Medtronic Closed-Loop Spinal Cord Stimulation System

NCT: NCT05177354

Date: 24FEB2023

Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	Evaluation of Long-term Patient Experience with a Medtronic Closed-Loop SCS System (Closed-Loop SCS study)
Clinical Investigation Plan Identifier	MDT21017
Study Product Name	Pain Rechargeable (RC) system with Inceptiv™ Implantable Neurostimulator (INS)
Sponsor/Local Sponsor	Medtronic Neuromodulation [redacted] Medtronic Australasia Pty Ltd [redacted]
Document Version	4.0
Version Date	06JAN023

Confidentiality Statement

[redacted]

[redacted]

1. Investigator Agreement and Signature Page

Study product Name	Pain RC system with Inceptiv™ INS
Sponsor	Medtronic Neuromodulation
Clinical Investigation Plan Identifier	Evaluation of Long-term Patient Experience with a Medtronic Closed-Loop SCS System (Closed-Loop SCS study)
Version Number/Date	4.0 06JAN2023
I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to comply with the Declaration of Helsinki, the Clinical Investigation Plan, and Good Clinical Practice, as well as local laws, regulations, and standards. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.	
Investigator's Signature	
Investigator's Name	
Institution	
Date	

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2. Glossary

Table 1: Glossary

Term	Definition
AE	Adverse Event
ADE	Adverse Device Effect
ASADE	Anticipated Serious Adverse Device Effect
CV	Curriculum Vitae
CFR	Code of Federal Regulation
CIP	Clinical Investigation Plan
CRO	Clinical Research Organization
CRF	Case Report Form
CTA	Clinical Trial Agreement
DD	Device Deficiency
DMC	Data Monitoring Committee
DoH	Declaration of Helsinki
DTL	Delegated Task List
EC	Ethics Committee
eCRF	Electronic Case Report Form
ECAPs	Evoke Compound Action Potentials
[redacted]	[redacted]
FAL	Foreseeable Adverse Event List
FD	Financial Disclosure
GCP	Good Clinical Practice
IB	Investigator's Brochure

[redacted]

[redacted]

Term	Definition
IC	Informed Consent
ICF	Informed Consent Form
IFU	Instructions For Use
INS	Implantable Neurostimulator
[redacted]	[redacted]
[redacted]	[redacted]
NSR	Non-Significant Risk
[redacted]	[redacted]
PHI	Protected Health Information
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
RA	Regulatory Authority
RC	Rechargeable
SF	Short Form
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCS	Spinal Cord Simulation
SSI	Significant Safety Issue
SADE	Serious Adverse Device Effect
TGA	Therapeutic Goods Administration
UAE	Unavoidable Adverse Event
USM	Urgent Safety Measure

[redacted]

[redacted]

Term	Definition
[redacted]	[redacted]
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analogue Scale

3. Synopsis

Table 2: Synopsis

Title	Evaluation of Long-term Patient Experience with a Medtronic Closed-Loop SCS System (Closed-Loop SCS study)
Clinical Study Type	Prospective, multi-center, randomized, single-blind, investigational, feasibility study
Product Name	Pain RC system with Inceptiv™ INS referred to as Inceptiv in this study
Sponsor/Funding Source	Medtronic Neuromodulation [redacted]
Local Sponsor	Medtronic Australasia Pty Ltd. [redacted]
Indication Under Investigation	The next generation spinal cord stimulator, Inceptiv, is indicated to aid in the management of chronic, intractable pain of the trunk and/or limbs. Patients with stable intractable Angina Pectoris or Peripheral Vascular Disease of Fontaine Stage III or higher will be excluded from the study.
Investigation Purpose	Characterize the efficacy of the next generation, rechargeable, spinal cord stimulator
Product Status	The Inceptiv spinal cord stimulator is investigational
Primary Objective	To demonstrate that the proportion of low-back and/or leg pain subjects having a reduction in overstimulation sensation with Neuro Sense On compared to Neuro Sense

[redacted]

	Off, at the randomization and in-clinic testing visit, exceeds a performance goal of 50%.
Secondary Objectives	1. To characterize the efficacy of spinal cord stimulation (SCS) therapy for the treatment of overall pain in low-back and/or leg pain subjects by evaluating the efficacy responder rate. The efficacy responder rate is defined as the percentage of low-back and/or leg pain implanted subjects who experience at least a 50% improvement in overall pain, as measured by the Visual Analogue Scale (VAS), from Baseline to the 3-Month Visit. 2. To characterize the efficacy responder rate of low-back pain and leg pain in low-back and/or leg pain subjects, as measured by the pain-specific VAS, from Baseline to the 3-Month Visit. The low-back responder rate will be characterized for subjects with baseline back VAS ≥ 60 mm, and the leg responder rate will be characterized for subjects with baseline leg VAS ≥ 60 mm.
[redacted]	[redacted]

[redacted]

	[redacted]
Study Design	Prospective, multi-center, randomized, single-blind, investigational, feasibility study. Eligible patients will be consented and enrolled, undergo a psychological evaluation, have an x-ray or MRI, as needed, be evaluated for baseline assessments, undergo an SCS trial and if successful, undergo the implant of a permanent INS. Following implant, subjects will have their SCS device settings optimized for the Neuro Sense feature. Following device optimization, subjects will be randomized to a sequence of Neuro Sense On and Neuro Sense Off for in-clinic testing. Subjects will then continue being followed periodically for a total study duration of up to 24-months.
Randomization	1:1 randomization (one of the two sequences): Neuro Sense On followed by Neuro Sense Off or Neuro Sense Off followed by Neuro Sense On
[redacted]	[redacted]

[redacted]

[redacted]

	[redacted]
Inclusion/Exclusion Criteria	**Inclusion Criteria:** 1. 18 years of age or older 2. Candidate is undergoing Medtronic SCS device trial for chronic, intractable pain of the trunk and/or limbs due to Failed Back Surgery Syndrome (FBSS), Complex Regional Pain Syndrome (CRPS), or other chronic neuropathic pain without history of surgical interventions. Note: *The sponsor recommends not enrolling patients with chronic pain due to conditions that do not have adequate evidence to support the use of SCS (e.g., post-herpetic neuralgia, focal CRPS etc.)* 3. If being treated for low-back and/or leg pain, o the baseline overall^ VAS is ≥ 60 mm and o baseline back and/or leg pain VAS is ≥60 mm. ^average overall pain in the back and/or leg in the 72 hours prior to the baseline visit, measured using VAS. 4. If being treated for upper limb pain – baseline VAS is ≥ 60 mm for upper limb pain 5. On stable (no change in dose, route, or frequency) prescribed pain medications being used for back and/or leg pain or upper limb pain, as determined by the investigator, for at least 28 days prior to device trial 6. Willing and able to provide signed and dated informed consent 7. Willing and able to comply with all study procedures and visits ***The sponsor strongly recommends only enrolling patients capable of comprehending and consenting in English.** **Exclusion Criteria:** 1. Indicated for an SCS device to treat stable intractable Angina Pectoris, Peripheral Vascular Disease of Fontaine Stage III or higher, or Diabetic Peripheral Neuropathy

[redacted]

	2. Previously trialed or implanted with spinal cord stimulator, peripheral or vagus nerve stimulator, deep brain stimulator or an implantable intrathecal drug delivery system 3. Currently participating, or plans to participate, in another investigational study unless written approval is provided by the Medtronic study team 4. Major psychiatric comorbidity or other progressive diseases that may confound study results, as determined by the Investigator 5. Serious drug-related behavioral issues (e.g., alcohol dependency, illegal substance abuse), as determined by the Investigator Note: *The Sponsor recommends excluding patients on ≥100 MME of opioids/day.* 6. Pregnant or planning on becoming pregnant (if female and sexually active, subject must be using a reliable form of birth control, be surgically sterile, or be at least 2 years post-menopausal) 7. Be involved in an injury claim or under current litigation Note: *this includes patients that are the beneficiary of a successful injury claim.*
Study Procedures and Assessments	**Study Visits** • Enrollment/Baseline • Device Trial • Trial Lead Explant • SCS Implant • Device Activation • Device Optimization (up to one-month) • Randomization and In-Clinic Testing • Visits (3-Month, 6-Month, 12-Month, 18-Month, and 24-Month) **Enrollment/Baseline:** Subjects are considered enrolled at the time the study-specific informed consent form is signed. Subjects in compliance with inclusion/exclusion criteria will be eligible to participate. VAS scores for overall, low-back and leg OR upper limb and neck pain will be collected. Subjects that meet inclusion criteria and none of the exclusion criteria will be asked about their pain and

	medical history, scheduled for a device trial and complete the required assessments. **Device Trial (≤ 28 days post Baseline assessment):** Subjects will be implanted with two percutaneous leads and stimulation will be applied using a wireless external neurostimulator. The trial-phase is not to exceed 10 days. **Trial Lead Explant:** Leads will be explanted at the end of the trial period. Self-reported pain relief will be collected. Subjects who have a 50% or greater reduction in pain will go onto a permanent SCS system implant in the study. **SCS Implant:** An Inceptiv device will be implanted and connected to the lead(s). **Device Activation:** The device will be turned on and the optimization period will begin. [redacted] **Randomization and In-clinic Testing:** Approximately 1-Month post Device Activation, subjects will undergo randomization and in-clinic testing. Subjects will be randomized to one of the two sequences: Neuro Sense On followed by Neuro Sense Off or Neuro Sense Off followed by Neuro Sense On. Subjects will be blinded to the settings tested. In each setting, subjects will perform a series of 3-5 activities, [redacted] which are designed to induce overstimulation. [redacted] Subjects will be asked to rate the intensity of the overstimulation sensation they experienced while

[redacted]

[redacted]

	performing the activity using a 5-point Likert scale after each activity. Subjects will be asked which setting they preferred following the testing of both settings. It is strongly recommended to program the SCS device with Neuro Sense On for the duration of the study. **Visits (3-, 6-, 12-, 18-, and 24-Months post Device Activation):** Following in-clinic testing, subjects will come in for regular visits and efficacy and safety of the therapy will be assessed. Unscheduled visits may occur as necessary. **Phone Calls:** Subjects will be called every week starting after Device Activation through the 3-Month Visit and monthly thereafter with an exception for the weeks or months when the subject has a study required visit. If the subject reports being Unsatisfied with the therapy, as determined by the phone call, the subject may be brought in for an Unscheduled visit for further therapy optimization. Alternatively, if the pain score reported by the subject during the phone call is ≥4, or if they report experiencing overstimulation the site should contact Sponsor Representative to further evaluate the need for therapy optimization; the Sponsor representative may contact the subject to troubleshoot over the phone prior to scheduling an in-clinic visit.
Safety Assessments	The following Adverse Events will be collected: device-related, procedure-related, therapy-related, and serious. All device deficiencies will be collected.

Statistics	For the primary objective, it is hypothesized that the proportion of low-back and/or leg pain subjects (p) having a reduction in overstimulation sensation during Neuro Sense On compared to Neuro Sense Off period exceeds a performance goal of 50%. H_0: $p \leq 50\%$ H_A: $p > 50\%$ The proportion of low-back and/or leg pain subjects with a reduction in overstimulation sensation during Neuro Sense On compared to Neuro Sense Off period will be calculated, with a one-sided 97.5% confidence lower bound. This proportion will be tested against 50% using a binomial exact test. The confidence lower bound needs to be greater than 50%, or equivalently, the p-value must be less than 0.025 to reject the null hypothesis. For the primary objective, PASS 2020 Tests for One Proportion was used to calculate the sample size, with a null proportion of 50%, and an alternative proportion of 80%; 28 subjects are needed to achieve more than 90% power with a one-sided test and alpha = 0.025. This is a subset of the total device implanted low-back and/or leg pain subjects.  The first secondary objective is to characterize the overall responder rate, which is defined as the percentage of low-back and/or leg pain implanted subjects who experience at least a 50% improvement in overall pain, as measured by the VAS, from Baseline to the 3-Month Visit. The other secondary objective is to characterize the responder rate separately for low-back or leg pain, as

	measured by the pain-specific VAS, from Baseline to the 3-Month Visit. The low-back responder rate will be characterized for subjects with baseline back VAS ≥ 60 mm, and the leg responder rate will be characterized for subjects with baseline leg VAS ≥ 60 mm. Up to 45 implanted subjects with low-back and/or leg pain are desired to characterize the responder rates at the 3-Month Visit. The proportion of responders will be presented for both secondary objectives, with 95% confidence intervals. Information from subjects with data available at baseline and the 3-Month Visit will be used for these objectives.  Adverse events and device deficiencies will be summarized using tables displaying the frequency and percentage of event, as well as number of subjects experiencing event. Adverse events will be summarized by seriousness as well.

4. Introduction

4.1 Background

Spinal cord stimulation (SCS) is a therapy for the treatment of chronic pain that relies on the application of mild electrical stimulation delivered to the dorsal column fibers of the spinal cord via a lead or leads implanted in the epidural space. The electrical stimulation used in the therapy is provided by an external neurostimulator during a screening trial, which is conducted to determine if SCS could work long-term for a patient. If a patient has a successful screening trial (typically defined as ≥ 50% pain relief), then a permanent implantable pulse generator (IPG) would be implanted in the patient and provide the electrical stimulation to the dorsal column via the epidurally placed leads.

Medtronic received US FDA approval for its first SCS IPG in 1984. In the nearly 40 years since that first approval other companies have entered this space, numerous clinical studies have been conducted and

real-world data sets collected demonstrating the efficacy and effectiveness of SCS in alleviating chronic pain, refractory to conventional treatment. In recent years, as knowledge has grown, attention has shifted towards understanding the impact of different stimulation parameters to further improve patient outcomes.

A variety of stimulation paradigms, involving different pulse rate, duty cycle, lead location and automatic vs. manual programming, have been successfully trialed in this patient population including: High frequency (≤10 kHz) stimulation[1], burst[2,3], dorsal root ganglion stimulation[4], combination of high frequency and low frequency[5], differential targeted multiplexing (DTM)[6] and closed loop SCS (e.g., position-adaptive)[7–9]. These therapy options are also characterized as paresthesia-based[1,10] or paresthesia-free[1,8], depending on the mode of pain-relief. Responder rates (≥50% pain relief) of over 80% have been reported in each of these studies; the pain relief was also found to be sustained long-term.[11,12,2,8] In addition to pain relief, patients also experienced improvements in quality of life, function, sleep quality and reduction/elimination of pain medication[2,3].

While the efficacy of SCS in alleviating chronic pain has been demonstrated for various indications, it is not without unwanted side effects. One such adverse effect, overstimulation, is the focus of this investigation. Overstimulation occurs when the intensity of the delivered stimulation reaches a level where a patient may experience discomfort or even pain. This event typically occurs when the distance between the spinal cord and the epidural lead(s) decreases, which may result in the spinal cord receiving a larger amount of stimulation than desired. [redacted]

Since 2011, Medtronic has utilized AdaptiveStim™ Technology to address overstimulation[9]. AdaptiveStim uses an accelerometer within the INS to sense a change in position. The AdaptiveStim feature allows for certain therapy intensities to be set for six or seven positions, depending on the model a patient has implanted. Based on feedback from the patient, a healthcare practitioner can set the desired intensity, and when a patient changes position into one of the pre-set positions, the intensity is automatically adjusted. This is an effective feature that began to address this therapy-limiting issue of overstimulation but given its limitation of only adjusting for certain positions and responding on the order of seconds, not milliseconds, Medtronic is seeking to improve upon the feature aimed at addressing overstimulation [redacted]

Medtronic's closed-loop algorithm, uses the evoked compound action potential (ECAP), which is the spinal cord's physiological response to stimulation,[13] to adjust the amplitude of stimulation, if required. ECAPs are the summed action potentials elicited from a nerve or group of nerves in response to a stimulus. Parker et al. were the first to report recording human ECAPs from the Dorsal Columns (DC) of the spinal cord using the lead that is used to deliver conventional SCS[13]. Prior to this, most ECAPs were recorded using invasive microelectrode recordings in animals. Since then, the group has reported further studies of spinal cord ECAPs, with various stimulation parameters, lead locations and spacing, from both humans and sheep[14,15]. [redacted]

[redacted]

Recordings of spinal cord activity in response to stimulation typically have two major components: the

[redacted]

[redacted]

Saluda then launched their pivotal trial at 20 sites in the United States, the EVOKE study, in 2017. EVOKE was a double blind, randomized controlled study, with conventional (open loop) SCS forming the control arm. One hundred and thirty-four patients with chronic back or leg pain, VAS score of >= 60 mm, refractory to conventional treatment, and Oswestry Disability Index of 41-80, and no previous experience with SCS, were enrolled and randomized. Eighty-two percent of the 125 patients that completed the 3-Month follow-up experienced >=50% pain relief compared to 60.2% in the open-loop group. The safety profile of the two-arms was similar. No adverse events were attributed to sensing ECAPs using closed-loop feedback stimulation. These outcomes were sustained through the 12-month and 24-month follow-ups. [18,19]

[redacted]

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[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.2 Purpose

The purpose of the Closed-Loop SCS study is to further our understanding of closed-loop SCS in patients implanted with the Inceptiv INS. The Closed-loop SCS study is a prospective, multi-center, randomized,

[redacted]

single-blind, investigational, feasibility study. This is a first-in-man study since the fully implantable Inceptiv device has not been studied in humans. The study will advance our knowledge on the long-term effects of the closed-loop feature on overstimulation.

