Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	Spinal Cord Stimulation (SCS) Research Study
Clinical Investigation Plan Identifier	MDT18036 / NCT03763708
Study Product Name	Medtronic Implantable Neurostimulation Systems
Sponsor/Local Sponsor	Medtronic, Inc 7000 Central Ave NE Minneapolis, Minnesota, 55432 U.S.A. +1-763-514-4000
Document Version and date	3.0, 06 June 2022

Confidentiality Statement

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
CRPS	Complex Regional Pain Syndrome
DD	Device Deficiency
DDD	Degenerative Disk Disease
eCRF	Electronic Case Report Form
[redacted]	[redacted]
FBS	Failed Back Syndrome
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HCO	Health Care Organization
HCP	Health Care Professional
HIPAA	Health Insurance Portability and Accountability Act
Hz	Hertz
IC/ICF	Informed Consent/Informed Consent Form
IRB	Institutional Review Board
ISO	International Organization for Standardization
µs	Microseconds
mA	Milliamps
[redacted]	[redacted]
EDC	Electronic Data Capture
RSD	Reflex Sympathetic Dystrophy
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCS	Spinal Cord Stimulation
[redacted]	[redacted]
V	Volts

3. Synopsis

Title	Spinal Cord Stimulation (SCS) Research Study
Clinical Study Type	Post-market
Product Name	Medtronic Implantable Neurostimulation 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/or limbs.
Investigation Purpose	To characterize the effects of stimulation parameters on pain relief and other cohort specific outcomes.
Product Status	All devices used in this study are commercially available and will be used within the intended approved indication.
Primary Objective	To characterize the pain scores, specific to the indication associated with SCS implant, with different SCS parameters.
[redacted]	[redacted]
Study Design	This is a prospective, multi-center, post-market study to characterize the effects of stimulation parameters on pain relief, [redacted] It is estimated that up to 360 subjects will be enrolled [redacted] in the United States. [redacted] The overall study duration, from first subject enrollment to last subject visit, is expected to last approximately 10 years. Multiple on-label stimulation parameters will be studied throughout the execution of this clinical investigational plan. [redacted]

	[redacted] A study cohort is defined as a group of subjects who share the same recommended programming parameters and follow-up visit cadence. [redacted] The longer enrollment period enables the research of SCS parameters over time as the science and technology in SCS develops. [redacted] he completion of the study is defined as the approval of the Final Clinical Study Report and closure of all sites.
Sample Size	It is estimated that up to 360 subjects will be enrolled. Considering the research interests in multiple stimulation settings and longer enrollment of the study, a sample size of up to 360 subjects is deemed to be reasonable to characterize the effects of changes to stimulation settings, as well as to provide data for consideration of future studies. The sample size for each on-label programming parameter group may vary based on the research interest.
Inclusion/Exclusion Criteria	<u>Inclusion Criteria:</u> 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 Medtronic neurostimulation system, for a labeled indication, and expected longevity of neurostimulator is at least 16 months 3. Willing and able to provide signed and dated informed consent 4. Capable of comprehending and consenting in English 5. Willing and able to comply with all study procedures and visits 6. Able to differentiate between pain associated with the indication for SCS implant and other types of pain, as determined by the investigator, or designee [redacted] <u>Exclusion Criteria:</u> To be included in this study, a patient must not meet any of the following exclusion criteria:

	1. Implanted with neurostimulation system for an off-label indication 2. Currently enrolled or planning to enroll in an interventional clinical study that could potentially confound the study results (co-enrollment in an interventional study is only allowed when documented pre-approval is obtained from the Medtronic study manager, or designee) 3. If female, pregnant or is of child-bearing potential and unwilling to use a medically acceptable form of birth control during the study 4. Has untreated major psychiatric comorbidity, as determined by the investigator, or designee 5. Has a non-rechargeable neurostimulator where the battery longevity is not able to be estimated with the battery longevity calculator
Study Procedures and Assessments	Upon obtaining informed consent, each subject will complete an Enrollment Visit [redacted] The following measures may be used during the study: [redacted]
Safety Assessments	Subjects will be assessed from enrollment through the end of the study for adverse events related to the following: • The SCS system and accessories (device-related) • SCS therapy (therapy-related) • SCS procedure (procedure-related) In addition, all device deficiencies reported during the study will be collected.

Statistics	Descriptive statistics will be reported for the primary [redacted] objectives. In addition, the statistical approach may vary based on the research question to be addressed in each cohort [redacted] Where applicable, hypothesis testing may be performed to characterize change from baseline. Hypothesis testing may not be performed on all cohorts. Sample sizes in cohorts with hypothesis testing will be estimated based on at least 80% power with a significance level of 0.05 for two-sided tests or 0.025 for one-sided tests. Sample sizes in cohorts with no hypothesis testing may vary depending on the research questions to be addressed. Device, procedure, and therapy related adverse events and device deficiencies will be presented in summary tables. [redacted]

4. Introduction

This post-market clinical study will be conducted with up to 40 sites and include subjects treated with SCS, consistent with FDA approved indications and instructions for use, using programming parameters within the capabilities of approved SCS devices. It is estimated that up to 360 subjects will be enrolled. [redacted] 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.

4.1 Background

Spinal cord stimulation (SCS) has been proven to be an effective therapy for pain relief. Three parameters are programmed to deliver stimulation in SCS systems: pulse width (µs), frequency (Hz), and amplitude (mA or V). Pulse width determines the number of neurons targeted for therapy; while

frequency affects the quality or feeling of the neurostimulation. Amplitude controls the stimulation intensity and may be adjusted above or below sensory perception thresholds. Most clinical trials are conducted using a range of parameters rather than a specific parameter set; therefore, no conclusions can be made about specific parameters.

Pulse width is the duration of each electric impulse in microseconds. As the duration of the stimulus increases, an increase in the recruitment of nerve fibers occurs. Limited clinical research has been conducted on pulse width optimization in SCS. In one single-blinded, prospective study, Yearwood et al. (2010) surveyed pulse widths from 50 to 1000 µs in 19 back pain subjects. Approximately 37% of subjects selected to increase their pulse width values as compared to their original program and the median pulse width of all final programs was 400 µs.[1] Abejon et al. (2015) conducted a clinical study examining 46 subjects programmed at a fixed frequency of 50 Hz and pulse widths between 50 - 1000 µs. Subjects achieved the best degree of satisfaction at pulse width 331.27+/- 227 µs and were dissatisfied at pulse widths exceeding 700 µs. Subjects preferred pulse widths ranging from 320-500 µs which agrees with the Yearwood study for support of longer pulse widths within the conventional range.[2]

Frequency or rate of stimulation is a parameter that may be modulated to produce different analgesic outcomes.[3] While the range of frequencies for most rechargeable implantable SCS devices (e.g., Medtronic RestoreSensor) is 2 – 1200 Hz, the conventional stimulation frequencies range from 50 to 120 Hz.[4] Since 2010, there has been a focus on using higher frequencies (1000 Hz -10 kHz) for stimulation; for which, there are publications reporting significant pain relief.[5,6] Several small studies have explored the upper limits of conventional SCS frequencies, 1000- 1200 Hz, and have reported that subjects who have lost pain relief from conventional SCS at lower frequencies could have pain relief restored at these

