DTM™-LE SCS Study

Clinical Investigational Plan V2.0

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Medtronic **Clinical Investigation Plan**	
Clinical Investigation Plan/Study Title	Differential-Target Multiplex Low Energy Spinal Cord Stimulation (DTM-LE SCS) Study
Clinical Investigation Plan Identifier	MDT20042
Study Product Name	Medtronic Intellis™ with AdaptiveStim™ Neurostimulation System
Sponsor	Medtronic, Inc. Medtronic Neuromodulation 700 Central Ave NE Minneapolis, MN, 55432 U.S.A. +1-763-514-4000
Document Version	2.0

Confidentiality Statement

1. Investigator Statement

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

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2. Glossary

Term	Definition
ADE	Adverse Device Effect
AE	Adverse Event
CDU	Clinical Data Upload
CFR	Code of Federal Regulation
CIP	Clinical Investigation Plan
CRF	Case Report Form
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DD	Device Deficiency
eCRF	Electronic Case Report Form
[redacted]	[redacted]
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IC	Informed Consent
INS	Implantable Neurostimulator
IRB	Institutional Review Board
LAR	Legally Authorized Representative
LE	Low Energy
MedDRA	Medical Dictionary for Regulatory Activities
NPU	Neuro Programmer Upload
[redacted]	[redacted]
[redacted]	[redacted]
PHI	Protected Health Information
[redacted]	[redacted]
RA	Regulatory Authority
RC	Rechargeable Cell
RDC	Remote Data Capture
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCS	Spinal Cord Stimulation
SID	Subject Identification
[redacted]	[redacted]
UAE	Unavoidable Adverse Event
VAS	Visual Analog Scale
WENS	Wireless External Neurostimulator

3. Synopsis

Title	Differential-Target Multiplex Low Energy Spinal Cord Stimulation (DTM-LE SCS) Study
Clinical Study Type	Post-Market
Product Name	Medtronic Intellis™ with AdaptiveStim™ Neurostimulation System
Sponsor	Medtronic, Inc. Medtronic Neuromodulation 700 Central Ave NE Minneapolis, MN, 55432 U.S.A. +1-763-514-4000
Indication under investigation	Approved indication of spinal cord stimulation as an aid in the management of chronic, intractable pain of the trunk and/or limbs.
Investigation Purpose	To evaluate the efficacy and energy use of a low energy DTM™ (DTM-LE) SCS therapy for pain relief
Product Status	All devices used in this study are commercially available and will be used within the intended approved indication and intended use
Primary Objective	To characterize changes in overall (back and leg) pain intensity, as measured by visual analog scale (VAS), from Baseline to 3-Month visit in subjects with devices programmed to DTM-LE SCS
Secondary Objective	To characterize programming parameters associated with energy use from Device Trial through 12-Month visit.
[redacted]	[redacted]

	[redacted]
Study Design	This is a prospective, multi-center, open-label, post-market study to evaluate the efficacy and energy use of a low energy DTM™ (DTM-LE) SCS therapy for pain relief. The study will be conducted in up to 15 sites in the United States. All eligible subjects will undergo an SCS Device Trial per labeling that includes intraoperative testing. If the final lead placements span [redacted] T8 to [redacted] T10 after trial lead implant and patient flexion, DTM-LE stimulation will be programmed for pain relief and comfort. DTM-LE SCS will deliver different, simultaneously running signals within the range of FDA-approved device capabilities to [redacted] different locations between [redacted] T8 and [redacted] T10 vertebral levels. [redacted] to achieve successful pain relief, defined as a subject-reported assessment with ≥50% improvement in overall pain from baseline. After a successful DTM-LE SCS Device Trial, subjects will proceed with the standard of care to an implant of a Medtronic Intellis™ with AdaptiveStim™ rechargeable neurostimulator. Post-implant and after the wound has healed, the device will be activated and programmed to the DTM-LE SCS parameters. Device activation will be Day 0 for the study. Subjects will complete post-implant visits at 1-, 3-, 6-, and 12-month. The primary endpoint will be evaluated at the 3-Month Visit.
Sample Size	Approximately 30 subjects are needed to provide data at 3-Month visit, with an estimated attrition of 40% between enrollment and implant and an estimated attrition of 10% between implant and 3-Month visit, up to 56 subjects may be enrolled into the study.
Inclusion/Exclusion Criteria	Inclusion Criteria: To be included in this study, a patient must meet the following inclusion criteria: 1. 18 years of age or older 2. Willing and able to provide signed and dated informed consent

	3. Capable of comprehending and consenting in English 4. Candidate per labeling for an SCS system (trial and implant) as an aid in the management of chronic, intractable pain of the trunk and/or limbs 5. Has moderate to severe back and leg pain, as determined by the investigator, or designee 6. Baseline VAS is ≥6 for overall pain 7. Baseline VAS is ≥6 for back or leg pain 8. ODI score of 21 to 80 out of 100 9. On stable (no change in dose, route, or frequency) pain medications (prescribed and over-the-counter) being used specifically for back and leg pain, as determined by the investigator or designee, for at least 28 days prior to enrolling in the study 10. Willing and able to comply with all study procedures and visits 11. Willing and able to not increase their pain medications (prescribed and over-the-counter) being used specifically for back and leg pain through the 3-month visit 12. Able to differentiate between pain associated with the indication for SCS implant and other types of pain, as determined by the investigator, or designee <u>Exclusion Criteria:</u> To be included in this study, a patient must not meet any of the following exclusion criteria: 1. Previously trialed or implanted with spinal cord stimulator, peripheral nerve stimulator, or an implantable intrathecal drug delivery system 2. Expected to be inaccessible for follow-up 3. Current diagnosis of moderate to severe central lumbar spinal stenosis with symptomatic neurogenic claudication as determined by the investigator, or designee 4. 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) 5. If female, is pregnant or is of child-bearing potential and unwilling to use a medically acceptable form of birth control during the study 6. Has untreated major psychiatric comorbidity, as determined by the investigator, or designee 7. Serious drug-related behavioral issues (e.g. alcohol dependency, illegal substance abuse), as determined by the investigator, or designee

	8. Unable to achieve supine or prone position 9. If subject is classified as vulnerable or requires a legally authorized representative (LAR) <u>Additional Inclusion Criteria (to be evaluated at Device Trial/Implant):</u> 1. Final lead placements span [redacted] T8 to [redacted] T10 after patient flexion at Device Trial 2. The subject reports ≥ 50% improvement in overall pain relief at the Device Trial End Visit 3. Final lead placements span [redacted] T8 to [redacted] T10 at Device Implant
Study Procedures and Assessments	Specific data and procedure requirements per visit are summarized in the Procedure Table. **Study Visits** • Enrollment/Baseline Visit • Device Trial Start Visit • Device Mid-Trial Visit (If necessary) • Device Trial End Visit • Device Implant Visit • Device Activation Visit • 1-Month Visit • 3-Month Visit • 6-Month Visit • 12-Month/Final Study Visit **Enrollment/Baseline Visit:** Subjects are considered enrolled at the time the study-specific informed consent (and HIPPA or other data protection authorization as required by local regulations) is signed. Subjects in compliance with inclusion/exclusion criteria will be eligible to participate. A VAS score for overall (back and leg), back, and leg pain will be collected. Subjects that do not have a VAS ≥ 6 cm for overall pain and a VAS ≥ 6 cm for either back or leg pain will be exited from the study. [redacted] Subjects that meet eligibility criteria will be scheduled for a device trial and the following will be collected: [redacted] • Demographics • Medical/surgical history • Pain medications