5. Objectives

5.1 Primary Objectives

To demonstrate that the proportion of low-back and/or leg pain subjects having a reduction in overstimulation sensation with Neuro Sense On compared to Neuro Sense Off, at the randomization and in-clinic testing visit, exceeds a performance goal of 50%.

Overstimulation is defined as an uncomfortable sensation of stimulation (intense tingling, shocking, jolting) brought about by protocol-prescribed activities [redacted]. This overstimulation sensation is transient and reversed by the subject returning to a neutral position.

5.2 Secondary Objectives

1. To characterize the efficacy of spinal cord stimulation (SCS) therapy for the treatment of overall pain (for low-back and/or leg pain subjects) by evaluating the efficacy responder rate. The efficacy responder rate is defined as the percentage of implanted subjects who experience at least a 50% improvement in overall pain, as measured by the Visual Analogue Scale (VAS), from Baseline to the 3-Month Visit.
2. To characterize the efficacy responder rate within in each type of pain (low-back or leg) for low-back and/or leg pain subjects, as measured by the pain-specific VAS, from Baseline to the 3-Month Visit. The low-back responder rate will be characterized for subjects with baseline back VAS ≥ 60 mm, and the leg responder rate will be characterized for subjects with baseline leg VAS ≥ 60 mm.

[redacted]

[redacted]

6. Study Design

The study is expected to be conducted at up to ten study sites located in Australia. Up to 140 subjects will be enrolled in the study to ensure up to 57 subjects with low-back and/or leg pain and up to 12 subjects with upper limb and/or neck pain are implanted with the study device.

Up to 110 Inceptiv devices may be used in the study. To reduce the possibility of atypical results from a site overly influencing the study, no more than 20% of the total implanted population will be from each site unless the site gets pre-approval from Medtronic for additional implants.

Subjects will be enrolled, and baseline data will be collected. Those meeting all inclusion criteria and no exclusion criteria will undergo a device trial. Subjects with sufficient pain relief during the trial will be implanted with the study device and undergo Device Optimization for 1-Month. Approximately 1-Month post Device Activation, subjects will undergo in-clinic testing. Subjects will be randomized at the in-clinic visit to one of the two sequences: Neuro Sense On followed by Neuro Sense Off or Neuro Sense Off followed by Neuro Sense On. Subjects will be blinded to the settings tested. In each setting, subjects will perform a series of activities and asked to rate the intensity of the overstimulation sensation they experienced while performing the activity using a 5-point Likert scale. [redacted] It is recommended that the Neuro Sense feature be turned ON at the end of the in-clinic testing visit, unless the patient prefers the Neuro Sense OFF setting. All subjects will then be followed for up to 24-months following device activation; scheduled study visits will occur at 3-, 6-, 12-, 18-, and 24-months post device activation.

[redacted]

6.1 Duration

The expected total study duration is approximately 48 months, representing approximately 24 months of enrollment and 24 months of subject follow-up. Subjects will exit the study after completion of their 24 Month Visit.

6.2 Rationale

Spinal Cord Stimulation is a well-established therapy for the treatment of chronic pain with numerous clinical studies demonstrating effective pain relief.[24–27,18,28] Recently, effective pain relief using conventional, low-dose therapy coupled with a closed-loop algorithm based on physiological feedback from the implanted subject has been demonstrated.[29] The use of a closed-loop algorithm in SCS is not a new concept. Medtronic first introduced an early form of a closed-loop algorithm based on positional changes in 2011,[28] which demonstrated benefit to patients with significant pain relief and convenience. Patients treated with SCS systems report under-stimulation or over-stimulation induced by movement.[30] The variation in perceived intensity is often attributed to changes in the distance between the implanted lead and the spinal cord resulting in increased or decreased numbers of dorsal column nerve fibers recruited during stimulation. Published pre-clinical and clinical feasibility data have demonstrated the feasibility to measure ECAPs in the spinal cord from the epidural space.[14,13,15] These studies support the use of features extracted from the ECAP as a measure of the level of neural recruitment to serve as a feedback signal for continuous adjustment of stimulation amplitude (i.e., closed-loop control).

The primary objective for this study is to demonstrate that the proportion of subjects having a reduction in overstimulation sensation with Neuro Sense On compared to Neuro Sense Off exceeds a performance goal of 50% which highlights the new device feature.

Additionally, secondary objectives to characterize improvement in pain has historically been used in SCS studies. [redacted]

7. Product Description

7.1 General

The Inceptiv System consists of investigational and market-released products.

[redacted]

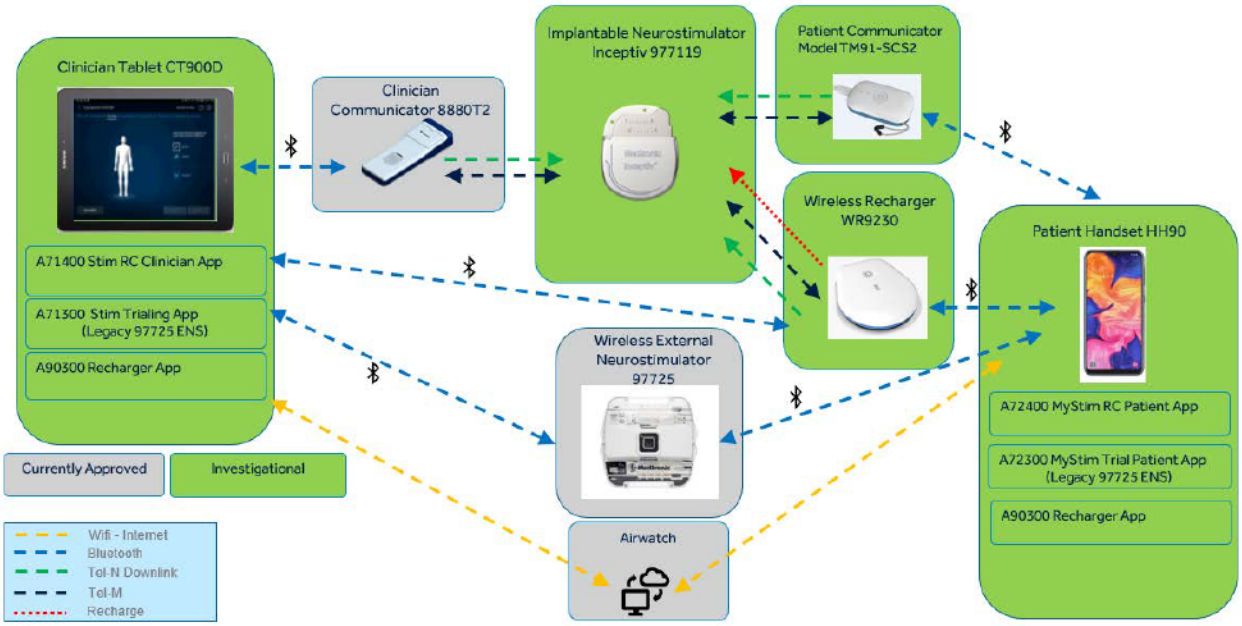


Figure 4: System Overview

The study will be conducted using the products described in Table 3. Instructions for use of the products used in this study are provided in their respective manuals or Investigator's Brochure.

Table 3: System Product Information

Product	Model	Manufacturer	Investigational or Market-released
Inceptiv Implantable Neurostimulator	977119	Medtronic	Investigational
Wireless External Neurostimulator	97725	Plexus	Market-released
Leads: Vectris™ SureScan™ MRI 1x8 Compact Or Specify™ SureScan™ MRI 5-6-5	977A260, 977A275, 977A290 977C165, 977C190	Medtronic	Investigational upon opening
Lead: Vectris™ 1x8 Compact	977D260, 977D275, 977D290	Medtronic	Market-released
Clinician Tablet	CT900D and/or CT900E	Samsung	Investigational

Product	Model	Manufacturer	Investigational or Market-released
Clinician Programmer Application (version 1.0.2576 or newer)	A71400	Medtronic	Investigational
Stimulation Trialing Clinician Programmer Application (version 2.0.247 or newer)	A71300	Medtronic	Investigational
Programmer Platform Software-Communication Manager Application (version 1.0.1213 or newer)	A901	Medtronic	Investigational
Patient Data Service Application (version 1.0.828 or newer)	A902	Medtronic	Investigational
Patient Handset	HH90	Samsung	Investigational
Patient Programmer Application (version 1.0.864 or newer)	A72400	Medtronic	Investigational
Patient Programmer Trialing Application (version 5.0.800 or newer)	A72300	Medtronic	Investigational
Patient Telemetry Communicator	TM91SCS2	Jabil	Investigational
Recharger Application (version 1.0.596 or newer)	A90300	Medtronic	Investigational
Recharger	WR9230	Jabil	Investigational
Recharger Subsystem SCS Therapy	RS7230	Jabil	Market-released
Communicator	8880T2	Plexis	Market-released
Connector Plug	B31060	Medtronic	Market-released
Boot	37500301, 37500302	Jabil	Market-released
Recharger Belt	FP9000 (S, M, L, XL)	Jabil	Market-released
Carrying Case	Not applicable	Protech	Market-released

All materials that may contact tissues and/or body fluids are presented in Table 4.

Table 4: Materials in contact with tissues and/or body fluids

Product	Model	Materials
Implantable Neurostimulator		
Inceptiv Implantable Neurostimulator	977119	• Titanium grade 9 Ti-3A1-2.5V

[redacted]

Product	Model	Materials
		• Titanium Grade 5 Ti-6Al-4V • Titanium Grade 1 • Polysulfone with 0.5% titanium dioxide; siloxane coated, • Liquid silicone rubber (Silastic® Q7-4850) with titanium dioxide • Enhanced-tear resistant (ETR) silicone rubber (Silastic® Q7-4735) • Silicone adhesive, (Nusil MED-2000)
Leads: Vectris™ SureScan™ MRI 1x8 Compact	977A260, 977A275, 977A290	• Epoxy, fluoropolymer, MP25N, platinum-iridium, polyurethane, tantalum • Anchor: Silicone rubber • Anchor dispenser tool: Polycarbonate, polytetrafluorooethyene, Stainless steel • Guidewire, needles, tunneling rod, tunneling tip, tube: Stainless steel • Stylets: Polpropylene, Stainless steel
Specify™ SureScan™ MRI 5-6-5	977C165, 977C190	• Platinum-iridium, Silicone rubber, Polyurethane, Titanium dioxide, MP35N, Epoxy • Anchor: Silicone rubber • Passing elevator: Acetal resin, Silicone rubber, Barium sulfate, • Lead blank: Silicone rubber, Barium sulfate • Tunneling tools: Stainless steel, Fluoropolymer • Torque wrench: Polymer, Stainless steel
External Neurostimulator		
Wireless External Neurostimulator	97725	• ABS/polycarbonate blend Cycoloy • Clear polyester film
Lead: Vectris™ 1x8 Compact	977D260, 977D275, 977D290	• Epoxy, fluoropolymer, MP35N, platinum-iridium, polyurethane, tantalum • Guidewire, needles: stainless steel • Stylet: Polpropylene, stainless steel
Clinician Programmer		
Clinician Tablet	CT900D and/or CT900E	Non-implantable
Clinician Programmer Application	A71400	Non-implantable

[redacted]

Product	Model	Materials
Stimulation Trialing Clinician Programmer Application	A71300	Non-implantable
Programmer Platform Software-Communication Manager Application	A901	Non-implantable
Patient Data Service Application	A902	Non-implantable
Recharger Application	A90300	Non-implantable
Patient Programmer		
Patient Handset	HH90	Non-implantable
Patient Programmer Application	A72400	Non-implantable
Patient Programmer Trialing Application	A72300	Non-implantable
Recharger Application	A90300	Non-implantable
Other		
Patient Telemetry Communicator	TM91-SCS2	Non-implantable
Recharger	WR9230	Non-implantable
Recharger Subsystem SCS Therapy	RS7230	Non-implantable
Communicator	8880T2	Non-implantable
Connector Plug	B31060	55D Polyurethane
Boot	37500301, 375003	Non-implantable
Recharger Belt	FP9000	Non-implantable
Carrying Case	Not applicable	Non-implantable

7.1.1 Inceptiv Implantable Neurostimulator

The Inceptiv implantable neurostimulator is a rechargeable, multiprogrammable device that delivers electrical stimulation through one or more leads. The stimulation settings are stored in programs to target specific effects or areas. A program is a specific combination of pulse width, rate, and intensity settings acting on a specific electrode combination.

Medtronic has developed an optional closed-loop feature to improve a patient's experience with SCS therapy, specifically targeting overstimulation. The closed-loop algorithm is able to sense the body's physiological ECAP response, and automatically react, based on the spinal cord's response to stimulation.

[redacted]

7.1.2 Vectris SureScan MRI 1x8 Compact

The percutaneous leads are connected to the implantable neurostimulator. Each lead has electrodes on the distal end; the proximal (connector) end fits into an 8-conductor connector. A stylet can be inserted into the proximal end of the lead to aid in positioning the lead.

7.1.3 Specify SureScan MRI 5-6-5

The surgical leads are connected to the implantable neurostimulator. The lead has 16 electrodes on the distal end; two proximal ends fit into 8-coductor connectors. Up to three low-back and/or leg subjects may be implanted with surgical leads.

7.1.4 Wireless External Neurostimulator

The Wireless External Neurostimulator is part of a neurostimulations system used for intraoperative testing during lead placement and for trial stimulation outside of the operating room.

7.1.5 Vectris MRI 1x8 Compact

The trial leads are connected to the wireless external neurostimulator. Each lead has electrodes on the distal end; the proximal (connector) end fits into an 8-conductor connector. A stylet can be inserted into the proximal end of the lead to aid in positioning the lead. The trial leads are contraindicated for long-term implantation and must be removed within ten days of implant.

7.1.6 Boot

The boot is an external single-use-only accessory that is used with the wireless external neurostimulator to adhere the wireless external neurostimulator externally to the patient's body during the duration of the trial period.

7.1.7 Clinician Tablet

The Clinician Tablet, a Samsung tablet with Android operating system, is a nonsterile, commercially available, off-the shelf, non-medical device. The Clinician Programmer Application and the Stimulation Clinician Trialing Programmer Application operate on this platform.

7.1.8 Clinician Programmer Application

The Clinician Programmer Application (CPA) is a mobile medical application designed for use by clinicians to interrogate and program medical devices. It is designed to configure and manage SCS therapy parameters by the clinicians for Inceptiv. The CPA will run on the Clinician Tablet which is a non-medical off-the-shelf tablet. Additionally, with the CPA, the Communication Manager Application (non-medical), and Patient Data Services Application (non-medical) will be utilized. The Communicator will serve as a telemetry bridge between the Clinician Tablet and Inceptiv.

