Electrically Evoked Compound Action Potentials Human Observation Medtronic Algorithm Comparison Study (ECHO MAC)

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Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	Electrically evoked compound action potentials human observation Medtronic Algorithm Comparison study (ECHO-MAC)
Clinical Investigation Plan Identifier	MDT19024
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Confidentiality Statement

1. Investigator Statement

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

Table of Contents

Table of Tables

Table of Figures

[redacted]

Glossary

Abbreviation	Term
ADE	Adverse Device Event
AE	Adverse Event
CFR	Code of Federal Regulations
CIP	Clinical Investigational Plan
CL	Closed Loop
CRF	Case Report Form
[redacted]	[redacted]
DC	Dorsal Column
DCN	Dorsal Column Nuclei
DD	Device Deficiency
DMC	Data Monitoring Committee
DoH	Declaration of Helsinki
EC	Ethics Committee
ECAPs	Evoked Compound Action Potentials
eCRFs	Electronic Case Report Forms
ENS	External Neurostimulator
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance and Portability and Accountability Act
IC	Informed Consent
ICs	Integrated Circuits
IDE	Investigation Device Exemption
IRB	Institutional Review Board
ISO	International Organization for Standardization
LAR	Legally Authorized Representative
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
OL	Open Loop
[redacted]	[redacted]
RDC	Remote Data Capture
[redacted]	[redacted]
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SCS	Spinal Cord Stimulation
SR	Significant risk
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
US	United States
WENS	Wireless External Neurostimulator

2. Synopsis

Title	Electrically evoked compound action potentials Medtronic Algorithm Comparison (ECHO-MAC)
Clinical Study Type	Non-significant Risk Investigational Device Exemption (IDE) pre-market study
[redacted]	[redacted]
Sponsor	Medtronic [redacted]
Indication under investigation	Spinal Cord Stimulation (SCS) as an aid in the management of chronic, intractable pain of the trunk and/or limbs.
Investigation Purpose	To evaluate the in-clinic performance of a closed-loop algorithm in SCS therapy with an ENS device.
[redacted]	[redacted]
Primary Objective	To demonstrate that the proportion of subjects with a reduction in overstimulation[a] sensation with SCS using a closed-loop (CL) algorithm compared with SCS in open-loop (OL) exceeds a performance goal of 50%. [a] 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's returning to a neutral position.
[redacted]	[redacted]
Primary Endpoint	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 score during OL and CL periods will be calculated for each subject. If the average intensity score during CL period is less than that from the OL period, the subject is considered as a subject with a reduction in overstimulation sensation during CL vs. OL period. The primary endpoint is the proportion of subjects with a reduction in overstimulation sensation among subjects who have in-clinic testing.
Study Design	This is a prospective, multi-center, randomized, single-blind, cross-over, non-significant risk IDE research study.
Randomization	Subject randomization will occur after a clear, measurable ECAP [redacted] is verified and the algorithm is set-up. Subjects will be randomized to the sequence of receiving OL and CL in-clinic testing. Subjects will be blinded to the settings tested.
Sample Size	Up to a total of 60 subjects may be enrolled at approximately 15 sites in the US.
Inclusion/Exclusion Criteria	**Inclusion Criteria:** To be included in this study, a patient must meet the following inclusion criteria: • 22 years of age or older • Candidate for or undergoing Medtronic SCS device trial for labeled indication* • Willing and able to provide signed and dated informed consent • Capable of comprehending and consenting in English • Willing and able to comply with all study procedures and visits • Clear, measurable ECAP ECAPs** *Candidate for or undergoing a Medtronic SCS device trial for labeled indication means that a clinical decision has already been made between a physician and the patient to undergo Medtronic SCS trialing to treat the patient's chronic pain. This decision is to be made prior to discussing with the patient whether to enroll in the study. **If during set up of the in-clinic testing, the subject does not have a clear, measurable ECAP [redacted] they will not move forward with testing or randomization and will be considered a screen failure. **Exclusion Criteria:** To be included in this study, a patient must not meet any of the following exclusion criteria: • Implanted electrical cardiac devices (e.g., pacemaker, defibrillator) • Currently enrolled or planning to enroll in an interventional clinical study that could potentially confound the study results (co-enrollment in an interventional study is only allowed

	when documented pre-approval is obtained from the Medtronic study manager or designee) • Pregnant or is of child-bearing potential and unwilling to use a medically acceptable form of birth control during the study • Has untreated major psychiatric comorbidity, as determined by the investigator or designee • Trialed with a permanent implant lead and extension ("buried lead trial") • If subject is classified as vulnerable or requires a legally authorized representative (LAR)
Study Procedures and Assessments	Subjects may be consented prior to implantation of their commercial trial system. Upon obtaining informed consent, each subject will complete 2 study-related in-clinic visits, which may occur on the same day. • Enrollment/Baseline Visit • In-clinic Testing Visit **Enrollment/Baseline Visit** Subjects are considered enrolled at the time the study-specific informed consent/HIPAA form or other data protection form as required by local regulations is signed. Data collection requirements for the Enrollment/Baseline Visit: • Eligibility • Informed Consent • Demographics • Medical and surgical history **In-clinic Testing Visit** The in-clinic testing will take place after a subject has been implanted with their SCS trial leads for at least 24 hours, and prior to removal of trial leads as a part of standard of care. Data collection requirements for the In-Clinic Testing Visit: • Commercial Trial device parameters • Commercial trial Lead Information • Images of commercial trial lead(s) • Medications • Algorithm set-up parameters • Randomization • ECAP recordings • Subject rating of stimulation sensation with Likert scale [redacted] • Subject blinding assessment after each testing period • Adverse Events/Device Deficiency Collection