	The baseline visit can be a stand-alone visit or can be performed on the same day as the Device Trial Start Visit. **Device Trial Start Visit (≤ 20 days post Baseline Visit)** Subjects will be implanted with two compact percutaneous leads per labeling. If subjects have leads spanning the [redacted] T8 to [redacted] T10 vertebral levels after trial lead implantation and flexion, they will continue in the study and DTM-LE stimulation will be programmed for pain relief and comfort. Imaging, device information, and programming parameters will be collected. **Device Mid-Trial Visit (If necessary)** Subjects will be called during the device trial by a sponsor representative (e.g., field clinical engineer) to assess effectiveness of stimulation parameters and facilitate re-programming, as needed. An in clinic mid-trial visit may be performed, if necessary, for issues (such as inadequate pain relief that requires in-clinic re-programming/device interrogation) that cannot be addressed over the phone. Imaging and programming parameters will be collected, if performed. **Device Trial End** Subjects will be trialed per standard of care and within device labeling limits while enrolled into the study. Subjects will come in for the Device Trial End Visit within 7 days of the device trial start. At the Device Trial End Visit, if a subject has ≥ 50% improvement in overall pain with DTM-LE SCS programming, they will have their trial leads explanted and will proceed to implant. If a subject does not have ≥ 50% improvement overall pain relief with DTM-LE SCS programming, they will be treated per standard of care and exited from the study. The outcome (i.e., success or failure) of the trial for those subjects that did not have a successful DTM-LE SCS trial will be recorded. Programming parameters will be collected. Images will be collected if performed. Trial lead explant must occur within 10 days of trial lead implant. **Implant (≤ 35 days post end of device trial)** Subjects who were DTM-LE SCS programming responders during the device trial and who met all eligibility criteria will be implanted with an Intellis™ with AdaptiveStim™ neurostimulation system including two compact percutaneous leads per labeling. Subjects who have leads spanning the [redacted] T8 to [redacted] T10 vertebral bodies will continue in the study. Imaging, programming parameters and device information will be collected. The stimulator will be “OFF” when the subject leaves this visit. **Device Activation Visit (9 – 16 days post implant)** The Device Activation Visit will take place 9-16 days after implant, pending wound healing. The stimulator will be turned “ON” at this visit and subjects

	will be programmed to DTM-LE SCS settings. Programming parameters will be collected. Imaging will be collected, if performed. **Post-Implant Telephone Calls** Subjects will be called weekly by delegated study site personnel post-device activation to assess their pain relief status up to the 3-Month Visit and then monthly following the 3-Month Visit. If an in-clinic visit falls on the week or month of a scheduled telephone call, the call will not be performed. If the subject reports inadequate pain relief, they may be contacted by a sponsor representative (e.g., field clinical engineer) to assess for re-programming and/or come in for an unscheduled visit. **Post Implant 1-, 3-, 6-, and 12-Month/Final Study Visit (±15 days post Device Activation)** Post implant visits will occur at 1-, 3-, 6-, and 12-month post device activation. At the 1-month visit, stimulation threshold testing will be performed in the upright and supine positions for each programmed group. Imaging and programming parameters will be collected through the 12-Month/Final Study Visit, if re-programming or imaging occurs. The following measures will be collected during follow-up: • VAS (all follow-up visits) [redacted]
Safety Assessments	This study will collect and characterize all device-related, therapy-related, and procedure-related adverse events and device deficiencies from the Device Trial Start Visit until study exit.
Statistics	The Confidence Intervals for One Mean module in statistical software PASS 11 was used to provide the following sample size justification: a sample size of 30 subjects produces a two-sided 95% confidence interval with a distance from the mean to the limits that is equal to 0.97 when the estimated standard deviation is 2.6. With estimated attrition of 40% between enrollment and implant and 10% between implant and 3-Month, to achieve approximately 30 subjects at 3-Month visit, up to 56 subjects may be enrolled into the study. For the primary objective, the mean change of overall pain intensity from baseline to 3-Month visit will be reported with a 95% confidence interval (CI). Primary analysis will use per-protocol analysis set who are implanted, follow DTM-LE SCS programming, and provide data at both baseline and 3-Month visits. Sensitivity analyses will use completers analysis set who are implanted and provide data at both baseline and 3-Month visits regardless of

	programming patterns, as well as implanted analysis set with multiple imputation (MI) for missing data. The secondary objective will be analyzed with descriptive statistics from Device Trial to 12-Month visit. Subjects who contribute to follow-up visits will be included in the analysis. [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.

4. Introduction

4.1 Background

Spinal Cord Stimulation (SCS) uses electrical signals to modulate the nervous system, resulting in pain relief. These signals are defined by programs comprised of parameter settings for the amplitude, frequency, pulse width, active electrodes, current distribution, and therapy cycle. The parameters can be modulated to produce programs for purposes such as improved pain relief and/or comfort, reduced side-effects, increased energy efficiency, or delay or prevent therapy habituation. There are multiple hypotheses to account for the mechanisms of action of different SCS parameters. Non-rechargeable SCS systems have a finite energy capacity that limits the parameter settings available to meet an acceptable implant longevity. Introduction of therapy cycling, alternating periods of therapy turned ON and OFF, may maintain or even improve outcomes associated with SCS while preserving battery life.[1,2,3,4] Recent studies have shown that effective pain relief of traditionally higher energy programs can be maintained at lower energy doses through reduction of parameters (frequency, pulse width, amplitude).[5,6,7.] Development of lower energy SCS programs would increase recharge interval or reduce daily recharge duration in rechargeable cell (RC) systems and enable an acceptable device longevity in non-

[1] Shatin D, Mullett K, Hults G. Totally Implantable Spinal Cord Stimulation for Chronic Pain: Design and Efficacy. PACE 9 (1986) 577-583

[2] Provenzano D, Yu C, Verrills P, Guirguis M, Harrison N, Bradley K. Pulse Dosing of 10 kHz Paresthesia-Independent Spinal Cord Stimulation Provides Same Efficacy with Substantial Reduction of Device Recharge Time. Abstract 2019

[3] Vesper J, Slotty P, Schu S, Poeggel-Kraemer K, Littges H, Van Looy P, Agnesi F, Venkatesan L, Van Havenbergh T. Burst SCS Microdosing Is as Efficacious as Standard Burst SCS in Treating Chronic Back and Leg Pain: Results From a Randomized Controlled Trial. Neuromodulation 2019; 22:1 190-193

[4] Deer TR, Patterson DG, Baksh J, Pope JE, Metha P, Raza A, Agnesi F, Chakravarthy K. Novel Intermittent Dosing Burst Paradigm in Spinal Cord Stimulation. [Article in Press] Neuromodulation 2020

[5] Thomson SJ, Tavakkolizadeh M, Love-Jones S, Patel NK, Gu JW, Bains A, Doan Q, Moffitt M. Effects of Rate on Analgesia in Kilohertz Frequency Spinal Cord Stimulation: Results of the PROCO Randomized Controlled Trial. Neuromodulation 2018 21:1 (67-76)

[6] Paz-Solis J, Thomson S, Jain R, Chen L, Huertas I, Doan Q. Customization of Neural Dose: Real-World Data Demonstrating The Relationship Between Frequency, Pulse-Width, And Amplitude In Achieving Sub-Perception SCS Pain Relief (The HALO Study). Abstract 2019

[7] Verdolin MH. Case Series of Subperception SCS trial of multiple energy doses at T9-10 for FBSS. NANS Abstract 2020

rechargeable systems for programs with higher frequency and/or pulse-width settings. Evidence is needed to guide best programming practice as well as future parameter options.