7.1.9 Patient Programming Application

The Patient Programming Application (PPA) will operate on the Patient Handset and be used by patients (and/or their caregivers) to manage their therapy provided by Inceptiv.

7.1.10 Stimulation Trialing Clinician Programmer Application

The Stimulation Trialing Clinician Programmer Application allows clinicians to program wireless external neurostimulators during trialing by adjusting the rate, pulse width and amplitude of the therapy provided to the patient.

7.1.11 Patient Programmer Trialing Application

The Patient Programmer Trial Application operates on the Patient Handset and will be used by patients to manage their therapy during a trial. The Patient Programmer Trial Application allows the patient to make therapy programming adjustments to the wireless external neurostimulator. The Patient Handset has a user interface display and Bluetooth interface to the wireless external neurostimulator. The Patient Handset is constrained to a Commercial-Off-The-Shelf Android mobile phone.

7.1.12 Patient Telemetry Communicator

The Patient Handset works in conjunction with the Patient Telemetry Communicator to provide the programming/controlling capabilities to patients. Specifically, a communication bridge is formed from the Patient Handset, using Bluetooth Low Energy (BLE) signals, through the Telemetry Module to Inceptiv, using Tel-M and Tel-Np communication protocols, respectively.

7.1.13 Communicator

The Communicator is considered part of the clinician programmer system. The Communicator was originally developed for use across Medtronic Neuromodulation therapies. It is a non-sterile, battery-operated, external device designed to create a communication bridge between the Mobile Platform and Inceptiv.

7.1.14 Connector Plug

The Connector Plug is a sterile device that is intended to be inserted into the unused connector of Inceptiv.

7.1.15 Recharger Subsystem

The Recharger Subsystem is a kit that is designed to support the patient in their recharge needs.

The fixation belt is intended to support the Recharger during a patient's recharge session; however, the patient may choose to hold the recharger manually or via other means. The Recharger Belt is not required for the recharger to achieve its intended purpose, which is to recharge the Inceptiv.

- Recharger and application
- Fixation Belt
- CD9000 Charging Dock + Power Adapter
- USB cord and AC adaptor (commercial, off-the-shelf non-medical devices)
- System carrying case (non-medical device)

7.2 Manufacturer

There are several manufacturers of the study products, see Table 3.

[redacted]

7.3 Packaging

The Inceptiv device and accompanying investigational products will be labeled "Exclusively for clinical investigations".

7.4 Intended Population

The study device is indicated for SCS as an aid in the management of patients with chronic, intractable pain of the trunk and/or limbs. Study eligibility criteria must be met to participate, see Section 9.

7.5 Equipment

The following equipment must be available at each study site to support study activities:

- Fluoroscopy/x-ray with electronic output

This equipment will be maintained/calibrated according to the study site's standard protocol. Maintenance and calibration reports may be monitored periodically by the monitor.

7.6 Product Use

Instructions for Inceptiv and accompanying products will be provided in the Investigator's Brochure. Refer to existing manuals for market released product.

7.7 Product Training Materials

Investigators will be chosen to participate in this study based on being qualified by training, education, and relevant experience appropriate for the use of spinal cord simulators. Study specific training will be conducted pertinent to the involvement of personnel conducting study activities and Investigator responsibilities. All Investigators and site personnel will be trained on the Clinical Investigation Plan (CIP) prior to their participation on the study.

7.8 Product Receipt and Tracking

Sites with these clinically labeled products will track disposition upon receipt or return of the products, as well as upon implant or explant of the product. Tracking includes dates and quantities received, used, explanted and returned. Lot/serial numbers and expiration dates will be documented and used for traceability. All of these elements will be entered on an electronic Case Report Form (eCRF).

7.9 Product Storage

Investigational product, once received at the study site, must be stored in a secure location at the study site. It is the responsibility of the investigator to correctly handle, store, and track the investigational products maintained at the study site. Investigational products will be used only in the clinical study according to the CIP.

7.10 Product Return

All explanted devices (devices or permanent leads) should be returned to Medtronic for analysis when permissible by local laws and regulations. If the products are explanted but not returned, a justification will be reported on the appropriate case report forms or disposition logs. To receive a Returned Product Mailer Kit, please contact your local Medtronic field personnel.

[redacted]

7.11 Product Accountability

Product delivery

Market-released products:

Commercially available product supply will be managed in a manner consistent with other market-released products.

Investigational products:

Investigational products will be distributed to a study site only when Medtronic has received all required documentation and has notified the study site of study site activation. Distribution of investigational product to study sites during the study will be managed by Medtronic and can only be ordered by Medtronic personnel.

Product receipt and tracking

Market-released products:

There are no additional local requirements related to the market-released product beyond what is collected by Medtronic on the eCRF, this is the Investigator's responsibility and should be recorded in the subject's medical records, but will not be collected by Medtronic.

Investigational products:

The study site is responsible for maintaining tracking of the investigational products during the study. The tracking method might vary, but could use either electronic or paper accountability logs provided by Medtronic. The accountability logs must be maintained at each study site and updated when the investigational product is received, opened, implanted, explanted, disposed of or returned to Medtronic. In addition to tracking the date of events, the accountability log tracks product information including, but not limited to, date, model/serial number, and expiration date for the received product, subject ID of the implanted subject, reason(s) for and method of destruction/disposal for explanted components not returned to Medtronic (if applicable), and name of the person responsible for return or destruction/disposal (if applicable).

Medtronic will perform periodic reconciliation of the investigational product to ensure traceability.

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/site shall:

- Investigator/site is qualified by training, education, and relevant experience appropriate to the use of the product and associated procedures (Spinal Cord Stimulation)
- Investigator/site expects to have adequate time and resources to conduct the study throughout the duration of the study (up to 24-months of follow up activities)

[redacted]

- Investigator/site has access to an adequate number of eligible subjects (enroll at least 1 patient per month)
- Investigator/site has the ability to comply with applicable Ethics Committee (EC) and regulatory requirements
- Investigator is not debarred, disqualified, or working under sanctions
- Site has adequate facilities for study subjects to complete study assessments
- Has ability to perform fluoroscopy/x-ray with electronic output

8.2 Study Site Activation

During the activation process (prior to subject enrollment), Medtronic will train study site personnel on the Clinical Investigation Plan, relevant standards and regulations, informed consent (IC), 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:

- Ethics Committee (EC) approval (and voting list when a site team member is an EC member) of the current version of the CIP and IC.
- EC approval or acknowledgement of subject-facing materials and subject recruitment/advertising (if applicable)
- Regulatory Authority (RA) approval or notification, if applicable
- Fully executed Clinical Trial Agreement (CTA)
- Financial disclosure
- CV of investigators and key members of the investigation study site team (as required). The signature on the CV must be dated within 3 years prior to the date of activation of the study site.
- Documentation of delegated tasks
- Sponsor technical support list
- Documentation of study training (a separate training document will overview topics and include details on the format of delivery including the CIP, informed consent process, data collection tools, regulations and the devices)
- Additional requirements imposed by local regulations, the EC and RA shall be followed, if appropriate.

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.

[redacted]

8.3 Role of the Sponsor Representatives

In addition to performing monitoring and auditing activities, 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
- Technical support under the supervision of a study Investigator, but no data entry, shall be performed by Medtronic personnel or their representatives at study sites

In addition, for this study, sponsor representatives may be authorized by the Principal Investigator to perform the following significant study related duties:

- Support study Investigators in performing the study trial and implant procedures including device programming, interrogations and transmission of study data
- Support data collection during the trial and implant procedure and device testing
- Support data collection during the study visits
- Contact subjects to troubleshoot their device settings
- Due to extenuating circumstances, trained Medtronic personnel may remotely assist with in-person technical support via live video streaming from a secure and compliant service. The live stream will not be recorded and will be accessible only to authorized sponsor technical support representative through a secure service during the visits

Any data collection completed by Medtronic personnel will be clearly identified as such.

9. Selection of Subjects

9.1 Study Population

The intended study population includes patients who are candidates for undergoing a SCS device trial per approved indications, except for patients indicated for an SCS device to treat stable intractable Angina Pectoris or Peripheral Vascular Disease of Fontaine Stage III or higher. Study eligibility criteria must be met to participate, see Section 9.

9.2 Subject Enrollment

When a subject and the Principal Investigator or authorized designee, as required, have personally signed and dated the Informed Consent Form (ICF), the subject is considered a subject enrolled in the study. The date the subject signed the ICF and other privacy language, if applicable must be documented in the subject's medical records.

Subjects will be screened to ensure they meet all the inclusion and none of the exclusion criteria prior to study enrollment.

[redacted]

9.3 Inclusion Criteria

The patient must meet for the following criteria to be included in the study:

1. 18 years of age or older
2. Candidate is undergoing a Medtronic SCS device trial for chronic, intractable pain of the trunk and/or limbs due to Failed Back Surgery Syndrome (FBSS), Complex Regional Pain Syndrome (CRPS), or other chronic neuropathic pain without history of surgical interventions.

   Note: *The sponsor recommends not enrolling patients with chronic pain due to conditions that do not have adequate evidence to support the use of SCS (e.g., post-herpetic neuralgia, focal CRPS etc.)*
3. If being treated for low-back and/or leg pain,
   - the baseline overall^ VAS is ≥ 60 mm and
   - baseline back and/or leg pain VAS is ≥60 mm.

   ^average overall pain in the back and/or leg in the 72 hours prior to the baseline visit, measured using VAS.
4. If being treated for upper limb pain, the baseline VAS is ≥ 60 mm for upper limb pain.
5. On stable (no change in dose, route, or frequency) prescribed pain medications being used for back and/or leg pain or upper limb pain, as determined by the Investigator, for at least 28 days prior to the device trial
6. Willing and able to provide signed and dated informed consent
7. Willing and able to comply with all study procedures

***The sponsor strongly recommends only enrolling patients capable of comprehending and consenting in English.**

9.4 Exclusion Criteria

The patient must not meet any of the following criteria to be included in the study:

1. Indicated for an SCS device to treat stable intractable Angina Pectoris, Peripheral Vascular Disease of Fontaine Stage III or higher, or Diabetic Peripheral Neuropathy
2. Previously trialed or implanted with a spinal cord stimulator, peripheral or vagus nerve stimulator, deep brain stimulator, or an implantable intrathecal drug delivery system
3. Currently participating, or plans to participate, in another investigational study unless written approval is provided by the Medtronic study team
4. Major psychiatric comorbidity or other progressive disease that may confound study results, as determined by the Investigator
5. Serious drug-related behavioral issues (e.g., alcohol dependency, illegal substance abuse), as determined by the Investigator

   Note: *The Sponsor recommends excluding patients on ≥100 MME of opioids/day.*

[redacted]

6. Pregnant or planning on becoming pregnant (if female and sexually active, subject must be using a reliable form of birth control, be surgically sterile, or be at least 2 years post-menopausal)
7. Be involved in an injury claim or under current litigation

   Note: *this includes patients that are the beneficiary of a successful injury claim.*

10. Study Procedures

10.1 Schedule of Events

Figure 5 and Figure 6 are flow diagrams of how subjects will complete the study.

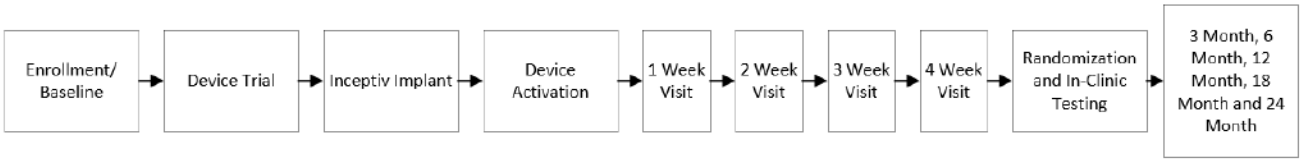


Figure 5: Study Flow Diagram

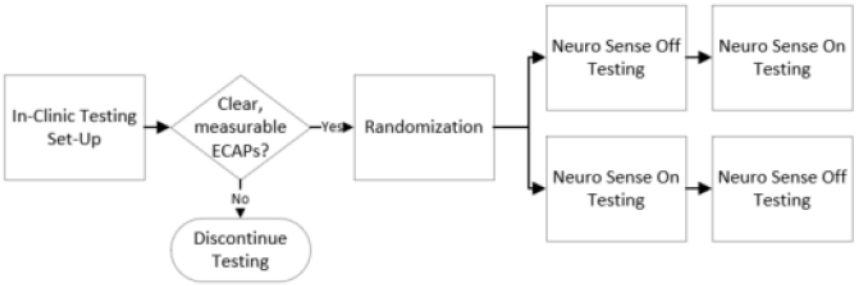


Figure 6: In-Clinic Testing Flow Diagram

10.2 Data Collection

Data collection requirements are summarized in Table 5 below.

Table 5: Data collection and study procedure requirements at subject visits

Study Procedures, Tasks and Data Collection	Enrollment/Baseline	Device Trial	Trial Lead Explant	Inceptiv Implant	Phone Calls[6]	Device Activation	Device Optimization (Weeks 1-4)	Randomization and In-Clinic Testing	Visits 3-, 6-, 12-, 18-, and 24-Months	Unscheduled	System Modification
Informed Consent Process	X										
Psychological Evaluation	X										
MRI or X-Ray	X[1]										
Inclusion/Exclusion Assessment	X										

[redacted]

Study Procedures, Tasks and Data Collection	Enrollment/Baseline	Device Trial	Trial Lead Explant	Inceptiv Implant	Phone Calls[6]	Device Activation	Device Optimization (Weeks 1-4)	Randomization and In-Clinic Testing	Visits 3-, 6-, 12-, 18-, and 24-Months	Unscheduled	System Modification
Demographics and Medical History	X										
Pain Medications	X	X	X	X	X	X	X	X	X	X	X
VAS	X								X		
[redacted]											
Fluoroscopy/X-Ray		X		X						X[5]	X[5]
Device Information		X		X							
Device Data		X	X	X		X	X	X	X	X	X
[redacted]											
Randomization Process								X	X[7]		
Algorithm Set-Up Parameters								X	X[7]		
ECAP recordings								X	X[7]		
Subject Rating of Stimulation Sensation with Likert Scale								X	X[7]		
[redacted]											
Adverse Events (AEs)	As they occur										
Device Deficiency (DD)	As they occur										
Study Deviations	As they occur										

[1]Optional
[2]For subjects with low-back and/or leg pain
[3]In subjects with upper limb pain
[4]For subjects with neck pain
[5]If necessary
[6]Every week starting after Device Activation through the 3-Month Visit and monthly thereafter except for the months when the subject has a study required visit
[7]At the 3- and 12-Month Visits only
[8]At the 3-, 12-, and 24-Month Visits only
[9]Starting at the end of the Device Activation visit through the 24-Month Visit

[redacted]

[redacted]

[6]Every week starting after Device Activation through the 3-Month Visit and monthly thereafter except for the months when the subject has a study required visit
[7]At the 3- and 12-Month Visits only
[8]At the 3-, 12-, and 24-Month Visits only
[9]Starting at the end of the Device Activation visit through the 24-Month Visit

10.3 Scheduled Visit Windows

Medtronic will provide the target dates and windows for each visit to the study site, as applicable. Should a subject miss a visit or the visit fall outside the pre-specified window, a study deviation must be reported and the original visit schedule maintained for subsequent visits. A late visit is preferred over a missed visit but must be accompanied by a study deviation. Visit windows are listed in Table 6.

