Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	Spinal Cord Stimulation (SCS) Dosing Study
Clinical Investigation Plan Identifier	MDT17046
Study Product Name	Medtronic RestoreSensor® (Models 97714 and 37714) Implantable Neurostimulation Systems
Sponsor	Medtronic, Inc 7000 Central Ave NE Minneapolis, Minnesota, 55432 U.S.A. +1-763-514-4000
Study Manager	[redacted]
Medical Expert	[redacted]
Document Version	Version 1.0, 22 Aug 2017

1. Investigator Statement

Participating investigators will be provided with a separate investigator agreement to document their obligations and commitment with respect to study conduct.

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2. Glossary

Abbreviation	Term
ADE	Adverse Device Effect
AE	Adverse Event
CIP	Clinical Investigation Plan
CFR	Code of Federal Regulations
DD	Device Deficiency
eCRF	Electronic Case Report Form
EQ-5D	European Quality of Life 5-Dimensions
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCO	Health Care Organization
HCP	Health Care Professional
HD	High Dose
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
INS	Implantable Neurostimulation System
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
NPU	Neuro Programmer Upload
ODI	Oswestry Disability Index
RDC	Remote Data Capture
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Events
SCS	Spinal Cord Stimulation
SSA	Satisfaction and Sensation Assessment
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analog Scale

3. Synopsis

Title	Spinal Cord Stimulation (SCS) Dosing Study
Clinical Study Type	Post-market feasibility
Product Name	Medtronic RestoreSensor® Neuromodulation Systems
Sponsor	Medtronic, Inc. 7000 Central Ave NE Minneapolis, Minnesota, 55432 U.S.A. +1-763-514-4000
Indication Under Investigation	Approved indication of spinal cord stimulation as an aid in the management of chronic, intractable pain of the trunk and limbs.
Investigation Purpose	To characterize the effects of amplitude titration on subject satisfaction and pain relief with high dose (HD) stimulation (90 µs and 1000 Hz) in subjects with back and leg pain being treated by SCS.
Product Status	All devices used in this study are commercially available and will be used within the intended approved indication.
Primary Objective(s)	To characterize the minimum amplitude as a percentage of perception threshold that maintains SCS therapy satisfaction.
Secondary Objective(s)	To characterize the minimum amplitude as a percentage of perception threshold that maintains overall pain relief.
Additional Objectives	[redacted]
Safety Objective	To characterize therapy and device related adverse events and device deficiencies.
Study Design	This is a prospective, multi-center, single-blind post-market feasibility study. This study will be conducted in the United States at no less than 2 sites. To reduce the possibility of atypical results from a site overly influencing the combined results, no more than 30 subjects will be enrolled at each site. Eligible subjects will receive four different programmed amplitude settings (80%, 60%, 40%, and 20%

	of perception threshold), each for approximately two weeks. Subjects will be blind to the different amplitude settings and will not be informed that the amplitude is being titrated down, beginning at 80% of perception threshold. The overall study duration, from first subject enrollment to last subject visit, is expected to last approximately 15 months. Each subject's participation in the study is expected to last approximately 12 weeks from enrollment. The completion of the study is defined as the approval of the Final Study Report and closure of all sites.
Sample Size	An estimated 60 subjects will be enrolled and screened for at least 40 subjects to proceed beyond the Baseline visit. A sample size of 40 subjects is reasonable to characterize the distribution of the minimum amplitude as a percentage of perception threshold that maintains SCS therapy satisfaction, as well as to provide data for consideration of future studies.
Inclusion/Exclusion Criteria	**Screening Eligibility** Inclusion Criteria: To be included in this study, a patient must meet the following inclusion criteria: 1. 22 years of age or older 2. Implanted with a RestoreSensor system (for back and leg pain) for at least 1 month 3. Has a program with only 1 anode and 1 cathode with 90 µs and 1000 Hz and the group that contains the program is used ≥ 50% (compared to the percent use of the other groups, if present) 4. Willing and able to provide signed and dated informed consent 5. Capable of comprehending and consenting in English 6. Capable of getting into the supine and sitting positions for perception threshold testing 7. Willing and able to comply with all study procedures and visits 8. On stable (no change in dose, route, or frequency) prescribed pain medications for at least 4 weeks before enrollment and willing to maintain dose during the study Exclusion Criteria: To be included in this study, a patient must not meet any of the following exclusion criteria: 1. Implanted with leads for peripheral nerve stimulation or an implantable intrathecal drug delivery system 2. Had a pain-related surgery in the previous 1 months of enrollment or the intent to undergo surgery during the period of the study 3. Implanted with quadripolar lead 4. Currently enrolled or planning to enroll in a potentially confounding clinical study during the course of the study (co-enrollment in concurrent

	studies is only allowed when documented pre-approval is obtained from the Medtronic study manager (or designee)) 5. Pregnant or is of child-bearing potential and unwilling to use a medically acceptable form of birth control during the study 6. Has untreated major psychiatric comorbidity, as determined by the investigator, or designee 7. Has serious drug-related behavioral issues (e.g., alcohol dependency, substance abuse), as determined by the investigator, or designee 8. Has unresolved major issues of secondary gain (ie, secondary reason not to report improvement in health condition), as determined by the investigator, or designee **Baseline Eligibility** To proceed on with the Baseline visit, the subject must meet the following inclusion criteria: 1. Has an average overall VAS pain score ≤ 4 based on the Baseline diary To proceed on with the Baseline visit, the subject must not meet any of the following exclusion criteria: 1. Has provided response to Baseline SSA as "Neutral", "Somewhat unsatisfied", or "Very unsatisfied" with the therapy 2. Completed less than 5 of the 7 days of the Baseline diary
Study Procedures and Assessments	Subjects will complete a screening visit, baseline/programming visit, three additional programming visits, and a final study visit. Each subject is expected to complete 6 study-related visits. The following assessment measures will be used during the study: • Satisfaction and Sensation Assessment (SSA) [redacted] • Visual Analog Scale (VAS) for pain within diary
Safety Assessment	Safety will be evaluated by the collection of device deficiencies and adverse events related to the following: • The implanted SCS system and accessories • Spinal cord stimulation therapy
Statistics	No hypothesis testing will be performed for the study. Descriptive statistics for the primary, secondary and additional objectives will be reported. Device and therapy related adverse events and device deficiencies will be presented in summary tables.

4. Introduction

This on-label, post-market feasibility clinical study will be conducted with at least 2 sites. It is estimated that 60 subjects will be enrolled and screened for at least 40 to proceed beyond the Baseline visit. The expected study commitment for each subject is intended to be approximately 12 weeks. The study will be conducted in accordance with this protocol, the ethical principles that have their origin in the Declaration of Helsinki, all applicable regulatory requirements (21 Code of Federal Regulations (CFR) §11 Electronic records; electronic signatures, 21 CFR §50 Protection of human subjects, 21 CFR§54 Financial disclosure by clinical investigators, 21 CFR §56 Institutional review boards, and 21 CFR §803 Medical device reporting), and will comply with Good Clinical Practices (GCP) as guidelines for this study.

Documentation for this study will be produced and maintained to ensure that a complete history of the study exists. Documents created for this study, including all versions of original documents, will be identifiable and appropriately stored to assure control and traceability of data related to this study.