Understanding of frequency modulation has been expanded from traditional stimulation at a range of around 40 – 100 Hz,[8] to stimulation in the range of hundreds to thousands of cycles-per-second or with burst patterns,[9,10,11] where the therapy provides pain relief while producing reduced or no sensation of stimulation (aka paresthesia). While sub-paresthesia threshold stimulation was initially shown to be effective using higher frequency and higher energy consumption parameters, the PROCO study demonstrated that frequencies from 10 kHz down to 1 kHz, at 50% paresthesia perception threshold, and with titration of pulse width and amplitude, could provide pain relief while reducing the mean charge per second by about a third.[5] This observation was extended with the HALO study, from 1 kHz down to 10 Hz, and the "rule of neural dosing" was introduced to describe the increase in pulse width and amplitude titration required with lower frequencies.[6] The Hi Lo Sham study similarly showed that targeted, sub-perception therapy produced similar pain relief for both a high and low energy program that were both superior to sham during a 3-day trial period.[7]

Therapy cycling is another strategy that has long been employed with traditional SCS where automatic on/off cycling mode has shown greater pain relief than patients stimulated continuously.[1] It is now being studied with otherwise higher energy consuming therapies. The 10kHz SCS Pulse Dosing study demonstrated that subthreshold, 10 kHz, 30 µs therapy could be cycled off from 50 up to 97% of the time and still maintain pain relief in a significant number of patients at 3 months.[2] The Burst SCS Microdosing study showed no difference in pain relief between the BurstDR waveform, Burst with 5 s on:5 s off, and Burst with 5 s on:10 s off.[3] This was expanded upon with the BOLD study, which tested cycling in 30 s increments from a 1:12 to a 1:3 paradigm and showed most patients were using the 1:12 option at 6 months.[4]

The understanding of mechanisms of action for SCS has recently been expanded to include the concept of glial cell modulation. Neural-glial cell interaction has been implicated in development of the chronic pain state.[12,13,14] Additionally, glia are electrically responsive cells in the spinal cord and outnumber neurons by 12:1.[15] The Differential Target Multiplexed™ waveform was designed to target neural and glial cells. Preclinical research suggests the ability of DTM™ SCS to impact neural-glial cell interaction, showing statistically significant reversal of pain behaviors compared to either low or high frequency

[8] Sharan A, Cameron T, Barolat G. Evolving patterns of spinal cord stimulation in patients implanted for intractable low back and leg pain. Neuromodulation. 2002;5(3):167–79. doi:10.1046/j.1525-1403.2002.02027.x.

[9] De Ridder D, Plazier M, Kamerling N, Menovsky T, Vanneste S. Burst spinal cord stimulation for limb and back pain. World neurosurgery . 2013; 80(5): 642-649.e1.

[10] Al-Kaisy A, Van Buyten JP, Smet I, Palmisani S, Pang D, Smith T. Sustained effectiveness of 10 kHz highfrequency spinal cord stimulation for patients with chronic, low back pain: 24-month results of a prospective multicenter study. Pain medicine 2013; Electronic Publication Date: 5 Dec 2013.

[11] De Ridder D, Vanneste S, Plazier M, van der Loo E, Menovsky T. Burst spinal cord stimulation: Toward paresthesia-free pain suppression. Neurosurgery.2010; 66: 986-990.

[12] Milligan ED, Watkins LR. Pathological and protective roles of glia in chronic pain. Nat Rev Neurosci. 2009 Jan;10(1):23-36.

[13] Vallejo R, Tilley DM, Vogel L, Benyamin R. The role of glia and the immune system in the development and maintenance of neuropathic pain. Pain Pract. 2010 May-Jun;10(3):167-84.

[14] De Leo JA, Tawfik VL, LaCroix-Fralish ML. The tetrapartite synapse: Path to CNS centralization and chronic pain. Pain. 2006; 122:17-21.

[15] Ruiz-Sauri A., Orduña-Valls J.M., Blasco-Serra A. et al. Glia to neuron ratio in the posterior aspect of the human spinal cord at thoracic segments relevant to spinal cord stimulation. Journal of Anatomy, vol. 235, no. 5, 2019, pp. 997-1006.

stimulation alone.[16,17,18,19,20] In addition, preclinical studies investigating the genome of nerve-injured animals suggests that the DTM™ waveform uniquely modulated gene expression compared to other frequencies alone.[17, 18, 19, 20, 21] This has presented a potential new factor to explain the SCS mechanism of action. In a randomized controlled trial, DTM™ SCS delivered superior back pain relief at the 3-month primary endpoint for patients with chronic back and leg pain, compared to conventional stimulation.[21]

With the desire to provide an advanced therapy and to continue to build on the DTM™ SCS theory, this study aims to employ a combination of energy reducing strategies (reduction in frequency and therapy cycling) to study a low energy DTM™ SCS derivative that may reduce recharge burden in RC systems and enable an acceptable device longevity in non-rechargeable systems while continuing to provide meaningful pain relief.

4.2 Purpose

The purpose of this study is to evaluate the efficacy and energy use of a low energy DTM™ (DTM-LE) SCS therapy for pain relief.

5. Objectives

5.1 Objectives

5.1.1 Primary Objective

To characterize changes in overall (back and leg) pain intensity, as measured by visual analog scale (VAS), from Baseline to 3-Month visit in subjects with devices programmed to DTM-LE SCS.

5.1.2 Secondary Objective

To characterize programming parameters associated with energy use from Device Trial through 12-Month visit.

[redacted]

[16] Cedeno D.L., Cass C.L., Kelley C.A., et al. Pre-clinical comparison of differential-target multiplexed scstm with low and high rate SCS. Neuromodulation 2019 22:3 (E185-)
[17] Cedeno D.L., Kelley C.A., Cass C.L., et al. Pre-clinical Comparison of Differential-Target Multiplexed SCS with Low and High Rate SCS. Presentation at ASRA 2018. San Antonio, Texas.
[18] Vallejo R, Smith W, Kelley C, et al. Neuron-glial inflammasome enhanced reversal by DTM-SCS relative to high rate and low rate SCS in a neuropathic pain model. American Society for Regional Anesthesiology and Pain Medicine (ASRA); November 14-17, 2019; New Orleans, LA. Abstract #480
[19] Vallejo R, Kelley C, Smith W, et al. Cell-specific targeting in neural tissue using Differential Target Multiplexed (DTM) SCS. American Society for Regional Anesthesiology and Pain Medicine (ASRA); November 14-17, 2019; New Orleans, LA. Abstract #513
[20] Vallejo R, Tilley D, Kelley C, et al. Proteomics of Differential Target Multiplexed-SCS applied to an animal model of neuropathic pain. American Society for Regional Anesthesiology and Pain Medicine (ASRA); November 14-17, 2019; New Orleans, LA. Abstract #509
[21] Fishman MA, Calodney A, Kim P, Slezak J, Benyamin R, Rehman A, Soto E, Yang T, Hacobian A, Griffith L, Yu C, Vallejo R. Prospective, Multicenter Feasibility Study to Evaluate Differential Target Multiplexed Spinal Cord Stimulation Programming in Subjects With Chronic Intractable Back Pain With or Without Leg Pain. [Article in Press] Pain Practice 2020

[redacted]

6. Study Design

This is a prospective, multi-center , open-label, post-market study to evaluate the efficacy and energy use of a low energy DTM™ (DTM-LE) SCS therapy for pain relief. The study will be conducted in up to 15 sites in the United States.