Table 6: Data collection and study procedure requirements at subject visits

Visit	Visit ranges
Enrollment/Baseline	Not applicable
Device Trial	≤ 28 days after Enrollment/Baseline
Device Trial Phone Calls	Daily, as needed
Device Trial Lead Explant	≤ 10 days from Device Trial
SCS Implant	≤ 60 days after end of Device Trial
Phone Calls	Weekly starting after Device Activation through the 3-Month Visit and monthly thereafter with an exception for the weeks or months when the subject has a study required visit.
Device Activation (Day 0)	9-16 days after implant: pending wound healing
[redacted]	[redacted]
Randomization and In-clinic Testing	30 days ± 5 days from Day 0 (visit may occur on the same day as Visit 4 if Visit 4 is occurring within window, and at the discretion of the PI)
3-Month	90 days ± 15 days from Day 0
6-Month	180 days ± 15 days from Day 0
12-Month	360 days ± 30 days from Day 0
18-Month	540 days ± 30 days from Day 0

[redacted]

Visit	Visit ranges
24-Month	720 days ± 30 days from Day 0

10.4 Prior and Concomitant Medications

Only prescribed medications used for the treatment of low-back, leg pain and upper limb pain will be collected during the study. [redacted] Any changes to subject's pain medications while they are enrolled in the study will be documented in the subject's medical records and the study database.

[redacted]

All medications used to treat adverse events (regardless of their reason prescribed) will be documented on an eCRF.

10.5 Subject Consent

Informed consent is defined as a legally effective documented confirmation of a subject's voluntary agreement to participate in a particular study after information has been given and explained to the subject on all aspects of the study that are relevant to the subject's decision to participate. This process includes obtaining an IC form and other privacy language as required by law that has been approved by the study site's EC and signed and dated by the subject. A subject may only consent after information has been given and explained to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate.

Prior to enrolling subjects, the IC and other privacy language as required by law must be approved by the EC. The document(s) must be controlled (i.e., versioned and dated) to ensure it is clear which version(s) were approved by the EC. Any adaptation of the sample IC must be reviewed and approved by Medtronic and the EC reviewing the application prior to enrolling subjects.

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, consent may be requested from subjects to confirm their continued participation.

The template IC will be provided under separate cover.

Prior to initiation of any study-specific procedures, IC must be obtained from the subject. Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize study sites to submit subject information to the study sponsor. The IC process must be conducted by the Principal Investigator or an authorized designee, and the IC Form and other privacy

[redacted]

language as required by law must be given to the subject in a language he/she is able to read and understand. The process of IC must be conducted without using coercion or undue improper influence on or inducement of the subject to participate by the investigator or other study site personnel. The IC process shall not waive or appear to waive subject's legal right. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

The subject must have ample time and opportunity to read and understand the IC form, to inquire about details of the study, and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the subject.

When the subject decides to participate in the study, the IC must be signed and personally dated by the subject and Investigator or authorized designee, as required by the IC, and ensured by the Principal Investigator or his/her authorized designee. If applicable, independent witness must be present throughout the entire informed consent process, and the written informed consent form and any other information related to the study must be read aloud and explained to the prospective subject. If applicable, witness shall also sign and personally date the consent form to attest that the information in the IC Form was accurately explained and clearly understood by the subject, and that informed consent was freely given.

A copy of the IC and other privacy language, signed and dated as required by law, must be provided to the subject.

If the IC is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study-related procedures. It is best practice for the IC process to be documented in the subject's case history, regardless of circumstance. In the event the subject cannot read and/or write, a witnessed (impartial third party) IC Form will be allowed, provided detailed documentation of the process is recorded in the subject's case history and the witness signs and dates the IC Form. In the event the subject cannot read and/or write, the IC process shall be obtained through a supervised oral process if the local regulation allows. An independent and impartial witness must be present during this process. The IC and any other information must be read aloud to the prospective subject. Whenever possible, either the subject shall sign and personally date the informed consent form. The witness signs and personally dates the IC attesting that the information was accurately explained and that informed consent was freely given.

The original of the signed IC must be filed in the hospital/clinical chart and/or with the subject's study documents.

The IC and other privacy language as required by law must be available for monitoring and auditing. Any Medtronic Field personnel who support the study procedure must be able to review the subject's signed and dated IC and verify its completeness prior to proceeding with the implant/download. In the event the Medtronic Field personnel identify IC as being incomplete, the study procedure will not be allowed to occur until the consent of the subject can be adequately and appropriately obtained.

10.6 Enrollment

A subject is considered enrolled when the subject and the Principal Investigator or authorized designee, impartial witness, as required, have personally signed and dated the informed consent. The date the subject signed the informed consent form, 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. Enrollment can be a stand-alone visit or can occur on the same day as screening. Once consent is obtained, report adverse events/deaths, study deviations and subject exits as they occur. No study-related procedures or testing may be conducted prior to completion of the informed consent process with a subject.

10.7 Pre-Procedure Screening

Following enrollment, perform a psychological examination to ensure the subject doesn't have any psychiatric comorbidities that could influence the ability to have a permanent SCS device. Alternatively, the results of a psychological examination performed in the last 6 months prior to enrollment in the study can be used after the medical professional reconfirms subject suitability for receiving a SCS system. Perform an x-ray, CT scan, or MRI, to confirm a permanent implant is appropriate. An existing x-ray, CT scan, or MRI can be used for this purpose, unless the investigator deems updated imaging is needed. Exit the subject from the study and complete an Exit eCRF if the subject is not suitable to move on to a device trial.

10.8 Baseline

Up to 140 subjects will be enrolled in the study to ensure up to 57 subjects with low-back and/or leg pain and up to 12 subjects with upper limb and/or neck pain are implanted with the study device. Of the 57 subjects with low-back and/or leg pain, it is recommended that at least 25 of those subjects have a baseline back VAS ≥ 60 mm. Assess and confirm eligibility to the study-specific inclusion/exclusion criteria. Each subject must be in compliance with all of the inclusion/exclusion criteria to be eligible to participate in this study. If it is determined that a subject is ineligible for the study, or if they withdraw early, a study exit must be recorded in the study database. Study assessments will be completed and activity goals will be collected.

The following information is required to be collected at the baseline visit:

- Inclusion/exclusion criteria
- Demographics
- Medical history
- Pain medications
- VAS
- [redacted]

10.9 Device Trial

Subjects will be implanted with two percutaneous leads and the exteriorized proximal end will be connected to a wireless external neurostimulator. The subject may perform a flexion maneuver prior to having fluoroscopy/x-ray performed of the lead location. The trial phase is not to exceed 10 days. Subjects will be contacted via phone during this phase regarding their device trial.

The following information is required to be collected at the device trial visit:

- Fluoroscopy/x-ray of trial lead location
- Device information for trial products
- Collect data files via the clinician programmer tablet and securely send to Medtronic
- Pain medication changes
- AEs/device deficiencies

10.10 Imaging

Anterior/posterior and lateral images, e.g., x-ray or fluoroscopy, of the trial lead(s) will be taken, including at least one anterior/posterior image that captures the vertebral level of the lead(s). An additional image of the externalization of the lead(s) may also be required for the device trial (for example, if not visible in the other images). The subject may perform a flexion maneuver prior to having fluoroscopy/x-ray performed of the lead location. Send the redacted images to Medtronic following all required timepoints.

10.11 Device Trial Lead Explant

All subjects will have their device interrogated. All reports (final) will be collected and leads will be explanted. Trial lead explant must occur on or before 10 days from the trial implant. Subjects who have 50% or greater reduction in pain will go onto a permanent INS implant in the study. If not, exit the subject from the study.

The following information is required to be collected at the trial lead explant visit:

- [redacted]
- Collect data files via the clinician programmer tablet and securely send to Medtronic
- Pain medication changes
- AEs/device deficiencies

10.12 Inceptiv Implant

Subjects will be implanted with the Inceptiv INS device and two percutaneous leads. Up to three low-back and/or leg pain subjects may be implanted with a surgical lead. If possible, the subject may perform a flexion maneuver prior to having fluoroscopy/x-ray performed of the lead location.

The following information is required to be collected at the INS implant:

- Device information for implanted products
- Fluoroscopy/x-ray images of final lead location
- Collect data files via the clinician programmer tablet and securely send to Medtronic
- Pain medication changes
- AEs/device deficiencies

[redacted]

10.13 Device Activation

The device activation visit will take place 9-16 days after implant, pending wound healing. Reschedule the visit if the wound has not healed. Programming will consist of therapy and Neuro Sense for subjects who have a measurable ECAP. Subjects will be educated on the use of their handset and recharger. Provide the subject the stimulation diary at the end of this visit.

The following information is required to be collected at the device activation visit:

- Collect data files via the clinician programmer tablet and securely send to Medtronic
- Pain medication changes
- AEs/device deficiencies

[redacted]

10.15 Randomization and In-Clinic Testing

In-Clinic Testing will occur within 30 days ± 5 days from Device Activation and again at the 3- and 12-Month Visits. A clear and measurable ECAP must be present in order to be randomized during in-clinic testing. Subjects will be randomized to either Neuro Sense On followed by Neuro Sense Off in-clinic testing, or Neuro Sense Off followed by Neuro Sense On testing. The subject will be blinded to the settings tested.

The following information is required to be collected during the in-clinic testing visit:

- [redacted]
- Randomization assignment
- Subject rating of stimulation sensation with Likert scale

[redacted]

[redacted]

- Collect data files via the clinician programmer tablet and securely send to Medtronic
- Pain medications
- AEs/device deficiencies

[redacted]

[redacted]

10.15.2 Methods of Assigning Subjects to Treatment Groups

Subjects who provide clear, measurable ECAPs at in-clinic testing setup will be randomized to receive either Neuro Sense On followed by Neuro Sense Off testing or Neuro Sense Off followed by Neuro Sense On testing in a 1:1 ratio, stratified by study site.

Permuted blocks (size 2 and 4) will be used to generate the randomization assignments in order to balance the subjects receiving each treatment assignment. Randomization allocation will be concealed from the subject, using a centralized automatic web-based data management system. Once assigned, the randomization assignment for the subject cannot be changed for that visit.

[redacted]

10.15.3 Blinding

The in-clinic testing phase of the study will be single blinded to reduce bias. The subject will not have knowledge of the therapy assigned during the in-clinic testing phases of the study. It is essential that study sites take special precaution to maintain the blind during the in-clinic testing. It is recommended that records and printouts that disclose the subject's randomization assignment be kept in the medical record and/or study file in envelopes, so as to protect the blinded status. Other options to maintain the blinding may be applied per investigational study site research procedure.

Medtronic personnel will be unblinded to randomization assignments.

10.15.4 Crossover

Crossover for this study visit is defined as the subjects receive either Neuro Sense On followed by Neuro Sense Off testing, or Neuro Sense Off followed by Neuro Sense On testing. All randomized subjects will crossover during the in-clinic testing. [redacted]

Every reasonable effort should be made to prevent unblinding of the subject.

10.16 Scheduled Visits

Subjects will be seen at 3-, 6-, 12-, 18-, and 24-Months.

10.16.1 3-, 6-, 12-, 18-, and 24-Month Visits

It is strongly recommended to program the SCS device with Neuro Sense On during the follow-up phase.

The following information is required to be collected at the visits:

- [redacted]
- VAS [redacted]

- [redacted]
- Collect data files via the clinician programmer tablet and securely send to Medtronic
- Pain medication changes
- AEs/device deficiencies

10.17 Phone Calls

Subjects will be called every week starting after Device Activation through the 3-Month Visit and monthly thereafter with an exception for the weeks or months when the subject has a study required visit. If the subject reports being Unsatisfied with the therapy, as determined by the phone call, the subject may be brought in for an Unscheduled visit for further therapy optimization. [redacted]

The following information is required to be collected during the phone calls:

- Pain Relief Status
  - [redacted]
  - Pain score on the 11-point Numeric Rating Scale (NRS) of 0 - 10; 0 being no pain and 10 being worst imaginable pain.
- [redacted]
- Pain medications changes
- AEs/device deficiencies

10.18 Unscheduled Visits

Unscheduled visits may occur if programming changes are required to correct programming errors, to reprogram for pain optimization, or for an AE. Whenever feasible, subjects should have their devices interrogated.

The following information is required to be collected during unscheduled visits:

- [redacted]
- Reason for visit
- If applicable, collect data files via the clinician programmer tablet and securely send to Medtronic
- Fluoroscopy/x-ray, if necessary
- Pain medications changes
- AEs/device deficiencies

10.19 Device Interrogation

For visits occurring at the study site, collect data files via the clinician programmer tablet and securely send to Medtronic. Source for the interrogation reports should be kept at the study site. It is recommended that data are not cleared during any interrogation.

[redacted]

10.20 System Modification

System modifications (e.g. lead or device revision, replacement, or explant) may occur in the study due to ineffective or loss of therapy, AEs, device deficiencies, or subject concerns that are not correctable by programming. In the event of a system modification, the visit schedule for the subject will remain unchanged. If the SCS device requires replacement, contact a member of the Medtronic study team as the decision to allow re-implant will be handled on a case-by-case basis. If the system is explanted, the explanted system will be returned to Medtronic. All explanted products should be returned to Medtronic for analysis when permissible by local laws and regulations. See Sections 7.10 and 7.11 for final product disposition details.

The following information is required to be collected during system modification visits:

- Changes to the implanted system
- Collect data files via the clinician programmer tablet and securely send to Medtronic
- Fluoroscopy/x-ray, if necessary
- Pain medications
- AEs/device deficiencies

10.21 Assessment of Efficacy

10.21.1 Overstimulation Sensation

All assessments will be documented in a paper format by the subject and transferred to the appropriate visit eCRF by authorized site personnel. For every overstimulation sensation brought about by protocol-prescribed activities, subjects will rate the intensity of the sensation in the following 5-point Likert scale:

- No overstimulation sensation (code=0)
- Weak overstimulation sensation (code=1)
- Moderate overstimulation sensation (code=2)
- Strong overstimulation sensation (code=3)
- Very strong overstimulation sensation (code=4)

[redacted]

10.21.3 Visual Analogue Scale

Pain will be assessed by VAS (0 – 100 mm). The VAS scale ranges from 0 mm meaning “no overall pain” and 100 mm meaning “worst overall pain imaginable.” Subjects will be asked to report pain intensity “in the last 72 hours” by marking a line perpendicular to the VAS line at the point that represents their pain intensity. Site personnel will determine the score by measuring the distance (mm) on the 100-mm line between the left, “no pain” anchor and the subject’s mark, measuring the total distance of the line (to ensure that it is 100 mm), and dividing the distance from the “no pain” mark to the subject’s mark by the total distance of the line. The scored VAS ranges from 0 – 100.

[redacted]

[redacted]

[redacted]

10.22 Assessment of Safety

To characterize all device-related, therapy-related, and procedure-related adverse events and device deficiencies. Adverse events and device deficiencies will be summarized using summary tables displaying the frequency and percentages, by study phase, and in total. Adverse events will be summarized by seriousness as well.

See Section 12 for further information on the collection of AEs and safety information.

10.23 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, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives,

[redacted]

microfilm or magnetic media, X-rays, subject files, device data and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the study).

Interrogation files will be collected and stored at the site. Pseudonymized copies of the interrogation files submitted to Medtronic should be sent via secure and compliant electronic file transfer services and/or secure mail.
Fluoroscopy or x-ray images shall be collected and stored on a CD/DVD or USB flash drive at the site. Pseudonymized copies of those images submitted to Medtronic shall be sent via secure and compliant electronic file transfer services and/or secure mail.

In general, eCRFs (or paper copies) may not serve as source documents. An exception may be the completion of 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.

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.

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

- Enrollment Notification
  - Study site assigned subject reference
- Baseline
  - Administrative information
- AE eCRF
  - Date study site became aware of event
  - Relatedness of adverse event
- Device Deficiency eCRF
  - Date study site became aware of event
- Subject Death
  - Date study site became aware of death
  - Relatedness of death
  - System explant information
- Deviations
  - Reason for deviation

10.24 Deviation Handling

A study deviation is defined as an event within a study that did not occur according to the CIP or the CTA.

Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. 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 visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness).

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g. the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary end point analysis). However, prior approval from Medtronic is required for such situations.

All study deviations must be reported on the CRF regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency. Multiple deviations of the same type at the same visit may be reported on one case report form.

