropped from 8.4 at baseline to 1.9 at twelve month follow-up. Average VAS leg pain scores were reduced from 5.4 at baseline to 1.6 at twelve months. The Senza™ high-frequency spinal cord stimulation system is authorized for sale in Europe and Australia. In 2015, Nevro received FDA approval for their Senza™ system.

[redacted]. The purpose of this study is to characterize the real-world outcomes of HR-SCS therapy as an aid in the management of chronic intractable pain of the trunk, including unilateral or bilateral pain associated with the following: failed back surgery syndrome, intractable low back pain using the Boston Scientific (BSC) PRECISION Spinal Cord Stimulator System with MultiWave Technology.

5. Device Description

Boston Scientific's Precision SCS System with MultiWave Technology is approved for sale in Europe (CE mark) [redacted]

The Precision SCS System with MultiWave Technology 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. The IPG is rechargeable and is recharged transcutaneously by a charging unit.

[redacted]

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

[redacted].

5.1. *Device Labeling*

Directions for use (DFU) will be provided to each Investigator. The commercial devices and packaging are physically identified and labeled as applicable. The device labeling contains the following information:

- Device description
- Model number
- Serial number / Lot number as applicable
- Device dimension (i.e. Length), as applicable
- Manufacturing location and date
- Expiration date ("use before date"), as applicable
- Storage temperature, as applicable.

6. Study Objectives

6.1. *Primary Objective*

The primary objective of this study is to characterize the real-world outcomes of high rate spinal cord stimulation (HR-SCS) therapy as an aid in the management of chronic intractable pain of the trunk, including unilateral or bilateral pain associated with the following: failed back surgery syndrome, intractable low back pain using the Boston Scientific (BSC) PRECISION Spinal Cord Stimulator System with MultiWave Technology.

7. Study Endpoints

7.1. *Primary Endpoint*

[redacted]

7.2. *Secondary Endpoints*

[redacted]

7.3. *Exploratory Endpoints*

[redacted]

7.4. *Health Economic Endpoints*

7.5. *Safety Parameters*

The study safety parameters include the following:

- Rate of occurrence of all device or procedure related adverse events (AEs), SAEs including serious adverse device events (SADEs), unanticipated serious adverse device effects (USADEs) through end of study.

8. Study Design

The study is a prospective, multi-center, single-arm study using Precision SCS System with MultiWave Technology .

The study is open label, thus the study participants, investigative site personnel, and the sponsor will not be blinded. All subjects will undergo permanent system implantation. The study design is shown in Figure 8-1.

8.1. *Scale and Duration*

The study will enroll up to 60 subjects at up to 10 centers in Europe. Enrollment is expected to take 4 months (approximately 1.5 subjects/site/month) and a subject's participation in the study, from the point of enrollment until study completion, should last approximately 12-15 months. The study is expected to last approximately 25 months from first patient enrolled until the end of study close-out activities.