4.1. Background

Spinal cord stimulation is an effective treatment for chronic, intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following conditions: failed back surgery syndrome (FBS) or low back syndrome or failed back, radicular pain syndrome or radiculopathies resulting in pain secondary to FBS or herniated disk, postlaminectomy pain, multiple back operations, unsuccessful disk surgery, degenerative disk disease/herniated disk pain refractory to conservative and surgical interventions, peripheral causalgia, epidural fibrosis, arachnoiditis or lumbar adhesive arachnoiditis, complex regional pain syndrome (CRPS), reflex sympathetic dystrophy (RSD), or causalgia. Spinal cord stimulation uses electrical pulses to activate or modulate the nervous system, resulting in pain relief. Stimulation parameters (amplitude, pulse width, frequency, electrodes) can be manipulated to provide patient-specific pain relief. Traditionally, parameters have been chosen to balance pain relief with comfortable paresthesia.

In the last several years, clinical evidence has emerged to suggest that paresthesia may not be required for pain relief.[1,2] Published studies have focused on two branded types of stimulation that seem to allow pain relief with either: 1) no paresthesia, as reported in studies on 10 kHz SCS, or HF10™ therapy[1,2,3,4,5] or 2) minimal paresthesia, as reported in studies on burst SCS, BurstDR.[6,7,8,9,10,11,12,13,14] The use of higher frequency stimulation of 1000 Hz with a pulse width of 90 µs has also been investigated for clinical outcomes as a consistent starting point for applying high dose (HD) stimulation.[15]

Conventional SCS therapy has primarily been driven by selecting an amplitude that creates paresthesia coverage without causing discomfort. There is evidence that the T9/T10 intervertebral disc space has been a common location to target stimulation for chronic low back pain and leg pain using conventional

parameters for over 20 years.[16,17,18,19] However, additional clinical work is needed to understand the effect of amplitude and electrode location when using HD stimulation.

The ability to characterize the relationship between amplitude and HD stimulation may help improve future clinical practice by optimizing subject therapy for pain relief. Furthermore, if lower amplitude settings produce effective pain relief, the battery output of the neurostimulator could be reduced consequently decreasing the required recharge frequency.

4.2. Purpose

The purpose of this study is to characterize the effects of amplitude titration on subject satisfaction and pain relief with high dose (HD) stimulation (90 µs and 1000 Hz) in subjects with back and leg pain being treated by SCS.

5. Objectives and Endpoints

5.1. Objectives

5.1.1. Primary Objectives

To characterize the minimum amplitude as a percentage of perception threshold that maintains SCS therapy satisfaction.

5.1.2. Secondary Objectives

To characterize the minimum amplitude as a percentage of perception threshold that maintains overall pain relief.

5.1.3. Additional Objectives

[redacted]

5.1.4. Safety Objectives

To characterize therapy and device related adverse events and device deficiencies.

6. Study Design

This is a prospective, multi-center, single-blind post-market feasibility study. This study will be conducted in the United States at no less than 2 sites. To reduce the possibility of atypical results from a site overly influencing the combined results, no more than 30 subjects will be enrolled at each site. Eligible subjects will receive four different programmed amplitude settings (80%, 60%, 40%, and 20% of perception threshold), each for approximately two weeks. Subjects will be blind to the different amplitude settings and will not be informed that the amplitude is being titrated down, beginning at 80% of perception threshold.

6.1. Duration

It is estimated that 60 subjects will be enrolled and screened for at least 40 subjects to proceed beyond the Baseline visit. The enrollment period is expected to last about 1 year. Enrolled subjects will have up to 6 study visits (including Screening, Baseline/Programming Visit #1, Programming Visits #2-4, and the Final Study Visit. Each of the four amplitude settings will be tested for approximately 2 weeks. Subjects' participation in the study is expected to last approximately 12 weeks from enrollment. The overall study duration, from first subject enrollment to last subject visit, is expected to last approximately 15 months. The completion of the study is defined as the approval of the Final Study Report and closure of all sites.

6.2. Rationale

[redacted]

[redacted]

[redacted]

7. Product Description

7.1. General Product Description

Subjects who have previously been implanted with a RestoreSensor implantable neurostimulator (INS), Model 97714 or 37714, system will be enrolled in this study. The implanted system consists of an INS, one or more leads, and applicable compatible extensions, anchors and accessories. Non-implanted system components include the clinician programmer and software application card, a patient programmer, an INS recharging system, and applicable accessories.

Table 1 contains the allowed model numbers of the key implanted components (leads and neurostimulators) of the neuromodulation system.

Table 1. Medtronic Market-Released SCS Products

Model Numbers	Name
Neurostimulators	
97714	RestoreSensor® SureScan® MRI Rechargeable neurostimulator
37714	RestoreSensor® neurostimulator
Leads	
977A1	Vectris™ SureScan® MRI Subcompact
977A2	Vectris™ SureScan® MRI 1x8 Compact
3776	Pisces Octad Subcompact
3777	Pisces Octad Standard
3778	Pisces Octad Compact
977C1	Specify SureScan MRI 5-6-5
977C2	Specify SureScan MRI 2x8
39565	Specify 5-6-5
39286	Specify 2x8

7.2. Product Return

All products are commercially available and no products will be provided as a part of this study. Subjects are to be implanted with their SCS system prior to enrollment. Subjects who require a system modification or explant will be exited prior to the procedure. Explanted devices should be returned through normal commercial methods.

7.3. Product Accountability

No product accountability will be required for the study.

Subjects who participate in the study beyond the Baseline visit will need to surrender their patient programmer to site personnel for the duration of the study. If the subject does not bring their patient programmer to the Baseline visit, the commencement of the first treatment period (80% perception threshold) will need to be postponed until the subject is able to bring their patient programmer to the site.

Site personnel will store each subject's patient programmer in a secure location. Each subject will be given back their patient programmer at the end of their participation in the study.

8. Selection of Subjects

8.1. Study Population

A Medtronic implantable neurostimulation system is indicated for spinal cord stimulation (SCS) 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 conditions:

- Failed Back Syndrome (FBS) or low back syndrome or failed back
- Radicular pain syndrome or radiculopathies resulting in pain secondary to FBS or herniated disk
- Postlaminectomy pain
- Multiple back operations
- Unsuccessful disk surgery
- Degenerative Disk Disease (DDD)/herniated disk pain refractory to conservative and surgical interventions
- Peripheral causalgia
- Epidural fibrosis
- Arachnoiditis or lumbar adhesive arachnoiditis
- Complex Regional Pain Syndrome (CRPS), Reflex Sympathetic Dystrophy (RSD), or causalgia

This study will enroll a sub-set of the population indicated for SCS systems. Subjects who meet the eligibility criteria listed in Sections 8.3-8.4 are eligible to be enrolled in the study.

8.2. Subject Enrollment

Subjects are considered enrolled at the time the study-specific Informed Consent Form (ICF) is signed. Each subject must meet all the inclusion criteria and no exclusion criteria to be eligible to participate in this study.