[1] Yearwood TL1, Hershey B, Bradley K, Lee D. Pulse width programming in spinal cord stimulation: a clinical study. Pain Physician. 2010 Jul-Aug;13(4):321-35.
[2] Abejón D1, Rueda P, del Saz J, Arango S, Monzón E, Gilsanz F. Is the introduction of another variable to the strength-duration curve necessary in neurostimulation? Neuromodulation. 2015 Apr;18(3):182-90; discussion 190. doi: 10.1111/ner.12223. Epub 2014 Aug 29.
[3] Miller JP, Eldabe S, Buchser E, Johanek LM, Guan Y, Linderoth B. Parameters of Spinal Cord Stimulation and Their Role in Electrical Charge Delivery: A Review. Neuromodulation. 2016; 19:373-384.
[4] Abejón D1, Cameron T, Feler C, Pérez-Cajaraville J. Electric parameters optimization in spinal cord stimulation. Study in conventional nonrechargeable systems. Neuromodulation. 2010 Oct;13(4):281-6; discussion 286-7. doi: 10.1111/j.1525-1403.2010.00290.x.
[5] Al-kaisy A, Palmisani S, Pang D, Sanderson K, Wesley S, Tan Y, McCammon S, Trescott A. Prospective, Randomized, Sham-Control, Double Blind, Crossover Trial of Subthreshold Spinal cord Stimulation at Various Kilohertz Frequencies in Subjects Suffering from Failed Back Surgery Syndrome (SCS Frequency Study). Neuromodulation. 2018 Jul;21(5):457-465.
[6] Kapural L, Yu C, Doust MW, Gliner BE, Vallejo R, Sitzman BT, Amirdelfan K, Morgan DM, Brown LL, Yearood TL, Bundschu R, Burton AW, Yang T, Benyamin R, Burgher AH. Novel 10-kHz High-Frequency Therapy (HF10 Therapy) Is Superior to Traditional Low-frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: The SENZA-RCT Randomized Controlled Trial. Anesthesiology. 2015 Oct; 123(4):851-60.

higher frequencies.[7, 8, 9] In the PROCO study, a published randomized controlled trial, Thompson et al (2017) showed equivalent pain relief for 1, 4, 7, and 10 kHz frequencies.[10]

Studies have tested sub-perception stimulation amplitudes, but maintained traditional frequency ranges (60 – 85 Hz) and pulse widths (210-390 µsec) in small groups of subjects or case reports.[11, 12, 13] In one small case series of neuropathic pain, parameters set at conventional frequency and pulse width settings at sub-perception amplitudes relieved neuropathic pain better than no stimulation but were less effective than supra-threshold stimulation. Recently, new programming algorithms claim to be effective at sub-perception amplitudes, but these algorithms include high frequencies[14, 15, 16] or long pulse widths.[17, 18] To date, there are no studies with a focus on surveying the range of amplitudes.

In addition, the recent studies evaluated various 'cycling' or 'pulsing' techniques wherein the stimulation paradigms are cycled on and off for specific times to improve battery longevity for non-rechargeable devices and time between recharges for rechargeable devices. This promising new approach has yet to be well characterized or understood as to which cycling parameters are the most efficacious. In conclusion, neurostimulators have the ability to stimulate in a wide range of on-label parameter settings; however, more can be understood about the effects of these parameters on patient pain relief or physiologic processes that are ultimately related to patient benefits. This study explores the on-label parameters to determine these effects.

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[7] Smith H1, Youn Y, Pilitsis JG. Successful use of high-frequency spinal cord stimulation following traditional treatment failure. Stereotact Funct Neurosurg. 2015;93(3):190-3. doi: 10.1159/000380825. Epub 2015 Apr 1.

[8] North JM1, Hong KJ2, Cho PY3. Clinical Outcomes of 1 kHz Subperception Spinal Cord Stimulation in Implanted Patients With Failed Paresthesia-Based Stimulation: Results of a Prospective Randomized Controlled Trial. Neuromodulation. 2016 Oct;19(7):731-737. doi: 10.1111/ner.12441. Epub 2016 May 17.

[9] Youn Y1, Smith H, Morris B, Argoff C, Pilitsis JG. The Effect of High-Frequency Stimulation on Sensory Thresholds in Chronic Pain Patients. Stereotact Funct Neurosurg. 2015;93(5):355-9. doi: 10.1159/000438998. Epub 2015 Oct 8.

[10] Thomson SJ1, Tavakkolizadeh M2, Love-Jones S3, Patel NK4, Gu JW5, Bains A6, Doan Q5, Moffitt M5. Effects of Rate on Analgesia in Kilohertz Frequency Spinal Cord Stimulation: Results of the PROCO Randomized Controlled Trial. Neuromodulation. 2018 Jan;21(1):67-76. doi: 10 1111/ner.12746. Epub 2017 Dec 8.

[11] Benyamin R1, Kramer J, Vallejo R. A case of spinal cord stimulation in Raynaud's Phenomenon: can subthreshold sensory stimulation have an effect? Pain Physician. 2007 May;10(3):473-8.

[12] Eddicks S, Maier-Hauff K, Schenk M, Müller A, Baumann G, Theres H. Thoracic spinal cord stimulation improves functional status and relieves symptoms in patients with refractory angina pectoris: the first placebo-controlled randomised study. Heart. 2007 May;93(5):585-90. Epub 2007 Jan 19.

[13] Wolter T1, Kiemen A, Porzelius C, Kaube H. Effects of sub-perception threshold spinal cord stimulation in neuropathic pain: a randomized controlled double-blind crossover study. Eur J Pain. 2012 May;16(5):648-55. doi: 10.1002/j.1532-2149.2011.00060.x. Epub 2011 Dec 19.

[14] Al-Kaisy A1, Palmisani S1, Smith TE1, Pang D1, Lam K2, Burgoyne W3, Houghton R4, Hudson E5, Lucas J2. 10 kHz High-Frequency Spinal Cord Stimulation for Chronic Axial Low Back Pain in Patients With No History of Spinal Surgery: A Preliminary, Prospective, Open Label and Proof-of-Concept Study. Neuromodulation. 2017 Jan;20(1):63-70. doi: 10.1111/ner.12563. Epub 2016 Dec 26

[15] Van Buyten JP1, Al-Kaisy A, Smet I, Palmisani S, Smith T. High-frequency spinal cord stimulation for the treatment of chronic back pain patients: results of a prospective multicenter European clinical study. Neuromodulation. 2013 Jan-Feb;16(1):59-65; discussion 65-6. doi: 10.1111/ner.12006. Epub 2012 Nov 30.

[16] Kapural L1, Yu C, Doust MW, Gliner BE, Vallejo R, Sitzman BT, Amirdelfan K, Morgan DM, Brown LL, Yearwood TL, Bundschu R, Burton AW, Yang T, Benyamin R, Burgher AH. Novel 10-kHz High-frequency Therapy (HF10 Therapy) Is Superior to Traditional Low-frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: The SENZA-RCT Randomized Controlled Trial. Anesthesiology. 2015 Oct;123(4):851-60. doi: 10.1097/ALN.0000000000000774.

[17] De Ridder D1, Vanneste S, Plazier M, van der Loo E, Menovsky Burst spinal cord stimulation: toward paresthesia-free pain suppression. Neurosurgery. 2010 May;66(5):986-90. doi: 10.1227/01.NEU.0000368153.44883.B3.

[18] De Ridder D1, Plazier M, Kamerling N, Menovsky T, Vanneste S. Burst spinal cord stimulation for limb and back pain. World Neurosurg. 2013 Nov;80(5):642-649.e1. doi: 10.1016/j.wneu.2013.01.040. Epub 2013 Jan 12.

4.2 Purpose

Medtronic, Inc. is sponsoring the SCS Research Study, a prospective, multi-center, post-market clinical study. The purpose of this study is to characterize the effects of stimulation parameters on pain relief [redacted]

5. Objectives and/or Endpoints

5.1 Objectives

5.1.1 Primary Objective

To characterize pain scores, specific to the indication associated with SCS implant, with different SCS parameters.

5.1.2 [redacted]

[redacted]

6. Study Design

This is a prospective, multi-center, post-market study to characterize the effects of stimulation parameters on pain relief [redacted] It is estimated that up to 360 subjects will be enrolled [redacted] in the United States. [redacted]

The overall study duration, from first subject enrollment to last subject visit, is expected to last approximately 10 years.

Multiple on-label stimulation parameters will be studied throughout the execution of this clinical investigational plan. [redacted]

[redacted] A study cohort is defined as a group of subjects who share the same recommended programming parameters and follow-up visit cadence. These stimulation parameters and visit cadence will be provided by Medtronic to each site per study cohort. [redacted] Cohorts with both rechargeable and non-rechargeable devices may explore on-label stimulation parameters [redacted]

The longer enrollment period enables the research of SCS parameters over time as the science and technology in SCS develops.

[redacted] The completion of the study is defined as the approval of the Final Clinical Study Report and closure of all sites.