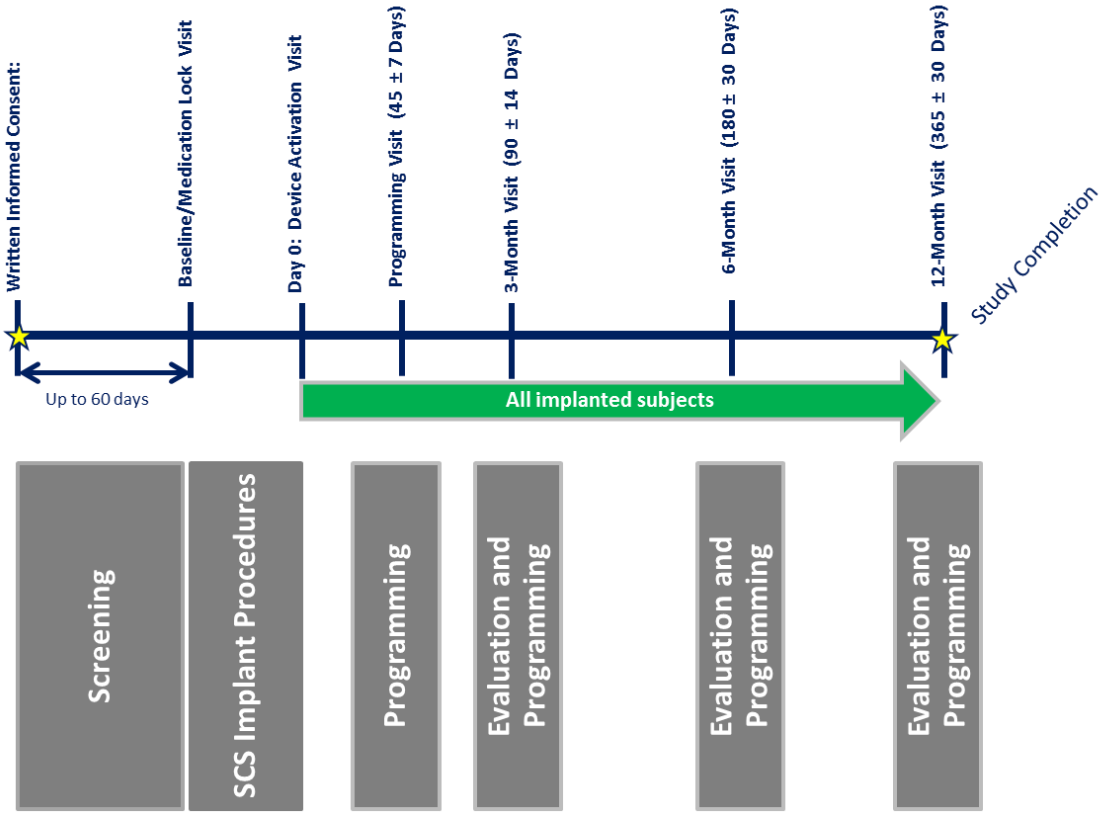

Figure 8-1: VELOCITY Study Design

8.2. *Treatment Assignment*

Eligible subjects, following written consent will receive stimulation [redacted]

8.3. *Justification for the Study Design*

The study is a prospective, multi-center, single-arm study using Precision SCS System with MultiWave Technology [redacted]. The purpose of the study is to characterize the real-world outcomes of HR-SCS therapy as an aid in the management of chronic intractable pain of the trunk, including unilateral or bilateral pain associated with the following: failed back surgery syndrome, intractable low back pain using the Boston Scientific (BSC) PRECISION Spinal Cord Stimulator System with MultiWave Technology.

A multi-center design will minimize the impact on treatment outcome that may potentially result from differences in patient selection, regional differences in the patient demographic, and differences in investigator technique and patient management.

A prospective study design will eliminate the bias associated with case selection in a retrospective review and will ensure that identical procedures are followed for data capture and review.

The primary efficacy endpoint will be measured at 3 months post-Activation of the SCS system because this represents duration sufficient for a subject to have their programming parameters optimized [redacted].

9. Subject Selection

9.1. *Study Population and Eligibility*

Study candidates will be drawn from the population of patients resident in pain management or surgical medical practices. The study eligibility criteria are listed in Sections **Error! R eference source not found.** and 0.

9.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see Table 9-1**)** will be considered for inclusion in this clinical investigation, provided no exclusion criterion (see Table 9-2) is met.

Table 9-1 Inclusion Criteria

Clinical Inclusion Criteria	[redacted]

9.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (Table 9-2) will be excluded from this clinical study.

Table 9-2 Exclusion Criteria

[redacted]	[redacted]

10. Subject Accountability

10.1. *Point of Enrollment*

A subject will be considered enrolled in the study at the time that the informed consent form is signed. No study-related procedures or assessments can take place until the informed consent form is signed. All enrolled subjects will be included in the study analyses.

[redacted]

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 device safety or performance, the investigator shall use local treatment protocols to determine the patient's options for therapy.

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 BSN (e.g., adverse event);
- Study non-compliance;
- Subject did not meet inclusion criteria or met an exclusion criteria after signing informed consent;
- Subjects not agreeing to a recommended revision;
- Lost to follow-up;
- Death of the subject.

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.

Subjects withdrawn after a successful implant will not be replaced and will be included in the site's overall total for trialed subjects.

10.3. *Subject Status and Classification*

Subjects who provide written informed consent but do not meet all of the study eligibility criteria will not be implanted. These subjects will be deemed as "enrolled but not implanted" and their reason for ineligibility will be documented in the EDC system. Enrolled subjects who are not implanted will not count towards the enrollment cap.
Subjects who sign consent, meet all eligibility criteria, and are implanted cannot be replaced.