In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the EC as well as Medtronic within five (5) working days. Reporting of all other study deviations should comply with EC policies and/or local laws and must be reported to Medtronic as soon as possible upon the study site becoming aware of the deviation. Reporting of deviations must comply with EC policies, local laws, and/or Regulatory Authority requirements. Refer to Investigator Reports, Table 8 for deviation reporting requirements and timeframes for reporting to Medtronic and/or Regulatory Authority.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, conduct additional training, terminate the investigation). Repetitive or serious investigator compliance issues may result in initiation of a corrective action plan with the investigator and study site, and in some cases, may necessitate suspending enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study. Medtronic will provide study site-specific reports to investigators summarizing information on deviations that occurred at the investigational study site on a periodic basis.

Examples of study deviations include but are not limited to:

- Failure to obtain proper IC
- Failure to collect required study data
- Inclusion/exclusion criteria not met
- Missing required device interrogation files
- Visits out of window

10.25 Subject Exit, Withdrawal or Discontinuation

10.25.1 Study Exit

A study exit eCRF is required for all subjects. Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing system and/or procedure related AEs are resolved or unresolved

with no further actions planned, or until official study closure, whichever occurs first. Following exit, subjects will continue to receive standard medical care as they would having received a commercially available SCS device and be followed per Investigator discretion. Upon exiting from the study, no further study data will be collected or study visits will occur for the subject. All data available through the time of the subject's exit will be used for analysis.

Subjects are urged to remain in the study as long as possible but may be exited from the study for any of the following situations:

- Study completed
- Subject lost to follow-up
- Subject death
- Subject did not meet inclusion/exclusion criteria
- Subject was not implanted with the study device
- Subject did not provide informed consent
- Subject chooses to withdraw (e.g., consent withdrawal, relocation to another geographic location)
- Investigator deems withdrawal necessary (e.g., medically justified, inclusion/exclusion criteria not met, failure of subject to maintain adequate study compliance)

Complete an Unscheduled Visit if the subject exits early, between visits and prior to the last study visit:

10.25.2 Study Completed

At the completion of the 24-Month Visit, subjects will be exited from the study. The 24-Month Visit and exit visit should be combined, and both a 24-Month Visit CRF and a Study Exit CRF need to be completed.

10.25.3 Lost to Follow-up

A subject is considered to be lost to follow-up if at least two attempts to contact the subject are unsuccessful. The method of attempt (e.g., one letter and one phone record, or two letters) must be documented in the subject's medical record. In addition, regulation set forth by the governing EC must be followed.

11. Risks and Benefits

11.1 Potential Risks

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of a product, from the business analysis phase through development, market release, and post-market surveillance. The risk analysis process for the Inceptiv system is being performed in accordance with ISO 14971, and will ensure that the level of risk is as low as possible prior to starting the study.

It is anticipated there are no incremental risks introduced to the subject as a result of participation in this study or with the implantation of the Inceptiv system. Any new identified risks will be communicated to Investigators and result in a CIP revision.

11.2 Foreseeable Risks

11.2.1 SCS Adverse Events Summary

The implantation of a SCS system involves risks that are similar to other spinal cord procedures. In addition to those risks associated with surgery, the following adverse events may occur with implantation or uses of a neurostimulation system.

- Allergic or immune system response to the implanted materials
- Infection
- Lead, extension, or neurostimulator erosion through the skin or migration
- Leakage of cerebrospinal fluid
- Loss of pain relief may return patients to their underlying pain condition
- Patients on anticoagulation therapies may be at greater risk for postoperative complications such as hematomas that can result in paralysis
- Persistent pain at the neurostimulator site
- Placement of the epidural lead-extension is a surgical procedure that may expose patients to risks of epidural hemorrhage, hematoma, or paralysis
- Radicular chest wall stimulation
- Seroma or hematoma at the neurostimulator site
- 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 nausea, diarrhea, incontinence, or constipation
- Stimulation-dependent bladder symptoms such as urinary retention, incontinence, or frequency
- Tissue damage at the implant site

11.2.2 Device/Software Deficiencies Risks

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

- Mechanical failure/damages of system components, e.g., lead fracture (increased impedance), or breach of insulation
- Migration or dislodgement of the lead(s)
- Programming and/or telemetry problems that might limit the capability to program or determine what parameters are programmed
- Automatic adjustment of output that might provide output that is below or above the desired values
- Outside electromagnetic interference (e.g., cardioversion, defibrillation, electrocautery etc.) might affect that output or programming of the system

[redacted]

11.2.3 Radiographic Risks

As part of the study, subjects may be required to have fluoroscopic or X-ray images taken of their device and/or leads that are additional to those required for commercial procedures. This represents a negligible amount of additive radiation exposure beyond imaging used as part of a standard trial lead placement. Winninger[41] found that the mean total fluoroscopy time for SCS trialing procedures (n = 110) averaged 133.4 s with a standard deviation of 84.8 s, with additional imaging required for implant of permanent leads and the INS. For example, five images are roughly the equivalent of 1.7 s of pulsed fluoroscopy at the lowest frame rate (3 pulses/s). This is much lower than the average time for the trialing procedure (at the most conservative estimate of 3 pulses/s) and under one-tenth of a standard deviation from the mean. Further, Schmid[42] found that 1 min. of pulsed fluoroscopy at 3 pulses/s (180 images— far above what is anticipated for this study beyond commercial procedures) for fluoroscopy-guided perineural/epidural injections of the lumbar spine (a reasonable analog to the thoracic imaging performed as part of this study) results in an effective dose of 0.07 mSv and 0.08 mSv in males and females, respectively. Pradhan[43] reports that cancer risk can't be estimated from doses below 100 mSv.

11.3 Risk Minimization

The potential risks associated with Inceptiv system were identified and risk control measures were defined. Any potential risks associated with this study are further minimized by selecting qualified investigators and training study personnel on the CIP.

In addition, Investigators will be actively involved in the implantation and follow-up of the subjects implanted with the SCS systems.

Risks will be minimized by careful assessment of each subject prior to, during, and after implant of the SCS. Prior to implant, it is recommended subjects undergo a complete physical evaluation.

Medtronic has further minimized the possibility of risks by performing required laboratory and pre-clinical testing prior to the Closed-Loop SCS study, implementing quality control measures into production processes, providing guidelines for subject selection and evaluation, and providing adequate instructions and labeling.

After implantation, subjects in the Closed-Loop SCS study will be followed at regular intervals to monitor the condition of the implanted system and the battery. At each required visit, the Investigator must interrogate the SCS to verify appropriate function and to evaluate pacing and sensing characteristics and to assess any adverse events. Informed consent will include description for the subject to understand that the subject should inform any health care personnel before any medical procedure, that they have an implanted SCS system. Additionally, if the subject will undergo a cardioversion or defibrillation, with the implanted SCS system, ensure that stimulation is turned off for the duration of the medical procedure. Please refer to the Investigator's Brochure, Information for Prescribers or the Patient Therapy Guide for additional information.

11.4 Potential Benefits

The Inceptiv system may offer no benefit. The potential benefit of having the Inceptiv system, above and beyond SCS therapy for the treatment of chronic pain, is the reduction of overstimulation events, if the closed-loop feature is enabled. The information gained from this study could result in the improved management of other patients with chronic pain. Additionally, information collected from this study may assist in the design of new product(s)/therapy(ies).

11.5 Risk-Benefit Rationale

The benefit of the study lies in the knowledge to be gained from the results and the potential to improve SCS therapy. All potential risks have been controlled to a level as far as possible. Any residual risk is determined to be acceptable given the expected benefit.

12. Adverse Events and Device Deficiencies

12.1 Adverse Events

AE definitions are provided in Table 7. The following AEs will be collected throughout the study duration, starting at the time of signing the IC:

- procedure related
- device related
- therapy related
- serious adverse events regardless of relatedness

Reporting of these events to Medtronic will occur on an AE eCRF. Each event must be reported separately. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened. A subset of AEs will be collected in this study as these are the most relevant to the study device and study design given no new or increased risk with the Inceptiv system.

UAE, listed in Table 7, need not be reported unless the adverse event worsens or is present outside the stated timeframe post-implant.

For AEs that require immediate reporting (see Table 9), initial reporting may be done by phone, fax, or on the eCRF completing as much information as possible. The completed AE CRF must be submitted to Medtronic as soon as possible.

Any medication/treatment associated with the treatment of an AE must be reported

Subject deaths are also required to be reported. Refer to Section 12.6 for Subject Death collection and reporting requirements.

Events that are not reportable for this study are:

- Sensation of stimulation (paresthesia)
    - Sensation of stimulation (e.g., tingling, buzzing) will not be reported as this may occur as part of this therapy.
    - Sensation of stimulation brought by protocol-prescribed activities (i.e. coughing, laughing, Valsalva) if transient and reversed by the subject returning to a neutral position (anytime occurred).
    - Overstimulation: uncomfortable sensation of stimulation (intense tingling, shocking, jolting) brought by protocol-prescribed activities if transient and reversed by the subject returning to a neutral position (as defined in Section 14.4).

[redacted]

- Transient periods of sensation or stimulation events that are uncomfortable to the subject that do not result in an intervention or are relieved by change in body position or decreasing therapy intensity

NOTE: Extended periods of sensation or overstimulation events that are uncomfortable to the subject (e.g. tingling, shocking, jolting) that result in intervention (e.g. reprogramming, turning the device off) will be reported.

12.2 Device Deficiency

The device deficiency definition is provided in Table 7. Device deficiency information will be collected throughout the study and reported to Medtronic. Note that device deficiency that result in an AE to the subject should be captured as an AE only. Device deficiencies that led to increasing pain, but still below baseline pain levels should be reported as only a device deficiency, not an AE.

Device deficiency that did not lead to an AE but could have led to a SADE (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate reporting (see Table 9).

12.3 Processing Updates and Resolution

For any changes in status of a previously reported adverse event or device deficiency (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 device deficiency 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 ongoing device and/or procedure related AEs, as classified by the investigator, are resolved, unresolved with no further actions planned, or until official study closure, whichever occurs first. At the time of study exit, all collected AEs with an outcome of "not recovered/not resolved", "recovering/resolving" or "unknown" must be reviewed and updates provided as applicable.

12.4 Definitions/Classifications

For the purposes of the clinical report, Medtronic will classify each adverse event according to ISO 14155:2020. 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. It is the responsibility of the Investigator to identify the occurrence of all AEs and device deficiencies and to ensure the required information is accurately documented in the medical records and reported to Medtronic.

Table 7: Adverse Event and Device Deficiency Definitions

General	
Adverse Event (AE)	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 and whether anticipated or unanticipated. 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. (ISO 14155:2020, 3.2)
Adverse Device Effect (ADE)	AE related to the use of an investigational medical device. Note 1: This definition includes AEs 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 an use error or from intentional misuse of the investigational medical device. Note 3: this includes 'comparator' if the comparator is a medical device (ISO 14155:2020, 3.1)
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. Note 1: DD include malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labeling. Note2: This definition includes device deficiencies related to the investigational medical device or the comparator. (ISO 14155:2020, 3.19)
Relatedness	
Device related (Those classified as Investigational in Table 3)	An adverse event that results from the presence or performance (intended or otherwise) of the Investigational components of Inceptiv system. • Inceptiv INS • Vectris SureScan MRI leads • Specify SureScan MRI 5-6-5 leads • Clinician Tablet • Clinician Programmer Application • Stimulation Trialing Clinician Programmer Application • Programmer Platform Software-Communication Manager Application • Patient Data Service Application • Patient Handset • Patient Programmer Application • Patient Programmer Trialing Application • Patient Telemetry Communicator

[redacted]

	• Recharger Application • Recharger
Procedure Related	An adverse event that occurs due to any procedure related to the trial, implant, explant or surgical modification of the Inceptiv system or any of the Inceptiv system components.
Therapy Related	An adverse event that occurs due to the therapy delivered by the Inceptiv system, should not include events that resulted from a malfunction of the device (i.e. hardware-related events).
Not Related	Relationship to the device or procedures can be excluded when: □ the event has no temporal relationship with the use of the device or procedure □ the event does not follow a known response pattern to the device (if the response pattern is previously known) and is biologically implausible; □ the discontinuation of 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 event; □ the event involves a body-site or an organ not expected to be affected by the device or procedure; □ the 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 device used for diagnosis, when applicable; In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event
Possible	The relationship 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 seems relevant and/or the event cannot reasonably be explained by another cause.
Causal relationship	The event is associated with the device or study 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 device use/application or procedures; □ the event involves a body-site or organ that

[redacted]

	the device or procedures are applied to; the device or procedures have an effect on; □ the event follows a known response pattern to the device (if the response pattern is previously known); □ the discontinuation of 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 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 device used for diagnosis, when applicable; In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.
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 pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE. (ISO 14155:2020, 3.45)
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2020, 3.44)
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk assessment. Note 1: Anticipated serious adverse device effect (ASADE) is an effect which by nature, incidence, severity or outcome has been identified in the risk assessment.

[redacted]

<table>
<tr><td></td><td>(ISO14155:2020 3.51)</td></tr>
<tr><td>Significant Safety Issue (SSI)</td><td>A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.
(NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016)</td></tr>
<tr><td>Urgent Safety Measure (USM)</td><td>A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety.

Note: This type of significant safety issue can be instigated by either the investigator or sponsor and can be implemented before seeking approval from ECs or institutions.
(NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016)</td></tr>
<tr><td>Serious Health Threat</td><td>Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons
NOTE 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.
(ISO 14155:2020, 3.46)</td></tr>
<tr><td>Unavoidable Adverse Events (UAE)</td><td>An Adverse Event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the Investigator's opinion.
Unavoidable AEs are not considered reportable unless the AE worsens or is present outside the stated timeframe.
Including, but not limited to:
<table>
<tr><th>Description</th><th>Timeframe (hours) from the Surgical Procedure</th></tr>
<tr><td>Anesthesia related nausea / vomiting</td><td>24</td></tr>
<tr><td>Low-grade fever (<100°F or <37.8°C)</td><td>48</td></tr>
<tr><td>Pain at the access site</td><td>72</td></tr>
<tr><td>Mild to moderate bruising / ecchymosis</td><td>168</td></tr>
<tr><td>Sleep problems (insomnia)</td><td>72</td></tr>
<tr><td>Back pain related to lying on table</td><td>72</td></tr>
</table></td></tr>
</table>

12.5 Reporting of Adverse Events and Device Deficiencies

All reportable AEs and device deficiencies must be recorded in the subject's medical record, the CRF and promptly to Medtronic. Investigators are required to keep records on all relevant observations.

Reportable adverse events and device deficiencies will include the following information, at a minimum:

- Date of event
- Diagnosis or description of the event
- Assessment of the seriousness and relationship to the product(s) under investigation and procedure (AE only)
- Model and identifiers (serial, lot number) for the involved device (if applicable)
- Treatment (AE only)
- Outcome and date of resolution (AE only)

It is the responsibility of the Investigator to identify the occurrence of reportable AEs and device deficiencies and to ensure the required information is accurately documented on the CRF.

12.5.1 Adverse Event and Device Deficiency Classification

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

Upon receipt of AE/ device deficiencies at Medtronic, a Medtronic representative will review the AE/ device deficiencies 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/ device deficiencies based on the information provided by the investigator. Copies of de-identified source documentation regarding an adverse event or device deficiency (e.g., clinician notes or summaries) will be provided to Medtronic upon request.

Regulatory reporting of AEs and device deficiencies will be completed according to local regulatory requirements. Refer to Table 9 for a list of required investigator and Medtronic reporting requirements and timeframes. It is the responsibility of both to abide by any additional AE reporting requirements stipulated by the EC responsible for oversight of the study.

For emergency contact regarding a USADE, SAE and/or SADE, contact a study representative immediately (refer to the study contact list provided in the study site's study documents binder/investigator site file or refer to the Sponsor contact information provided on the title page).

AEs will be classified according to the standard definitions as outlined below in Table 8.