8.3. Inclusion Criteria (Screening Visit)

To be included in this study, a patient must meet the following inclusion criteria:

1. 22 years of age or older
2. Implanted with a RestoreSensor system (for back and leg pain) for at least 1 month
3. Has a program with only 1 anode and 1 cathode with 90 µs and 1000 Hz and the group that contains the program is used ≥ 50% (compared to the percent use of the other groups, if present).
4. Willing and able to provide signed and dated informed consent
5. Capable of comprehending and consenting in English
6. Capable of getting into the supine and sitting positions for perception threshold testing
7. Willing and able to comply with all study procedures and visits
8. On stable (no change in dose, route, or frequency) prescribed pain medications for at least 4 weeks before enrollment and willing to maintain dose during the study

8.4. Exclusion Criteria (Screening Visit)

To be included in this study, a patient must not meet any of the following exclusion criteria:

1. Implanted with leads for peripheral nerve stimulation or an implantable intrathecal drug delivery system
2. Had a pain-related surgery in the previous 1 month of enrollment or the intent to undergo surgery during the period of the study
3. Implanted with quadripolar lead
4. Currently enrolled or planning to enroll in a potentially confounding clinical study during the course of the study (co-enrollment in concurrent studies is only allowed when documented pre-approval is obtained from the Medtronic study manager (or designee))
5. Pregnant or is of child-bearing potential and unwilling to use a medically acceptable form of birth control during the study
6. Has untreated major psychiatric comorbidity, as determined by the investigator, or designee
7. Has serious drug-related behavioral issues (e.g., alcohol dependency, substance abuse), as determined by the investigator, or designee
8. Has unresolved major issues of secondary gain (ie, secondary reason not to report improvement in health condition), as determined by the investigator, or designee

8.5. Baseline Eligibility Criteria

To proceed on with the Baseline visit, the subject must meet the following inclusion criteria:

1. Has an average overall VAS pain score ≤ 4 based on the Baseline diary

To proceed on with the Baseline visit, the subject must not meet any of the following exclusion criteria:

1. Has provided response to Baseline SSA as “Neutral”, “Somewhat unsatisfied”, or “Very unsatisfied” with the therapy
2. Completed less than 5 of the 7 days of the Baseline diary

9. Study Procedures

9.1. Schedule of Events

Table 2 reflects the study procedures, tasks, and data collection by each visit and Figure 1 is a study visit diagram. Subjects will be required to come into the clinic for the following 6 study visits:

- Screening
- Baseline /Programming Visit #1
- Programming Visit #2
- Programming Visit #3
- Programming Visit #4
- Final Study Visit

A telephone call will be placed to the subjects one week before each clinic visit to remind them to begin completing the diary.

Table 2. Study Procedures, Tasks, and Data Collection by Visit

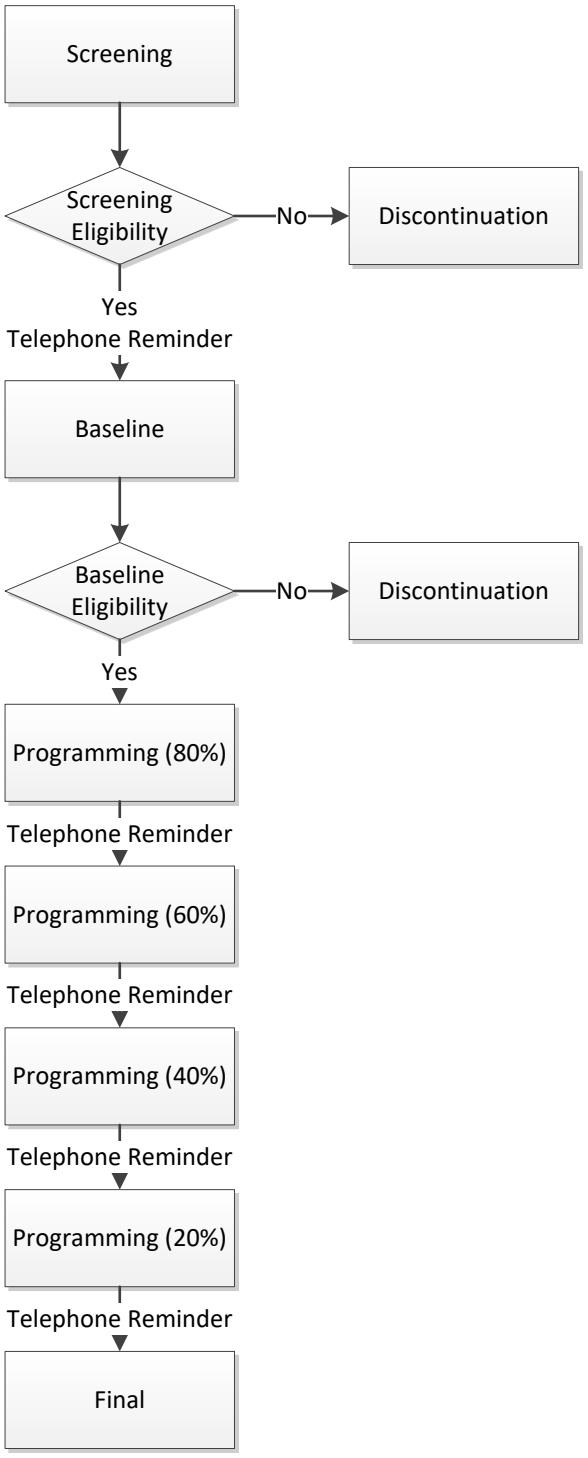
Study Procedures, Tasks, and Data Collection (row) by Visit (column)	Screening	Baseline/ Programming #1	Programming #2	Programming #3	Programming #4	Final Study Visit
Informed Consent	√					
Screening Eligibility	√					
Demographics	√					
Medical/Surgical History	√					
Pain Medications	√					
Device Information	√					
Baseline Eligibility		√				
[redacted]						
Collect Patient Programmer		√				
Imaging		√*				
Perception Thresholds		√				√
Telephone Call**		√	√	√	√	√
Pain Diary (distribute)	√ (Baseline)	√ (80%)	√ (60%)	√ (40%)	√ (20%)	
Pain Diary (collect completed)		√ (Baseline)	√ (80%)	√ (60%)	√ (40%)	√ (20%)
Device Interrogation Programming & Upload (initial and final)	√	√	√	√	√	√
SSA		√	√	√	√	√
AE/DD	√	√	√	√	√	√
Lead Identification						√***
Return Patient Programmer						√

* On the day of the Baseline visit, or during the study, subjects must have imaging performed.

** A telephone call will be placed to the subjects one week before they return to the clinic to remind them to begin completing the diary.

*** Will only be performed with subjects who have two leads implanted; may take place at a separate visit.

Figure 1: Study Visit Diagram



9.2. Subject Screening

Subjects may be recruited through the investigator's practice and referring physicians. It is recommended to recruit subjects who live within a reasonable distance from the site.

Potential subjects may be identified through chart reviews or as new or existing patients attend clinic visits. If subjects are recruited from outside the investigator's practice, sites are to ensure that appropriate release for access to the subject's records (paper and/or electronic) is obtained. Any subject recruitment materials disseminated to subjects (advertisements, handouts, posters, social media) must be approved by the Institutional Review Board (IRB) prior to use.

Recruited subjects will be screened by the principal investigator or authorized site personnel by reviewing the study's inclusion and exclusion criteria. All subjects must be consented in accordance with the protocol, and IRB requirements, prior to any study-specific procedures. Subjects who do not meet any of the inclusion or who meet exclusion criteria may not be rescreened.

9.3. Subject Consent

The informed consent process will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and with 21CFR§50 Protection of Human Subjects.

Prior to entering the study, the principal investigator or qualified designee will explain to each subject the purpose and nature of the study, procedures, expected study duration, available alternative therapies, and the benefits and risks involved with study participation and the potential treatment. Subjects will be given a copy of the IRB-approved ICF/Health Insurance and Portability and Accountability Act (HIPAA) form and any other written information. In addition, subjects will be given adequate time to review the document and to ask questions and will be informed of their right to withdraw from the study at any time without prejudice. Subjects must be able to read and comprehend the ICF written in English. After this explanation and review period, and before any study-specific procedures have been performed, the subject will voluntarily sign and date the ICF/HIPAA form. The date the subject signs the ICF/HIPAA form represents the date the subject is considered enrolled in the study; subjects are considered enrolled in the study upon signing the ICF/HIPAA.

The principal investigator, or appropriately delegated personnel, will document the informed consent process, including the date of consent and name of the person conducting the consent process in the subject's medical record. The original signed ICF/HIPAA should also be placed in the subject's medical record. Subjects must complete the informed consent process prior to any study-related procedures or testing being conducted. If the informed consent process is obtained the same day the subject begins participating in study-related procedures, it should be clearly documented in the subject's case history that consent was obtained prior to participation in any study-related procedures.