	
Safety Assessments	This study will collect and characterize all [redacted] system-related, SCS therapy-related, and study procedure procedure-related adverse events and device deficiencies from the In-clinic Testing Visit until study exit. Sensation of overstimulation (e.g. intense tingling, shocking, jolting) will not be reported as adverse events as this may occur as part of the procedures of this study. **Exception**: Extended periods of sensation or stimulation events that are uncomfortable to the subject (e.g. shocking, jolting) that result in intervention (e.g. changing programming settings, turning the device off) will be reported.
Statistics	For the primary objective, it is hypothesized that the proportion of subjects with a reduction in overstimulation sensation during CL compared to OL period exceeds a performance goal of 50%. H_0: $p \leq 50\%$ H_A: $p > 50\%$ The proportion of subjects with a reduction in overstimulation sensation during CL compared to OL 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, if the p-value is less than 0.025 to declare a study success. PASS 2020 Group-Sequential Tests for One Proportion in a Fleming Design module was used to calculate the sample size, with a null

	proportion of 50%, an alternative proportion of 75%, and one interim analysis at 70% of sample size, 42 subjects are needed to achieve more than 90% power with a one-sided alpha = 0.025 test. [redacted] To account for an estimated 30% attrition between enrollment and randomization, up to 60 subjects may be enrolled into the study. A 30% attrition rate was based on historical attrition rates from similar studies, as well as to account for the subjects who don't have clear, measurable ECAPS. [redacted] The primary analysis for the primary objective will follow the intent-to-treat (ITT) principle by including all the subjects randomized. The subjects who are randomized but have missing average scoring of overstimulation sensation during OL and/or CL period will be imputed using Multiple Imputation (MI). Two sensitivity analyses, one tipping point analysis using ITT population and one completer's analysis using all the subjects who finish the in-clinic testing and provided the scoring of overstimulation sensation. [redacted] Adverse events and device deficiencies will be summarized using summary tables displaying the frequency and percentages. Adverse events will be summarized by seriousness as well.

3. Introduction

3.1 Background

Overstimulation in SCS occurs when the intensity of the delivered stimulation reaches a level where a patient may experience discomfort or even pain. Overstimulation 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. This change in distance may happen quickly (on the order

of milliseconds) and may be caused by events such as sneezing, coughing or positional changes, all of which occur constantly throughout the day as patients go about their lives.

Since 2011, Medtronic has utilized AdaptiveStim™ Technology to address overstimulation. AdaptiveStim uses an accelerometer within the implantable neurostimulator (INS) to sense a change in position. The AdaptiveStim feature allows for certain therapy intensities to be set in either one of six or seven positions, depending on the model a patient has implanted. Either a patient or 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, [redacted]

Evoked compound action potentials (ECAPs) are the summed action potentials elicited from a nerve or group of nerves in response to stimulation. When the dorsal columns (DC) of the spinal cord are stimulated, action potentials propagate caudally toward the dorsal horn of the spinal segment that it innervates and rostrally toward the brain. Parker et al[1)]. were the first to report recording ECAPs from the DC of the spinal cord– applying and building on decades of ECAPs research in the auditory system. As more fibers are activated due to an increase in stimulation reaching the spinal cord, the ECAP amplitude grows in a linear fashion. Sensing an ECAP and measuring its amplitude allows for a feedback mechanism to inform therapy intensity based on the compounded response of the spinal cord to stimulation.

[redacted]

[redacted]

3.2 Purpose

Medtronic is sponsoring the ECHO-MAC study, a prospective, multi-center, randomized, single-blind, cross-over, non-significant risk IDE pre-market study. The purpose of this study is to evaluate the in-clinic performance of a closed-loop algorithm in SCS therapy [redacted]

4. Objectives and/or Endpoints

4.1 Objectives

4.1.1 Primary Objective(s)

To demonstrate that the proportion of subjects with a reduction in overstimulation[a] sensation with SCS using a CL algorithm compared with SCS in OL exceeds a performance goal of 50%.

[a] 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's returning to a neutral position.

[redacted]

5. Study Design

This is a prospective, multi-center, randomized, single-blind, cross-over, non-significant risk IDE study. This study will be conducted in the United States with up to 15 sites.

Up to 60 subjects are expected to be enrolled in the study to allow for at least 42 subjects for analysis.

The in-clinic testing will occur during a single office visit, at the end of the standard commercial SCS trial.

To reduce the potential for site-related bias, each site will contribute up to 10 enrolled subjects. The per-study site enrollment cap may be increased upon Sponsor approval.

5.1 Duration

The expected total study duration is approximately 6 months. The duration of a subject's participation is approximately 2 weeks from enrollment, although this may vary depending on when enrollment occurs relative to the SCS device trial. Enrolled subjects will have up to 2 study visits - Enrollment and the In-clinic Testing Visit, which may occur on the same day. The In-clinic Testing Visit is expected to last up to 3 hours and subjects will be discontinued at the end of the visit.

The study may also be stopped on recommendation of the Data Monitoring Committee (DMC), see stopping guidelines in Section 12.

5.2 Rationale

Patients treated with SCS systems often report over-stimulation induced by movement[2)] . The variation in perceived intensity is often attributed to changes in the distance between the implanted lead and

spinal cord resulting in increased or decreased numbers of dorsal column nerve fibers recruited during stimulation. Published pre-clinical and clinical feasibility data, [redacted] have demonstrated it is possible to measure ECAPs in the spinal cord from the epidural space[1),3),4)]. 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., CL control).

[redacted]

6. Product Description

[redacted]

[redacted]

6.2 Packaging

The labeling will indicate that the devices are for investigational use only, “CAUTION: Investigational Device. Limited by Federal Law (USA) to Investigational Use.” The Instructions for Use will be provided under separate cover.

6.3 Intended Population

A Medtronic implantable neurostimulation system is indicated for Spinal Cord Stimulation (SCS) as an aid in the management of chronic, intractable pain of the trunk and/or limbs.
Subjects who meet the eligibility criteria listed in Sections 8.3-8.4 are eligible to participate in this study.

6.4 Product Receipt and Tracking

The [redacted] System and accessories will be hand-carried by the Medtronic Engineer to the site along with a Product Delivery Note that will include product description, serial/lot number and quantity received. Site personnel delegated to product accountability will indicate they have received the

product by signing and dating the product delivery note and a copy will be kept in the sites Regulatory Binder.

6.5 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.

6.6 Product Return

At the conclusion of the study, the [redacted] System and any remaining system accessories will be returned to Medtronic. [redacted]

6.7 Product Accountability

The [redacted] System and accessories are considered investigational in the United States. All investigational product will be distributed to a study site only when Medtronic has received all required documentation and has notified the study site of site activation. Distribution of an investigational product to study sites during the study will be managed by Medtronic and can only be ordered by Medtronic personnel.

The study site is responsible for maintaining tracking of the investigational devices during the study. The product will be tracked at the site using electronic accountability logs provided by Medtronic. The accountability logs must be maintained at each study site and updated when the investigational product is received, opened, used, and 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 subject, reason(s) for and method of destruction/disposal for used 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.

7. Study Site Requirements

7.1 Investigator/Investigation Site Selection

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

The principal investigator shall:

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

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

7.2 Study Site Activation

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

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

- IRB approval (and voting list, as required by local law) of the current version of the CIP and IC
- Fully executed CTA
- CV/medical license of investigators and key members of the investigation study site team (as required)
- Documentation of delegated tasks
- Documentation of study training
- Financial disclosure

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.