Table 8: Event Classification Responsibilities

What is Classified	Who Classifies	Classification
Relatedness*	Investigator, Sponsor	• Relationship to the: ○ Device: ▪ Inceptiv INS ▪ Vectris SureScan MRI leads ▪ Specify SureScan MRI 5-6-5 leads

[redacted]

What is Classified	Who Classifies	Classification
		▪ Clinician Tablet ▪ Clinician Programmer Application ▪ Stimulation Trialing Clinician Programmer Application ▪ Programmer Platform Software-Communication Manager Application ▪ Patient Data Service Application ▪ Patient Handset ▪ Patient Programmer Application ▪ Patient Programmer Trialing Application ▪ Patient Telemetry Communicator ▪ Recharger Application ▪ Recharger o Procedure o Therapy
Expectedness	Sponsor	USADE
Seriousness	Investigator	SAE, device deficiencies with SADE potential
	Sponsor	SAE, device deficiencies with SADE potential
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator

*Adverse events that are classified as having a relationship of possible, probable or causal to the investigational device or procedure or therapy are considered to be related to the investigational medical device and are classified as ADEs.

12.5.2 Adverse Event and Device Deficiency Reporting Requirements

Regulatory reporting of AEs and device deficiencies will be recorded and reported according to local regulatory requirements. It is the responsibility of the Investigator and the sponsor to abide by the AE reporting requirements stipulated by local law and the study site's EC.

Table 9: Reporting Requirements

All SAEs and DDs with potential SADE	
Investigator submit to:	
Medtronic	Without unjustified delay. (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.b)
Ethics Committee	Submit per local reporting requirements.
Institution	Submit to Institution per local reporting requirements.
Regulatory authorities	Submit per local reporting requirements.
Sponsor submit to:	
Investigators	Submit to investigator per local reporting requirements.
Regulatory authorities	Submit to regulatory authority per local reporting requirements.
Ethics Committee	Submit to EC per local reporting requirements.
Unanticipated Serious Adverse Device Effects (USADEs)	
Investigator submit to:	
Medtronic	Submit to the sponsor per local reporting requirements.
Regulatory Authority	Submit to regulatory authority per local reporting requirements.
Ethics Committee, Institution	Report to their institution without undue delay and no later than 72 hours of the Principal Investigator becoming aware of the event. (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.g)
Sponsor submit to:	
Investigator	Submit to the investigator per local reporting requirements.
Regulatory authorities	Submit to regulatory authority per local reporting requirements.
Ethics Committee	Submit to EC per local reporting requirements.
Significant Safety Issues (SSI) and Urgent Safety Measure (USM)	
Investigator submit to:	
Medtronic, Ethics Committee, Institution	• Urgent Safety Measure (USMs): Within 24 hours

[redacted]

	(NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.c) • All other significant safety issues: without undue delay and no later than 72 hours of the principal investigator becoming aware of the event (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.g)
Regulatory Authority	Submit to regulatory authority per local reporting requirements.
Institution	Submit to Institution per local reporting requirements.
Sponsor submit to:	
Investigator	Submit to the investigator per local reporting requirements.
Regulatory authorities	Submit to regulatory authority per local reporting requirements.
Ethics Committee	Submit to EC per local reporting requirements.
Institution	Submit to Institution per local reporting requirements.
All other reportable AEs	
Investigator submit to:	
Medtronic	Submit to the sponsor per local reporting requirements.
Regulatory Authority	Submit to regulatory authority per local reporting requirements.
Ethics Committee	Submit to EC per local reporting requirements.
Sponsor submit to:	
Regulatory authorities	Submit to regulatory authority per local reporting requirements.
Ethics Committee	Submit to EC per local reporting requirements.
All other Device Deficiencies	
Investigator submit to:	
Medtronic	Submit to the sponsor per local reporting requirements.
Regulatory Authority	Submit to regulatory authority per local reporting requirements.
Ethics Committee	Submit to EC per local reporting requirements.
New information that may adversely affect safety of the subjects or the conduct of the study	
Investigator submit to:	

[redacted]

Medtronic	Submit to the sponsor per local reporting requirements.
Ethics Committee	Submit to EC per local reporting requirements.
Sponsor submit to:	
Investigator	Submit to investigators per local reporting requirements.
Regulatory authorities	Submit to regulatory authority per local reporting requirements.
Ethics Committee	Submit to EC per local reporting requirements.

12.6 Subject Death

All subject deaths must be reported by the investigator to Medtronic on an AE form (AE with outcome of fatal) as soon as possible after the investigator first learns of the death. In case of death, there should be only one AE with the outcome of death.

In the event of a subject's death, it is recommended that the implanted system be explanted and returned to Medtronic for analysis whenever possible per local process. Local laws and procedures must be followed where applicable. If any system component is returned to Medtronic, internal return product reporting systems may be used to gather additional information about the returned device/component.

A copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic clinical study team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records, if available should be sent to the Medtronic clinical study team. If an autopsy is conducted, a copy of the autopsy report should also be sent to the Medtronic clinical study team if available and allowed by state/local law. When the death occurs at a remote study site, it is the investigative study site's responsibility to attempt retrieval of information about the death. Additionally, device disposition information should be updated.

In summary, the following data will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Relatedness to device, therapy and/or procedure
- Device interrogation information/reports (if available and allowed by state/local law)
- Device disposition information
- Death summary/hospital records (if available and allowed by state/local law)
- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and allowed by state/local law)

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 Regulatory Authority, as applicable, for the following incidents immediately upon learning of them and is not limited to AEs and device deficiencies 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. Committees and Organizations

13.1 Clinical Research Organization (CRO)

CROs will not be used in this study.

13.2 Data Monitoring Committee (DMC)

A DMC is not needed for this study. Instead, regular meetings will be held by Sponsor personnel, including the Medical Advisor, to review AEs and device deficiencies, identify potential trends in safety data during the clinical study, and to ensure consistent reporting.

14. Statistical Design and Methods

This section presents statistical considerations for the study design and provides a high-level description of planned analysis and reporting. More details will be given in a separate Statistical Analysis Plan (SAP) that will be approved before data freeze or lock for analysis. Any deviation to the pre-specified statistical analyses will be noted in the study report.

14.1 General Aspects of Analysis

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.

General descriptive statistics for categorical and continuous variables will be used: categorical variables will be summarized as counts and percentages; continuous variables will be presented using mean,

standard deviation, median, quartiles and range, as applicable. All confidence intervals will be presented as two-sided 95% confidence intervals, unless otherwise pre-specified.

14.1.1 Analysis Sets

- The **All Consented Set** (ACS) will include all subjects who signed the study specific ICF and enrolled in the study.
- The **Full Analysis Set** (FAS) will include all device-implanted subjects.
- The **Primary Analysis Set** (PAS) will follow the intent-to-treat (ITT) principle to include randomized low-back and/or leg pain subjects who will be used for the primary objective, i.e., the first 28 randomized low-back and/or leg pain subjects who provide the primary endpoint.
- The **Complete Case Set** (CCS) will include all device-implanted subjects who have data available at baseline and follow-up. This set is defined for each outcome measure at each follow-up visit.

[redacted]

14.1.2 Handling Missing Data

Missing data are a potential source of bias when analyzing study data. A rigorous study design and execution will help prevent the incidence of missing data from occurring as described in Section 14.9. The primary objective will use the PAS with the Multiple Imputation (MI) methodology for missing data if there is greater than 5% of subjects with missing values. Details of the imputation method are described in Section 14.4.1.6. The secondary objectives will use the FAS with the MI methodology for missing data if there is greater than 5% of subjects with missing values, as described in Sections 14.5.1.4 and 14.5.2.4. All other objectives will be analyzed using the CCS unless otherwise specified in the SAP. The ACS and FAS subjects will be used for demographic analyses and safety reporting.

[redacted]

14.1.4 Disposition of Subjects

Subject disposition will be illustrated in a flow diagram. Subject visits will be tabulated and compliance to visit schedule will be summarized. Attrition will be identified and summarized.

14.1.5 Demographics and Other Baseline Characteristics

The subjects' baseline demographics will be summarized with standard descriptive summary statistics, including counts and percentages for categorical variables, and mean, standard deviation, median, and range for continuous variables.

14.1.6 Other Characteristics

The subjects' other characteristics, such as questionnaire responses, may be summarized with standard descriptive summary statistics, including counts and percentages for categorical variables, and mean, standard deviation, median, and range for continuous variables.

14.1.7 Adjusting for Multiple Comparisons

As the only hypothesis test in this study is for the single endpoint of the primary objective, adjustments for multiple comparisons are not required.

14.2 Analysis Execution

The primary objective analysis will occur after 28 randomized low-back and/or leg pain subjects finish the in-clinic testing, and one final study analysis will occur after all subjects complete the study. The primary objective analysis is described in Section 14.4. A final report will be prepared once all data collection has ended and all subjects have completed the study and have been exited.

14.3 Interim Analysis

No interim analyses will be performed in this study.

14.4 Primary Objective

The primary objective is to demonstrate that the proportion of low-back and/or leg pain subjects having a reduction in overstimulation sensation with Neuro Sense On compared to Neuro Sense Off, at the randomization and in-clinic testing visit, exceeds a performance goal of 50%.

Overstimulation is defined as an uncomfortable sensation of stimulation (intense tingling, shocking, jolting) brought about by protocol-prescribed activities [redacted]. This overstimulation sensation is transient and reversed by the subject returning to a neutral position.

14.4.1.1 Hypothesis

It is hypothesized that the proportion of low-back and/or leg pain subjects with a reduction in overstimulation sensation during Neuro Sense On compared to Neuro Sense Off period exceeds a performance goal of 50%.

H_0: $p \leqslant 50\%$

[redacted]

H_A: p > 50%

14.4.1.2 Endpoint definition and derivation

For every overstimulation sensation brought about by protocol prescribed activities, subjects will rate the intensity of the sensation in the following 5-point Likert scale:

- No overstimulation sensation (code=0)
- Weak overstimulation sensation (code=1)
- Moderate overstimulation sensation (code=2)
- Strong overstimulation sensation (code=3)
- Very strong overstimulation sensation (code=4)

The average intensity scores during Neuro Sense On and Neuro Sense Off period will be calculated for each individual subject. If the average intensity score during Neuro Sense On period is less than that from the Neuro Sense Off period, the subject is considered as a subject with a reduction in overstimulation sensation during Neuro Sense On vs. Neuro Sense Off period. The proportion of subjects with a reduction in overstimulation sensation among subjects who have in clinic testing need to exceed a performance goal of 50%.

14.4.1.3 Performance Requirements

The null hypothesis will be rejected if the one-sided 97.5% lower confidence bound is greater than 50%.

14.4.1.4 Rationale for Performance Criteria

The Neuro Sense On setting is an additional feature to control overstimulation to be added to an existing device. It is expected that this feature will help majority of the subjects. The 50% performance goal is selected to ensure that majority of the low-back and/or leg pain subjects meet the criterion with 95% confidence.

14.4.1.5 Analysis Methods

The proportion of low-back and/or leg pain subjects with a reduction in overstimulation sensation during Neuro Sense On compared to Neuro Sense Off period will be calculated, with a one-sided 97.5% confidence lower bound. This proportion will be tested against 50% using a binomial exact test. The confidence lower bound needs to be greater than 50%, or equivalently, the p-value must be less than 0.025 to reject the null hypothesis.

[redacted]

[redacted]

14.4.1.6 Determination of Subjects/Data for Analysis

The analysis for this objective will follow the ITT principle by including all the low-back and/or leg pain subjects randomized for the primary analysis (PAS). If there is greater than 5% of subjects with missing values, then the subjects who are randomized but have missing average scoring of overstimulation sensation during Neuro Sense On and/or Neuro Sense Off period will be imputed using Multiple Imputation (MI). Prior to the use of MI, the distributions of the continuous variables will be assessed for normality and transformation may be considered if they are not normally distributed. [redacted]

Following imputation, the objective will be evaluated using MI analysis method.

[redacted]

14.5 Secondary Objectives

14.5.1 Secondary Objective 1: Overall Responder Rates

This objective is to characterize the efficacy of spinal cord stimulation (SCS) therapy for the treatment of overall pain (for low-back and/or leg pain subjects) by evaluating the efficacy responder rate. The efficacy responder rate is defined as the percentage of implanted subjects who experience at least a 50% improvement in overall pain, as measured by the Visual Analogue Scale (VAS), from Baseline to the 3-Month Visit.

[redacted]

14.5.1.1 Hypothesis

There is no hypothesis test for this objective. The purpose is to characterize the overall efficacy responder rate at the 3-Month Visit.

14.5.1.2 Endpoint definition and derivation

A responder will be any low-back and/or leg pain subject who demonstrates at least a 50% improvement (percent change) in overall pain as measured by the VAS, calculated as follows:

- Absolute change (Δ) at the subject level will be calculated as:

$$\Delta = VAS_{Follow\text{-}up} - VAS_{Base}$$

  Where VAS_{Base} and $VAS_{Follow\text{-}up}$ are the value of the overall VAS pain score at baseline and follow-up, respectively. A negative value indicates an improvement (reduction) in pain.

- Percentage change at the subject level will be calculated as 100 times the absolute change divided by the baseline value.

$$\text{Percentage change} = 100*\Delta / VAS_{Base}$$

14.5.1.3 Analysis Methods

A point estimate of the proportion of responders, along with a 95% confidence interval, will be presented for this objective.

14.5.1.4 Determination of Subjects/Data for Analysis

Information from low-back and/or leg pain subjects who provide data at baseline and the 3-Month Visit (low-back and/or leg pain subjects from the CCS) will be used for this objective.

As a sensitivity analysis, if there is greater than 5% of subjects with missing values, any subjects who were device-implanted (FAS) but are missing their VAS scores at the 3-Month Visit will be imputed using Multiple Imputation (MI). Prior to the use of MI, the distributions of the continuous variables will be assessed for normality and transformation may be considered if they are not normally distributed. [redacted] Following imputation, the objective will be evaluated using MI analysis method.

[redacted]

14.5.2 Secondary Objective 2: Pain-Specific Responder Rates

This objective is to characterize the efficacy responder rate within in each type of pain (low-back or leg) for low-back and/or leg pain subjects, as measured by the pain-specific VAS, from Baseline to the 3-

[redacted]

Month Visit. The low-back responder rate will be characterized for subjects with baseline back VAS ≥ 60 mm, and the leg responder rate will be characterized for subjects with baseline leg VAS ≥ 60 mm.

14.5.2.1 Hypothesis

There is no hypothesis test for this objective. The purpose is to characterize the pain-specific efficacy responder rate at the 3-Month Visit.

14.5.2.2 Endpoint definition and derivation

A responder will be any low-back and/or leg pain subject who demonstrates at least a 50% improvement (percent change) in pain-specific score as measured by the VAS, calculated as follows:

- Absolute change (Δ) at the subject level will be calculated as:

$$\Delta = VAS_{Follow\text{-}up} - VAS_{Base}$$

  Where VAS_{Base} and $VAS_{Follow\text{-}up}$ are the value of the back or leg VAS pain score at baseline and follow-up, respectively. A negative value indicates an improvement (reduction) in pain.

- Percentage change at the subject level will be calculated as 100 times the absolute change divided by the baseline value.

$$\text{Percentage change} = 100*\Delta / VAS_{Base}$$

14.5.2.3 Analysis Methods

A point estimate of the proportion of responders, along with a 95% confidence interval, will be presented for each pain category within the secondary objective. Additional results, such as the proportion of responders by pain category and site, may be provided as well.

14.5.2.4 Determination of Subjects/Data for Analysis

Information from subjects who provide data at baseline and the 3-Month Visit (CCS) will be used for this objective. For the analysis of back pain responder rate, the subset of CCS subjects with a baseline back VAS ≥ 60 mm will be used. For the analysis of leg pain responder rate, the subset of CCS subjects with baseline leg VAS ≥ 60 mm will be used.

As a sensitivity analysis, if there is greater than 5% of subjects with missing values, any subjects who were device-implanted (FAS) but are missing their VAS scores at the 3-Month Visit will be imputed using Multiple Imputation (MI). Prior to the use of MI, the distributions of the continuous variables will be assessed for normality and transformation may be considered if they are not normally distributed. [redacted]

Following imputation, the objective will be evaluated using MI analysis method.