A template informed consent will be provided by Medtronic under separate cover. Any changes to the ICF template must be approved by Medtronic and the reviewing IRB prior to initiation of subject enrollment or for any changes during the study.

Any new information developed during the study which might affect the subject's understanding of the informed consent or the study, or the subject's decision to continue to participate, will be brought to the subject's attention by the principal investigator or site staff.

9.4. Study Visit Procedures

Subjects will be assessed for eligibility to the study-specific inclusion/exclusion criteria through the Baseline visit.

9.4.1. Screening Visit

The Screening visit will commence after each subject has been enrolled. Subjects who do not meet all eligibility criteria will be exited from the study.

During the Screening visit the following will be collected:

- Subject demographics
- Medical and surgical history
- Device information
- Pain medication usage

Each subject's device will be interrogated and a report session will be generated to capture the subject's initial active therapy settings.

Eligibility criteria will be evaluated to ensure subjects have a program with only 1 anode and 1 cathode with 90 µs and 1000 Hz and the group that contains the program is used ≥ 50%. Any additional programs and groups within each subject's device will be removed during this visit.

Each subject's device will be set to the program with only 1 anode and 1 cathode with 90 µs and 1000 Hz, being used upon entry into the study, for a Baseline period lasting at least 2 weeks.

A report session will be generated to capture the subject's final active therapy settings.

Subjects will be provided with a multi-day diary and asked to record their VAS pain scores for the last 7 days of the Baseline period. A telephone call will be placed to the subjects one week before they return to the clinic to remind them to begin completing the diary. Subjects should bring their completed diary with them to the Baseline visit.

9.4.2. Baseline/Programming Visit #1

The Baseline/Programming Visit #1 will be targeted to take place at least 2 weeks after the Screening visit. At the beginning of the Baseline visit, subjects will return their completed diary, complete the Subject Satisfaction Assessment (SSA), and baseline eligibility criteria will be assessed.

To proceed on with the Baseline visit, the subject must meet the following inclusion criteria:

1. Has an average overall VAS pain score ≤ 4 based on the Baseline diary

To proceed on with the Baseline visit, the subject must not meet any of the following exclusion criteria:

1. Has provided response to Baseline SSA as "Neutral", "Somewhat unsatisfied", or "Very unsatisfied" with the therapy
2. Completed less than 5 of the 7 days of the Baseline diary

Subjects who do not meet Baseline eligibility criteria will be exited from the study and will be considered a screen failure.

[redacted]

On the day of the Baseline visit, or during the course of the study, subjects must have imaging performed (eg, fluoroscopy or x-ray), which will be annotated with a vertebral marker.

Each subject's device will be interrogated and a report session will be generated to capture the subject's initial active therapy settings.

The perception threshold and description of the sensation will be collected for Setting 1 (90 µs and 1000 Hz) with subjects in both the supine and sitting positions. [redacted]

Table 3: Perception Threshold Settings

	Pulse Width	Frequency
Setting 1	90 µs	1000 Hz
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Each subject's device will be programmed with four groups at 90 µs and 1000 Hz. The active anode and cathode in each group will remain the same as what the subject used during the Baseline period and should remain the same for the duration of the study. The only difference between the four groups will be the amplitude, which will be set to 80%, 60%, 40%, and 20% of the determined amplitude perception thresholds in the sitting and supine positions with AdaptiveStim™ enabled. If subjects are unable to reach a perception threshold at 90 µs and 1000 Hz, the maximum amplitude allowed by the device (9.9 volts) will be used as the perception threshold.

Subjects will begin their first treatment period programmed to the group with 80% perception threshold and AdaptiveStim™ enabled.

At the conclusion of programming, a report session will be generated to capture the subject's final active therapy settings.

Subjects will be asked to give their patient programmer to site personnel for the remaining duration of the study. If the subject does not bring their patient programmer to the Baseline visit, the commencement of the first treatment period (80% perception threshold) will need to be postponed until the subject is able to bring their patient programmer to the site. Once a subject exits the study, their patient programmer will be returned. Subjects will be informed, although they will not have access to their patient programmer during the study, they can turn their device off using their recharger. During the study, patients may need to recharge their device more or less often and should check their device daily to verify whether recharging is needed.

Subjects will be provided a diary to record their VAS pain scores for the last week of the follow-up period prior to coming back into the clinic. A telephone call will be placed to the subjects one week before they return to the clinic to remind them to begin completing the diary.

9.4.3. Programming Visits #2, #3, and #4

Beginning approximately two weeks after the Baseline visit, in accordance with the targeted windows in Section 9.4.6, subjects will return to the clinic for Programming Visit #2 and should bring back their completed diary. After Programming Visit #2, subjects will return to the clinic about every two weeks for Programming Visits #3 and #4.

During Programming Visits #2, #3, and #4, subjects will be asked to complete the SSA to reflect their satisfaction of the last therapy setting. Subjects will also record on the SSA whether they have felt any stimulation sensations during the last follow-up period and, if so, to describe the sensation.

Each subject's device will be interrogated and a report session will be generated to capture the subject's initial active therapy settings.

With the device programmed to 90µs and 1000 Hz, the amplitude will be programmed based on the perception thresholds obtained in the supine and sitting positions during the Baseline visit as follows:

- Programming Visit #2: 60% of Baseline perception threshold
- Programming Visit #3: 40% of Baseline perception threshold
- Programming Visit #4: 20% of Baseline perception threshold

If subjects are unable to reach a perception threshold at 90 µs and 1000 Hz, the maximum amplitude allowed by the device (9.9 volts) will be used as the perception threshold.

At the conclusion of programming, a report session will be generated to capture the subject's final active therapy settings.

Subjects will be provided a diary to record their VAS pain scores for the last week of each follow-up period. Subjects should bring back their completed diary each time they return to the clinic at the end of a follow-up period. A telephone call will be placed to the subjects one week before they return to the clinic to remind them to begin completing the diary.

9.4.4. Final Study Visit

During the Final Study visit, subjects will be asked to complete the Satisfaction and Sensation Assessment (SSA).

Each subject's device will be interrogated and a report session will be generated to capture the subject's initial active therapy settings.

The perception threshold and description of the sensation will be collected for Setting 1 (90 µs and 1000 Hz) with subjects in both the supine and sitting positions. [redacted]

Table 4: Final Perception Threshold Settings

	Pulse Width	Frequency
Setting 1	90 µs	1000 Hz
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

At the end of the visit, subjects will have their patient programmers returned to them and be programmed to a setting per standard of care.

[redacted]

9.4.5. Telephone Reminders

One week prior to each programming visit, subjects will be called and reminded to begin completing the pain diary. Subjects should also be reminded to bring back their completed diary at each visit.

9.4.6. Target Windows

The following visit windows, Table 5, should be targeted when scheduling study visits. If a subject is unable to return within the target visit window, a protocol deviation will not be required if the minimum 3 days of diary data are captured sometime after the first week of the period.

Table 5: Target Visit Windows

Visit	Target Windows
Baseline/Programming Visit 1	At least 2 weeks + 7 days of Screening visit
Programming Visit 2	Within 2 weeks +/- 3 days Programming Visit 1
Programming Visit 3	Within 2 weeks +/- 3 days Programming Visit 2
Programming Visit 4	Within 2 weeks +/- 3 days Programming Visit 3
Final Study Visit	Within 2 weeks +/- 3 days Programming Visit 4

9.5. Medications

All medications prescribed for the treatment of pain will be collected during the Screening visit. Only subjects who are on stable (no change in dose, route, or frequency) prescribed pain medications for at least 4 weeks prior to screening and willing to maintain the dose during the study are eligible for participation. Any prescribed changes to a subject's pain medications while they are enrolled in the study will be collected.