Up to 56 subjects are expected to be enrolled in the study to allow for approximately 30 subjects to complete the 3-Month Visit. All implanted subjects with devices activated will be followed through the 12-Month/Final Study Visit. The study sample size accounts for expected attrition; therefore, subjects who discontinue prior to study completion will not be replaced.

All eligible subjects will undergo an SCS Device Trial per labeling that includes intraoperative testing. If the final lead placements span [redacted] T8 to [redacted] T10 after trial lead implant and patient flexion, DTM-LE stimulation will be programmed for pain relief and comfort. DTM-LE SCS will deliver different, simultaneously running signals within the range of FDA-approved device capabilities at [redacted] unique locations between [redacted] T8 and [redacted] T10 vertebral levels and will be programmed within the following limits:

[redacted]

[redacted] on [redacted]

After a successful DTM-LE SCS Device Trial, subjects will proceed with the standard of care to an implant of a Medtronic Intellis™ with AdaptiveStim™ rechargeable neurostimulator. Approximately 9-16 days post-implant, after the wound has healed, the device will be activated and programmed using DTM-LE SCS.

Device activation will be Day 0 for the study. Subjects will complete follow-up visits at 1-, 3-, 6-, and 12-months. The primary endpoint will be evaluated at the 3-Month visit.

Subjects may be enrolled at approximately 15 study sites in the US, with no more than 10 subjects enrolled at any individual study site. Enrollment will be competitive across study sites. The per-study site enrollment cap may be increased upon Sponsor approval.

6.1 Duration

The expected total study duration is approximately 2 years. Enrolled subjects will have up to 10 scheduled visits including Baseline, Device Trial (up to 3 visits), Device Implant, Device Activation, Post Implant (1-month, 3-month, and 6-month visit) and Final Study (12-month visit). Subjects' participation in the study is expected to last up to 14 months from enrollment (>1 month for screening, baseline, implant and recovery; 12 months of required follow-up until study closure); however, this may vary based on the time between the device trial end and device implant.

6.2 Rationale

This study will evaluate the efficacy and energy use of a low energy DTM™ (DTM-LE) SCS therapy for pain relief. The data collected will provide insight into the efficacy of programming settings that utilize energy reducing strategies and has the potential to shape future clinical practices that may reduce recharge burden in rechargeable systems and enable an acceptable device longevity in non-rechargeable systems. Furthermore, the study may contribute evidence to support the evolution and flexibility of the DTM™ SCS therapy. The study design builds on existing pre-clinical and clinical evidence supporting the use of a DTM™ waveform and facilitates additional data collection to further understand the use of a low energy DTM™ waveform in the management of pain relief for subjects with chronic, intractable pain of the trunk and/or limbs.

7. Product Description

7.1 General

The Intellis™ with AdaptiveStim™ Technology neurostimulation system will be used in this study. Neurostimulation systems include a neurostimulator, lead(s), extension(s), programmers, and accessories. This study will include only Medtronic commercially available products used within their intended approved indication. Products will be obtained through normal commercial channels and will not be provided as a part of this study.

The implanted components of the Intellis™ with AdaptiveStim™ system include the following:

- Model 97715 Intellis™ with AdaptiveStim™ neurostimulation system
- Model 977D260 Vectris™ 1x8 Compact Trial Screening Lead Kit
- Models 977A260, 977A275, and 977A290 Vectris™ SureScan™ MRI 1x8 Compact Lead Kits
- Models 97791 and 97792 Injex™ Anchor Accessory Kits

The non-implanted components of the Intellis™ with AdaptiveStim™ system include the following:

- Model 97725 Wireless External Neurostimulator
- Model 97745 Patient Controller
- Model 375003 Boot for Wireless External Neurostimulator
- Model 97755 Recharger
- Model 8880T2 Communicator
- Other accessories used (e.g., tunneling tools, needle kits, wrenches, or screws)

7.2 Manufacturer

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

7.3 Packaging

The devices that will be used in this study have been approved or cleared by the FDA for spinal cord stimulation as an aid in the management of chronic, intractable pain of the trunk and/or limbs. The devices specified in Section 7.1 will be shipped in their commercially available form which includes packaging and labeling.

7.4 Intended Population

In the United States a Medtronic implantable neurostimulation system is indicated for spinal cord stimulation (SCS) systems as an aid in the management of chronic, intractable pain of the trunk and/or limbs-including unilateral or bilateral pain associated with the following conditions according to product labeling:

- Failed Back Syndrome (FBS) or low back syndrome or failed back
- Radicular pain syndrome or radiculopathies resulting in pain secondary to FBS or herniated disk
- Post Laminectomy pain

- Multiple low back operations
- Unsuccessful disk surgery
- Degenerative Disk Disease (DDD)/herniated disk pain refractory to conservative and surgical interventions
- Peripheral causalgia
- Epidural fibrosis
- Arachnoiditis or lumbar adhesive arachnoiditis
- Complex Regional Pain Syndrome (CRPS), Reflex Sympathetic Dystrophy (RSD), or Causalgia

7.5 Product Use

The Medtronic Intellis™ with AdaptiveStim™ Technology Neurostimulation System and related components and accessories are commercially available for SCS in the United States and shall be used in accordance with commercial labeling. Exposure to the study product is considered from the time the subject is first exposed to the neurostimulation system, at the beginning of the device trial, until the product is explanted, or the subject discontinues from the study, if later.

7.6 Product Training Materials

Only investigators who are trained and experienced in implanting neurostimulation spinal cord stimulation systems will perform the implant procedures required for this clinical study.

7.7 Product Return

All products are commercially available, and no products will be provided from Medtronic as a part of this study. All explanted devices (devices or leads or activators, etc.) should be returned to Medtronic for analysis when permissible by local laws and regulations. If the products are explanted but not returned, a justification will be reported on the appropriate case report forms or disposition logs. To receive a Returned Product Mailer Kit, please contact your local Medtronic field personnel.

7.8 Product Accountability

All products are commercially available, and no products will be provided from Medtronic as a part of this study; therefore, no device accountability or traceability is required.