6.1 Duration

It is estimated that up to 360 subjects will be [redacted] The overall study duration, from first subject enrollment to last subject visit, is expected to last approximately 10 years. The completion of the study is defined as the approval of the Final Clinical Study Report and closure of all sites.

6.2 Rationale

Patients who receive neurostimulation therapy typically have chronic, intractable pain of the back and/or limbs that is not sufficiently managed with medications or other more conservative treatments. Oftentimes, this chronic pain is due to or associated with failed back surgery syndrome, complex regional pain syndrome or diabetic peripheral neuropathy. [19,20,21,22,23]

[19] Frey ME, Manchikanti L, Benyamin RM, Schultz DM, Smith HS, Cohen SP. Spinal cord stimulation for patients with failed back surgery syndrome: a systematic review. Pain Physician. 2009 Mar-Apr; 12(2):379-97.
[20] Taylor RS. Spinal cord stimulation in complex regional pain syndrome and refractory neuropathic back and leg pain/failed back surgery syndrome: results of a systematic review and meta-analysis. J Pain Symptom Manage. 2006 Apr; 31(4 Suppl):S13-9.
[21] Turner JA, Loeser JD, Bell KG. Spinal cord stimulation for chronic low back pain: a systematic literature synthesis. Neurosurgery. 1995 Dec;37(6):1088-95.
[22] Turner JA, Loeser JD, Deyo RA, Snaders SB. Spinal cord stimulation for patients with failed back surgery syndrome or complex regional pain syndrome: a systematic review of effectiveness and complications. Pain. 2004 Mar; 108(1-2):137-47.
[23] Duarte RV, Andronis L, Lenders MW, de Vos CC. Quality of life increases in patients with painful diabetic neuropathy following treatment with spinal cord stimulation. Qual Life Res. 2016 Jul;25(7):1771-7. doi: 10.1007/s11136-015-1211-4.

Most clinical studies reporting on the pain-relieving effects of SCS are observational case studies with no appropriate comparator or systematic reviews of the aforementioned. There are prospective studies that demonstrate at least 50% pain relief or improvement in function in 60% of CRPS patients implanted with SCS systems[24, 25, 26, 27, 28], 50 to 60% of FBSS patients.[29,30,31, 28] and 50-63% in Painful Diabetic Peripheral Neuropathy patients.[23] However, a number of clinical reviews report that the pain-relieving effect of SCS can diminish over time.[32] While there is a deficiency of multiple evidence-based studies demonstrating efficacy of long term SCS, there are even fewer studies that provide sufficient data regarding SCS parameter effects (eg, frequencies, pulse widths, cycling duties, etc.) on clinical outcomes along with long term effects. Research studies are needed to address the gap in our knowledge of SCS parameters and how they differentially, but effectively, modulate central nervous system mechanisms that drive chronic intractable pain, the underlying causes, or relief from pain.

7. Product Description

7.1 General

This study involves commercially available devices used within their intended approved indication.

Subjects who have previously been implanted with a Medtronic neurostimulation system (ie, neurostimulator, lead(s), extension(s), and accessories) will be enrolled in this study. For non-rechargeable neurostimulation systems, systems must be able to have the battery longevity be calculated with the commercial application on a clinician programming tablet (e.g., Vanta™ with AdaptiveStim™). Non-rechargeable neurostimulators where the battery longevity can only be calculated manually are excluded from the study. Table 7-1 contains a list including examples of, but not limited to, FDA-approved neurostimulators that may be used in the study.

[24] Harke H, Gretenkort P, Ladleif HU, Rahman S. Spinal cord stimulation in sympathetically maintained complex regional pain syndrome type I with severe disability. A prospective clinical study. Eur J Pain. 2005 Aug;9(4):363-73.
[25] Oakley JC, Weiner RL. Spinal cord stimulation for complex regional pain syndrome: a prospective study of 19 patients at two centers. Neuromodulation. 1999 Jan;2(1):47-50.
[26] Kemler MA, Barendse GAM, van Kleef M, de Vet HCW, Rijks CPM, Furnee CA, van den Wildenberg FAJM. Spinal cord stimulation inpatients wit chronic reflex sympathetic dystrophy. New Eng J Med. 2000; 343(9):618-624.
[27] Chivukula S, Tempel ZJ, Weiner GM, Gande AV, Chen CJ, Ding D, Moossy JJ. Cervical and cervicomedullary spinal cord stimulation for chronic pain: Efficacy and outcomes. Clin Neurol Neursurg. 2014 Dec; 127:33-41.
[28] Deer TR, Skaribas IM, Haider N, Salmon J, Kim C, Nelson C, Tracy J, Espinet A, Lininger TE, Tiso R, Archacki MA, Washburn SN. Effectiveness of Cervical Spinal Cord Stimulation for the Management of Chronic Pain. Neuromodulation 2014; 17:265-271.
[29] Burchiel KJ, Anderson VC, Brown FD, Fessler RG, Friedman WA, Pelofsky S, Weiner RL, Oakley J, Shatin D. Prospective, multicenter study of spinal cord stimulation for relief of chronic back pain. Spine (Phila Pa 1976). 1996 Dec 1;21(230:2786-94.
[30] Thomson SJ, Tavakkolizadeh M, Love-Jones S, Patek NK, Gu JW, Bains A, Doan Q, Moffitt M. Effects of Rate on Analgesia in Kilohertz Frequency Spinal Cord Stimulation: Results of the PROCO Randomized Controlled Trial. Neuromodulation. 2018 Jan;21(1):67-76. Epub 2017 Dec 8.
[31] Kapural L, Yu C, Doust MW, Gliner BE, Vallejo R, Sitzman BT, Amirdelfan K, Morgan DM, Brown LL, Yearwood TL, Bundschu R, Burton AW, Yang T, Benyamin R, Burgher AH. Novel 10-kHz High-frequency Therapy (HF10 Therapy) Is Superior to Traditional Low-frequency Spinal Cord Stimulation for the Treatment of Chronic Back and Leg Pain: The SENZA-RCT Randomized Controlled Trial. Anesthesiology. 2015 Oct;123(4):851-60.
[32] Kumar K, Hunter G, Demeria D. Spinal cord stimulation in treatment of chronic benign pain: challenges in treatment planning and present status, a 22-year experience. Neurosurgery. 2006 Mar; 58(3):481-96.

Table 7-1: Medtronic FDA-Approved Neurostimulators

Model Number	Name
977006	Vanta™ with AdaptiveStim™
97716	Intellis™
97715	Intellis™ with AdaptiveStim™
97714	RestoreSensor® SureScan® MRI
37714	RestoreSensor™
97713	RestoreAdvanced® SureScan® MRI
37713	RestoreAdvanced™
97712	RestoreUltra® SureScan® MRI
37712	RestoreULTRA™
37711	Restore™

7.2 Manufacturer

The neurostimulation systems are manufactured by Medtronic, Inc. with operational headquarters in Minneapolis, Minnesota 55432-5604, USA.

7.3 [redacted]

7.4 Product Return

All products are commercially available, and no products related to the neurostimulation system will be provided from Medtronic as a part of this study.

When explanting a device (e.g., replacement, cessation of therapy, or postmortem), or when disposing of accessories, if possible, return the explanted device with completed paperwork to Medtronic for analysis and disposal. To allow for device analysis, do not autoclave the device or expose the device to ultrasonic cleaners. Dispose of any unreturned components according to local environmental regulations.

[redacted]

7.5 Product Accountability

No product accountability is required for the study. All products are considered commercially available, and Medtronic will not be providing products related to the neurostimulation system for this study.

Subjects who participate in the study may be asked to surrender their patient programmer to site personnel for follow-up periods (for example, if a subject is implanted with a neurostimulator that can be turned off using a recharger and does not require a patient programmer for recharging).

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

[redacted].

8. Study Site Requirements

8.1 Investigator/Investigation Site Selection

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation.

The principal investigator shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation
- Be experienced in the field of application and training in the use of spinal cord stimulation
- Be able to demonstrate that the proposed investigational study site:
  - Has the required number of eligible subjects needed within the recruitment period
  - Has one or more qualified investigators, a qualified investigational study site team, and adequate facilities for the foreseen duration of the clinical investigation

Study site personnel qualification and training will be completed and documented prior to participation in this study.