10.4. *Enrollment Controls*

The overall enrollment in the study will be capped at 60 implanted subjects. Per site enrollment will be capped initially at 10 implanted subjects. The initial cap of 10 implanted subjects at any one site can be increased based upon written communication of sponsor approval.

The study will implement a formal *Enrollment Communication Plan*. [redacted]

10.5. *End-of-Study Action Plan*

The End-of-Study Action Plan (ESAP) defines the actions to be taken when a subject reaches the end of their study participation. At the time of subject withdrawal or during the last study follow-up visit the ESAP will be implemented.

All ESAP decisions made by a subject need to be documented in the subject's source documents.

When each enrolled subject completes the study, or withdraws, the subject exits the study. If the subject is implanted, the subject may continue to use the system per the applicable Directions for Use and should be followed according to standard, routine medical care.

11. Study Methods

11.1. *Data Collection*

There are a number of different study assessments required at each visit. The data collection schedule is provided in Table 11-1. Full descriptions for all assessments are provided in Section **Error! Reference source not found.**.

Table 11-1: Data Collection Schedule

	Screening	Baseline Visit [2]	SCS Implant Procedure	Device Activation Visit	Programming Visit	3-Month Visit	6-Month Visit	12-Month Visit / End of Study	Unscheduled Study Visits
	(Up to 60 days following Informed Consent)		Up to 45 days from BL		45 ± 7 days post-Activation Visit	90 ± 14 days post-Activation Visit	180 ± 30 days post-Activation Visit	365 ± 30 days post-Activation Visit	
Informed Consent (ICF)	x								
Inclusion/Exclusion Criteria Evaluation	x								
Demography		x							
Medical History		x							
Concomitant Medications (pain-related) [2]	x	x	o	o	o	x	x	x	o
Adverse Event (AE)	x	x	x	x	x	x	x	x	x
Dispense Daily Diary [4]	x				x		x		
Collect Daily Diary		x				x		x	
Oswestry Disability Index version 2.1a (ODI v2.1a)		x				x	x	x	
Pain Intensity numerical rating scale (NRS)[3]		x				x	x	x	
Patient Global Impression of Change (PGI-C)						x	x	x	
Percent Pain Relief (PPR)						x	x	x	
Procedure Information			x						
Programming				x	o	o[1]	o[1]	o[1]	o
Resource Utilization Inventory (RUI)		x				x	x	x	
Short Form Health Survey 36 items (SF-36 v2)		x				x	x	x	

x - required o - optional

1 - subjects' device may be programmed as needed after completion of assessments

2 - Subject's opioid medications will be locked at the Baseline and remain unchanged up to 3-month post Activation Visit

3 - NRS is being done per subject interview

4 - Subjects will receive a 7-day diary to be completed prior to the next visit. The diary may be completed in a 15-day window prior to the Visit.

11.2. *Screening Period (Up to 60 days following Informed Consent)*

All interested patients will undergo a screening period during which their eligibility into the study will be determined.

Written Informed Consent must be obtained for all subjects who are potential study candidates. A subject is considered enrolled only after the subject signs and dates the ICF:

- Subjects will be asked to sign the Informed Consent form before any study-specific tests or procedures are performed;
- The context of the study must be fully explained and the subjects must be given the opportunity to ask questions and have those questions answered to their satisfaction;
- Study personnel should explain that even if a subject agrees to participate in the study and signs an ICF, certain procedures might demonstrate that the patient is not eligible to continue participation;
- The Informed Consent form is study-specific and must be approved by the Ethics Committee (EC).

During the Screening period, eligibility criteria as described in Sections 9.2 and 9.3 will be evaluated. If a subject fails study eligibility, they will be withdrawn from the study.

Subjects will complete a 7-day daily diary (consecutive) to document their pain scores and return the diary to the site staff at the Baseline Visit. This diary may be completed in a 15-day window prior to the Baseline Visit.

11.3. *Baseline Visit (Medication Lock)*

During the Baseline Visit, a detailed evaluation of subjects' disease state and its impact on their health will be performed. Subjects will be asked about any adverse events since their last study visit (if any). Subjects will return their completed diary to the site staff.