8. Study Site Requirements

8.1 Investigator/Investigation Site Selection

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

The principal investigator shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation
- Be experienced in the field of application and training in the use of spinal cord stimulation

- Be able to demonstrate that the proposed investigational study site:
  - Has the required number of eligible subjects needed within the recruitment period
  - Has one or more qualified investigators, a qualified investigational study site team and adequate facilities for the foreseen duration of the clinical investigation

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

8.2 Study Site Activation

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

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

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

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

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

8.3 Role of the Sponsor Representatives

Sponsor representatives who are qualified and trained on the protocol may participate in the conduct of the study under the direct supervision of the principal investigator as described below. The principal investigator or other study site personnel designated on the delegation of authority form must collect all required data, record the study activities, and be responsive to the subject's needs during an activity performed by a sponsor representative. Sponsor representatives may provide support at the study site as required for the study under supervision of the Principal Investigator, including:

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

Medtronic personnel 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

9. Selection of Subjects

9.1 Study Population

The intended study population is patients with chronic intractable back and leg pain.

9.2 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 of the inclusion and none of the exclusion criteria to be eligible to participate in this study. A subject who does not meet inclusion/exclusion criteria or who discontinues prior to implant for any other reason (e.g. fails device trial, cannot be implanted due to hardware, etc.) will be considered a screen fail. Subjects will continue to be followed in the study once device activation after implant has been completed, except in the case of early withdrawal.

9.3 Inclusion Criteria

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

1. 18 years of age or older
2. Willing and able to provide signed and dated informed consent

3. Capable of comprehending and consenting in English
4. Candidate per labeling for an SCS system (trial and implant) as an aid in the management of chronic, intractable pain of the trunk and/or limbs
5. Has moderate to severe back and leg pain, as determined by the investigator, or designee
6. Baseline VAS is ≥6 for overall pain
7. Baseline VAS is ≥6 for back or leg pain
8. ODI score of 21 to 80 out of 100
9. On stable (no change in dose, route, or frequency) pain medications (prescribed and over-the-counter) being used specifically for back and leg pain, as determined by the investigator or designee, for at least 28 days prior to enrolling in the study
10. Willing and able to comply with all study procedures and visits
11. Willing and able to not increase their pain medications (prescribed and over-the-counter) being used specifically for back and leg pain through the 3-month visit
12. Able to differentiate between pain associated with the indication for SCS implant and other types of pain, as determined by the investigator, or designee

Additional inclusion criteria, to be evaluated at device trial/implant:

1. Final lead placements span [redacted] T8 to [redacted] T10 after patient flexion at Device Trial
2. The subject reports ≥ 50% improvement in overall pain relief at the Device Trial End Visit
3. Final lead placements span [redacted] T8 to [redacted] T10 at Device Implant

9.4 Exclusion Criteria

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

1. Previously trialed or implanted with spinal cord stimulator, peripheral nerve stimulator, or an implantable intrathecal drug delivery system
2. Expected to be inaccessible for follow-up
3. Current diagnosis of moderate to severe central lumbar spinal stenosis with symptomatic neurogenic claudication as determined by the investigator, or designee
4. 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)
5. If female, pregnant or is of child-bearing potential and unwilling to use a medically acceptable form of birth control during the study
6. Has untreated major psychiatric comorbidity, as determined by the investigator, or designee
7. Serious drug-related behavioral issues (e.g. alcohol dependency, illegal substance abuse), as determined by the investigator, or designee
8. Unable to achieve supine or prone position
9. If subject is classified as vulnerable or requires a legally authorized representative (LAR)

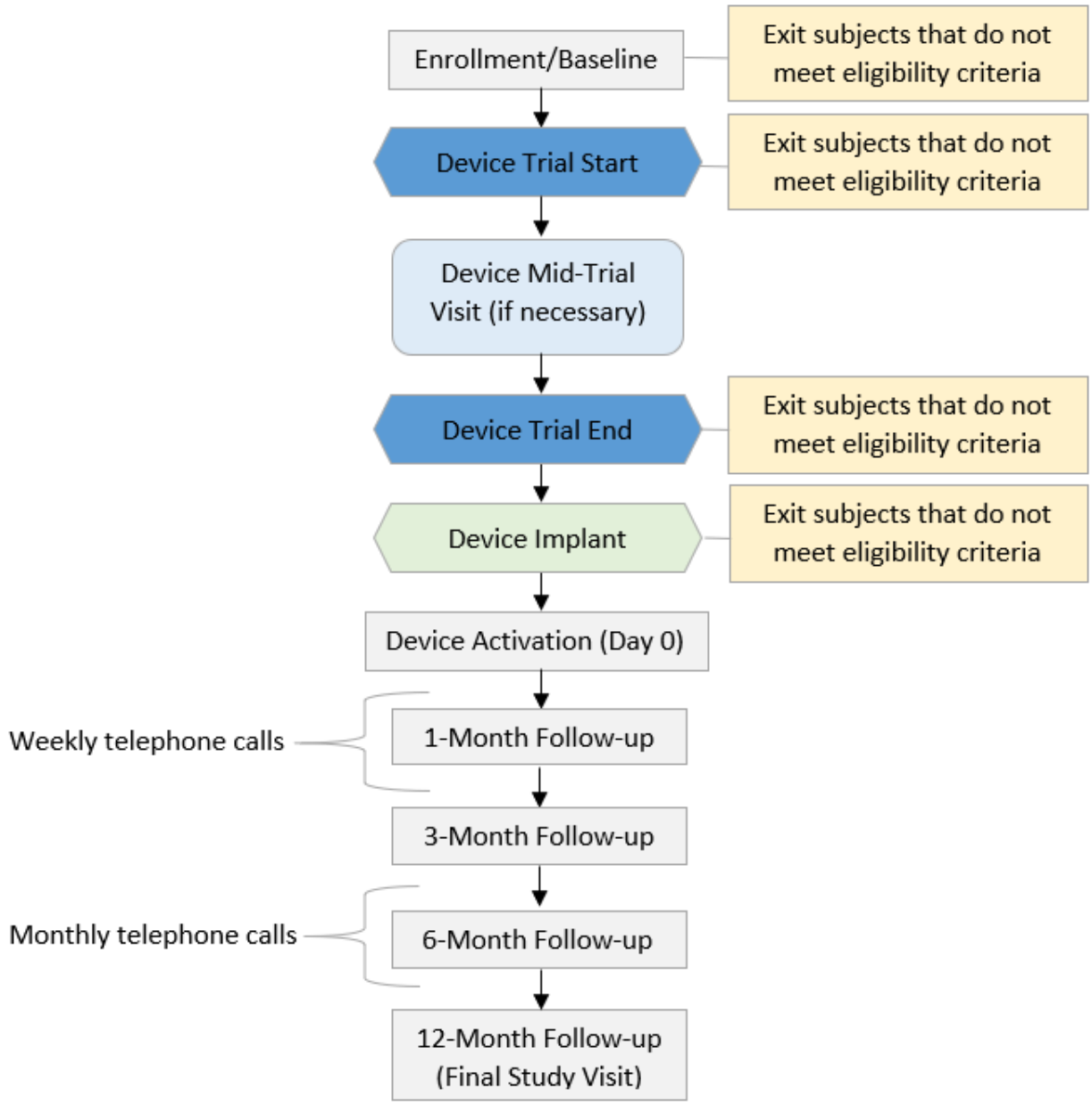
10. Study Procedures

10.1 Schedule of Events

Figure 10-1 is a flow diagram of how subjects will complete the study. Subjects will be required to come into the clinic for up to 10 study visits:

- Enrollment/Baseline Visit
- Device Trial Start Visit
- Device Mid-Trial Visit (if necessary)
- Device Trial End Visit
- Device Implant Visit
- Device Activation Visit (Day 0)
- 1-Month Visit
- 3-Month Visit
- 6-Month Visit
- 12-Month/Final Study Visit