8.2 Study Site Activation

During the site activation process (prior to subject enrollment), Medtronic will train study site personnel on the clinical investigation plan (CIP), relevant standards and regulations (as required), informed consent (IC), programming, and data collection and reporting tools. If new members join the study site team, they will receive training on the applicable study requirements relevant to their role before contributing to the study.

Prior to performing study related activities, all regulatory requirements shall be fulfilled, including, but not limited to the following:

- IRB approval (and voting list, as required by local law) of the current version of the CIP and IC.
- Fully executed Clinical Trial Agreement (CTA)

- CV/medical license of investigators and key members of the investigation study site team (as required).
- Documentation of delegated tasks.
- Documentation of study training.

In addition, all participating study site staff must be trained on the current version of the CIP as well as on the applicable study requirements depending on their role and must be delegated by the principal investigator to perform study-related activities.

Medtronic will provide each study site with documentation of study site/investigator readiness; this letter must be received prior to performing study-related activities.

8.3 Role of the Sponsor Representatives

In addition to performing monitoring and auditing activities, qualified and trained sponsor representatives may provide support at the study site as required for the study under supervision of the Principal Investigator, including:

- Provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- [redacted]

These activities will be performed under the supervision of the investigator, or appropriately delegated study personnel, and will not bias the outcome of study, affect the quality of research data, or compromise the rights and welfare of human subjects. Any data collection completed by Medtronic personnel will be clearly identified as such.

9. Selection of Subjects

9.1 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 all conditions approved by the FDA at the time of initiation of any individual cohort.

This study will enroll a sub-set of the population indicated for SCS systems. Subjects who meet the eligibility criteria listed in Sections 9.3-9.4 are eligible to be enrolled in the study.

9.2 Subject Enrollment

When a subject and the principal investigator or authorized designee, as required, have personally signed and dated the IC, the subject is considered enrolled in the study. The date the subject signed the IC must be documented in the subject's medical records.

Subjects will be screened to ensure they meet all of the inclusion and none of the exclusion criteria prior to being eligible to participate in the study. Subjects may be enrolled in multiple cohorts to test different on-label programming parameter groups.

9.3 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 Medtronic neurostimulation system, for a labeled indication, and expected longevity of neurostimulator is at least 16 months
3. Willing and able to provide signed and dated informed consent
4. Capable of comprehending and consenting in English
5. Willing and able to comply with all study procedures, and visits
6. Able to differentiate between pain associated with the indication for SCS implant and other types of pain, as determined by the investigator, or designee

[redacted]

9.4 Exclusion Criteria

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

1. Implanted with neurostimulation system for an off-label indication
2. Currently enrolled or planning to enroll in an interventional clinical study that could potentially confound the study results (co-enrollment in an interventional study is only allowed when documented pre-approval is obtained from the Medtronic study manager, or designee)
3. If female, pregnant or is of child-bearing potential and unwilling to use a medically acceptable form of birth control during the study
4. Has untreated major psychiatric comorbidity, as determined by the investigator, or designee
5. Has a non-rechargeable neurostimulator where the battery longevity is not able to be estimated with the battery longevity calculator

10. Study Procedures

10.1 Schedule of Events

All subjects will be scheduled for an Enrollment visit. The informed consent may occur during the Enrollment visit or at a time prior to the Enrollment visit. [redacted]

[redacted]

[redacted]

10.1.1 [redacted]

[redacted]

[redacted]

10.1.2 [redacted]

[redacted]

[redacted]

[redacted]

10.2 Data Collection

Study procedures, tasks, and data collection requirements by visit are summarized in Table 10-1 below.

[redacted]

Table 10-1: Data collection and study procedure requirements at subject visits

Study Procedures, Tasks, and Data Collection	Enrollment	[redacted]	[redacted]	Final Study Visit	[redacted]
IC[a]	X				
Eligibility	X	X			

Study Procedures, Tasks, and Data Collection	Enrollment	[redacted]	[redacted]	Final Study Visit	[redacted]
Demographics	X				
Medical/Surgical History	X	Updates as they occur			
Device Information	X				
Location of Pain[b]	X		X	X	
[redacted]	X		X	X	
[redacted]	X		X	X	
[redacted]	X		X	X	
[redacted]	X		X	X	
[redacted]	X		X	X	X
[redacted]	X	X	X	X	X
[redacted]		X	X	X	X
[redacted]	X	Updates as they occur			
[redacted]	X				
[redacted]		X			
[redacted]		X			
[redacted]		X	X	X	X
[redacted]		X	X	X	X
[redacted]	X	X	X	X	
[redacted]					
AEs	As they occur				
DD	As they occur				
System modifications	As they occur				
Study deviations	As they occur				
Death	As they occur				

Study Procedures, Tasks, and Data Collection	Enrollment	[redacted]	[redacted]	Final Study Visit	[redacted]

[redacted]

10.3 [redacted]

10.4 Subject Screening

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 should be pre-screened by the principal investigator or authorized site personnel by reviewing the study's inclusion and exclusion criteria prior to enrollment.

All subjects must be consented in accordance with the protocol, and IRB requirements, prior to completion of any study-specific procedures.

10.5 [redacted]

[redacted]

10.6 Subject Consent

Investigators shall consider for enrollment all subjects who meet eligibility requirements for study participation to avoid any bias in the subject population. Prior to enrolling subjects, each investigational site's IRB will be required to approve the CIP, the informed consent form (ICF) and HIPAA/data protection authorization or other privacy language, and any other written study information to be provided to the subjects (e.g. CA Bill of Rights if applicable, subject assessments etc.). The document(s) must be controlled (i.e. version number and date) to ensure it is clear which version(s) were approved

by the IRB. Any adaptation of the informed consent form must be reviewed by Medtronic and approved by the IRB prior to enrolling subjects. The ICF will be provided under separate cover.

Patient informed consent is defined as legally effective, documented confirmation of a subject's voluntary agreement to participate in a clinical study after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate. The informed consent process will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and in accordance with 21 CRF Part 50.

Prior to entering the study, the principal investigator, or appropriately delegated designee, will explain to each subject all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation including, but not limited to, the following: purpose and nature of the study, study procedures, expected study duration, available alternative therapies, and the benefits and risks involved with study participation and the potential treatment.

The investigator shall seek such consent only under circumstances that provide the prospective subject sufficient opportunity to consider whether to participate, and that minimize the possibility of coercion or undue influence. No informed consent, whether oral or written, may include any exculpatory language through which the subject is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

Subjects are considered enrolled at the time the study specific ICF is signed. If a subject enrolls for participation in multiple cohorts, a new consent form will be signed for each subsequent cohort. Informed consent must be obtained from the subject prior to initiation of any study-specific procedures. Subjects must be able to personally sign and date the consent form to participate in this study. Signing and dating of the ICF or HIPAA authorization or other data protection form by a legally authorized representative will not be permitted for this study. Subjects will be required to sign and date a HIPAA authorization or other data protection form as required by local regulations before participating sites can collect, use and submit subject information to the study sponsor. The Consent Form and Authorization to Use and Disclose Personal Health Information/ Research Authorization/other legally required privacy language must be given to the subject in a language he/she is able to read and understand. Only subjects capable of reading and understanding English are eligible to participate in this study.

If the informed consent form is obtained the same day the subject begins participating in study-related procedures, it will be documented in the subject's case history that consent was obtained prior to participation in any study-related procedures.

The original signed ICF must be filed in the hospital/clinical chart and/or with the subject's study documents. A copy of the informed consent form and signed Authorization to Use and Disclose Personal

Health Information/Research Authorization/other legally required privacy language must be provided to the subject.

The informed consent form and Authorization to Use and Disclose Personal Health Information/Research Authorization/other legally required privacy language must be available for monitoring and auditing.

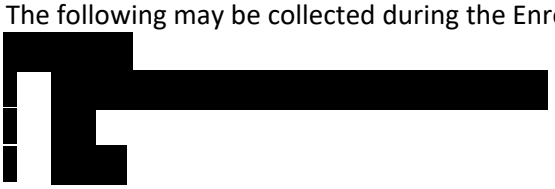
Any changes to a previously approved informed consent form throughout the course of the study must be submitted and approved by Medtronic and the IRB reviewing the application before being used to consent a prospective study subject. The document(s) must be controlled (i.e. versioned and dated) to ensure it is clear which version(s) were approved by the IRB.