The following assessments will be completed at the Baseline Visit to obtain baseline information on subjects:

- Pain Intensity: Numerical Rating Scale (NRS) as evaluated by study personnel interview
- Oswestry Disability Index version 2.1a (ODI v2.1a)
- Resource Utilization Inventory (RUI)
- Short Form Health Survey 36 items (SF-36 v2)
- 7-day Subject Diary

Subject's opioid medications will be locked at this visit and remain unchanged (no change type/dose/route) up to 3-month post Activation Visit.

End of Visit Information:
Subjects should be reminded not to make any changes to their opioid medications (type/dose/route).

11.4. *SCS Implant Procedure (s)*

Subjects will have up to 45 days to receive their Precision SCS Implant after the Baseline visit. Subjects will undergo a screening trial and implant procedure based on the sites' standard of care.

- Information related to the procedure, devices, etc. will be documented.
- Only BSC percutaneous leads may be used. Surgical/Paddle leads may not be used.
- Intraoperative Testing may be performed per standard of care
- The IPG may be programmed but, following the completion of programming, the device will be OFF until the Device Activation Visit
- The use of acute opioid pain medication for procedural discomfort is allowed, per site's routine care.

End of Visit Information: Following the implant procedure, instructions related to follow up care will be provided per standard of care.

- Subjects are to contact the site in an event that any additional intervention is warranted, to report a suspected adverse event, etc.
- Subjects should be reminded not to make any changes to their opioid medications (type/dose/route)
- If device implantation is unsuccessful, subjects will be followed for 2 weeks post implantation in an attempt to assess for procedure related adverse events, if they occur. These subjects will be withdrawn from the study.

11.5. *Device Activation Visit*

At the Device Activation Visit, subjects will be programmed at high rate settings for optimal therapy. Subjects will be asked about any adverse events since their last study visit (if any). Information related to programming will be collected. Subjects may have as many visits as needed to obtain optimal programming settings.

End of Visit Information:

- Subjects should be reminded not to make any changes to their opioid medications (type/dose/route);
- Instructions related to charging and use of device should be provided per standard of care.

11.6. *Programming Visit (45 ± 7 days post-Activation Visit)*

At the Programming Visit, subjects' device will be programmed to receive optimal settings. Subjects will be asked about any adverse events since their last study visit (if any). Information related to programming will be collected.

End of Visit Information:

- Subjects should be reminded not to make any changes to their opioid medications (type/dose/route);
- Instructions related to charging and use of device should be provided per standard of care;
- Subjects will receive a 7-day diary to be completed prior to the 3-Month Visit. The diary may be completed in a 15-day window prior to the Visit.

11.7. *3-Month Visit (90 ± 14 days post-Activation Visit)*

At the 3-Month Visit, subjects' will return to the clinic for programming and evaluation. Subjects will be asked about any adverse events since their last study visit (if any). Subjects will return their 7-day diary to the site staff.

The following assessments will be completed at 3-Month Visit prior to device programming.

- Pain Intensity: Numerical Rating Scale (NRS) as evaluated by study personnel interview
- Percent Pain Relief (PPR)
- Patient Global Impression of Change (PGI-C)
- Oswestry Disability Index version 2.1a (ODI v2.1a)
- Resource Utilization Inventory (RUI)
- Short Form Health Survey 36 items (SF-36 v2)
- 7-day Subject Diary

Per standard of care, subjects' device may be programmed as needed after completion of assessments. Information related to programming will be collected. Subjects' opioid medications may be adjusted as needed and change during the rest of the course of the study. Changes to opioid medications should be documented.

End of Visit Information:

- Instructions related to charging and use of device should be provided per standard of care.

11.8. *6-Month Visit (180 ± 30 days post-Activation Visit)*

At the 6-Month Visit, subjects' will return to the clinic for programming and evaluation. Subjects will be asked about any adverse events since their last study visit (if any).

The following assessments will be completed at 12-Month Visit prior to device programming.

- Pain Intensity: Numerical Rating Scale (NRS) as evaluated by study personnel interview
- Percent Pain Relief (PPR)
- Patient Global Impression of Change (PGI-C)
- Oswestry Disability Index version 2.1a (ODI v2.1a)
- Resource Utilization Inventory (RUI)
- Short Form Health Survey 36 items (SF-36 v2)

Per standard of care, subjects' device may be programmed as needed after completion of assessments. Information related to programming will be collected. Subjects' opioid medications may be adjusted as needed and change during the rest of the course of the study. Changes to opioid medications should be documented.