Figure 10-1: Study Visit Diagram



10.2 Data Collection

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

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

Study Procedures, Tasks, and Data Collection (row) by Visit (column)	Enrollment/Baseline Visit	Device Trial Start Visit	Device Mid-Trial Visit [e]	Device Trial End Visit	Device Implant Visit	Device Activation Visit	1-, 3-, 6-, and 12-Month/Final Study Visit	Post-implant Phone Calls	Unscheduled Visits
Informed Consent Process	√								
Demographics	√								
Inclusion/Exclusion Criteria	√	√		√	√				
VAS – overall, back, and leg	√						√		√
Medical/Surgical History	√								
[redacted]									
Programming Parameters[f]		√	√[b]	√[b]		√	√		√[b]
[redacted]									
Imaging		√			√	√[d]	√[d]		√[d]
Device information (model, serial/lot number)		√			√				
Pain relief/programming feedback								√	
[redacted]									
Initial and final setting device interrogation report(s)		√	√[b]	√	√	√	√		√[b]
AE/DD		√	√	√	√	√	√	√	√
Pain Medications	√	√	√	√	√	√	√	√	√

[redacted]

[b]Perform activity only if unit reprogrammed

[redacted]

[d]If acquired

[e]Not a required study visit, only performed if necessary

[f]May include electrode impedance measurements

10.3 Visit Windows

Study visit windows are summarized in Table 10-2 below and will be targeted when scheduling study visits. Should a subject miss a visit or the visit fall outside the pre-specified window, a study deviation must be reported, and the original follow-up schedule maintained for subsequent visits.

Data analyses include visits, regardless of whether the visit occurs within the window. Therefore, a late visit is preferred over a missed visit but must be accompanied by a deviation report.

Table 10-2: Study Visit Target Windows

Study Visit	Target Window
Baseline	N/A
Device Trial Start	≤ 20 days after Baseline visit
Device Trial End	≤ 7 days after Device Trial Start
Device Implant	≤ 35 days after Device Trial End
Device Activation - **Day 0**	9-16 days after Device Implant; pending wound healing
1-Month	30 days ± 10 days after **Day 0**
3-Month	90 days ± 15 days after **Day 0**
6-Month	180 days ± 30 days after **Day 0**
12-Month	360 days ± 30 days after **Day 0**

10.4 Subject Screening

Potential subjects may be identified through chart reviews or as new/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 medical records (paper and/or electronic) is obtained. Any subject recruitment materials disseminated to subjects (advertisements, handouts, posters, social media) must be approved by the Institutional Review Board (IRB) prior to use.

Recruited subjects should be pre-screened by the principal investigator or authorized site personnel by reviewing the study's inclusion and exclusion criteria prior to enrollment. All subjects must be consented in accordance with the CIP and IRB requirements prior to any study-specific procedures.

10.5 Prior and Concomitant Medications/Therapies

Only medications used specifically for the treatment of back and/or leg pain will be collected during the study. Pain medications will be collected at baseline and any changes to pain medications will be collected throughout the study. Only subjects who are on a stable dose (no new medications, discontinued, or changes in dose, route, or frequency) of all prescribed and over the counter pain medications for back and/or leg pain, in the opinion of the investigator (or designee), for at least 28 days prior to screening will be eligible for participation in the study. Subjects must be willing and able to not increase their pain medications (including prescribed and over-the-counter) specifically for back and leg pain, as defined above, through the 3-Month Visit unless there is a need to mitigate a safety concern (e.g., adverse event). Decreases in pain medications are allowed after enrollment. Any changes to subject's pain medications while they are enrolled in the study will be documented in the subject's medical records and the pain medications eCRF.

The addition of pain medications for the relief of surgical discomfort after device trial and implant procedures is allowed. Pain medications prescribed for post-operative pain management are not

considered an increase in pain medications if the medication is ceased prior to the date of the Device Activation Visit.

Subjects that have previously been trialed or implanted with spinal cord stimulator, peripheral nerve stimulator, or an implantable intrathecal drug delivery system will not be eligible to participate in the study.

10.6 Subject Consent

Informed consent is defined as a legally effective documented confirmation of a subject's voluntary agreement to participate in a particular study after information has been given and explained to the subject on all aspects of the study that are relevant to the subject's decision to participate. This process includes obtaining an IC form and 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 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 ICF 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. Subjects must be able to personally sign and date the consent form to participate in this study.

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.

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.

10.7 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. At the Baseline visit, subjects will be consented prior to any study-related procedures or testing being conducted. Subjects in compliance with inclusion/exclusion criteria will be eligible to participate. A VAS score for overall (back and leg), back, and leg pain will be collected. Subjects that do not have a VAS ≥ 6 cm for overall pain and a VAS ≥ 6 cm for either back or leg pain will be exited from the study. [redacted]. Subjects that meet eligibility criteria will proceed with the remaining data collection for the baseline visit and will be scheduled for a device trial. The baseline visit can be a stand-alone visit or can be performed on the same day as the Device Trial Start Visit.

The following information will be collected at the baseline visit:

- Informed Consent
- Inclusion/Exclusion Criteria
- Demographics
- Medical/surgical history
- VAS
- [redacted]
- Pain Medications

10.8 Device Trial

The Device Trial Start Visit must occur within 14 days of the Baseline Visit. Subjects will have up to 3 Device Trial Visits:

- Device Trial Start Visit
- Device Mid-Trial Visit (if necessary)
- Device Trial End Visit

10.8.1 Device Trial Start (≤ 20 days post-Baseline)

All eligible subjects will undergo an SCS Device Trial per labeling that includes intraoperative testing. Subjects will be implanted with two Medtronic compact percutaneous leads as a part of the device trial procedure. No devices will be provided by the sponsor as a part of this study. A flexion maneuver will be performed. If subjects have leads spanning the [redacted] T8 to [redacted] T10 vertebral levels after trial lead implant and flexion maneuver, they will continue in the study and DTM-LE stimulation will be programmed for pain relief and comfort. The most recent fluoroscopy/x-ray will be used to confirm lead location. DTM-LE SCS will deliver different, simultaneously running signals within the range of FDA-approved device capabilities to [redacted] different locations between [redacted] T8 and [redacted] T10 vertebral levels and will be programmed within the following limits:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted] During this visit, subjects will be provided with a patient programmer and wireless external neurostimulator (WENS) and educated on their use. Subjects will be informed how they can turn their device off, if needed.

The following information will be collected at the Device Trial Start Visit:

- Device Information
- Programming parameters/device interrogation report(s) with initial and final settings
- Imaging (post flexion maneuver)
- Changes to pain medications
- AEs/DDs

10.8.2 Device Mid-Trial (If necessary)

Subjects will be called during the device trial by a sponsor representative (e.g., field clinical engineer) to assess effectiveness of stimulation parameters and facilitate re-programming, as needed. Subjects may come in for a study visit during the trial, if necessary, for issues (such as inadequate pain relief that

requires in-clinic re-programming/device interrogation) that cannot be addressed over the phone. Imaging may be performed to assess for lead migration if deemed necessary by the investigator.