The investigator must notify the subject of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's willingness to participate in the study. If relevant, approval may be requested from subjects to confirm their continued participation.

10.7 Enrollment Visit

A subject is considered enrolled when the consent process has been finalized. The date the subject signed the IC and Data Protection Authorization, as required by law, must be documented in the subject's medical records. A log of all subjects enrolled in the study should be maintained.

The following may be collected during the Enrollment visit,



[redacted]

[redacted]

10.8 [redacted]

Subjects will be queried for adverse events, device deficiencies [redacted] In addition, information will be collected on the visit case report form for any events that, as determined by the investigator, are not reportable as an adverse event but may influence accuracy of pain reporting by the subject.

[redacted]

[redacted]

Table 10-2: Range of Programmable Neurostimulator Settings

	Frequency	Pulse-width	Amplitude
Vanta	40 to 130 Hz	60 to 450 µs	0-25.5 mA per electrode; 0 to 100 mA per program
Intellis	2 to 1200 Hz	60 to 1000 µs	0-25.5 mA per electrode; 0 to 100 mA per program
RestoreSensor, RestoreUltra	2 to 1200 Hz	60 to 1000 µs	0 to 10.5 V

	Frequency	Pulse-width	Amplitude
Restore, RestoreAdvanced	2 to 130 Hz	60 to 450 µs	0 to 10.5 V

[redacted]

[redacted]

[redacted]

For subjects with non-rechargeable neurostimulators, estimated battery longevity of the programmed active study settings will be calculated on the clinician programmer prior to the end of the visit. The estimated battery longevity with the study settings will be reviewed with the investigator and compared to that of the settings programmed at the beginning of the visit, if applicable. [redacted]

[redacted]

[redacted]

During the follow-up period, subjects with rechargeable devices may need to recharge their device more or less often; therefore, subjects should be instructed to check their device daily to verify whether recharging is needed.

[redacted]

10.9 [redacted].

[redacted] subjects will be queried for adverse events, device deficiencies, [redacted] In addition, information will be collected on the visit case report form for any events that, as determined by the investigator, are not reportable as an adverse event but may influence accuracy of pain reporting by the subject.

[redacted]

[redacted]

[redacted]

[redacted]

Each subject's device will be programmed to commercially-available settings [redacted] such as those shown in Table 10-2 at [redacted]

[redacted]

During each follow-up period, subjects with rechargeable devices may need to recharge their device more or less often; therefore, subjects should be instructed to check their device daily to verify whether recharging is needed.

[redacted]

[redacted] subjects will be queried for adverse events, device deficiencies, [redacted] In addition, information will be collected on the visit case report form for any events that, as determined by the investigator, are not reportable as an adverse event but may influence accuracy of pain reporting by the subject.

[redacted]

[redacted]

If re-programming occurs, each subject's device will be interrogated, and a report session will be generated to capture the subject's therapy settings at the beginning and end of the visit, including electrode impedance measurements. For subjects with non-rechargeable neurostimulators, the current battery level for the neurostimulator, along with the estimated battery life remaining will be reviewed on the clinician programmer.

Each subject's device may, if applicable, be re-programmed to commercially-available settings [redacted] such as those shown in Table 10-2, [redacted]

During each follow-up period, subjects with rechargeable devices may need to recharge their device more or less often; therefore, subjects should be instructed to check their device daily to verify whether recharging is needed.

10.11 Final Study Visit

Upon completion of the last follow-up period, subjects will complete the Final Study Visit. [redacted] Subjects will be queried for adverse events, device deficiencies, [redacted] In addition, information will be collected on the visit case report form for any events that, as determined by the investigator, are not reportable as an adverse event but may influence accuracy of pain reporting by the subject.

[redacted]

The following may be collected during the Final Study visit, [redacted]

[redacted]

[redacted]. Subjects will be programmed to a setting per standard of care prior to exiting the study.

[redacted]

10.12 [redacted]

Subjects may be called during their participation in the study to reinforce study compliance [redacted]

10.13 Imaging

Subjects may be asked to have fluoroscopic or X-ray images taken of their implanted lead(s) as part of the study, unless imaging taken prior to the subject's enrollment or as part of their standard of care are available and allow for the anatomical location of the active contacts to be defined. If the subject does not have adequate imaging available, imaging may be performed, at no more than 1 visit throughout the study, to obtain anterior/posterior and lateral fluoroscopy or X-ray views that allow for the anatomical location of the active contacts to be defined. Standard of care images taken during the subject's participation, but not required by the study, may also be collected.

[redacted]

[redacted]

10.14 [redacted]

[redacted]

10.15 [redacted]

[redacted]

10.16 System Modification

If a subject's neuromodulation system is revised or replaced during the study, documented approval is required from the Medtronic study manager, or designee, for the subject to proceed with the study.

10.17 [redacted]

10.17.1 [redacted]

[redacted]

10.17.2 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.18 [redacted]

10.18.1 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

10.18.3 [redacted]

[redacted]

10.18.4 [redacted]

10.18.5 [redacted]

10.18.6 Imaging

Images may be collected at a single visit to characterize the anatomical location of the active contacts when pertinent to the stimulation parameters being tested.

10.18.7 [redacted]

10.18.8 [redacted]

10.18.9 [redacted]

10.19 Assessment of Safety

Subjects will be assessed from enrollment through the end of the study for adverse events related to the following:

- The SCS system and accessories (device-related)
- SCS therapy (therapy-related)
- SCS procedure (procedure-related)

In addition, all device deficiencies reported during the study will be collected.

10.20 Recording Data

Data entered must be traceable to source documents. Source documentation is defined as the first-time data appear, and may include original documents, data, and records (e.g., hospital records, clinical and office charts, procedure reports, subjects' diaries, images, and device data).

In general, eCRFs (or paper copies) may not serve as source documents. An exception may be the completion of QoL Questionnaires and clinical scales. Source documentation for data elements not routinely captured in medical records may vary from study site to study site; the study site may use source document worksheets if identified as source documents.

The investigator must ensure the availability of source documents from which the information on the eCRFs was derived. The type and location of source documents should be documented. Where printouts of electronic medical records, are provided as source documents, or where copies of source documents are retained as source documents, those should be certified. Certification must contain (1) the signature of the individual making the copy, (2) the date the copy was made and (3) a statement attesting to the accuracy and completeness of the copy.

The source documents must be made available for monitoring or auditing by Medtronic's representative or representatives of the competent authorities and other applicable regulatory agencies.

10.20.1 Case Report Form Data

This study will use an electronic data capture (EDC) 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. [redacted] Data from the subject assessments will be entered into the database by delegated 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.

10.20.2 [redacted]

[redacted]

10.20.3 Image Data

Site personnel will redact, at a minimum, the subject's name and label each image with the Subject's ID prior to securely sending them to Medtronic.

After receipt by Medtronic, the images may be evaluated by a qualified reader to define and characterize the locations of the active contacts. Medtronic will keep all copies of the images that they receive in a secure location and may use them for other business purposes outside of this study.

10.20.4 [redacted]

10.21 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.

10.22 Subject Exit, 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.

Examples of reasons for study exit include the following:

- Normal study completion
- Subject adverse event
- Subject death
- Subject lost to follow-up
- Investigator decides to terminate the subject's participation in the study (for example, due to lack of compliance, violation of/change in eligibility criteria)
- Subject becomes pregnant
- Medtronic requests subject be discontinued
- Subject voluntarily withdraws from the study
- 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

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 discontinues 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 a device, procedure, or therapy-related adverse event or device deficiency, the appropriate event eCRFs should also be completed.

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.

11. Risks and Benefits

11.1 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. Furthermore, there are additional risks associated with subjects taking part in this study which are stated in Section 11.1.1.5

11.1.1 Foreseeable Risks

11.1.1.1 Risks of Surgery

Implanting a neurostimulation system has risks similar to other spinal procedures, including spinal fluid leak (spinal fluid collection under the skin), headaches, swelling, bruising, bleeding, infection, or paralysis.