End of Visit Information:

- Instructions related to charging and use of device should be provided per standard of care;
- Subjects will receive a 7-day diary to be completed prior to the 12-Month Visit. The diary may be completed in a 15-day window prior to the Visit.

11.9. *12-Month Visit (365 ± 30 days post-Activation Visit) - End of Study*

At the 12-Month Visit, subjects' will return to the clinic for programming and evaluation. Subjects will be asked about any adverse events since their last study visit (if any). This Visit will be End of Study Visit and subjects will be followed per End of Study Action Plan as described in Section 10.5. Subjects will return their 7-day diary to the site staff.

The following assessments will be completed at 12-Month Visit prior to device programming.

- Pain Intensity: Numerical Rating Scale (NRS) as evaluated by study personnel interview
- Percent Pain Relief (PPR)
- Patient Global Impression of Change (PGI-C)

- Short Form Health Survey 36 items (SF-36 v2)
- Resource Utilization Inventory (RUI)
- Oswestry Disability Index version 2.1a (ODI v2.1a)
- 7-day Subject Diary

Per standard of care, subjects' device may be programmed as needed after completion of assessments. Information related to programming will be collected. Subjects' opioid medications may be adjusted as needed and change during the rest of the course of the study. Changes to opioid medications should be documented.

End of Visit Information:

- Instructions related to charging and use of device should be provided per standard of care.

11.10. *Unscheduled Study Visits*

Subjects may have as many unscheduled study visits as needed for programming (e.g., reprogramming, replacement, revision) or evaluation of adverse events.

11.11. *Revision or Replacement of Leads, Extensions and/or IPGs*

During the course of 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 on 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. Any replacements or revisions performed during the course of the study must be documented. Acute opioid pain medications may be taken per standard of care.

11.12. *Study Completion*

All subjects permanently implanted with an IPG will be followed through completion of the End of Study visit (12-months post-Activation Visit). The End of Study Action Plan (see Section 10.5) defines the actions to be taken when the subject reaches the end of their study participation.

11.13. *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

investigation center team with a statement that it is a true reproduction of the original source document.

Table 11-2: 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 investigational site
Imaging films/prints documenting lead(s) location	Retained at investigational site
Assessments and questionnaires	Retained at investigational site and/or electronic data collection platform / EDC
Clinician programmer printouts/electronic files for programming information	Retained at investigational site

12. Statistical Considerations

12.1. *Primary Endpoint*

The primary endpoint for this study is low back responder rate at 3 months post-activation, [redacted].

12.1.1. Hypotheses

[redacted]

[redacted]

[redacted]

12.1.2. Sample Size

The required sample size for this study was calculated based on the following assumptions:

[redacted]

12.1.3. Statistical Methods

For the primary endpoint, statistical testing will be performed to determine if the low back pain responder rate with HR-SCS is superior to the OPC of this study.

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

12.2. *Secondary Endpoints*

[redacted]

[redacted]

12.3. *Exploratory Endpoints*

A number of exploratory endpoints are included in this study to explore the effect of treatment on additional outcomes.

The exploratory endpoints are intended to generate hypotheses for future study. Consequently, no correction for multiple testing will be performed for the exploratory endpoints. All exploratory endpoints will be clearly identified as such in study reports.

12.4. *Health Economic Endpoints*

A number of health economic endpoints are included in this study to measure the economic value of the treatment.

[redacted].

12.5. *Safety Parameters*

Safety parameters include the Rate of occurrence of all device or procedure related adverse events (AEs), SAEs including serious adverse device events (SADEs), unanticipated serious adverse device effects (USADEs) through end of study.

For time-to-event variables, Kaplan-Meier plots will be provided. The Cox proportional hazards regression model will be used to assess the effects of risk factors on the time-to-event variables.

12.6. *Analysis Sets*

All primary and secondary endpoints will be analyzed on both intent-to-treat and a per-protocol basis.

[redacted]

12.6.1. Safety Analysis Set

In the safety analysis, all subjects who sign the IRB-approved written Informed Consent form will be included.

12.7. *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. Consequently, consecutively eligible subjects will be randomly allocated into the study, minimizing

selection bias. Boston Scientific will report to the ethic committee any evidence of fraud, including deliberate tampering with the selection of subjects.