7.3 Role of the Sponsor Representatives

Sponsor representatives may provide support at the study site as required for the study under supervision of the Principal Investigator or delegated site personnel, including:

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

- Provide technical support at visits under the supervision of a study investigator
- Perform monitoring and auditing activities

In addition, for this study, sponsor representatives may be authorized by the principal investigator to perform the following trial related duties:

- Support study investigators in performing the study trial/implant procedure
- Support data collection during the trial/implant procedure and device testing
- Support data collection during visits
- Perform device programming, device interrogation, and device download including printing or uploading of device information
- Identify location of active lead contacts using images
- Collect stimulation thresholds
- Discuss any issues with programming or subject compliance with the principal investigator or other site personnel

Sponsor representatives may not perform the following:

- Practice medicine, provide medical diagnoses or make decisions related to subject treatment/care
- Discuss a subject's condition or medical treatment with the subject or a member of the subject's family
- Assist the subject by direct physical contact except as required by the specific protocol-related task to be conducted
- Complete source documents or entry into the electronic medical record
- Enter data on eCRFs, with the exception of Medtronic Use Only fields/forms

8. Selection of Subjects

8.1 Study Population

The intended study population is patients who are a candidate for or undergoing a Medtronic SCS device trial for labeled indication. A clinical decision has already been made between a physician and the patient to undergo Medtronic SCS trialing to treat the patient's chronic pain. This decision is to be made prior to discussing with the patient whether to enroll in the study.

8.2 Subject Enrollment

A subject is considered enrolled into the study when the subject and the principal investigator or authorized designee, as required, have personally signed and dated the IC. The date the subject signed the IC and data protection authorization, 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.

8.3 Inclusion Criteria

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

- 22 years of age or older
- Candidate for or undergoing Medtronic SCS device trial for labeled indication*
- Willing and able to provide signed and dated informed consent
- Capable of comprehending and consenting in English
- Willing and able to comply with all study procedures and visits
- Clear, measurable ECAPs**

*Candidate for or undergoing a Medtronic SCS device trial for labeled indication means that a clinical decision has already been made between a physician and the patient to undergo Medtronic SCS trialing to treat the patient's chronic pain. This decision is to be made prior to discussing with the patient whether to enroll in the study.

**If during set up of the in-clinic testing, the subject does not have a useable ECAP [redacted] they will not move forward with testing or randomization and will be considered a screen failure

8.4 Exclusion Criteria

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

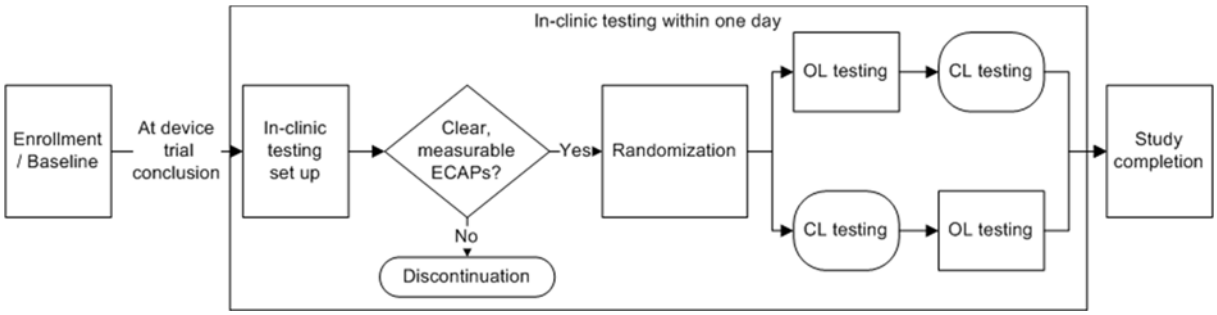
- Implanted electrical cardiac devices (e.g., pacemaker, defibrillator)
- Currently enrolled or planning to enroll in an interventional clinical study that could potentially confound the study results (co-enrollment in an interventional study is only allowed when documented pre-approval is obtained from the Medtronic study manager or designee)
- Pregnant or is of child-bearing potential and unwilling to use a medically acceptable form of birth control during the study
- Has untreated major psychiatric comorbidity, as determined by the investigator or designee
- Trialed with a permanent implant lead and extension ("buried lead trial")
- If subject is classified as vulnerable or requires a legally authorized representative (LAR)Study Procedures

9. Schedule of Events

Figure 9-1 is a flow diagram of how subjects will complete the study. Subjects will be required to come into the clinic for 2 study visits, although they could occur on the same day:

- Enrollment
- In-clinic Testing Visit

Figure 9-1: Study Visit Diagram



9.1 Data Collection

Study procedures, tasks and data collection requirements are summarized in Table 9-1 below.

Table 9-1 Study Procedures, Tasks, and Data Collection by Visit

Study Procedures, Tasks, and Data Collection (row) by Visit (column)	Enrollment	In-Clinic Testing
Informed Consent	✓	
Eligibility	✓	
Demographics	✓	
Surgical and Medical History	✓	
Medications		✓
Commercial Trial Lead Information		✓
Commercial Trial device parameters		✓
Images of commercial trial lead(s)		✓
Algorithm set-up parameters		✓
Randomization		✓
ECAP recordings		✓
Subject rating of stimulation sensation with Likert scale		✓
[redacted]		✓
Adverse Event/Device Deficiency collection		✓

9.2 Subject Screening

Subjects may be recruited through the investigator's practice and referring physicians.

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

Recruited subjects will be screened by the principal investigator or authorized site personnel by reviewing the study's inclusion and exclusion criteria. All subjects must be consented in accordance with

the protocol and IRB requirements prior to any study-specific procedures. Subjects who do not meet any of the inclusion or who meet exclusion criteria may not be rescreened.

All subjects that are considered for the study should be included on the study screening log. The reason for non-eligibility, as determined by the Investigator should also be recorded on the study pre-screening log. The screening log serves as a method for Medtronic to assess selection bias in the trial.

9.3 Prior and Concomitant Medications/Therapies

All prescribed medications will be collected during the In-clinic Testing Visit.

9.4 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 and a/an Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law that has been approved by the study site's IRB/ 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 site and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be approved by the IRB. The document(s) must be controlled (i.e. versioned and/or dated) to ensure it is clear which version(s) were approved by the IRB. Any adaptation of the sample IC must be reviewed and approved by Medtronic and the IRB 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.

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 Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be given to the subject in a language, he/she is able to read and understand. Only subjects capable of reading and understanding English are eligible to participate in this study. Signing and dating of the IC or HIPAA authorization or other data protection form by a legally authorized representative will not be permitted for this study. 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.