[redacted]

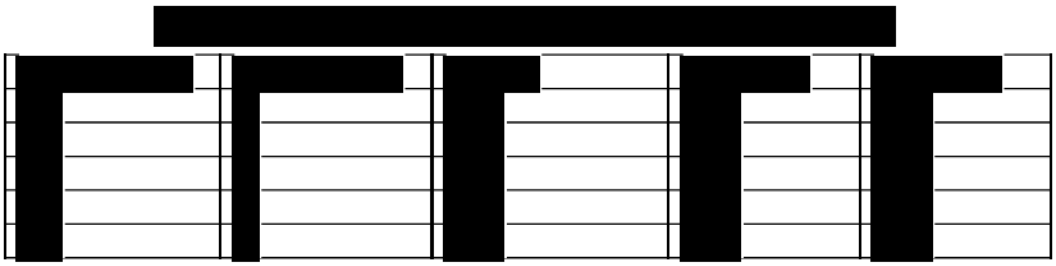
[redacted]

[redacted]

14.7 Safety Assessment

To characterize all device-related, therapy-related, and procedure-related adverse events and device deficiencies from the start of the device trial until study exit. Adverse events and device deficiencies will be summarized using summary tables displaying the frequency and percentages of events as well as the number of subjects experiencing events, by study phase, and in total. Adverse events will be summarized by seriousness as well.

[redacted]



For the primary objective, a subset (28) of the total device implanted low-back and/or leg pain subjects are needed to evaluate the endpoint. For the secondary objectives, up to 45 implanted subjects with low-back and/or leg pain are desired to characterize the responder rates at the 3-Month Visit. Up to 9 implanted subjects with upper limb and/or neck pain are desired to characterize the population at the 3-Month Visit.

[redacted]

[redacted]

14.9 Minimization of Bias

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

- Subjects' in-clinic testing sequences are randomized with stratification at each site. This is to ensure subjects get equal opportunities to start with either Neuro Sense On or Off testing.
- Subjects are blinded to the Neuro Sense On or Neuro Sense Off testing settings. This is to ensure that the knowledge of testing settings is not going to influence the subjects' assessment of overstimulation sensation.
- Missing data are a potential source of bias when analyzing study data. A rigorous study design and execution will help prevent the incidence of missing data from occurring. All efforts will be made to ensure patient visits are completed with limited attrition to ensure interpretability of study results.
- To reduce the possibility of atypical results from a site overly influencing the combined results, the maximum number of subjects to be enrolled at a single study site is limited to 18 and cannot be increased without prior sponsor approval.
- A statistical analysis plan will be developed prior to analyzing data which will document all prespecified analyses and analysis methods.
- All study investigators will be trained on and required to follow the CIP.
- All study investigators and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials.
- All sites will use the same version of the CIP and standardized case report forms.
- Monitoring will be conducted to verify adherence to the CIP.

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

This study will be conducted in compliance with international ethical and scientific quality standards, known as GCP. GCP includes review and approval by an independent EC before initiating a study, continuing review of an ongoing study by an EC, and obtaining and documenting the freely given informed consent of a subject before initiating the study.

The Closed-Loop SCS study was designed to reflect the GCP principles outlined in ISO 14155:2020 and other international clinical requirements outlined below. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators. In

[redacted]

accordance with ISO 14155:2020, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical investigation. All Investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation. Adverse Event and Device Deficiency handling is ISO 14155:2020 compliant for all with the exception that only those AEs that are device related, procedure related, therapy related or serious, will be collected. Non-subject AEs will not be collected. Only the most relevant AEs to the study device and study design are being collected because no new or increased risk were identified for the subject or person handling the Inceptiv system.

Subjects will receive the study device free of charge and a modest amount of money to reimburse for travel to required visits.

Medtronic contracts with participating institutions/investigators through a clinical trial agreement that defines the scope and responsibilities and associated compensation related to carrying out the obligations under a clinical study sponsored by Medtronic.

The principles of the Declaration of Helsinki (DoH) have been implemented through the IC process, EC approval, study training, clinical trial registration, pre-clinical testing, risk-benefit assessment and publication policy.

Ultimately, all study sites will follow and comply with:

- Principles of DoH
- ISO 14155:2020
- 21 CFR Part 11 (Electronic Records, Electronic Signatures)
- The Clinical Trial Agreement
- The procedures described within this CIP
- Local EC Requirements

The study will be publicly registered in accordance with the DoH. In addition, the study may be registered in local regulatory databases where required by local law.

Approval of the CIP and CIP amendments is required from the following groups prior to any study procedures at a study site:

- Medtronic
- Principal Investigators
- An independent medical EC

Similarly, approval of subsequent revisions to the CIP is required at each study site from the above mentioned groups prior to implementation of the revised CIP at the study site.

[redacted]

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 ICF 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 to 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 EC 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

Data will be collected using an electronic data management system for studies. Case Report Form (CRF) data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to study sites for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained by Medtronic in accordance with applicable regulations.

All records and other information about subjects participating in this study will be treated as confidential. Data will be transferred and processed by Medtronic or a third party designated by Medtronic in a key coded form, unless it's impossible to pseudonymize for instance, where the subject's name cannot be removed from the data carrier, such as diagnostic images.

Procedures in the CIP require source documentation. Source documentation will be maintained at the study site. Source documents, which may include worksheets, subject medical records, programmer printouts, and interrogation files, must be created and maintained by the investigational study site team.

The Investigator will clearly mark clinical records to indicate that the subject is enrolled in this clinical investigation. The Investigator is responsible for completion and sign off of eCRFs.

[redacted]

The data reported on the CRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. See Section 10.31 for CRFs and data collection elements that may be considered source.

Device data from transmissions will be uploaded to secure servers. Device data collected at office visits will be sent to Medtronic. Upon receipt, device data will be maintained with databases and retrieved for analysis and reporting.

16.3 Direct Access to Source Data/Documents

Medtronic may conduct audits at participating study sites. The purpose of an audit is to verify the performance of the monitoring process and the study conduct, independently of the personnel directly involved in the study. Regulatory agencies may also perform inspections at participating study sites. The investigator and/or institution shall permit Medtronic, EC and Regulatory agencies direct access to source data and documents during monitoring, audits and regulatory inspections.

16.4 Confidentiality

All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential. Study sites will assign a unique Subject ID to each subject. Records of the subject ID relationship will be maintained by the study site. The subject ID number is to be recorded on all study documents to link them to the subject's medical records at the study site. Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data. To maintain confidentiality, the subject's name or any other Protected Health Information (PHI) should not be recorded on any study document other than the ICF. This scenario will be covered in the ICF. In the event a subject's name/PHI is included for any reason, it will be blinded as applicable. In the event of inability to blind the identification (e.g., digital media), it will be handled in a confidential manner by the authorized personnel. Data relating to the study might be made available to third parties (for example in case of an audit performed by Regulatory Authority), provided the data are treated as confidential and that the subject's privacy is guaranteed. No identifiable subject information will be published.

16.5 Liability

16.5.1 Insurance (Australia)

Medtronic Australasia Pty Ltd is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical study liability insurance coverage 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 EC.

16.6 CIP Amendments

Any revisions or amendments to the CIP or IC document, along with a statement of justification for the changes, will be submitted to all affected RAs and governing ECs, according to applicable regulations. Approval by ECs must be obtained prior to implementing a CIP revision at the study site.

[redacted]

16.7 Record Retention

All study-related documents (including applicable Source Documents, CRFs, Investigator Site File, electronic data etc.) must be retained for a period of at least 2 years after market-release in his/her region and after study closure (or longer if required by local law).

No study document or image will be destroyed without prior written agreement between Medtronic and the Investigator. The Investigator should take measures to prevent accidental or premature destruction of documents. Should the Investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to Medtronic.

Medtronic will retain the study records according to Medtronic corporate policy and record retention schedule.

16.7.1 Investigator Records

The Investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. CRFs must be maintained and signed electronically within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of 15 years (or longer as local law or hospital administration requires) after product approval or the date on which the investigation is terminated or the date that the records are no longer required for purposes of supporting a pre-market approval application.

- All correspondence between the EC, sponsor, monitor, Regulatory Authority and the Investigator that pertains to the Investigation, including required reports.
- Subject's case history records, including:
  - Signed and dated IC by subject and Investigator
  - Observations of AEs/DDs
  - Medical history
  - Trial, Implant, Testing and visit data
  - Documentation of the dates and rationale for any deviation from the protocol
- List of investigation study sites
- Financial Disclosure
- Subject screening log & ID log (if applicable)
- Normal value(s)/range(s) for clinical laboratory test (if applicable)
- Lab certificate (if applicable)
- Device Disposition Logs containing Model and serial numbers of devices delivered to the study site, subject IDs of the subjects implanted, received dates of devices, implant/used dates, explant dates, returned-to-sponsor dates and reasons, all persons who received, used or disposed each device, and method of disposal/destruction.
- Non implantable device Disposition Logs containing Model and serial/lot numbers, subject IDs of the subjects receiving device, receive and return date by patient,

[redacted]

returned-to-sponsor dates, disposal /destruction date, all persons who received device from sponsor or subject, returned or disposed/destruct device, and reason and method of disposal/destruction.

- All approved versions of the CIP, IC, Investigator Brochure
- Signed and dated CTA
- CV signed and dated of Principal Investigators and key members of investigation study site team (as required by applicable regulations
- Documentation of delegated tasks
- EC approval documentation. Written information that the investigator or other study staff, when member of the EC, did not participate in the approval process. Approval documentation must include the ECs composition, where required per local law.
- Regulatory Authority notification, correspondence and approval, where required per local law.
- Study training records for study site staff
- Insurance certificates
- Shipping records of investigational devices
- Equipment maintenance records, if applicable
- Any other records that local regulatory agencies require to be maintained
- Final Study Report including the statistical analysis

16.7.2 Sponsor Records

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

- All correspondence which pertains to the investigation
- Investigational device traceability record containing Model and serial numbers of devices, shipping date and name and address of person that received shipped device, location (if different than person shipped to), transfer and receipt by Medtronic dates.
- Non implantable device traceability records containing Model and serial/lot numbers, shipping date and name and address of person that received shipped device, location (if different than person shipped to), transfer and receipt by Medtronic dates.
- Sample of label attached to investigational device
- Signed Investigator Trial Agreements, Financial Disclosure and current signed and dated 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
- Randomization records
- Copies of all EC approval letters and relevant EC correspondence and EC voting list/roster/letter of assurance

[redacted]

- Names of the institutions in which the study will be conducted
- Regulatory Authority correspondence, notification and approval as required by national legislation
- Insurance certificates
- Names/contact addresses of monitors
- Monitoring visit reports
- Case Report Forms
- Statistical analyses and underlying supporting data
- Final report of the study
- The CIP, Investigator's Brochure summary and 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 retain records and reports per Medtronic standards and applicable regulations.

16.8 Reporting Requirements

16.8.1 Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the Sponsor of all CRFs, AEs and adverse device effects (reported per the country-specific collection requirements), device deficiencies, deaths, and any deviations from the CIP. If any action is taken by an EC with respect to this 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 above for investigator records.

Safety data investigator reporting requirements are listed in Section 12. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 11: Investigator reports applicable for all geographies per Medtronic requirements

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval	Sponsor and Relevant Authorities, where applicable per local requirements	Report if required by local law.

[redacted]

Report	Submit to	Description/Constraints
Progress Report	Sponsor and EC	Provide if required by local law or EC.
Study Deviations	Sponsor and EC	Any deviation from the CIP shall be recorded together with an explanation for the deviation. Deviations shall be reported to the sponsor who is responsible for analyzing them and assessing their significance. Note: When relevant, ethics committees or the appropriate Regulatory Authority should be informed. (ISO 14155:2020) In the event the deviation involves a failure to obtain a subject's consent, or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the EC as well as Medtronic within five (5) working days **Australia:** Report any suspected breaches to the sponsor and confirmed serious breaches to their institution (research governance office) within 72 hours of becoming aware or notified of the same; provide any follow-up information as required and work with the institution or sponsor, as appropriate, to implement any corrective and preventative actions **Australia - Serious Breach:** A breach of Good Clinical Practice or the protocol that is likely to affect to a significant degree: a) The safety or rights of a trial participant, or b) The reliability and robustness of the data generated in the clinical trial. Note: this guidance's definition of serious breach differs from the definition in the Australian Code for the Responsible Conduct of Research and is about deviations from the requirements of Good Clinical Practice or the clinical trials protocol. (NHMRC Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods 2018)
Final Report	ECs and relevant authorities	This report must be submitted as per local requirements.

16.8.2 Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below. In addition to the reports listed below, Medtronic shall, upon request of the reviewing EC or Regulatory Authority provide accurate, complete and current information about any aspect of the investigation. Safety data Medtronic reporting requirements are listed in Section 12.

[redacted]

Table 12: Sponsor reports for Australia

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, EC, and relevant authorities	Provide prompt notification of termination or suspension and reason(s). (ISO 14155:2020)
Recall and device disposition	Investigators, EC, relevant authorities	Notification as per local requirements.
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the CRFs and the final report of the clinical investigation. (ISO 14155:2020) Study site specific study deviations will be submitted to investigators periodically. Report serious breaches to the reviewing EC and PI within 7 calendar days of confirming a serious breach has occurred and provide follow-up when required. (NHMRC Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods 2018)
Withdrawal of approval by TGA or EC or approving authority	TGA, EC	Notify TGA of withdrawal of ethics approval. In case of revocation of CTN or CTX approval status by TGA, sponsor to notify EC and sites. In case of withdrawal of authorization from approving authority, communicate information to the EC and to TGA (Australian Clinical Trial Handbook, version 2.4, Aug 2021)
Completion of clinical trial	TGA	Notify TGA of the completion of a clinical trial after the trial has been completed at all sites along with the reason the clinical trial ceased (e.g. concluded normally, insufficient recruits, etc.) (Australian Clinical Trial Handbook, version 2.4, Aug 2021)

[redacted]

Report	Submit to	Description/Constraints
Annual safety reports, single case adverse events, clinical study report	TGA	Submit upon request from TGA (Australian Clinical Trial Handbook, version 2.4)
USADEs for Australia and international / safety report / updated IB / approved product information	Investigator and EC	Per EC requirements, but at least annually: • Annual safety report including: a summary of the evolving safety profile of the trial, a brief description and analysis of new/relevant findings, implications of safety data to the risk-benefit ratio for the trial, a description of any measures taken or proposed to minimize risks (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods, November 2016, section C.1.i) • An updated/addenda of IB or IFU, if appropriate (e.g. when an IB is no longer maintained) (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods, November 2016, section C.1.h)
Action with respect to safety that has been taken by another country's regulatory agency (relevant to an ongoing clinical trial in Australia)	TGA	Without undue delay and no later than 72 hours of the trial sponsor becoming aware of the action (Australian Clinical Trial Handbook, version 2.4)

16.9 Publication and Use of Information

Publications from the Closed-Loop SCS study will be handled according to Standard Operating Procedures and as indicated in the CTA.

16.9.1 Publication Committee

Medtronic may form the Closed-Loop SCS study Publication Committee from study Investigators and Advisors. Medtronic personnel may serve as members of the committee. This committee will manage study publications with the goal of publishing findings from the data. The Publication Committee will develop the final Publication Plan as a separate document.

The Publication Committee's role is to: 1) manage elements addressed in the publication plan as outlined here, 2) develop the final Publication Plan under separate cover, 3) execute the Publication Plan, 4) oversee the publication of primary, secondary and ancillary study results, 5) review and

prioritize publication proposals, 6) provide input on publication content, and 7) determine authorship. In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan.

Membership in the Publication Committee does not guarantee authorship. The committee will meet at as needed.

16.9.2 Management of Primary, Secondary, and Ancillary Publications

The Publication Committee reviews, prioritizes, and manages all publications including primary, secondary and ancillary publications. Primary and secondary publications are those that address analyses of any or all primary objectives or secondary objectives, respectively, as specified in the CIP.

An ancillary publication is any publication that does not address the study objectives identified in the CIP. They include publications proposed and developed by other Medtronic departments or entities, clinicians participating in this study, and clinicians not participating in this study. The committee will work with Medtronic to ensure that requests do not present conflicts with other proposals, are not duplicative, and to determine which ancillary publication proposals, if any, will be supported.