9.6. Assessment of Efficacy

9.6.1. Satisfaction and Stimulation Assessment (SSA)

Subjects will be asked to indicate their satisfaction with the therapy and details pertaining to any stimulation sensations. The SSA will include questions such as the following:

- Overall how satisfied or unsatisfied are you with this therapy?
  - Very satisfied
  - Somewhat satisfied
  - Neutral
  - Somewhat unsatisfied
  - Very unsatisfied
- Specify reason for this response?

- Have you felt any stimulation sensations?
  - No
  - Yes, specify the following:
    - Occasional or Continuous
    - Pleasant or Unpleasant
    - Position when felt (lying on back, lying on front, lying on right, lying on left, mobile, reclining, upright, other)

9.6.2. Visual Analog Scale (VAS) in Pain Diary

Pain will be assessed using the VAS in a pain diary. The VAS is a 10 cm line, with "No pain" on left and "Worst pain imaginable" on the right.

Subjects will record their overall, back, and leg pain using a paper pain diary once a day for a 7-day period prior to the scheduled study visits. For the initial baseline pain diary, completed prior to the baseline visit, subjects are required to complete at least 5 of the 7 days to ensure diary compliance during the study.

For the scheduled follow-up visits, the subject will be reminded to complete the diary for a 7-day period prior to the scheduled follow-up visit and the last 3 days of the diary will be used for the assessment.

The pain diary questionnaire will consist of questions such as the following:

- Please rate your pain by making a vertical slash mark through the line that best describes your average overall pain during the last 24 hours. (Line with “No pain” on left and “Worst pain imaginable” on the right)
- Please rate your pain by making a vertical slash mark through the line that best describes your average back pain during the last 24 hours. (Line with “No pain” on left and “Worst pain imaginable” on the right)
- Please rate your pain by making a vertical slash mark through the line that best describes your average leg pain during the last 24 hours. (Line with “No pain” on left and “Worst pain imaginable” on the right)

[redacted]

[redacted]

[redacted]

[redacted]

9.7. Assessment of Safety

Safety will be evaluated by the collection of device deficiencies and adverse events related to the following:

- The implanted SCS system and accessories
- Spinal cord stimulation therapy

9.8. Recording Data

This study will use a remote data capture (RDC) system to collect study required Case Report Form (CRF) information. Electronic CRFs (eCRFs) will be provided by the sponsor; required data will be taken from source documents and directly entered into the study database via the eCRFs by the appropriately delegated site personnel, in accordance with applicable regulations. Source documentation for pain diaries and subject assessments will be captured in a paper format and completed confidentially by the subject only. Data from the paper assessments will be entered into the database by authorized site personnel.

Representatives from the clinical site may not make changes to the diaries except for administrative entries.

The principal investigator, or appropriately delegated personnel, are responsible for entering data on the eCRFs. The principal investigator, or appropriately delegated personnel, is required to approve all data on eCRFs via electronic signature.

9.8.1. Programming Data

Through device interrogations with the 8840 N'Vision® Clinician Programmer, parameter data (eg, session data files) will be collected from the neurostimulator.

Report Link is a commercially available tool, which will be used during this study that allows clinicians to electronically transfer and save session data files as a PDF document from the 8840 N'Vision® Clinician Programmer to the computer. Those PDF files can be printed to local or network printers and stored into electronic medical record systems, and uploaded into the Neuro Programmer Upload (NPU) application.

The NPU is an application designed to capture programmer interrogation output reports (eg, "session data reports") from the 8840 N'Vision Clinician Programmer and store them within a Medtronic database for analysis and reporting.

[redacted]

[redacted]

9.9. Deviation Handling

A deviation is defined as an instance(s) of failure to follow, intentionally or unintentionally, the requirements of the clinical investigation plan (CIP). The investigator is not allowed to deviate from the CIP, except under emergency circumstances to protect the rights, safety and well-being of human subjects.

Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. If the deviation affects subject's rights, safety and well-being, or the scientific integrity of the study, prior approval from IRB is also required. Prior approval is not required when a deviation is necessary to protect the safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g. subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness).

All study deviations must be reported on the eCRFs regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency.

Study deviations must be reported to Medtronic as soon as possible upon the site becoming aware of the deviation. Reporting of deviations must comply with IRB policies, local laws, and/or regulatory agency requirements.

Medtronic is responsible for reviewing deviations, assessing the effectiveness of the CIP, confirming appropriate deviation reporting requirements are met, identifying site trends that require action. Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and site, and in some cases, necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study.

9.10. Subject Withdrawal or Discontinuation

A subject has the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the principal investigator or institution. Subjects will be provided standard medical care by their physician after their study participation ends.

The study sample size accounts for expected attrition, thus exited subjects will not be replaced.

Examples of reasons for study exit include the following:

- Subject death
- Subject lost to follow-up
- Subject voluntarily withdraws from the study
- Subject becomes pregnant
- Investigator terminates the subject's participation in the study due to lack of compliance, violation of/change in eligibility criteria
- Any clinical laboratory abnormality, inter-current illness, or other medical condition or situation occurs such that continued study participation would not be in the best interest of the subject
- Normal study completion

A study exit eCRF will be completed for all enrolled subjects; the reason for withdrawal shall be recorded on the study exit eCRF. If a subject exits from the study prior to normal completion, the eCRFs for visits that have occurred up to the point of withdrawal as well as the study exit eCRF should be completed. If a subject exits due to an adverse event or device deficiency, the appropriate event eCRFs should also be completed.

If the subject proceeds beyond the Baseline/Programming Visit #1 but chooses to withdraw from the study early; if they are willing, the Final Study Visit procedures may be completed prior to study exit.

If a subject requires a system modification or replacement during the study, they should be exited from the study.

In the case that the subject is determined to be lost to follow-up, details of a minimum of two attempts and the method of attempt (e.g., one letter and one phone record or two letters) to contact the subject must be recorded in the subject's medical records. In addition, regulations set forth by the governing IRB must be followed.

10. Risks and Benefits

10.1. Potential Risks

This is a post-market study and subjects will be treated in accordance with the labeled instructions for use and indications for Medtronic's SCS therapy. There are foreseeable risks that exist for all SCS patients regardless of whether they are in the study. There are no expected new or increased risks associated with this clinical study.

10.1.1. Foreseeable Risks

10.1.1.1. Spinal Cord Stimulation Adverse Events Summary

The implantation of a spinal cord stimulation system involves risks that are similar to other spinal procedures. In addition to those normally associated with surgery, implantation or use of a

neurostimulation system includes, but is not limited to, the following risks:

- Allergic or immune system response to the implanted materials
- Infection
- Lead, extension, or neurostimulator erosion through the skin or migration
- Leakage of cerebrospinal fluid
- Loss of pain relief may return patients to their underlying pain condition
- Patients on anticoagulation therapies may be at greater risk for postoperative complications such as hematomas that can result in paralysis
- Persistent pain at the neurostimulator site
- Placement of the epidural lead-extension is a surgical procedure that may expose patients to risks of epidural hemorrhage, hematoma, or paralysis
- Radicular chest wall stimulation
- Seroma or hematoma at the neurostimulator site
- Stimulation-dependent gastrointestinal symptoms such as diarrhea, incontinence or constipation
- Stimulation-dependent bladder symptoms such as urinary retention, incontinence or frequency
- Change in stimulation, possibly related to cellular changes around the electrode(s), shifts in electrode position, loose electrical connections, lead or extension fractures, which has been described by some patients as uncomfortable stimulation (jolting or shocking sensation).
- Formation of reactive tissue around the lead in the epidural space can result in delayed spinal cord compression and paralysis, requiring surgical intervention. Time to onset can range from weeks to many years after implant.
- The safety and effectiveness of this therapy has not been established for pregnancy, unborn fetus, or delivery. The study procedures may involve unknown risks for female subjects, their embryo or fetus (unborn child), or delivery if they become pregnant. For this reason, pregnant females have been excluded from participating in this study. Female subjects must agree to not become pregnant during the study by using a medically acceptable method of birth control; an identified pregnancy will result in immediate study withdrawal.