A copy of the IC and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language, signed and dated as required by law, must be provided to the subject and his/her authorized designee.

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.

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

Consistent with the Declaration of Helsinki (DoH), vulnerable adults (i.e. those subjects mentally incapable of giving consent) are excluded from this protocol. Any subjects with mental incompetence (e.g. Alzheimer's, dementia, psychiatric disorders, developmental disorders) should be assessed for vulnerable status. This protocol defines vulnerable adult as those subjects mentally incapable of giving consent, in the Investigator's opinion. The Investigator should consider the definition of vulnerable adult per ISO 14155, which defines vulnerable adults as: "individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of a retaliatory response. For example, this could include Individuals with loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving IC. Other vulnerable subjects could include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention.

9.5 Enrollment/Baseline

A subject is considered enrolled when the consent process has been finalized. The date the subject signed the IC and Data Protection Authorization, as required by law, must be documented in the subject's medical records. A log of all subjects enrolled in the study should be maintained. The enrollment/ baseline visit can be a stand-alone visit or can be performed on the same day prior to the in-clinic testing.

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

- Informed Consent
- Eligibility
- Demographics
- Surgical and Medical History

9.6 In-Clinic Testing

The in-clinic testing will take place after the subject has been implanted with an SCS device trial lead for at least 24 hours, completed their commercial trialing phase, and prior to their percutaneous trial lead(s) being removed per standard of care. At the In-clinic Testing Visit, following imaging and set up of the CL algorithm, the subject will be randomized to either OL testing followed by CL testing or CL testing followed by OL testing. The subject will be blinded to the settings tested.

The following information is required to be collected at the In-clinic Testing Visit:

- Commercial trial device parameters
- Commercial trial lead information
- Images of commercial trial lead(s)
- Medications
- Algorithm set-up parameters
- Randomization
- ECAP recordings
- Subject rating of stimulation sensation with Likert scale
- [redacted]
- Subject blinding assessment after each testing period
- Adverse Events/Device Deficiency Collection

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.7 Imaging

Anterior/posterior and lateral images, e.g., x-ray or fluoroscopy, of the subjects' trial lead(s) will be taken, including at least one anterior/posterior image that captures the vertebral level of the trial lead. An additional image of the externalization of the lead(s) may also be required (for example, if not visible in the other images). [redacted]

Site personnel will deidentify each image and label with the subject's ID prior to securely sending them to Medtronic.

9.8 Randomization and Treatment Assignment

Subjects who give informed consent, fulfill the inclusion and exclusion criteria, and provide clear, measurable ECAPs at in-clinic testing setup will be randomized to receive either OL followed by CL testing or CL followed by OL 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 and to help prevent the next treatment assignment from being guessed by site personnel. Randomization allocation will be concealed from the clinician and subject, using a centralized automatic web-based data management system. Once assigned, the randomization assignment for the subject cannot be changed. The randomization details are outlined under separate cover in a Randomization Plan.

9.8.1 Blinding

The study will be single-blind to reduce bias. The subject will not have knowledge of the in-clinic testing assigned for the duration of the study. It is essential that study sites take special precaution to maintain the blind for the entire portion of the subject's participation in the study. A blinding assessment will be completed after each testing period in order to assess adequacy of blinding on the subject.

9.8.2 Crossover

Crossover in this particular study is defined as the subjects receive either OL followed by CL in-clinic testing, or CL followed by OL in-clinic testing. All randomized subjects will crossover. [redacted]

9.9 Assessment of Efficacy

Subject assessments will be performed by appropriately trained, qualified and delegated site personnel according to the usual practices at the site.

9.9.1 Subject Assessment

9.9.1.1 Overstimulation Sensation

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

- 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 of intensity scores during the OL and CL period will be calculated for each individual subject regarding the overstimulation sensation. If the average of intensity scores during the CL period is less than that from the OL period, the subject is considered to have experienced a reduction in overstimulation sensation during CL vs. OL 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%. Since this is a feature to control overstimulation with approved stimulation parameters, the 50% performance goal is selected so that majority of the subjects meet the criterion with 95% confidence.

[redacted]

9.10 Assessment of Safety

This study will collect and characterize all device-related, therapy-related, and procedure-related adverse events and device deficiencies from the time the subject is enrolled until study exit. See Section 11 for further information on the collection of AEs and safety.

9.11 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' assessments or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, X-rays, and subject files).

In general, eCRFs (or paper copies) may not serve as source documents. Source documentation for data elements not routinely captured in medical records may vary from study site to study site; the study site may use source document worksheets if identified as source documents.

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

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

This study will use a remote data capture (RDC) system to collect study required Case Report Form (CRF) information. Electronic CRFs (eCRFs) will be provided by the sponsor; required data will be taken from source documents and directly entered into the study database via the eCRFs by the appropriately delegated site personnel, in accordance with applicable regulations. Source documentation for patient in-clinic testing assessment will be completed confidentially by the subject only. Data from the subject assessment will be entered into the database by delegated site personnel. The principal investigator, or appropriately delegated personnel, are responsible for entering data on the eCRFs. The principal investigator, or appropriately delegated personnel, is required to approve all data on eCRFs via electronic signature.

9.12 Deviation Handling

A study deviation is defined as an instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CIP, IRB, or CTA. The investigator is not allowed to deviate from the CIP, except under emergency circumstances to protect the rights, safety and well-being of human subjects. Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to protect the safety, rights or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g. subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness). 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 IRB as well as Medtronic within five (5) working days. Reporting of all other study deviations should comply with IRB policies, RA requirements, and/or local laws and must be reported to Medtronic as soon as possible upon the study site becoming aware of the deviation.

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 (e.g. required subject assessments)
- Inclusion/exclusion criteria not met
- Missing required device interrogation files
- Visits outside of window

9.13 Subject Exit, Withdrawal or Discontinuation

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

If a subject is withdrawn from the study, the reason for withdrawal shall be recorded on a study exit eCRF and in the subject's medical record. Examples of reasons for study exit include the following:

- Eligibility criteria not met
- Pregnancy
- Subject death
- Subject lost to follow-up (LTFU)
- 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)
- Adverse events
- Normal study completion

A study exit eCRF, including reason for exit, is required for all subjects and will be completed for any enrolled subject who permanently discontinues from the study or completes the protocol-required study follow-up and has completed the study. 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.

9.13.1 Study Completed

At the completion of the In-clinic Testing Visit, subjects will be exited from the study.

9.13.2 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, regulations set forth by the governing IRB must be followed.