Subjects on anticoagulation therapy may be at higher risk for problems after surgery such as hematomas that could result in paralysis

11.1.1.2 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 risks associated with surgery, the following adverse events may occur with implantation or use of a neurostimulation system. Certain adverse events may necessitate surgical intervention.

- Allergic or immune system response to the implanted materials
- Infection
- Lead, extension, or neurostimulator erosion through the skin or migration
- Leakage of cerebrospinal fluid
- Lack of effective therapy or loss of therapeutic effect resulting in return of baseline symptoms
- 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
- 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.
- Stimulation-dependent gastrointestinal symptoms such as diarrhea, incontinence, or constipation
- Stimulation-dependent bladder symptoms such as urinary retention, incontinence, or frequency
- Tissue damage at the implant site

11.1.1.2.1 Pregnancy

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.

11.1.1.3 System Revision Risk

The following neurostimulators: RestoreSensor, RestoreUltra, RestoreAdvanced, and Restore will require replacement 9 years or earlier from the date a subject received it, regardless of the number of times the neurostimulator is recharged.

The Intellis neurostimulators will provide at least 9 years of operation before replacement is recommended.

The Vanta neurostimulator is non-rechargeable and will require a system revision at the end of service. The time for this battery duration depends on the programming parameters for each person and can be estimated using the estimated battery longevity feature on the Clinician tablet.

It is possible that the system will need to be revised (explanted, replaced, or repositioned) earlier than the expected duration for each neurostimulator. Possible reasons for revision/explant may include infection, malfunction, and migration of the system components. The risks associated with system revision are equivalent to the commercially available systems.

11.1.1.4 Risks Associated with the Recharging System

The recharger, antenna, and belt 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. Subjects should check for skin irritation or redness near the neurostimulator during recharging.

11.1.1.5 Study-Specific Risks

As part of the study, subjects may be asked to have fluoroscopic or X-ray images taken. This may be beyond what is standard of care. A slight increase in cancer risk may exist for people exposed to radiation. Following the fluoroscopic procedure, the skin area exposed to the x-rays could react to produce an effect similar to a sun burn. A skin reaction, if it occurs at all, could show up from a few hours to a few weeks after the procedure, and usually goes away on its own.

Parameters used during the study may not be effective, which could result in an increased level of pain. Additionally, study parameters may cause an uncomfortable level of stimulation in acute or ambulatory settings.

Depending on the programmed parameters the subject was using when they entered the study, it is possible subjects with rechargeable devices may need to recharge more frequently during one or more treatment periods. Depending on their programming parameters the subject was using when they entered the study, it is possible that subjects with non-rechargeable devices may require a revision surgery of their neurostimulator sooner than if they did not enter the study.

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

11.1.1.6 Additional Risks and Information

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

11.2 Risk Minimization

At any time during the study, subjects will be able to turn their device OFF using their patient programmer or 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).

For patients with non-rechargeable devices, the programming settings will be closely monitored to minimize the risk of battery depletion that is sooner than their expected battery duration. [redacted] the duration of the estimated battery duration with the proposed settings will be calculated by using the application on the clinician tablet. This time will be compared to the patient's baseline estimated battery duration. For newly implanted patients (i.e., subjects that have less than two weeks of stimulation after implantation), the baseline estimated battery duration will be calculated based on appropriate parameters and intensities used for standard-of-care programming. For patients with stable programming settings, the baseline estimated battery duration will be calculated using their baseline programming settings.

[redacted]

[redacted] the estimated battery longevity of new settings will be evaluated compared to baseline settings. If the investigator (or designee) determined that the estimated longevity is not adequate, the physician may discuss with the subject and energy settings may be adjusted [redacted] the investigator (or designee) will evaluate if the subject Is a candidate [redacted]

[redacted] If the subject is determined not to be a candidate, the subject will be programmed per standard of care and exited from the study.

[redacted] the estimated battery longevity will be calculated compared to the current study settings. The programmer will compare the estimated battery duration of any new settings to that of the current programming settings and monitor current battery level.

At any point in the course of the study, the patient may exit the study and continue with their standard of care for any reason, including concern over battery usage. In addition, the current battery level and estimated battery life of the neurostimulator will be reviewed [redacted] to further minimize the likelihood of any unexpected battery usage.

Further mitigations reside in careful construction of the study. This includes selecting an appropriate patient population via inclusion/exclusion screening and closely monitoring subject progress and events reported for the study. Additionally, qualified investigators with proper SCS therapy experience will be selected, which includes trained personnel to perform any additional imaging taken as a part of the study.

Labeling that contains precautions, warnings, and contraindications, as well as instructions on the use of the devices are available to investigators who may provide this information to subjects.

11.3 Potential Benefits

There may be no direct medical benefit to subjects participating in the study. 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. The SCS settings used during this study may reduce subjects' pain intensity, return subjects to a more fully functional status, improve their quality of life, or limit unwanted side effects. The SCS settings used in this study may also prolong the battery longevity of non-rechargeable neurostimulators or increase time between recharging for rechargeable devices. These benefits cannot be guaranteed due to the investigational nature of this study.

The primary anticipated benefit of this study is to help Medtronic with the understanding of SCS therapy and assist with the design of future studies and product improvements. The information gathered from this study could also help clinicians optimize therapy for their patients.

11.4 Risk-Benefit Rationale

Subjects participating in this study will be exposed to risks from commercial SCS therapy that have been deemed, through existing PMA approval, to be outweighed by the benefits of treating chronic, intractable pain within approved indications. Additional risks that exist due to participation in the study, including reduced efficacy and uncomfortable stimulation have been minimized by mitigations within the study design, and will be properly communicated to potential subjects. The additional risk of earlier

battery depletion resulting in device replacement for patients with non-rechargeable devices has been minimized by estimating the battery longevity and will be properly communicated to potential subjects.

12. Adverse Events and Device Deficiencies

12.1 Adverse Events

AE definitions are provided in Table 12-1. Each event is defined according to International Organization for Standardization (ISO) 14155. 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.

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 SCS system and accessories (device-related)
- SCS therapy (therapy-related)
- SCS procedure (procedure-related)

Each event will be classified according to 5 different levels of causality using the following terms:

- Not Related
- Unlikely
- Possible
- Probable
- Causal

Only events that are classified as possible, probable or causal are considered to be related for data analysis.

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, procedure, accessories, or therapy.

Events that are not reportable for this study are:

- Lack of pain relief

- Pain symptoms will be collected as part of the efficacy measures

- Sensation of stimulation (paresthesia)
  - Sensation of stimulation (e.g. tingling, buzzing) will not be reported as this may occur as part of this therapy. **Exception: Sensation or stimulation events that are uncomfortable to the subject (e.g. shocking, jolting) will be reported.**
- Adverse events unrelated to
  - Implanted SCS system, accessories or surgical procedure
  - Spinal cord stimulation 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.

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 be updated when there is a change to the information provided on the form (e.g. change in intervention, outcome, relatedness, etc.).

12.2 Device Deficiency

The DD definition is provided in Table 12-1. DD information will be collected throughout the study and reported to Medtronic on a device event eCRF, one for each device deficiency. Note that DD that results in an AE to the subject should be captured as an AE only.

12.3 Processing Updates and Resolution

For any changes in status of a previously reported adverse event or DD (i.e. change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE or DD form. All AEs must be followed until the AE has been resolved, is unresolved with no further actions planned, the subject dies or exits the study, or until study closure, whichever occurs first.

In the event that a subject is exited from the study prior to study completion, all efforts should be made to continue following the subject until all unresolved system or procedure related AEs, as classified by the investigator, are resolved, unresolved with no further actions planned, or 30 days post study exit, whichever occurs first.

At the time of study exit, all collected adverse events that are unresolved must be reviewed and an update to the original AE must be reported.