10.1.1.2. Device Deficiencies Risks

The use of SCS systems includes risk of the following device deficiencies:

- Mechanical failure/damage of system components, eg, premature battery depletion, lead fracture (increased impedance), or breach of insulation
- Migration or dislodgement of the lead(s)
- Migration, dislodgement, or flipping of the neurostimulator
- Programming and/or telemetry problems that might limit the capability to program or determine what parameters are programmed
- Potential coupling or telemetry problems during recharging may cause inconsistency or limit battery charge restoration

- Over-discharge of the neurostimulator battery may shorten battery life, permanently damage the battery, and/or result in the need for a replacement
- Premature battery depletion resulting in the need for a replacement

10.1.1.3. Risks Associated with the Recharging System

- The recharger, antenna, belt and holster are not sterile, and contact with the wound could cause an infection. The recharger is not intended to be used on an unhealed wound.
- Use of rechargeable neurostimulation systems may be associated with adverse events including heating sensation, discomfort, blistering not caused by heating, skin irritation, or redness near the implanted neurostimulator during or after recharging. Patients should check for skin irritation or redness near the neurostimulator during or after recharging.

[redacted]

10.1.1.5. Additional Risks and Information

Additional information including precautions, warnings, and contraindications is included within the packaged labeling of each system component.

Parameters used during the study may not be effective. Additionally, because the amplitude level will be titrated down, some subjects may not receive effective therapy after a certain threshold is reached, which could result in an increase level of pain. Furthermore, prescribed pain medications should remain stable (no change in dose, route, or frequency) during the study.

Depending on the programmed parameters the subject was using when they entered the study, it is possible subjects may need to recharge more frequently during one or more treatment periods.

There may be additional risks related to this study, other than the ones described, that are not yet known.

10.1.1.6. Mitigation of Risks

At any time during the study, subjects will be able to turn their device OFF using their Patient Recharger. Furthermore, a subject has the right to withdraw from the study at any time and for any reason (eg, due to insufficient pain relief).

10.2. Potential Benefits

There may be no direct benefit from participation in the study. The SCS settings used during this study may reduce subjects' pain intensity, return subjects to a more fully functional status, and/or improve their quality of life. Additionally, with stimulation delivered at sub-perception threshold amplitudes, subjects may avoid uncomfortable or even intolerable stimulation sensations, such as painful paresthesia. During the study subjects will have increased interaction with physicians or medical staff compared to routine clinical care, which may provide some indirect health benefits. Another possible benefit for participating in this study may be a reduction in the number of required recharging sessions for individual subjects.

Data from this study may have the anticipated benefit of helping Medtronic with the understanding of SCS therapy and assisting with the design of future studies and product improvements. The information gathered from this study could also help clinicians optimize therapy for their patients.

10.3. Risk-Benefit Rationale

Neurostimulation therapies, such as SCS, are used as an aid in the management of chronic, intractable pain that cannot be effectively managed with medications and/or other conservative treatments alone. Patients considered for neurostimulation therapy have typically had pain of long duration and have failed multiple therapeutic paths.

Medtronic has carefully designed and tested the RestoreSensor® Neurostimulation Systems for the approved indications. Medtronic has completed an extensive risk analysis to ensure the identification of potential hazards and subsequent mitigation of these hazards to eliminate them entirely or reduce them to an acceptable level. With existing PMA approval for the commercially available RestoreSensor® Neurostimulation Systems, an established safety profile of probable benefit outweighing risk already exists for SCS Therapy for chronic low back and/or leg pain. In most cases SCS is a reversible procedure that can be turned off or removed. Moreover, stimulation parameters are adjustable to minimize or reverse complications and maximize therapeutic effects.

The study investigates the relationship between amplitude dose, therapy satisfaction, and pain relief in subjects being actively treated with SCS using HD parameters (90 µs and 1000 Hz). The system output and programming parameters used with the SCS Dosing study are within the approved ranges of the commercially available RestoreSensor® Neurostimulation Systems. The anticipated benefits of the clinical outcomes of SCS therapy per the study design outweigh the overall risk.

11. Adverse Events and Device Deficiencies

11.1. Definitions

Adverse Event (AE): (ISO 14155:2011 3.2)
Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

NOTE 1: This definition includes events related to the investigational medical device or the 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 investigational medical devices.

Adverse Device Effect (ADE): (ISO 14155:2011 3.1)
Adverse event related to the use of an investigational medical device.

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or 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): (ISO 14155:2011 3.37)
Adverse event that

a) led to death,
b) led to serious deterioration in the health of the subject, that either resulted in
   1) a life-threatening illness or injury, or
   2) a permanent impairment of a body structure or a body function, or
   3) in-patient or prolonged 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) led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Device Effect (SADE): (ISO 14155:2011 3.36)
Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE): (ISO 14155:2011 3.42)
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: 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 (DD): (ISO 14155:2011 3.15)
Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

NOTE: Device deficiencies include malfunctions, use errors, and inadequate labeling.

Malfunction: (ISO 14155:2011 3.27)
Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP.

Use Error: (ISO 14155:2011 3.43)
Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

NOTE 1: Use error includes slips, lapses, and mistakes.

NOTE 2: An unexpected physiological response of the subject does not in itself constitute a use error.

11.2. Classifications

Each adverse event is classified according to ISO 14155:2011. Where the definition indicates “device”, it refers to any device used in the study. This might be the device under investigation, or any market released component of the system.

All reportable adverse events will be classified using the responsibility matrix in Table 6.

Table 6: Event Classification Responsibilities

What is Classified	Who Classifies	Classification Parameters
Relatedness	Investigator	Therapy related Device related
Seriousness	Investigator	SAE/SADE
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Medtronic	MedDRA term assigned based on the data provided by investigator

11.3. Recording of Adverse Events

Adverse Event (AE) information will be collected from the time the subject has been enrolled until they are discontinued from the study. AE information will be reported to Medtronic on an adverse event eCRF, one for each Adverse Event.

Only those AEs which are related to the following will be collected:

- The implanted SCS system and accessories
- Spinal cord stimulation therapy

It is the responsibility of the investigator to identify the occurrence of adverse events and device deficiencies and to ensure all required information is accurately documented on the eCRF. See the eCRFs for the information to be reported for each adverse event.

Documented pre-existing conditions are not considered adverse events unless the severity of the condition has worsened and is related to the implanted SCS system, accessories, or therapy.

For adverse events that require immediate reporting, initial reporting may be done by phone, fax, or e-mail, or on the eCRF by completing as much information as is available. The adverse event eCRF must be completed as soon as possible.

In case the investigator requires information from the sponsor in an emergency, the investigator can contact the Medtronic study team using the contact details provided in Section 11.6.

The clinical course of each adverse event must be followed until the adverse event is resolved or the subject is in a stable condition. “Ongoing” adverse events must be assessed at each study visit. The adverse event eCRF should to be updated when there is a change to the information provided on the form (e.g. change in intervention, outcome, relatedness, etc.).