10. Risks and Benefits

10.1 Potential Risks

This study will enroll subjects who are planning to have an SCS device trial regardless of participation in the study (i.e., subjects will not be selected for a SCS device trial in order to facilitate participation in the study). All risks associated with the Medtronic spinal cord stimulation device trial are pre-existing and are not introduced by the conduct of the study.

The [redacted] System will maintain stimulation parameters (e.g. amplitude, pulse width) within the approved bounds of the commercially available Medtronic SCS systems (Intellis, Restore, etc.). The [redacted] System will be operated in accordance with labeled instructions for use, developed specifically for this study.

It is anticipated that the risks associated with the [redacted] System will be similar to those of the commercial SCS device trial system external neurostimulator (ENS) which are described below. In addition to risks normally associated with surgery, commercial SCS device trialing includes, but is not limited to, the following risks:

- Allergic or immune system response to the implanted materials
- Infection
- Lead or extension 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
- 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
- Stimulation-dependent gastrointestinal symptoms such as diarrhea, nausea, incontinence or constipation
- Stimulation-dependent bladder symptoms such as urinary retention, incontinence or frequency
- Change in stimulation, possibly related to cellular changes around the electrode(s), shifts in electrode position, loose electrical connections, lead or extension fractures, which has been described by some patients as uncomfortable stimulation (jolting or shocking sensation).
- Formation of reactive tissue around the lead in the epidural space can result in delayed spinal cord compression and paralysis, requiring surgical intervention. Time to onset can range from weeks to many years after implant.
- The safety and effectiveness of this therapy has not been established for pregnancy, unborn fetus, or delivery. The study procedures may involve unknown risks for female subjects, their

embryo or fetus (unborn child), or delivery if they become pregnant. For this reason, pregnant females have been excluded from participating in this study. Female subjects must agree to not become pregnant during the study by using a medically acceptable method of birth control; an identified pregnancy will result in immediate study withdrawal.

- Wireless telemetry control of both commercial SCS devices and the [redacted] System could unintentionally change the operation of an existing implanted electrical device.

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 [redacted] system is being performed in accordance with ISO 14971, and will ensure that the level of risk is acceptable prior to starting the study.

10.1.1 Radiographic Risks

As part of the study, subjects will be required to have fluoroscopic or X-ray images (less than or equal to 5) taken of their device trial leads. This represents a negligible amount of additive radiation exposure beyond imaging used as part of a standard trial lead placement. Wininger et al. 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[6]. 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 well under one-tenth of a standard deviation from the mean. Further, Schmid et al. [7] found that 1 min. of pulsed fluoroscopy at 3 pulses/s (180 images—over 36 times more imaging than that anticipated for this study) 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[7]. Pradhan[8] reports that cancer risk can't be estimated from doses below 100 mSv[8]. Following the fluoroscopic procedure, the skin area exposed to the x-rays could react to produce an effect similar to a sun burn. A skin reaction, if it occurs at all, could show up from a few hours to a few weeks after the procedure, and usually goes away on its own.

10.1.2 Study Specific Risks

Although secure electronic systems will be used, data will be anonymized, and other measures will be taken in this study to protect subject privacy there is not a guarantee of absolute confidentially and privacy; therefore, there is a slight risk of a loss of subject privacy in case of a data breach involving a subject's protected health information.

Use of the [redacted] System can pose risks to the subject that are incremental to or unique from those from commercial trialing, including:

- Temporary or transient uncomfortable sensation (e.g., shock or jolting) from the stimulation pulse(s)
- Temporary discomfort resulting from device heating or exposed electronics in the event of electrical/mechanical failure of a system component
- Discomfort resulting from an activity requested during the study

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

10.2 Risk Minimization

The potential risks associated with the [redacted] system were identified and have been successfully mitigated. Any potential risks associated with this study are further minimized by selecting qualified investigators and training study personnel on the CIP. Medtronic has also attempted to minimize risk to subjects implementing a DMC to review safety issues as part of the study.

Prior to participating in the study, subjects will be fully consented. Should the subject experience intolerable stimulation at any point during the study, the subject or researcher may turn off stimulation or change the stimulation settings. Furthermore, the subject may discontinue from the study at any time.

10.3 Potential Benefits

There may be no direct benefit from participation in the study.

[redacted]

10.4 Risk-Benefit Rationale

Medtronic has carefully tested the [redacted] System and completed a risk assessment of system use and ECHO-MAC study procedures to ensure the identification of potential hazards and subsequent mitigation of these hazards to eliminate them entirely or reduce them as far as possible. Study-specific risks to the subject that are incremental to commercial trialing are expected to primarily consist of potential transient discomfort, as detailed above. Subjects will be provided stimulation within the current approved output range of Medtronic stimulation devices. There may be other discomforts and risks related to SCS therapy and/or this study that are not foreseen at this time due to the difference between the currently approved Medtronic SCS systems and the external system to be used for this study.

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

The anticipated benefits of this clinical study outweigh the overall risk. Subjects may not benefit directly from their participation in the study. The study will assess the feasibility to record ECAPs, with Medtronic's leads using a CL system and responsively adjust stimulation. The knowledge gained from this study may benefit future patients through the better understanding of SCS therapy.

11. Adverse Events and Device Deficiencies

11.1 Adverse Events

AE definitions are provided in Section 11.3. Because this study has been determined to be NSR, only Adverse Events related to the [redacted] System, SCS therapy, or study procedures will be collected. Adverse Events will be collected beginning at the In-clinic Testing Visit through subject discontinuation. Each event will be classified according to 5 different levels of causality using the following terms (defined in Table 11-1):

- Not related
- Unlikely
- Possible
- Probable
- Causal

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

Reporting of these events to Medtronic will occur on an AE Form. Each event must be reported separately. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened and meets reporting criteria.

Subject deaths are also required to be reported Refer to Section 11.5 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. **Exception:** Extended periods of sensation or stimulation events that are uncomfortable to the subject (e.g. shocking, jolting) that result in intervention (e.g. changing programming settings, turning the device off) will be reported.

11.2 Device Deficiency

Device deficiencies (DD) reported during the study will be collected beginning at the In-clinic Testing Visit through subject discontinuation. Note that DD that result in an AE to the subject should be captured as an AE only. The DD definition is provided in Section 11.3.

11.3 Definitions/Classifications

Each event is defined according to International Organization for Standardization (ISO) 14155:2020 and 21 CFR§812.3(s). Where the definition indicates "device" it refers to any device used in the study. This might be device under investigation, or any commercially available component of the system.

Adverse Event (AE): (ISO 14155:2020 3.2)
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 the use of investigational medical devices or comparators.

Adverse Device Effect (ADE): (ISO 14155:2020 3.1)
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 use error or from intentional misuse of the investigational medical device.