12.8. *Number of Subjects per Investigative Site*

In order to enroll up to 60 subjects, up to 10 investigative sites will be included. The number of subjects at each site will capped at 10 subjects per site. Sponsor approval must be obtained in writing to enroll beyond the site-specific cap of 10 subjects.

12.9. *Eligibility of Subjects, Exclusions, and Missing Data*

[redacted]

12.10. *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). [redacted]

12.10.1. Interim Analyses

[redacted]

[redacted]

[redacted]

12.10.2. Subgroup Analyses

[redacted]

[redacted]

12.10.3. Justification of Pooling

Analyses will be performed using data pooled across various sites/institutions. Multivariate analysis techniques, including contingency tables and logistic regression for binary outcomes and analysis of variance for continuous measures, will be used to assess differences among study sites to justify pooling data across sites.

12.10.4. Multivariable Analyses

[redacted]

[redacted]

12.11. *Changes to Planned Analyses*

[redacted]. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

13. Data Management

13.1. *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. All changes made to the clinical data will be captured in an electronic audit trail and available for review by Boston Scientific Corporation (BSC) 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 EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

13.1.1. 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.

13.1.2. Direct Data Upload

For quality assurance purposes and validation, technical data on the SCS device, stored in the BSC Field Clinical Engineer/Field Clinical Specialist's (FCE) Clinician Programmer, will be collected using direct data upload to a secure BSC server. BSC FCEs, who assist in programming the device settings per routine care, will upload the Clinician Programmer database files to a secure server stored in a restricted location at BSC.

13.2. ***Study Assessments***

[redacted]

[redacted]

13.3 Data Retention

The Investigator or Investigational site will maintain, at the investigative site, in original format 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 local regulations. It is BSC's responsibility to inform the Investigator when these documents no longer need to be maintained.

The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator 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.

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

16 Device/Equipment Accountability

No device accountability will be required, because this study will be using commercially available devices. Compliance

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 clinical investigation plan, ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

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

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

- Report to BSC, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE.
- Report to the IRB/EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE, 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.
- 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 EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the device when it is used/operated by the subject.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, 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.

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. Only trained, experienced, licensed physicians are allowed to perform study procedures (e.g., IPG and Permanent Lead Implantation).

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 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 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 EC approval and renewals will be obtained throughout the duration of the study as required by local/country or EC requirements. Copies of the Investigator's reports and the 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 Field Clinical Engineer/Field Clinical Specialist

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

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

Typical tasks may include the following.

- Interrogating the device or programming device parameters to investigator-requested settings as specified in the protocol as well as operating investigational equipment
- Performing device 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 from programmers and other equipment
- Entering technical data on technical source form as long as the responsible HCP verifies and signs the completed worksheet
- Print out programming reports directly from the clinician programmer and provide original to clinical site as source documentation
- Provide technical expertise/support to subjects during office visits and/or during teleconference calls with the principal investigator or their delegated site staff and the subject.

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

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

Boston Scientific personnel will not do the following.

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

- Enter data in electronic data capture systems or on paper case report forms

17.5 Insurance

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

18 Monitoring

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

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

19 Potential Risks and Benefits

Subjects who take part in this study are subject to similar risks shared by all subjects who receive this device but are not participating in this study. In addition, this study is set up to collect data through questionnaires and interviews. To complete these additional questionnaires and interviews the subject will spend additional time at the hospital and/or doctor's office. They may have an increased number of visits to the hospital and/or doctor's office compared to standard of care.

19.1 Risks Associated with the Commercial Device(s)

There are no known incremental risks associated with use of the commercial device within this study setting.

19.2 Risks associated with Participation in the Clinical Study

The subject might find it difficult, uncomfortable, or tiresome to complete study visits, diary, and/or questionnaires. They may be uncomfortable with the medication lock requirements.

19.3 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.

Please refer to the Directions for Use Manual for procedures that should not be used while the SCS lead/s remains implanted.

19.4 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.

The PRECISION Spinal Cord Stimulation System with MultiWave Technology is indicated as an aid in the management of chronic intractable pain. Based on clinical and post-market experience, the anticipated risks associated with the use of the PRECISION™ system are predicted to be acceptable compared to the expected benefits in the reduction of symptoms. The treatment is reversible in that the device may be turned off or explanted at any time for any reason.