11.4. Recording of Device Deficiencies

Device deficiencies are events associated with a medical device that do not result in an adverse event for the subject. Device deficiency information will be collected throughout the study and reported to Medtronic on a device event eCRF, one for each device deficiency.

11.5. Reporting of Adverse Events and Device Deficiencies

It is the responsibility of the Investigator to abide by the adverse event reporting requirements and to also follow the reporting requirements of the IRB. Unanticipated Serious Adverse Device Effects (USADE), must be reported to Medtronic within 24 hours of the effect, and to the IRB as required.

11.6. Emergency Contact Details

In case of an emergency or to immediately report an Adverse Event, the investigators can contact the study team [redacted]

11.7. Deaths

The investigator must notify Medtronic immediately and the IRB, as required, after learning of a subject's death, regardless of whether or not the death is related to the device system or therapy. The investigator should also attempt to determine, as conclusively as possible, whether such deaths are related to the device system or therapy. If the death is evaluated as device-related or therapy-related, and unanticipated, the event will be reported as an USADE by Medtronic to the FDA. Deaths will be captured by a study exit eCRF and an adverse event eCRF if related to the device system or therapy.

If an autopsy is conducted, a copy of the report should be provided to Medtronic. Medtronic requests that all device system components that were being used at the time of the death be returned to Medtronic for analysis per Section 7.2. Requested death certificates and/or source documentation should be provided to Medtronic. If the death occurs at a location remote from the study site, it is the study site's responsibility to make every attempt to retrieve all pertinent information related to the subject's death and submit the investigator's death summary of the known events surrounding the death to Medtronic.

12. Data Review Committees

This study will not use a Clinical Events Committee or Data Monitoring Committee. Instead, all reported adverse events and device deficiencies will be reviewed by a Medtronic Medical Advisor to ensure consistent reporting. Regular meetings will be held by Medtronic personnel, including the Medical Advisor, to review adverse events and identify potential trends in safety data during the clinical study.

13. Statistical Design and Methods

13.1. General Statistical Considerations

Data analysis will be performed by Medtronic-employed statisticians or designees. A validated statistical software package will be used for the analyses of the study results (e.g., SAS).

The Statistical Analysis Plan (SAP) will be developed prior to data analysis and will include a comprehensive description of the statistical methods and reports to be included in the final study report. Any change to the data analysis methods described in the CIP will require an amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP, and the justification for making the change, will be described in the clinical study report.

13.1.1. Sample Size Justification

An estimated 60 subjects will be enrolled in order for at least 40 subjects to proceed beyond the Baseline visit. A sample size of 40 subjects is reasonable to characterize the distribution of the minimum amplitude as a percentage of perception threshold that maintains SCS therapy satisfaction, as well as to provide data for consideration of future studies.

13.1.2. Investigation Site Pooling

The investigators of this study will conduct the study according to a common protocol and use the same CRFs to collect study data. The site study personnel will be trained prior to the study initiation at each site. Periodic study monitoring by Medtronic will ensure compliance with protocol requirements.

There is no a priori provision to exclude any sites from the analysis. The data from all sites will be pooled for analysis. To reduce the possibility of atypical results from a site overly influencing the combined results, no more than 30 subjects will be enrolled at each site.

13.1.3. Other Specific Considerations

Adjustment for Baseline Covariates

There is no plan to make adjustment for baseline covariates for the primary objective.

Handling Missing Data

Missing data are a potential source of bias when analyzing study data. A rigorous study design and execution will help prevent the incidence of missing data from occurring.

The analysis of the primary and secondary objectives will use subjects who provide data.

Adjustment for Multiple Endpoints

As there is no hypothesis testing, adjustment for multiple endpoints is not required.

Interim Analysis

There is no planned interim analysis for the primary and secondary objectives in this study.

13.1.4. Reports

[redacted]

13.2. Demographics

Demographics and baseline characteristics will be summarized in the report for all subjects who complete the Baseline visit and meet the Baseline eligibility requirements.

13.3. Primary Objective

To characterize the minimum amplitude as a percentage of perception threshold that maintains SCS therapy satisfaction.

13.3.1. Hypothesis

There is no hypothesis testing for the primary objective. The purpose of the primary objective is to characterize the minimum amplitude that maintains SCS therapy satisfaction.

13.3.2. Experimental Design

The measurement of SSA is described in Section 9.6.1. Subject dissatisfaction with the therapy is defined as subjects choosing either 'somewhat unsatisfied' or 'very unsatisfied'. The SSA is collected at baseline and scheduled follow-up visits.

13.3.3. Analysis Methods and Presentation Format

The frequency and percentage of subjects satisfied with the therapy will be summarized at baseline and scheduled follow-up visits. The percentage of amplitude from perception threshold for maintaining subjects' satisfaction with the therapy will be summarized too.

13.3.4. Determination of Subject for Analysis

Subjects who provide data will be included in the analysis.

13.4. Secondary Objective

To characterize the minimum amplitude as a percentage from perception threshold that maintains overall pain relief. Maintaining overall pain relief is defined as having ≤ 2 points increase in average overall pain VAS during study follow-up.

13.4.1. Hypothesis

There is no hypothesis testing for the secondary objective. The purpose of the secondary objective is to characterize the minimum amplitude that maintains overall pain relief of equal or less than 2 points increase in average overall VAS pain scores.

13.4.2. Experimental Design

The measurement of pain score is described in Section 9.6.2. For baseline, an average overall VAS pain score is calculated using all 7 days of the diary. For scheduled follow-up visits, an average overall VAS pain score is calculated using the last 3 days of the diary prior to the scheduled visit, to ensure that there

is no residual treatment effect from the previous period. The pain scores are collected at baseline and scheduled follow-up visits.

13.4.3. Analysis Methods and Presentation Format

The mean and standard deviation of the pain score will be summarized at each follow-up visit. The percentage of amplitude from perception threshold for maintaining overall pain relief will be summarized.

13.4.4. Determination of Subject for Analysis

Subjects who provide data will be included in the analysis.

13.5. Additional Objectives

[redacted]

13.6. Safety Objective

To characterize therapy and device related adverse events and device deficiencies.

13.7. Statistical Result Presentation

Statistical results will be presented in the reports according to the standard clinical study report template.

14. Ethics

14.1. Statements of Compliance

The study will be conducted in accordance with this protocol, the ethical principles that have their origin in the Declaration of Helsinki, all applicable regulatory requirements (21CFR§50 Protection of Human Subjects, 21CFR§56 IRB, and 21CFR§54 Financial Disclosure of Clinical Investigators, and 21CFR§803 Medical Device Reporting) and will comply with Good Clinical Practices (GCP) as a guideline for this study. The principles of the Declaration of Helsinki have been implemented in this study by means of the patient informed consent process, IRB approval, risk benefit assessment, study training, clinical trial registration on http://clinicaltrials.gov/, and publication policy. Study Investigators will be required to sign an Investigator Agreement stating their intent to adhere to applicable regulations.

The study will not begin at any site until an IRB letter approving the protocol, the ICF, and any other subject-facing documents is received by Medtronic.

Details related to stipends provided to study subjects are outlined in the subject ICF.

15. Study Administration

15.1. Monitoring

Medtronic is responsible to the regulatory agencies for ensuring the proper conduct of this study in terms of adherence to applicable regulations, protocol compliance, and the validity and accuracy of the study data entered on eCRFs. Medtronic will assign Medtronic personnel, or designee, as monitors to aid in ensuring study staff understanding of the applicable regulations, and to assess and ensure principal investigator and study staff's understanding of the protocol, reporting requirements, and data validity. The principal investigator and study staff will provide the Medtronic monitors with complete and direct access to primary source data (eg, paper and electronic hospital/clinical charts, appointment books, laboratory records) that support the data on the eCRFs as well as other documentation supporting the conduct of the study. Monitors will perform source data verification and routine reviews of study-related regulatory documents during scheduled monitoring visits and work to secure compliance should any deficiencies be observed.