12.4 Definitions/Classifications

Table 12-1: Adverse Event and Device Deficiency Definitions

General	
Adverse Event (AE):	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):	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):	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):	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Device Deficiency (DD):	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:	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:	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.
Relatedness	
Device Related (includes all implantable components and features, associated introduction tools, operational and installed software and programmers as defined in the CIP, see Section 7.1)	An AE that results from the presence or performance of any component of the system. Neurostimulator-related: An AE that results from the presence or performance (intended or otherwise) of the neurostimulator. Lead-related: An AE that results from the presence or performance (intended or otherwise) of the lead. Extension-related: An AE that results from the presence or performance (intended or otherwise) of the extension. External Study Device-related: An AE that results from the presence or performance (intended or otherwise) of an external study device (e.g. programmer, ENS).
Therapy Related	Event related to therapy delivery by device. Normally therapy-related events resolve when the device is turned off or reprogrammed. This category should not include events that resulted from a malfunction of the device (i.e. hardware-related events).
Procedure Related	An AE that occurs due to any procedure related to the implantation or surgical modification of the system.
Seriousness	

Serious Adverse Event (SAE)	AE that led to any of the following a) death, b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic disease, 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) fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Causality	

Not Related	Relationship to the device or procedures can be excluded when: – the event is not a known[1] side effect of the product category the device belongs to or of similar devices and procedures; – the event has no temporal relationship with the use of the investigational device or the procedures; – the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; – the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; – the event involves a body-site or an organ not expected to be affected by the device or procedure; – the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); – the event does not depend on a false result given by the investigational device used for diagnosis[2], when applicable; – harms to the subject are not clearly due to use error; – In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event. [1]When the event is not a known side effect of the product category the device belongs to or of similar devices and procedures, generally is considered "not related". Yet, the unexpected effect shall not be excluded from evaluation and reporting. [2]If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer) or might not be diagnosed with the correct disease or condition.
Unlikely	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Causal Relationship	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: – the event is a known side effect of the product category the device belongs to or of similar devices and procedures; – the event has a temporal relationship with investigational device use/application or procedures; – the event involves a body-site or organ that the investigational device or procedures are applied to; – the investigational device or procedures have an effect on; – the serious event follows a known response pattern to the medical device (if the response pattern is previously known); – the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); – other possible causes (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; – harm to the subject is due to error in use; – the event depends on a false result given by the investigational device used for diagnosis[1], when applicable; – In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event. [1]If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition.

12.5 Reporting of Adverse Events and Device Deficiencies

12.5.1 Adverse Event and Device Deficiency Classification

All AE and DD will be reviewed by a Medtronic representative. AEs will be classified according to the definitions provided.

Upon receipt of AE at Medtronic, a Medtronic representative will review the AE/DD for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. Medtronic will utilize MedDRA for Regulatory Activities, to assign a MedDRA term for each AE based on the information provided by the investigator.

Regulatory reporting of AEs and DDs will be completed according to local regulatory requirements. Refer to Section 12.5.2 for a list of required investigator and Medtronic reporting requirements. It is the responsibility of both to abide by any additional AE reporting requirements stipulated by the IRB responsible for oversight of the study.

AEs and DDs will be classified according to the standard definitions as outlined below:

Table 12-2: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator Sponsor	Therapy-related Procedure-related Device-related
Seriousness	Investigator Sponsor	SAE
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator

12.5.2 Adverse Event and Device Deficiency Reporting Requirements

It is the responsibility of the investigator to abide by the adverse event reporting requirements below and to also follow the reporting requirements of the IRB.

In case of an emergency or to immediately report a subject death or SADE, the investigators can contact the study team.

Table 12-3: Adverse Event and Device Deficiency Reporting Requirements

ADEs	
Investigator shall submit to:	
Medtronic	Submit in a timely manner after the investigator first learns of the effect.
IRB	Submit to IRB per local reporting requirement.
Sponsor Shall Submit to:	
IRB	Submit to IRB per local reporting requirement.
SADEs	
Investigator shall submit to:	

Medtronic	Submit in a timely manner after the investigator learns of the event or of new information in relation to an already reported event.
IRB	Submit to IRB per local reporting requirement.
Sponsor shall submit to:	
IRB	Submit to IRB per local reporting requirement.
Investigators	Submit per local reporting requirement.
All other reportable AEs	
Investigator shall submit to:	
Medtronic	Submit in a timely manner after the investigator first learns of the event.
IRB	Submit to IRB per local reporting requirement.
Device Deficiencies	
Investigator shall submit to:	
Medtronic	Submit in a timely manner after the investigator first learns of the event.
IRB	Submit to IRB per local reporting requirement.

12.6 Subject Death

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 device, procedure, or therapy-related. The investigator should also attempt to determine, as conclusively as possible, whether such deaths are related to the device system, procedure, or therapy. Deaths will be captured by a study exit eCRF and an adverse event eCRF if related to the device system, procedure, 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. 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.

12.7 Product Complaint Reporting

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. The reporting of product complaints by the clinical team must be done according to the local Standard Operating Procedures. Medtronic will notify the RAs (e.g. CA) as applicable for the following incidents immediately upon learning of them and is not limited to AEs and DDs only:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have

led to the death or serious deterioration in the state of health of a patient, user, or other person.

- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- Any serious deterioration in the state of health, including:
  - Life-threatening illness or injury
  - Permanent impairment of a body function or permanent damage to a body structure
  - A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure

13. Data Review Committees

This study will not use a Clinical Events Committee or Data Monitoring Committee. [redacted]

14. Statistical Design and Methods

14.1 General Aspects of Analysis

This is a non-randomized study to characterize procedural learnings and explore effects of SCS programming on subject's pain symptoms [redacted]

Continuous measures will be reported as N, means, medians, standard deviations, minimums and maximums. Categorical measures will be reported as percentages or frequency distributions. Summaries will be completed for all subjects in a given analysis set (pooled across all study sites). If hypothesis testing will be performed for a specific cohort, sample size estimates will be calculated to insure at least 80% power with a significance level of 0.05 for two-sided tests, and 0.025 for one-sided tests.

Data analysis will be performed by Medtronic-employed statisticians or designees. A validated statistical software package (e.g., SAS version 9.4 or higher) will be used to analyze the study results.

The cohort-specific Statistical Analysis Plan (SAP) will be developed prior to data analysis and will include a comprehensive description of the statistical methods to be included in the Final Clinical Study Report for that cohort. 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. [redacted]

For each of the objectives the available data will be summarized and missing data will be discussed. The main analysis of the study objectives will be based on available data and missing data will not be imputed.

[redacted]

14.2 Interim Analysis

Study cohort reports will be generated when data collection has ended in the cohort and all subjects in the cohort have completed the last visit/been exited. [redacted]

14.3 Primary Objective(s)

To characterize subjects' pain scores, specific to the indication associated with SCS implant, with different SCS parameters.

Hypothesis: [redacted]

Endpoint definition and derivation: [redacted]

Analysis Methods: Means and standard deviations of pain scores may be summarized at enrollment, follow-up, and final study visits. Pain scores may also be summarized by different subgroups, and within-subject change may also be calculated at each visit. [redacted]

Determination of Subjects/Data for Analysis : All subjects who provide data at each time point will be included in the analysis (Completer's analysis) as the primary analysis of this study objective, and no imputation methods are planned for missing data. [redacted]

14.4 [redacted]

- [redacted]

14.5 Safety Assessment

Device, procedure, and therapy related adverse events, serious adverse events, and device deficiencies will be presented in summary tables within each study cohort report. If applicable, some high-level descriptive analyses may be performed by utilizing data across study cohorts.

14.6 Sample Size Determination

It is estimated that up to 360 subjects will be enrolled. Considering the research interests of multiple stimulation settings and longer enrollment of the study, a sample size of up to 360 subjects is deemed to be reasonable to characterize the effects of changes to stimulation settings, as well as to provide data for consideration of future studies.