NOTE 3: This includes 'comparator' if the comparator is a medical device.

Serious Adverse Event (SAE): (ISO 14155:2020 3.45)
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 diseases, 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) foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment

NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE.

Serious Adverse Device Effect (SADE): (ISO 14155:2020 3.44)
Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Adverse Device Effect (UADE): (21 CFR§812.3(s))
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Unanticipated Serious Adverse Device Effect (USADE) (ISO 14155:2020, 3.51)
Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment

NOTE 1: ASADE is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

Serious Health Threat (ISO 14155:2020 3.46)
Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons

NOTE 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

Device Deficiency (DD): (ISO 14155:2020 3.19)
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.

Table 11-1: Levels of Causality

Level of Causality	Definition
Not Related	Relationship to the device or procedures can be excluded when:

Level of Causality	Definition
	• the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; • the event has no temporal relationship with the use of the investigational device or the procedures; • the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; • the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; • the event involves a body-site or an organ not expected to be affected by the device or procedure; • the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); • the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; • harms to the subject are not clearly due to use error; • In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event
Unlikely	• The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained
Possible	• The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
Probable	• The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.

Causal relationship	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when:
	• The event is a known side effect of the product category the device belongs to or of similar devices and procedures;
	• The event involves a body-site or organ that
	  ○ The investigational device or procedures are applied to;
	  ○ The investigational device or procedures have an effect on:

Level of Causality	Definition
	• The serious event follows a known response pattern to the medical device (if the response pattern is previously known; • The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); • Other possible causes (e.g, an underlying concurrent illness/clinical condition and/or an effect of another device, drug or treatment) have been adequately ruled out; • Harm to the subject is due to error in use; • The event depends on a false result given by the investigational device used for diagnosis, when applicable; • In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

11.4 Reporting of Adverse Events

It is the responsibility of the Investigator to adhere to the adverse event reporting requirements as stated within the protocol and to their IRB reporting requirements. In case of an emergency or to immediately report a subject death and/or SADE, contact a study representative (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).

11.4.1 Adverse Event and Device Deficiency Classification

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

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

Regulatory reporting of AEs and DDs will be completed according to local regulatory requirements. Refer to Table 11-2 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 IRB responsible for oversight of the study. AEs will be classified according to the standard definitions as outlined below:

Table 11-2: Event Classification Responsibilities

What is Classified	Who Classifies	Classification Parameters
Relatedness	Investigator, Medtronic	Study procedure-related [redacted] System-related SCS Therapy-related
Seriousness	Investigator, Medtronic	SAE/SADE
Expectedness	Medtronic	UADE, USADE
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Medtronic	MedDRA term assigned based on the data provided by the Investigator

11.4.2 Adverse Event and Device Deficiency Reporting Requirements

Regulatory reporting of AEs and DDs 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 IRB.

Table 11-3: Reporting Requirements

ADEs	
Investigator shall submit to:	
Medtronic	Submit in a timely manner (within 3 weeks) after the investigator first learns of the effect.
IRB	Submit to IRB per local reporting requirement.
Sponsor shall submit to:	
IRB	Submit to IRB per local reporting requirement.
SADEs	
Investigator shall submit to:	
Medtronic	Submit in a timely manner (within 3 weeks) after the investigator learns of the event or of new information in relation to an already reported event.
IRB	Submit to IRB per local reporting requirement.
Sponsor shall submit to:	
IRB	Submit to IRB per local reporting requirement.
Investigators	Submit per local reporting requirement.
UADE and USADEs	

Investigator shall submit to:	
Medtronic	Submit immediately, but no later than72 hours after the investigator learns of the event or of new information in relation to an already reported event.
IRB	Submit to IRB per local reporting requirement.
Sponsor shall submit to:	
IRB	Submit to IRB per local reporting requirement.
Investigators	Submit per local reporting requirement.
All Other Reportable AEs	
Investigator shall submit to:	
Medtronic	Submit in a timely manner (within 3 weeks) after the investigator first learns of the event.
IRB	Submit to IRB per local reporting requirement.
Device Deficiencies	
Investigator shall submit to:	
Medtronic	Submit in a timely manner (within 3 weeks) after the investigator first learns of the deficiency.
IRB	Submit to IRB per local reporting requirement.

11.5 Subject Death

The investigator must notify Medtronic immediately, but no later than72 hours of the investigator's/site's first knowledge of the event) and the IRB, as required, after learning of a subject's death, regardless of whether or not the death is device-, procedure- or therapy-related. The investigator should also attempt to determine, as conclusively as possible, whether such deaths are related to the [redacted] system, procedure or therapy. Deaths will be captured by a study exit CRF and an adverse event CRF if related to the [redacted] System, study procedure or SCS therapy.

If an autopsy is conducted, a copy of the report should be provided to Medtronic. Requested death certificates and/or source documentation should be provided to Medtronic.

11.6 Product Complaint Reporting

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. The reporting of product complaints by the clinical team must be done according to the local

Standard Operating Procedures. Medtronic will notify the RAs (e.g. CA) as applicable for the following incidents immediately upon learning of them and is not limited to AEs and DDs only:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.

12. Data Review Committees

The DMC will be responsible for safeguarding the scientific integrity of the study and assessing the accumulating data on safety of the device/therapy and interventions during the study. The DMC will be responsible for safeguarding the interests of the study participants and for monitoring the overall conduct of the study. To enhance the integrity of the study, the DMC may also formulate recommendations related to the selection, recruitment, and retention of subjects, their management, improvement of adherence to protocol-specified regimens and procedures for data management and quality control.

The DMC will be advisory to the sponsor. The DMC may provide recommendations for early termination of the study. In order to recommend early termination of the study for efficacy, the primary objective must meet the predetermined decision boundaries. In addition, other considerations for early stopping for efficacy will include, but are not limited to, the magnitude of effect, data quality, and consistency of results across sites. Review and consensus by the entire committee is required in order to recommend that the study should be stopped.

The DMC will monitor the event rates of the study, and if necessary, they may recommend randomizing more subjects and/or extending follow-up in order to ensure the minimum number of events occur.

Statistical decision boundaries for the study are outlined in the statistical methods section of this document. These are to be used only as guidelines by the DMC when deciding whether the study should continue as no statistical methods can adequately capture the complexity of all data in a study.

13. 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 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.

13.1 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.

13.1.1 Analysis Sets

Enrolled Analysis Set: includes all consented subjects.

Intent-to-treat (ITT) Analysis Set: includes all subjects who are randomized.

Completer Analysis Set: includes subjects who are randomized and provide assessment for overstimulation sensation at both OL and CL in-clinic testing periods.

13.1.2 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.