15.2. Medtronic Representative Role

Medtronic representatives who are qualified and trained on the protocol and applicable study regulations may participate in the conduct of the study under the direct supervision of the principal investigator as described below. The principal investigator, or delegated personnel, must be present to collect source documentation, record the study activities, and to be responsive to the subject's needs during an activity performed by a Medtronic representative.

Medtronic personnel may perform the following:

- Provide technical support during follow-up visits
- Perform device programming, device interrogation, device download while under the direction of the investigator
- Discuss any issues with programming or subject compliance with the principal investigator or site personnel

Medtronic personnel may not perform the following:

- Practice medicine, provide medical diagnoses or make decisions related to subject treatment/care
- Express opinions about the product under study
- Assist the subject by direct physical contact except as required by the specific protocol-related task to be conducted
- Discuss a subject's condition or medical treatment with the subject or a member of the subject's family
- Provide the subject with any form/questionnaires related to the products under investigation
- Enter data on eCRFs, except for administrative Medtronic use only forms

15.3. Data Management

This study will use the Oracle Clinical Remote Data Capture (RDC) system, which allows the study centers to enter data directly to the eCRF in the sponsor's database over a secure internet connection. This system controls user access, ensures data integrity, and maintains audit trails. It is a fully validated system.

The principal investigator will ensure that only appropriately delegated study personnel are given access to the electronic eCRF system; user IDs and passwords may not be shared.

The principal investigator is responsible for the overall quality (completeness and accuracy) of the data entered on the eCRFs and in all other required reports. Data reported on the eCRFs, must be derived from and consistent with source documents, unless otherwise stated in this section or the study monitoring plan. If discrepancies in source are identified (eg, during monitoring), these need to be corrected or justified in a documented rationale, signed and dated by the principal investigator, or authorized delegate, to be maintained as a part of the subject's records. The principal investigator will review all data entries on a regular basis and ensure any corrections are appropriately made and documented.

The eCRF may be considered source for the following data collection elements:

- Investigator assessment of adverse event relatedness
- Detail pertaining to and reason for protocol deviation

Even when the eCRF may be considered as source, an alternative method of source documentation is always strongly encouraged.

Required data will be recorded on the appropriate eCRFs at the time of or promptly after each subject's visit. Only authorized persons can complete eCRFs. eCRFs will be approved by the principal investigator, or authorized delegate with an electronic signature.

Medtronic personnel will perform routine edit and consistency checks, in-house and during monitoring visits, for items such as missing data or inconsistent data. Identified data inconsistencies will be resolved by use of data queries; investigators and site personnel will review data queries and respond to them in a timely manner. The resolved discrepancy will become a part of the eCRF record for the subject. At the end of the study, the data will be frozen and will be retained indefinitely by Medtronic.

User access to the RDC system will be granted to each individual based on his or her delegation of authority. If a person only authorized to complete eCRFs makes changes to an already signed eCRF, the system will require the investigator, or authorized delegate, to re-sign the eCRF.

15.4. Direct Access to Source Data/Documents

Source data are defined as all information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation necessary for the reconstruction and evaluation of the clinical investigation. A source document is a printed, optical, or electrical document containing source data. Examples of source documents include the following: hospital records, laboratory notes, device accountability records, photographic negatives, radiographs, records kept at the investigational site, and at laboratories involved in the clinical investigation.

The principal investigator is responsible for ensuring source data and documents are complete, legible and accurate; and entries are made in a timely manner by appropriately delegated study staff.

The principal investigator and site personnel will provide the Medtronic monitor(s) with direct access to source data that support the data on the CRFs as well as other documentation supporting the conduct of the study.

Medtronic or third-party auditors representing Medtronic may perform Quality Assurance audits to verify the performance of the monitoring process and study conduct, and to ensure compliance with applicable regulations. Representatives for regulatory bodies, such as the FDA, may also perform site inspections related to this clinical study. The principal investigator, site personnel, and institution will provide auditors with direct access to primary source data and all study-related documentation.

Medtronic will investigate suspected cases of fraud or misconduct as appropriate.

15.5. Confidentiality

All records and other information about subjects participating in this clinical study will be treated as confidential. Subject confidentiality will be maintained throughout the clinical study to the extent permitted by law. That is, every attempt will be made to remove subject identifiers from clinical study documents. For this purpose, a unique subject identification code (study - site - subject number) will be assigned and used to allow identification of all data reported for each subject. This will also ensure that the information can be tracked back to the source data.

Study data may be made available to third parties, e.g., in the case of an audit or inspection performed by regulatory authorities, provided the data are treated confidentially and that the subject's privacy is guaranteed. The identity of a subject will never be disclosed if study data are published. Only anonymized data will be analyzed and published.

15.6. Liability

Medtronic, Inc. is a wholly owned subsidiary of Medtronic, PLC, which as the parent company of such entity maintains appropriate clinical study liability insurance coverage, as applicable and as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the IRB. In addition, subject compensation, indemnification, and insurance may be addressed within a separate clinical trial agreement.

15.7. CIP Amendments

Amendments to the CIP may be initiated by Medtronic to address changes to the conduct of the study.

Amendments to the CIP, and associated documents, must be approved by Medtronic and submitted to the IRBs for approval prior to implementation except when necessary to eliminate an immediate or apparent immediate hazard to participating subjects.

15.8. Required Reports and Records

15.8.1. Investigator Records

Documentation for this study will be produced and maintained to ensure that a complete history of the study exists. Documents created for this study, including all versions of original documents, will be identifiable and appropriately stored to assure control and traceability of data related to this study.

The principal investigator is responsible for the ensuring that all essential study documentation is retained and accessible for 2 years (or longer as local law or hospital administration requires) after the

investigation is terminated or completed. The retention period may be longer if required by Medtronic or regulatory requirements. Medtronic will be responsible for notifying sites of extensions to the 2-year minimum record retention requirements. The principal investigator will ensure that essential study documents are not destroyed until written permission has been obtained from Medtronic. Medtronic will be notified in writing of any transfer of study documentation.

15.8.2. Investigator Reports

The principal investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, reportable adverse events, device deficiencies, deaths, and any deviations from the CIP. If any action is taken by an IRB with respect to this clinical study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described in Section 15.8.1 for investigator records.

15.9. Publication and Use of Information

[redacted]

[redacted]

15.10. Suspension or Early Termination

Early termination is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single center. Suspension is a temporary postponement of study activities related to enrollment. This is possible for the whole study or a single center.

Medtronic reserves the right to suspend or terminate the study or an individual study site at any time.

Possible reasons for considering study suspension or termination of the study include but are not limited to:

- Adverse events associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic

Possible reasons for clinical investigator or center termination or suspension include but are not limited to:

- Failure to obtain initial IRB approval or annual renewal of the study
- Persistent non-compliance to the clinical study CIP (e.g. failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups)
- Lack of enrollment
- Noncompliance to regulations and the terms of the clinical trial agreement (e.g. failure to submit data in a timely manner, failure to follow-up on data queries and monitoring findings in a timely manner, etc.)
- IRB suspension of the center
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)

- Investigator request (e.g. no longer able to support the study)

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17. Appendices

There are no appendices within this clinical investigational plan.

18. Version History

Version	Summary of Changes	Author(s)/Title
[redacted]	[redacted]	[redacted]