The following information will be collected at the Device Mid-Trial Visit, if conducted:

- Programming parameters/device interrogation report(s) with initial and finial settings
- Imaging (if performed)
- Changes to pain medications
- AEs/DDs

10.8.3 Device Trial End

Subjects will be trialed per standard of care and within device labeling limits while enrolled into the study. Subjects will come in for the Device Trial End Visit within 7 days of the device trial start. At the Device Trial End Visit, if a subject has ≥ 50% improvement in overall pain with DTM-LE SCS programming, they will have their trial leads explanted and will proceed to implant. If a subject does not have ≥ 50% overall pain relief with DTM-LE SCS programming, they will be treated per standard of care and exited from the study. The outcome of the trial for those subjects that did not have a successful DTM-LE SCS trial will be recorded (success or failure). Trial lead explant must occur within 10 days of trial lead implant. Imaging may be performed to assess for lead migration if deemed necessary by the investigator.

The following information will be collected at the Device Trial End Visit:

- Percent Improvement in Overall Pain
- Programming parameters/device interrogation report(s) with initial and finial settings
- Imaging (if performed)
- Changes to pain medications
- AEs/DDs

10.9 Device Implant (≤ 35 days post Device Trial End)

Subjects who report a positive device trial (≥ 50% improvement in overall pain) with DTM-LE SCS parameters and who meet eligibility criteria will be implanted with a Model 97715 Intellis™ with AdaptiveStim™ neurostimulation system including two Model 977A260/75/90 Vectris™ leads per standard of care and within device labeling. No products will be provided from Medtronic as a part of this study. Prior to system implant, eligibility criteria must be re-confirmed by the investigator and documented in source records. Subjects who have leads spanning the [redacted] T8 to [redacted] T10 vertebral levels will continue in the study. Once in the recovery room, the device will be interrogated to measure electrode impedances and make sure that the device programming is ”OFF”. Device interrogation report(s) will be uploaded via CDU.

The following information will be collected at the Device Implant Visit:

- Device Information
- Programming parameters/device interrogation report(s) with initial and finial settings
- Imaging

- Changes to pain medications
- AEs/DDs

10.10 Device Activation (Day 0; 9-16 days after implant)

The Device Activation visit will take place 9-16 days after implant, pending wound healing. If wound has not healed, the Device Activation Visit will be rescheduled. Device Activation is considered Day 0 for the purpose of calculating the post implant visits and telephone calls. Imaging may be performed to assess for lead migration if deemed necessary by the investigator. The subject's most recent imaging should be referenced for programming. The stimulator will be turned "ON" at this visit and the subject will be programmed within the following limits:

During this visit, subjects will be educated on the use of their patient programmer/recharger. Subjects will be informed how they can turn their device off, if needed. Device interrogation report(s) with initial and final programmed settings will be uploaded via CDU.

The following information will be collected at the Device Activation Visit:

- Programming parameters/device interrogation report(s) with initial and finial settings
- Imaging (if performed)
- Changes to pain medications
- AEs/DDs

10.11 Post Implant Telephone Calls

Subjects will be called by delegated study site personnel post-device activation to assess pain relief status and confirm that their stimulator is on. Subjects will also be assessed for AEs (new or existing) and asked about any pain medication changes. Phone calls will be performed weekly up to the 3-Month Visit and then monthly following the 3-Month Visit. If an in-clinic visit falls on the week or month of a scheduled telephone call, the call will not be performed. If the subject reports inadequate pain relief, the subject will be called by a sponsor representative (e.g., field clinical engineer) to assess if re-programming is required. The subject may come in for an unscheduled visit, if necessary, for issues that cannot be addressed over the phone.

The following information will be collected during phone calls:

- Pain relief/programming feedback
- Changes to pain Medications
- AEs/DDs

10.12 Post-Implant Scheduled Visits

10.12.1 1-Month Visit

The 1-Month visit will occur 30 days ± 10 days after device activation (Day 0). Following the completion of all subject assessments required for this visit (see below), AdaptiveStim™ as well as the Position Diary will be turned ON and the device will be oriented. AdaptiveStim™ will then be turned OFF and stimulation threshold testing will be performed in the upright and supine positions for all programmed groups. AdaptiveStim™ may be turned back on, if needed, on an individual basis with sponsor approval. Before configuring AdaptiveStim™ Technology, it is recommended to allow a 4-week healing period after implanting the neurostimulator to allow time for the implanted components to stabilize. If there is not a ≥ 50% decrease in the VAS for overall pain collected at the visit compared to the Baseline VAS for overall pain, the subject may be re-programmed within the following limits:

[redacted]

Device interrogation report(s) with initial and final programmed settings will be uploaded via CDU. Imaging may be performed to assess for lead migration if deemed necessary by the investigator.

The following information will be collected during the 1-Month Follow-up visit:

- VAS

[redacted]

- Programming parameters/device interrogation report(s) with initial and finial settings
- Imaging (if performed)
- Changes to pain medications
- AEs/DDs

10.12.2 3-Month Visit

The 3-Month visit will occur 90 days ± 15 days after device activation (Day 0). If there is not a ≥ 50% decrease in the VAS for overall pain collected at the visit compared to the Baseline VAS for overall pain, the subject may be re-programmed. If re-programming occurs, device interrogation report(s) with initial

and final programmed settings will be uploaded via CDU. Imaging may be performed to assess for lead migration if deemed necessary by the investigator.

The following information will be collected during the 3-Month Follow-up visit:

- VAS
- [redacted]
- Programming parameters/device interrogation report(s) with initial and finial settings
- Imaging (if performed)
- Changes to pain medications
- AEs/DDs

10.12.3 6-Month Visit

The 6-Month visit will occur 180 days ± 30 days after device activation (Day 0). If there is not a ≥ 50% decrease in the VAS for overall pain collected at the visit compared to the Baseline VAS for overall pain, the subject may be re-programmed. If re-programming occurs, device interrogation report(s) with initial and final programmed settings will be uploaded via CDU. Imaging may be performed to assess for lead migration if deemed necessary by the investigator.

The following information will be collected during the 6-Month Follow-up visit:

- VAS
- Programming parameters/device interrogation report(s) with initial and finial settings
- Imaging (if performed)
- Changes to pain medications
- AEs/DDs

10.12.4 12-Month/Final Study Visit

The 12-Month/Final Study visit will occur 360 days ± 30 days after device activation (Day 0). At the completion of this visit subjects will be programmed per standard of care and exited from the study. Imaging may be performed to assess for lead migration if deemed necessary by the investigator.

The following information will be collected during the 12-Month Follow-up visit:

- VAS
- [redacted]

- Programming parameters/device interrogation report(s) with initial and finial settings
- Imaging (if performed)
- Changes to pain medications
- AEs/DDs

10.13 Unscheduled Visits

Unscheduled visits may occur if programming changes are required to correct programming errors, to reprogram to optimize pain control, or as needed for an AE or DD. Whenever feasible, subjects should have their devices interrogated. Imaging may be performed to assess for lead migration if deemed necessary by the investigator and subjects may be re-programmed, if necessary.

The following information may be collected at unscheduled follow-up visits:

- VAS
- Reason for the visit
- Programming parameters/device interrogation report(s) with initial and finial settings
- Imaging (if performed)
- Changes to pain medications
- AEs/DDs

10.14 Device Interrogation

For visits occurring at the study site, device interrogation report(s) with initial and final interrogation settings as well as electrode impedance measurements must be obtained and uploaded via CDU when programming occurs, if applicable. Source for the interrogation reports should be kept at the study site. It is recommended that data are not cleared during any interrogation.