The primary analysis of the primary objective will include subjects who are randomized (ITT Analysis Set) with the Multiple Imputation (MI) methodology for missing data. Details of the imputation method are described in Section 13.4. Sensitivity analyses will be performed for the primary objective using Completer Analysis Set.

13.1.3 Multiple Endpoints

As there is one primary objective, adjustment for multiple endpoints is not required.

[redacted]

[redacted]

13.2 Analysis Execution

Two formal analyses are planned for this study, [redacted] one final analysis will occur after all subjects complete the study. Interim Analysis is described in Section 13.3. A final report will be prepared once all data collection has ended and all subjects have completed the study and have been exited.

13.3 Interim Analysis

One planned interim analysis will be conducted under the auspices of the data monitoring committee (DMC) assigned to this study. The DMC will disseminate interim results only if absolutely necessary. Any such dissemination will be documented and described in the final study report. Study sites will not receive information about interim results unless they need to know for the safety of their subjects.

[redacted]

13.4 Primary Objective

To demonstrate that the proportion of subjects with a reduction in overstimulation sensation with SCS using a CL algorithm compared with SCS in OL 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's returning to a neutral position.

13.4.1 Hypothesis

It is hypothesized that the proportion of subjects with a reduction in overstimulation sensation during CL compared to OL period exceeds a performance goal of 50%.

H_0: $p \leq 50\%$

H_A: $p > 50\%$

13.4.2 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 OL and CL period will be calculated for each individual subject. If the average intensity score during CL period is less than that from the OL period, the subject is considered as a subject with a reduction in overstimulation sensation during CL vs. OL period. The proportion of subjects with a reduction in overstimulation sensation among subjects who have in-clinic testing is the primary endpoint.

13.4.3 Performance Requirements

The null hypothesis will be rejected if the one-sided 97.5% lower confidence bound is greater than 50% or, equivalently, if the p-value is less than 0.025.

[redacted]

13.4.5 Analysis Methods

The proportion of subjects with a reduction in overstimulation sensation during CL compared to OL 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, if the p-value is less than 0.025 to declare a study success. This implies that among the total 42 randomized subjects, equal or more than 28 subjects need to have a reduction in overstimulation sensation for the study to declares a success at the final analysis.

[redacted]

[redacted]

13.4.6 Determination of Subjects/Data for Analysis

The primary analysis for the primary objective will follow the ITT principle by including all the subjects randomized (ITT Analysis set). The subjects who are randomized but have missing average scoring of overstimulation sensation during OL and/or CL 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.

Two sensitivity analyses will be performed. One sensitivity analysis of tipping point analysis will be performed using the ITT Analysis Set. Another sensitivity analysis will be performed including all the subjects who finish the in-clinic testing and provided the scoring of overstimulation sensation for both OL and CL periods (Completer Analysis Set).

[redacted]

[redacted]

13.6 Safety Assessment

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

13.7 Sample Size Determination

PASS 2020 Group-Sequential Tests for One Proportion in a Fleming Design module was used to calculate the sample size, with a null proportion of 50%, an alternative proportion of 75%, and one interim analysis at 70% of sample size, 42 subjects are needed to achieve more than 90% power with a one-sided alpha = 0.025 test.

[redacted]

To account for a 30% attrition between enrollment and randomization, up to 60 subjects may be enrolled into the study. A 30% attrition rate was based on historical attrition rates from similar studies, as well as to account for the subjects who don't have a clear, measurable ECAP.

13.8 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 OL or CL testing.
- Subjects are blinded to the OL or CL 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 follow-ups 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 10 and cannot be increased without prior sponsor approval.

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

14. Ethics

14.1 Statement(s) of Compliance

The ECHO-MAC study will be conducted in accordance with this protocol, the ethical principles that have their origin in the Declaration of Helsinki (DoH), all applicable regulatory requirements (21CFR§50 Protection of Human Subjects, 21CFR§56 IRB, 21CFR§812 IDE and 21CFR§803 Medical Device Reporting) and will comply with the concepts of Good Clinical Practices (GCP) outlined in ISO 14155:2020 with the exception of Adverse Event collection. The principles of the DoH have been implemented in this study by means of the patient informed consent process, IRB approval, risk benefit assessment, study training, clinical trial registration on http://clinicaltrials.gov/, and publication policy. Study Investigators will be required to sign an Investigator Agreement stating their intent to adhere to applicable regulations.

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

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.

15. Study Administration

15.1 Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study site in order to ensure that the study is conducted in accordance with the CIP, the CTA, and the applicable regulatory

and local requirements. Medtronic, or delegates, must therefore be allowed direct access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the IC, Research Authorization (where applicable) and CTA.

15.2 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. Monitoring for the study, including site qualification visits, 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 IRB approval and review of the study, maintenance of records and reports, and review of source documents against subject CRFs in accordance to the study-specific monitoring plan. Monitors review study site regulatory and study compliance by identifying observations of non-compliance and communicating those observations along with recommendations for preventative/corrective actions to study site personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular study site.

15.3 Data Management

Medtronic personnel will perform routine edit and consistency checks for items such as missing data or inconsistent data. Identified data inconsistencies will be resolved by use of data discrepancies; investigators and center personnel will review data discrepancies and respond to the discrepancies in a timely manner. The resolved discrepancy will become a part of the CRF record for the subject.

The Oracle Clinical Remote Data Capture (RDC) system is a fully validated system and 21CFR§11 Part E compliant. The RDC system controls user access, ensures data integrity, and maintains an audit trail of entries, and changes, and corrections in the CRFs. User access will be granted to each individual based on his or her delegation of authority for the study and completion of the required training.

The Principal Investigator, or designated representative, is responsible for the accuracy, completeness and timeliness of the data submitted and must review all data for accuracy and provide his/her approval of the CRF and sign each form with an electronic signature. If a person only authorized to complete CRFs makes changes to an already signed CRF, the system will require the principal investigator, or authorized delegate, to re-sign the CRF.

The investigator will clearly mark clinical records to indicate that the subject is enrolled in this clinical investigation.

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 9.11 for CRFs and data collection elements that may be considered source.

15.4 Direct Access to Source Data/Documents

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

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

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

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

15.5 Confidentiality

All 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 SID to each subject. Records of the subject/SID relationship will be maintained by the study site. The SID 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. In the US, "Protected Health Information" (PHI) will be maintained in compliance with the HIPAA of 1996. To maintain confidentiality, the subject's name or any other PHI should not be recorded on any study document other than the IC. This scenario will be covered in the IC. 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 RA), provided the data are treated as confidential and that the subject's privacy is guaranteed. No identifiable subject information will be published.