The committee may decide that no publications, including abstracts, will be published prior to the end of the study or with individual study site data. Requests for publications on study objectives utilizing subset data (e.g., regional) will be evaluated for scientific validity and the ability of Medtronic to provide resources.

16.9.3 Criteria for Determining Authorship

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria.

Authors, including Medtronic personnel, must at a minimum meet all of the conditions below:

- Substantial contributions to conception and design of the work, or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Decisions regarding authorship and contributor-ship will be made by the committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.

All Investigators not listed as co-authors may be acknowledged as the “Medtronic Closed-Loop SCS Study Investigators” and will be individually listed according to the guidelines of the applicable scientific journal when possible and affiliation. Any other contributors will be acknowledged by name with their specific contribution indicated.

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16.9.4 Transparency

Transparency of clinical study results will be maintained by the following means:

- A final report, describing the results of all objectives and analysis, will be distributed to all investigators, ECs and CAs of participating countries when required by local law
- Registering and posting the study results on a publicly accessible database, e.g., ClinicalTrials.gov, based on the posting rules stipulated
- Submitting for publication the primary study results after the study ends
- Disclosing conflicts of interest (e.g., financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- Making an individual study sites study data accessible to the corresponding investigator after the completion of the study, if requested

16.10 Suspension or Early Termination

16.10.1 Planned Study Closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a study that occurs when Medtronic and/or regulatory requirements have been satisfied per the CIP and/or by a decision by Medtronic or RA), whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing EC oversight is required until the overall study closure process is complete. Refer to Section 10.33 for additional information regarding study exit procedures.

16.10.2 Early Termination or Suspension

Early Termination is the closure of a study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single study site Suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single study site. In the event the whole study or a single study site is suspended, blinding of the subject randomization assignment should be maintained whenever possible.

16.10.2.1 Study-wide termination or suspension

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

- AEs associated with the device 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 or Regulatory Authority
- Technical issues during the manufacturing process

16.10.2.2 Investigator/study site termination or suspension

Possible reasons for investigator or study site termination or suspension include but are not limited to:

- Failure to obtain initial EC approval or annual renewal of the study

[redacted]

- Persistent non-compliance to the clinical investigation (e.g. failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-up visits)
- Lack of enrollment
- Noncompliance to regulations and the terms of the CTA (e.g. failure to submit data in a timely manner, failure to follow-up on data queries and monitoring observations in a timely manner, etc.)
- EC suspension of the study site
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g., no longer able to support the study)

16.10.3 Procedures for Termination or Suspension

16.10.3.1 Medtronic-initiated and regulatory authority-initiated

- Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the Regulatory Authority, where required
- In the case of study termination or suspension for reasons other than a temporary EC approval lapse, the investigator will promptly inform the EC
- In the case of study termination, the investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare

16.10.3.2 Investigator-initiated

- The Investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The Investigator will promptly inform the institution, where required per regulatory requirements
- The Investigator will promptly inform the EC
- The Investigator will promptly inform the regulatory authorities
- The Investigator will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare

16.10.3.3 Ethics Committee-initiated

- The Investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days

[redacted]

- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with EC policy or its determination that an overriding safety concern or ethical issue is involved
- The Investigator will inform his/her institution, where required per local requirements
- The Investigator will promptly inform the subjects, or legally-authorized designees or guardians and/or the personal physician of the subjects, with the rationale for the study termination or suspension
- The Investigator will promptly inform the Regulatory Authority

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18. Appendices

18.1 Appendix A: Foreseeable Adverse Events

Potential risks associated with the Inceptiv system, associated harms, and adverse events, as well as risk minimization are discussed in more detail in Section 11. The information provided in this section includes additional reference information and may collectively assist in identifying those events for a given device or therapy that are unexpected in nature. The foreseeable adverse event information consists of rates of adverse events reported from previous Medtronic studies evaluating SCS systems.

The implantation of the Inceptiv system involves surgery, therefore, standard adverse events associated with a surgical procedure may be experienced (e.g., anesthesia complications, injury, infections, bleeding, exacerbation of pre-existing conditions, healing complications). However, the focus of this section is to address in more detail, those events that are foreseeable due to the implantation, use, performance, and/or presence of the system under investigation or comparable systems.

Treatment required for procedure and/or device/system related adverse events may include medication, device reprogramming, device modification (e.g., repositioning, electrical abandonment, surgical removal), or other surgical or medical remedies.

Adverse Events Reported in Previous Medtronic Clinical Studies

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18.2 Appendix B: Participating Investigators and Institutions

A final list of participating Investigators (names, address, professional positions) and institutions (names and address) has not been finalized and will be distributed under separate cover.

[redacted]

19. Version History

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
1.0/19AUG2021	Not Applicable, New Document	Not Applicable, New Document	Not Applicable, New Document	Not Applicable, New Document	[redacted]
2.0/08FEB2022	Term "Neuro Sense" was removed throughout unless it is in reference to a programming setting or randomization assignment	Business decision	None	All	[redacted]
2.0/08FEB2022	Added inclusion criteria recommendation to only enroll patients capable of comprehending and consenting in English	Translated documents not available	None	None	[redacted]

[redacted]

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
2.0/08FEB2022	Edited inclusion criterion 3 to include patients with back and/or leg pain	to be aligned with device indications and representative of the general pain population	Affects some of the Secondary and Additional Objectives. The analysis populations for the affected Secondary/ Additional Objectives were clarified to include those with baseline back or leg pain VAS ≥ 60mm.	None	[redacted]
2.0/08FEB2022	Inclusion Criterion 3 has been modified to define eligible patients as those with back and/or leg pain patients with 1. baseline overall VAS ≥ 60mm and	Edited Inclusion Criterion 3 for clarity	Affects some of the Secondary and Additional Objectives. The analysis populations for the affected Secondary/ Additional Objectives were	None	[redacted]

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Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
	2) back and/or leg pain ≥ 60mm		clarified to include those with baseline back or leg pain VAS ≥ 60mm.		
2.0/08FEB2022	Rephrased Sections 4.2, 6 and 9.1	Administrative change	None	None	[redacted]
2.0/08FEB2022	Deleted duplicated text in Section 6.2	Administrative change	None	None	[redacted]
2.0/08FEB2022	Updated some model application numbers in Table 3, 4 and Figure 4	Administrative change	None	IB	[redacted]

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Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
2.0/08FEB2022	Changed "will" to "may" for the flexion maneuver in Sections 10.9, 10.10, 10.12 and 11.2.3	Some sites may not routinely perform this	None	Investigator's Brochure	[redacted]
2.0/08FEB2022	Added the UEFI-15 in Section 10.16.1	Administrative change	None	None	[redacted]
2.0/08FEB2022	Removed "from the start of the device trial until study exit" from Section 10.22	A device deficiency could occur before use of the device	None	None	[redacted]
2.0/08FEB2022	Added examples of electromagnetic interference in Section 11.2.2	Administrative change	None	Investigator's Brochure	[redacted]

[redacted]

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2.0/08FEB2022	A sentence was modified to provide an example of what additional radiation exposure a patient may face, as not all study participants may require 5 additional scans in Section 11.2.3	Administrative change	None	None	[redacted]
2.0/08FEB2022	Added instructions for device programming prior to medical procedures in Section 11.3	New information	None	Informed Consent Form and Investigator's Brochure	[redacted]
2.0/08FEB2022	Removed CRO information in Section 13	Administrative change	None	None	[redacted]

[redacted]

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2.0/08FEB2022	Removed the requirement for initials to be used in Section 16.7.1	Name is acceptable for person who received the devices	None	None	[redacted]
2.0/08FEB2022	Updated the Australian Clinical Trial Handbook version in Section 16	Administrative change	None	None	[redacted]
2.0/08FEB2022	Updated the synopsis and statistical analyses sections to reflect the change in subject populations used for each analysis (due to the modification of the inclusion/exclusion criteria).	Necessary update due to modification of the inclusion/exclusion criteria.	Could impact the ability to adequately estimate the responder rate in the low-back or leg populations if we are unable to enroll a large enough number of subjects within each indication.	Will impact the SAP (not yet complete) and other documents will be affected by the inclusion/exclusion criteria modification.	[redacted]

[redacted]

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2.0/08FEB2022	"HR" removed from HREC and Inceptive corrected to Inceptiv throughout	Administrative change	None	None	[redacted]
3.0/21OCT2022	Changed visit window between Enrollment and Trial to 28 days	The previous 14-day window was too short to schedule for the Trial procedure.	None	Informed Consent Form	[redacted]
3.0/21OCT2022	Updated to 056-F275 vE Clinical Investigation Plan Template	Requirement to update to most current template. No template changes impacted content of the CIP.	None	None	[redacted]
3.0/21OCT2022	Added the following Note to the Exclusion Criteria #5 "Note: *The Sponsor recommends excluding patients on ≥100 MME of opioids/day.*"	To ensure ability to comply with study-related activities described in the protocol.	None	None	[redacted]

[redacted]

[redacted]

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3.0/21OCT2022	Added clarification to Exclusion Criteria #7 "Note: *this includes patients that are the beneficiary of a successful injury claim.* "	Provided clarification.	None	None	[redacted]
3.0/21OCT2022	Updated Inclusion Criteria #2 to add clarity on types of pain syndromes that would be eligible by adding text "due to Failed Back Surgery Syndrome (FBSS), Complex Regional Pain Syndrome (CRPS), or other chronic neuropathic pain without history of surgical interventions. " An	Clarify appropriate candidates for consideration.	None	None	[redacted]

[redacted]

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	additional note was added stating *"The sponsor recommends not enrolling patients with chronic pain due to conditions that do not have adequate evidence to support the use of SCS (e.g., post-herpetic neuralgia, focal CRPS etc.)"*				
3.0/21OCT2022	Updated Exclusion Criteria #1 to include Diabetic Peripheral Neuropathy	Clarify appropriate candidates for consideration.	None	None	[redacted]
3.0/21OCT2022	Updated Section 10.7 to allow use of existing psychological evaluation within the	Allows greater flexibility for sites in scheduling as well as not to increase burden by repeating	None	None	[redacted]

[redacted]

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	previous 6 months with reconfirmation of suitability for SCS in lieu of requiring a new psychological evaluation.	evaluations unnecessarily.			
3.0/21OCT2022	Updated Section 10.7 to allow CT-scan in addition to MRI and X-ray as well as to require imaging to be reviewed whereas it was left to investigator discretion alone.	Allows greater flexibility for sites in leveraging existing imaging or in obtaining new imaging if a potential subject cannot have MRI or X-ray. Also ensures investigators review imaging on file, or obtains new imaging, to assess if the subject should continue in the study.	None	None	[redacted]

[redacted]

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3.0/21OCT2022	Removed "Intensity Score for Overstimulation" in Section 10.21.1 as it was an error in the paragraph structure, not needed.	Grammatical update.	None	None	[redacted]
3.0/21OCT2022	Updated Section 10.21.12 to correct the error noting that PROMIS-29 is a 10 point scale, to indicate that it is an 11 point scale since it ranges from 0-10.	Error correction.	None	None	[redacted]
3.0/21OCT2022	Replaced "enrolled" with "implanted" in section 14.1.3 to align with Section 6	Limits the total number of implanted patients from each site to minimize bias.	None	None	[redacted]

[redacted]

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3.0/21OCT2022	Updated Figure numbers in the text of Section 10.1 as they referenced the wrong figures.	Error correction.	None	None	[redacted]
3.0/21OCT2022	Updated Table numbers in the text of Safety Section 12.1, 12.2, and 12.5.1 to align with correct Tables within those sections.	Error correction.	None	None	[redacted]
3.0/21OCT2022	Reorganized text in Section 12.1 for events that are not reportable and added a NOTE below the bulleted items to clarify when to report.	Provided clarification.	None	None	[redacted]

[redacted]

[redacted]

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3.0/21OCT2022	Clarified asterisk footer under Table 8: Event Classification Responsibilities to indicate that therapy-related also fall into ADE classification.	Clarification.	None	None	[redacted]
3.0/21OCT2022	Updated Clinician Tablet Model to include CT900E in addition to CT900D in Table 3 and Table 4	Hardware manufacturer will eventually phase out the CT900D, so this update allows for the updated hardware to be used.	None	Investigator's Brochure	[redacted]
3.0/21OCT2022	Added "or newer" to software versions in Table 3. Also corrected programmer platform software-communication manager application version from 1.0.12123 to 1.0.1213	To allow for software updates to launch during study conduct. Version utilized will be noted on all session reports and/or logs. Also corrected typo in programmer platform software-communication	None	None	[redacted]

[redacted]

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		manager application version number.			
3.0/21OCT2022	Added Note *"If the subject reports overstimulation/discomfort from stimulation in between study visits but has not documented in the Stimulation Diary, please request the subject to complete the diary during the visit."* in section 10.16.1	Additional guidance to sites on stimulation diary expectations.	None	None	[redacted]
3.0/21OCT2022	Updated Section 10.17 to clarify Phone Calls start at time of Device Activation as	Provides more detail to sites on how to assess when unscheduled visits and/or therapy	None	Informed Consent Form	[redacted]

[redacted]

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	well as implement NRS collection in addition to satisfaction. Added an expectation on assessment for overstimulation events. Added detail on steps to take if NRS is 4 or more to ensure subjects have therapy optimized when needed.	optimization may be needed. This also ensures they are aware of overstimulation events the subject may have experienced.			
3.0/21OCT2022	In Section 10.23, removed "and (3) a statement attesting to the accuracy and completeness of the copy" as it is not an ISO requirement. Also removed	Update based on study design and ISO requirements.	None	None	[redacted]

[redacted]

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	System Modification from the bulleted list as it was template language that doesn't apply to this protocol.				
3.0/21OCT2022	Updated Section 14.9 to indicate the study site enrollment cap is 18 instead of 17.	Aligns with site communication and expectation that the cap should be 20%.	None	None	[redacted]
3.0/21OCT2022	Removed the words "assessed for" from "assessed for AEs/device deficiencies" in applicable visit sections as AE and DD updates might not be new, but updates on existing.	Clarity on data collection expectation.	None	None	[redacted]

[redacted]

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3.0/21OCT2022	Removed "ADE" from second bullet in Section 16.7.1 as ADE is encompassed within the AE category.	Removed redundancy.	None	None	[redacted]
4.0/06JAN2023	Updated Section 6.1 Duration to change enrollment period from 12 month to approximately 24 months	Enrollment taking longer than anticipated	None	Informed Consent Form	[redacted]
4.0/06JAN2023	Updated sample size calculation in section 14.8 to reflect a higher attrition rate	A higher-than-expected attrition rate has been observed so far. The new expected attrition rate more closely reflects the attrition rate being observed in the study.	None	Informed Consent Form	[redacted]

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4.0/06JAN2023	Updated number of subjects to be enrolled from 90 to 140 throughout the document.	A higher-than-expected attrition rate has been observed so far. The new expected attrition rate more closely reflects the attrition rate being observed in the study.	None	Informed Consent	[redacted]
4.0/06JAN2023	Minor grammatical errors	Administrative change	None	None	[redacted]
4.0/06JAN2023	Changed from 50 implanted subjects for lower back and leg pain to up to 57 and changed 12 subjects for upper limb/neck may be implanted and up to 25 upper limb and/or neck	Concern with higher attrition rate	None	None	[redacted]

[redacted]

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	pain subjects may be enrolled				
4.0/06JAN2023	Removed requirement for a phone call when subject has an in office visit for Optimization	Patient will be seen weekly during the Optimization period, so a weekly phone call is not necessary as long as the subject is seen in office	None	Informed Consent	[redacted]
4.0/06JAN2023	Changed Randomization and In Clinic Testing window to allow for overlap with 4 week visit	Allows for subject to combine 4 week Optimization and Randomization and in Clinic Testing when stable on therapy at the discretion of the PI	None	none	[redacted]

[redacted]

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4.0/06JAN2023	Removed Doi references in the Reference Table	Doi numbers were incorrect	None	None	[redacted]

[redacted]