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
- Safety review processes by Boston Scientific
- Monitoring visits

19.5 Anticipated Benefits

The reported benefit of the PRECISION SCS System with MultiWave Technology may include:

- Reduction in the intensity of chronic low back pain
- Reduction in the intensity of chronic leg pain
- Improvement in physical functioning (disability)

- Reduction in pain-related medication use
- Reduction in the occurrence of side-effects of pain-related medications accompanied by reduction in opioid use (e.g. sleep disturbances, constipation, reduction in mental acuity)

19.6 Risk to Benefit Rationale

The risk evaluation for the PRECISION SCS System with MultiWave Technology determined that all hazards attributed to the PRECISION SCS System with MultiWave Technology 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 PRECISION SCS System with MultiWave Technology to treat chronic intractable pain outweighs the remaining residual risk. As the overall residual risk meets BSN's criteria, the PRECISION SCS System with MultiWave Technology is acceptable for use in a clinical setting.

19.7 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 Definitions and Classification

Adverse event definitions are provided in **Error! Reference source not found.**.

Table 20-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	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 (any procedure in the clinical investigation plan). NOTE 3: For users or other persons, this definition is restricted to events

Table 20-1: Safety Definitions

Term	Definition
	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: a) Led to death, b) Led to serious deterioration in the health of the subject, that either resulted in: a life-threatening illness or injury, or a permanent impairment of a body structure or a body function, or in-patient or prolonged hospitalization of existing hospitalization, or medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) Led to 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 Serious Adverse Device Effect (USADE) *Ref: ISO 14155-2011* *Ref: MEDDEV 2.7/3 12/2010*	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.

Underlying diseases 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 a specific SAE (see Table 20-1 for AE definitions).

Any AE experienced by the subject after informed consent, whether during or subsequent to the procedure, must be recorded in the eCRF.

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

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, or follow-up visits, 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, 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.
6. 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
7. Clinically significant worsening of the pattern of intensity or distribution of Baseline pain symptoms should be reported as an AE.
8. 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.

20.2 Relationship to Study Device(s)

The Investigator must assess the relationship of the AE to the study device or procedure. See criteria in **Error! Reference source not found.**

Table 20-2: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Unrelated	The adverse event is determined to be due to a concurrent illness or effect of another device/drug and is not related to the investigational product.
Related	d) The adverse event is determined to be potentially related to the investigational product, and an alternative etiology is equally or less likely compared to the potential relationship to investigational product, or e) There is a strong relationship to investigational product, or recurs on re-challenge, and another etiology is unlikely, or There is no other reasonable medical explanation for the event.

The Investigator must assess the potential relationship of all adverse events to the **device and procedure.** All **device** related adverse events will be assessed according to their relationship to one of the following sub-categories:

- **Device Hardware-Related AEs:** AEs that can reasonably be attributed to the mere physical presence of the device or to deficiency of the device (i.e., an allergic response to device materials).
- **Stimulation-Related AEs:** AEs that can reasonably be attributed to the effects of stimulation. A relationship to stimulation may be determined by demonstrating a predictable response to the alternating between stimulation-on and stimulation-off settings. However, a relationship to stimulation may also be reported without demonstrating a predictable response to the alternating between the stimulation-on and stimulation-off settings if in the opinion of the Investigator the AE is potentially related to stimulation.
- **Procedure Related AEs:** AEs that can reasonably be attributed to a **study protocol required procedure.**

20.3 Investigator Reporting Requirements

The communication requirements for reporting to BSC are as shown in **Error! Reference s ource not found.**3.

Table 20-3: Investigator Reporting Requirements

Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study

Table 20-3: Investigator Reporting Requirements

Serious Adverse Event including Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information	• Within 2 business days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (unidentified) for reported event	• When documentation is available
Adverse Event	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 (e.g. Recommend within 10 business days) after becoming aware of the information • Reporting required for adverse events related to procedure, hardware and stimulation. • Reporting is required through the end of the study.
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete Device Deficiency eCRF with all available new and updated information	• Within 2 business day of first becoming aware of the event and as per local/regional regulations • Reporting required through the end of the study

Note:

- AEs related to device/procedure, SAEs, SADEs, Device Deficiencies and USADEs will be collected from the time of informed consent through end of study. SAEs and Device Deficiencies may be reported via phone, fax or email if the electronic data capture (EDC) system is unavailable. The paper SAE Notification Form or Device Deficiency Notification Form should be used to report SAEs and/or device deficiencies during this time.
- Subjects should be instructed to contact their physician immediately if they experience any adverse event rather than wait for a scheduled visit.