15.6 Liability

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

15.7 CIP Amendments

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

15.8 Record Retention

All study-related documents 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). Medtronic will inform the investigator/study site when these documents are no longer required to be retained.

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.

15.8.1 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 two years (or longer as local law or hospital administration requires) after product approval or the date on which the investigation is terminated.

- All correspondence between the IRB, sponsor, monitor, RA and the investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:

- Signed and dated IC (In U.S., signed by subject)
- Observations of AEs/ADEs/DDs
- Medical history
- Implant and follow-up data
- Documentation of the dates and rationale for any deviation from the protocol

- Subject ID log
- All approved versions of the CIP and IC
- Signed and dated CTA
- CV of principal investigators and key members of investigation study site team (as required by applicable regulations)
- Documentation of delegated tasks
- IRB approval documentation. Written information that the investigator or other study staff, when member of the IRB, did not participate in the approval process. Approval documentation must include the IRBs composition, where required per local law
- Study training records for study site staff
- Final Study Report including the statistical analysis.

15.8.2 Sponsor Records

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

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

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

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

15.9 Reporting Requirements

15.9.1 Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects, device deficiencies, deaths, and any deviations from the clinical investigation plan. If any action is taken by an IRB 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 11. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 15-1: Investigator Reports

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC approval (either suspension or termination)	Sponsor	The investigator must report a withdrawal of approval by the reviewing IRB/EC of the investigator's part of the investigation within 5 working days. (21 CFR 812.150(a)(2))
Progress report	Sponsor and IRB/EC	The investigator must submit this report to the sponsor and IRB/EC at regular intervals, but in no event less than yearly intervals. (21 CFR 812.150 (a)(3)).
Study deviations	Sponsor and IRB/EC	Notice of deviations from the CIP to protect the life or physical wellbeing of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations. If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects, the deviation must be approved by Medtronic, the IRB/EC, and the FDA/applicable RA. If the deviation does not affect these issues then only Medtronic must approve it. (21 CFR 812.150(a)(4))
Failure to obtain IC prior to investigational device use	Sponsor and IRBs/ECs	If an investigator uses a device without obtaining IC, the investigator shall report such use within 5 working days after device use. (21 CFR 812.150(a)(5))
Final report	Sponsor IRBs/ECs Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or completion or termination of the investigator's part of the investigation. (21 CFR 812.150(a)(6))
Other	IRB/EC and FDA	An investigator shall, upon request by a reviewing IRB/EC, FDA or any other RA, provide accurate, complete, and current information about any aspect of the investigation. (21 CFR 812.150(a)(7))

15.9.2 Sponsor Reports

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

15.10 Publication and Use of Information

Medtronic may publish the results from the ECHO-MAC study. These publication activities may include abstracts, presentations/posters to scientific meetings, and manuscripts. Specific requirements regarding publication of study data will be provided in the publication plan. All proposed publications must be reviewed and approved by Medtronic prior to publication. If required by a publisher, the principal investigator agrees to obtain all necessary authorizations from study subjects prior to submitting study-related information for publication.

15.11 Suspension or Early Termination

15.11.1 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 IRB oversight is required until the overall study closure process is complete. Refer to Section 9.13 for additional information regarding study exit procedures.

15.11.2 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.

15.11.2.1 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 system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic or RA (where the study is operating under RA)
- Technical issues during the manufacturing process

15.11.2.2 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 IRB approval or annual renewal of the study
- Persistent non-compliance to the clinical investigation (e.g. failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-ups)
- Lack of enrollment

- Noncompliance to regulations and the terms of the 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.)
- IRB 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)

15.11.3 Procedures for Termination or Suspension

15.11.3.1 Medtronic-initiated and regulatory authority-initiated

- Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the RAs where required
- In the case of study termination or suspension for reasons other than a temporary IRB approval lapse, the investigator will promptly inform the IRB
- 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

15.11.3.2 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 IRB
- 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

15.11.3.3 IRB -initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days
- Subject enrollment must stop until the suspension is lifted
- Subjects already enrolled should continue to be followed in accordance with IRB 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 and/or the personal physician of the subjects, with the rationale for the study termination or suspension

16. References

1) Parker JL, Karantonis DM, Single PS, Obradovic M, Cousins MJ. (2012) Compound action potentials recorded in human spinal cord during neurostimulation for pain relief. Pain 153:593-601.
2) Schade, Cristy M., David M. Schultz, Nancy Tamayo, Sudha Iyer, and Eric Panken. 2011. "Automatic Adaptation of Neurostimulation Therapy in Response to Changes in Patient Position: Results of the Posture Responsive Spinal Cord Stimulation (PRS) Research Study." Pain Physician 14 (5): 407–17.
3) Parker JL, Karantonic DM, Single PS, Obradovic M, Laird J, Gorman RB, Ladd LA, Cousins MJ. (2013) Electrically evoked compound action potentials recorded from the sheep spinal cord. Neuromodulation 16:295-303.
4) Cameron, Tracy, Milan Obradovic, Robert B. Gorman, Nastaran H Shariati, John L. Parker, Peter S. Single, Michael L. Cousins, Linda Critchley, Dean M. Karantonis, and Marc Russo. 2015. "Evaluating Spinal Cord Stimulation Incorporating Feedback Control Using Evoked Compound Action Potential." Neuromodulation 18 (2): e101.
5) U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research., U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research. & U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. *Health Qual Life Outcomes* 4**,** 79 (2006). https://doi.org/10.1186/1477-7525-4-79
6) Wininger KL, Deshpande KK, and Deshpande KK. 2010. Radiation exposure in percutaneous spinal cord stimulation mapping: a preliminary report. Pain Physician. 2010 Jan-Feb; 13(1):7-18..
7) Schmid, G., et al. "Effective Dose of CT- and Fluoroscopy-Guided Perineural/Epidural Injections of the Lumbar Spine: A Comparative Study." Cardiovasc Intervent Radiol (2006) 29: 84-91
8) Pradhan, A S. "On the risk to low doses (<100 mSv) of ionizing radiation during medical imaging procedures – IOMP policy statement." J Med Phys. 2013 Apr-Jun; 38(2): 57-58
9) Fleiss JL. The statistical basis of meta-analysis. Stat Methods Med Res. 1993; 2(2):121-45

17. Appendices

There are no appendices within this clinical investigational plan.

18. Version History

Version	Summary of changes	Author(s)/Title
1.0	Not Applicable, New Document	[redacted]
2.0	• [redacted] • Section 9.6 In-clinic testing - added blinding assessments • [redacted] • Section 13 Statistical Design and Methods - added additional statistical details	[redacted]