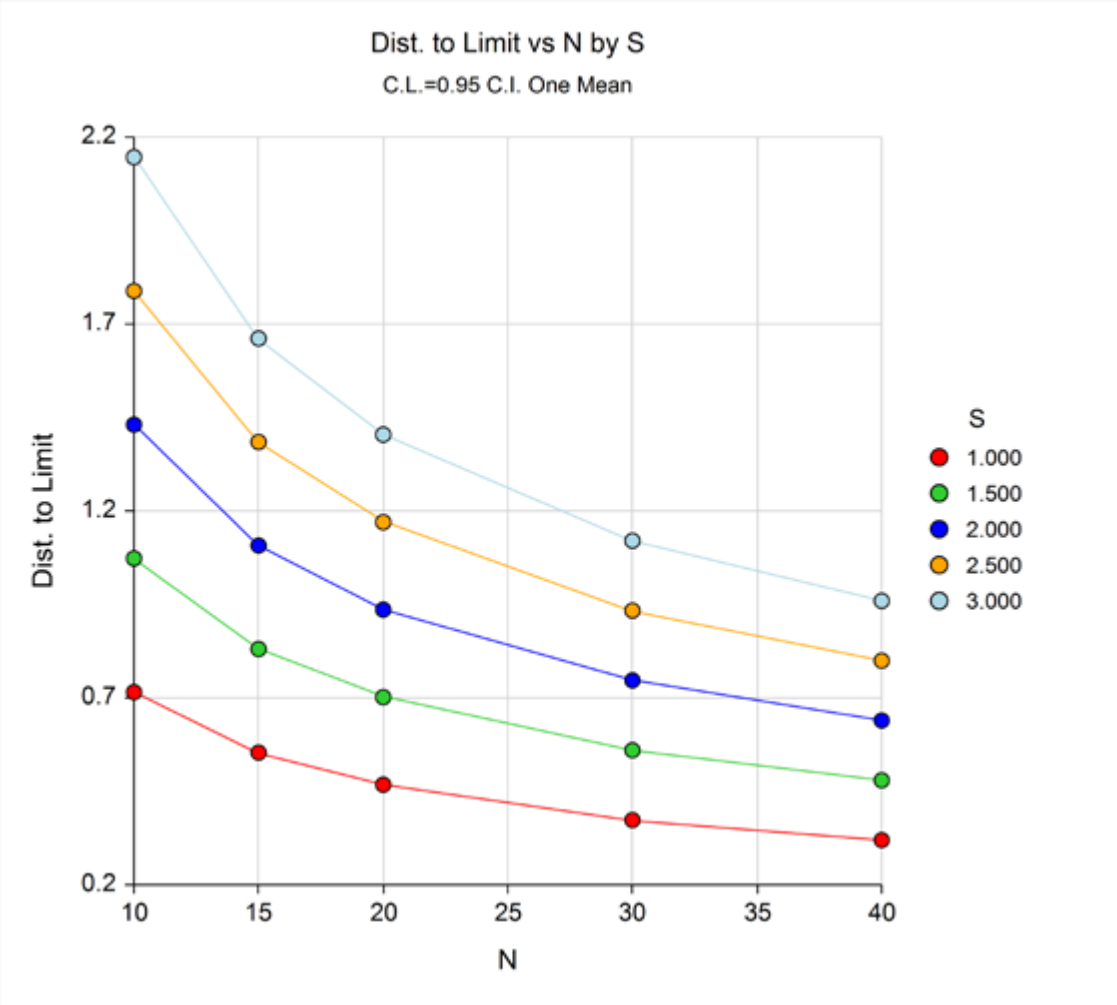
The sample size for each programming parameter group may vary based on the research interests, [redacted] Table 14-1 and Figure 14-1**.** show precision estimates (the distance from mean to limits) by sample size and standard deviation of [redacted] A sample size of 30 produces a two-sided 95% confidence interval with the precision that is equal to 0.93 when the estimated standard deviation is 2.5.

Sample sizes in cohorts with hypothesis testing will be estimated based on at least 80% power with a significance level of 0.05 for two-sided tests or 0.025 for one-sided tests. [redacted]

Table 14-1: Precision by sample size and standard deviation [redacted]

Sample size (N)	Standard deviation (S)				
	1.0	1.5	2.0	2.5	3.0
10	0.72	1.07	1.43	1.79	2.15
15	0.55	0.83	1.11	1.38	1.66
20	0.47	0.70	0.94	1.17	1.40
30	0.37	0.56	0.75	0.93	1.12
40	0.32	0.48	0.64	0.80	0.96

Figure 14-1: Precision by sample size and standard deviation [redacted]



14.7 Minimization of Bias

Selection of subjects, treatment of subjects, and evaluation of study data are potential sources of bias. Methods that may be incorporated in the study design to minimize potential bias include (but are not limited to):

- Limiting subject enrollment in a specific cohort to no more than 25% of total cohort sample size.
- Performing sensitivity analyses beyond the main analysis for the primary objective.

In summary, potential sources of bias that may be encountered in this study have been considered and minimized by careful study design.

15. Ethics

15.1 Statement(s) 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.

16. Study Administration

16.1 Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study site in order to ensure that the study is conducted in accordance with the CIP, the CTA, and the applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed direct access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the IC, Research Authorization (where applicable) and CTA. The principal investigator should also be available during monitoring visits.

16.1.1 Monitoring Visits

Frequency of monitoring visits may be based upon subject enrollment, study compliance, number of adverse events, number of deviations, observations from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents will be reviewed at each study site. Monitoring for the study, including site initiation visits, interim monitoring visits, and closeout visits, will be done in accordance with the study-specific monitoring plan.

Monitoring visits may be conducted periodically to assess study site progress, the investigator's adherence to the CIP, regulatory compliance including, but not limited to, IRB approval and review of the study, maintenance of records and reports, and review of source documents against subject CRFs in accordance to the study-specific monitoring plan. Monitors review study site regulatory and study compliance by identifying observations of non-compliance and communicating those observations along with recommendations for preventative/corrective actions to study site personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular study site.

16.2 Data Management

This study will use an Electronic Data Capture (EDC) 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 is fully validated and controls user access, ensures data integrity, and maintains audit trails.

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 locked and will be retained indefinitely by Medtronic.

User access to the EDC 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.

16.3 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.

16.4 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.

16.5 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.

16.6 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.

16.7 Record Retention

16.7.1 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 ensuring 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.

16.7.2 Sponsor Records

Medtronic shall maintain the following accurate, complete, and current records:

- All correspondence which pertains to the investigation
- Sample of label attached to investigational device
- Signed Investigator Trial Agreements and CV of principal investigator and key members of the investigation study site team (as required by local law), delegated task list
- All approved IC templates, and other information provided to the subjects and advertisements, including translations
- Copies of all IRB approval letters and relevant IRB correspondence and IRB voting list/roster/letter of assurance
- Names of the institutions in which the study will be conducted
- Monitoring visit reports
- Statistical analyses and underlying supporting data
- Final report of the study
- The CIP, study related reports, and revisions
- Study training records for study site personnel and Medtronic personnel involved in the study
- Any other records that local regulatory agencies require to be maintained.

Medtronic records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in stored in secured file cabinets at Medtronic during the course of this study.

After closure of the study, Medtronic will archive records and reports indefinitely.

16.8 Reporting Requirements

16.8.1 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 16.7.1 for investigator records.

16.8.2 Sponsor Reports

Medtronic shall prepare and submit complete, accurate, and timely reports as required per geography and IRB reporting requirements. In addition, Medtronic shall, upon request of the reviewing IRB, provide accurate, complete and current information about any aspect of the investigation.

16.9 Publication and Use of Information

The study will be registered at http://clinicaltrials.gov before first enrollment in the study. Study data and results will be made available as required per regulations.

Medtronic must be notified of any intent to publish data stemming from this clinical study.

Medtronic has developed a separate publication plan that will provide detailed information about a publication committee, if applicable, authorship selection, publication process, and handling requests for data. Publications will be governed by the terms of the investigator agreement and publication plan.

16.10 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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18. Appendices

There are no appendices within this clinical investigational plan.

19. Version History

Version	Summary of changes	Author(s)/Title
1.0	• Initial Release	[redacted] Principal Clinical Research Specialist
2.0	• Updated language throughout document to transfer from 056-F275, Clinical Investigation Plan Template v3.0 to vC. • Administrative Updates [redacted]	[redacted] Principal Clinical Research Specialist [redacted] Principal Statistician
3.0	• Updated to 056-F275, Clinical Investigation Plan Template vC to Rev D [redacted] • Updated background/rationale in accordance with other amendment updates	[redacted] Principal Clinical Research Specialist [redacted] Principal Statistician