20.4 Boston Scientific Device Deficiencies

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and labeling errors) will be documented and reported to BSC. If possible, the 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.

Boston Scientific will be notified of all device deficiencies, failures, malfunctions and product nonconformities with respects to the products in use in the study. Report all these events in the appropriate eCRF.

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

And, 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.

20.5 Reporting to Regulatory Authorities / IRBs / ECs / Investigators

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

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

21 Informed Consent

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

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

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

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

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

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

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

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

requested by the site's IRB/EC. The IRB/EC will determine the subject population to be re-consented.

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

22 Committees

22.1 Safety Monitoring Process

To promote early detection of safety issues, the BSC 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 Safety Office, which is responsible for coordinating the collection of information for the subject dossier from the sites. During regularly scheduled monitoring activities, clinical research monitors will support the dynamic reporting process through their review of source document and other data information.

23 Suspension or Termination

23.1 Premature Termination of the Study

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

23.1.1 Criteria for Premature Termination of the Study

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

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development of the device.

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

Any investigator, or IRB/ EC in the VELOCITY Study may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to

Boston Scientific. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

23.3 Requirements for Documentation and Subject Follow-up

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

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

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

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

23.4 Criteria for Suspending/Terminating a Study Site

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled 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 site participation, all study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/EC and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the site will continue to be followed according to the protocol and the end of study action plan. The Principal Investigator at the site must make provision for these follow-up visits unless BSC notifies the investigational site otherwise.

The sponsor may also consider transferring active subjects from the site that is being closed to another approved study site within geographic area.

Possible reasons for suspending/terminating a study center include:

- Persistent non-compliance with protocol;
- Repeated failure to complete CRFs in a timely manner;
- Failure to obtain written Informed Consent;

- Failure to report UADE within 1 business day after "becoming aware date" and SAE within 2 business days after becoming aware date to BSC;
- Loss of (or unaccounted for) investigational product inventory;
- Failure to enroll subjects.

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. In accordance with the Corporate Policy for the Conduct of Human Subject Research, BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific Corporation adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

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26 Abbreviations and Definitions

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

Table 26-1: Abbreviations

Abbreviation/Acronym	Term
ADE	adverse device effect
AE	adverse event
BSC	Boston Scientific Corporation
BSN	Boston Scientific Neuromodulation
CFR	Code of Federal Regulations
CI	confidence interval
CMM	conventional medical management
CP	clinician programmer
CR	conventional rate
CRC	clinical research coordinator
CRF	Case report form
CRO	contract research organization
CR-SCS	conventional rate spinal cord stimulation
DFU	directions for use
DSM-IV	The Diagnostic and Statistical Manual of Mental Disorders (DSM), 4th edition
EC	ethics committee
eCRF	electronic case report form
EDC	electronic data capture
ESAP	end of study action plan
ETS	external trial stimulator
FBSS	failed back surgery syndrome
FCE	Field Clinical Engineer/Field Clinical Specialist
HCP	health care provider
HR	high rate
HR-SCS	high rate spinal cord stimulation
Hz	hertz
ICF	informed consent form
ICMJE	International Committee for Medication Journal Editors
IDE	investigational device exemption
IPG	implantable pulse generator
ISO	International Organization for Standardization
ITT	intent-to-treat

kHz	kilohertz
LTTS	Long-Term Therapy Selection
mA	milliamps
MRI	magnetic resonance imaging
NRS	numerical rating scale
PGI-C	Patient Global Impression of Change assessment - see Section 13 for a detailed description
PPR	percent pain relief
Programming	The process of turning on and adjusting the stimulation parameters (amplitude, pulse width, rate, polarity) on an implantable pulse generator or external trial stimulator to arrive at optimal therapeutic parameters
PW	pulse width
RC	remote control
RCT	randomized controlled trial
RF	radio frequency
RUI	Resource Utilization Inventory assessment - see Section 13 for a detailed description
SADE	serious adverse device effect
SAE	serious adverse event
SCS	spinal cord stimulation
SF-36v2	Short Form 36 Health Survey ver 2 - see Section 13 for a detailed description
Sth	sensory threshold
UADE	unanticipated adverse device effect
USADE	unanticipated serious adverse device effect