10.15 Imaging

Fluoroscopy or x-ray images will be obtained at Device Trial and Permanent Implant. Images may also be obtained at any other time the investigator feels is necessary to perform images per standard of care. Any images collected for the study will be annotated with a vertebral marker and the distal electrode on each lead will be annotated to reflect which one is electrode 0 and which is electrode 8.

10.16 System Modification

A system modification will be reported in the event the initially implanted device requires invasive modification. System modifications (e.g. lead or device revision, replacement, or explant) may occur due to ineffective or loss of therapy, adverse event, or device deficiency. In the event of a system modification, the follow-up schedule for the subject will remain unchanged. If a system modification occurs, contact a member of the Medtronic study team as the decision to allow the subject to continue with the study will be handled on a case-by-case basis.

The following information will be collected for a system modification:

- Device interrogation report(s) with initial and final programmed settings from the old and new implantable neurostimulator (INS) uploaded via CDU, if replaced and subject remains in the study
- If any portion of the implanted system is replaced, record all changes in source documentation and device identification CRF (e.g. new lead model/serial number)
- AEs/DDs

All explanted product should be returned to Medtronic for analysis when permissible by local laws and regulations. See Section 7.7 for product return details.

10.17 Assessment of Efficacy

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

10.17.1 Visual Analog Scale (VAS)

Pain will be assessed using a VAS (0-10 cm) with 0 cm meaning “no pain” and 10 cm meaning “worst pain imaginable”. Overall pain is defined as a combination of back and leg pain, but not pain from other body parts. Subjects will be asked to report their average pain intensity (overall, back, and leg) that is related to their SCS device treatment “in the last 24 hours” by marking a line perpendicular to the VAS line at the point that represents their pain intensity. Site personnel will determine the score by measuring the distance (cm) on the 10-cm line between the left, “no pain” anchor and where the subject’s mark meets the line. The total length of the line will be measured (to ensure that it is 10 cm) and the distance from the “no pain” mark to the subject’s mark divided by the total distance of the line will be recorded. The scored VAS ranges from 0 – 10.

The VAS will be collected during the Enrollment/Baseline, 1-, 3-, 6-, and 12-Month visits. The VAS will also be collected at any unscheduled visits, as applicable.

[redacted]

[redacted]

[redacted]

10.17.8 Pain Medications

Only medications used specifically for the treatment of back and/or leg pain will be collected during the study. Pain medications will be collected at baseline and any changes to pain medications will be collected throughout the study.

[redacted]

10.17.11 Programming Parameters

Programming parameters will be collected during the Device Trial, Device Implant, Device Activation, 1-, 3-, 6-, and 12-Month visits. Programming parameters will also be collected at unscheduled visits, as applicable. Imaging collected as a part of standard of care will also be collected during the study to be used in reference to programming.

10.18 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 12 for further information on the collection of AEs and safety.

10.19 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.

10.19.1 Case Report Form Data

This study will use a remote data capture (RDC) system to collect study required Case Report Form (CRF) information. Electronic CRFs (eCRFs) will be provided by the sponsor; required data will be taken from source documents and directly entered into the study database via the eCRFs by the appropriately

delegated site personnel, in accordance with applicable regulations. [redacted] Data from the subject assessments will be entered into the database by delegated site personnel. Representatives from the clinical site may not make changes to the diaries except for administrative entries. The principal investigator, or appropriately delegated personnel, are responsible for entering data on the eCRFs. The principal investigator, or appropriately delegated personnel, is required to approve all data on eCRFs via electronic signature.

10.19.2 Programming Parameter Data

Through device interrogations with the Model A710 Intellis Clinician Programmer Application/8880T2 Communicator, programming and device data (eg, session data files) will be collected from the neurostimulator. These data will be electronically transferred as a PDF file to a computer at the study site using Clinical Data Upload (CDU). Those PDF files can then be stored as a source document at the site and be uploaded into the Neuro Programmer Upload (NPU) application. The NPU application is designed to capture programming and device data (eg, "session data reports") and store them within a Medtronic database for analysis and reporting. If programming and device data are not able to be uploaded into NPU, these data may be securely transferred to Medtronic.

10.19.3 Image Data

Images collected during the study will be annotated with a vertebral marker and the highest electrode on each lead will be annotated to reflect which one is electrode 0 and which is electrode 8. Site personnel will redact, at a minimum, the subject's name and label each image with the Subject's ID prior to sending them to Medtronic via upload to a secure file sharing application. Medtronic will keep all copies of the images that they receive in a secure location and may use them for other business purposes outside of this study.

10.20 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

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

- Eligibility criteria not met
- Pregnancy
- Failure to follow study requirements
- 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. Prior to exiting a subject from the study, it is recommended to follow the subject until all ongoing device, therapy, and/or procedure related AEs are resolved or unresolved with no further actions planned. Following exit, subjects will continue to receive standard medical care. 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. If discontinuation is because of safety or lack of effectiveness, the subject may be asked to be followed for collecting safety data outside the clinical investigation.

10.21.1 Study Completed

At the completion of the 12-month follow-up/final study visit, subjects will be exited from the study, both a 12-month follow-up/final study visit CRF and a Study Exit CRF need to be completed.

10.21.2 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.

10.21.3 Conditional Disengagement

After a subject is enrolled every effort should be made to keep the subject in the study. However, it is recognized that there are circumstances where limited data may be collected, or study exit will need to occur. In these cases, we will consider either modified data collection requirements where subjects may conditionally disengage in study procedures but data from the subject can still be collected because the subject has not revoked consent, or exit when study participation is completely ended.

Subjects may be conditionally disengaged from study procedures for any of the following reasons:

- Subject chooses to disengage (e.g., follow-up schedule cannot be adhered to, study burden too large, relocation to another geographic location but telephone follow-up still acceptable)
- Investigator deems conditional disengagement necessary (e.g. medically justified)

If the subject wishes to disengage from the study, or the investigator deems it necessary, the study site is required to document the reason. Prior approval from the study team is required and data collection requirements no longer apply, but study sites are encouraged to collect as much data as possible on the regular CRFs.

11. Risks and Benefits

11.1 Potential Risks

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of a product, from the business analysis phase through development, market release, and post-market surveillance. This is a post-market study and subjects will be treated in accordance with the labeled instructions for

use and indications for Medtronic's SCS therapy. There are foreseeable risks that exist for all SCS patients regardless of whether they are in the study. Furthermore, there are additional risks associated with subjects taking part in this study which are stated in Section 11.1.1.5 and there may be additional risks related to this study, other than the ones described below, that are not yet known.

11.1.1 Foreseeable Risks

11.1.1.1 Risks of Surgery

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

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

11.1.1.2 Spinal Cord Stimulation Adverse Events Summary

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

- Allergic or immune system response to the implanted materials
- Infection
- Lead, extension, or neurostimulator erosion through the skin or migration
- Leakage of cerebrospinal fluid
- Loss of pain relief may return patients to their underlying pain condition
- Patients on anticoagulation therapies may be at greater risk for postoperative complications such as hematomas that can result in paralysis
- Persistent pain at the neurostimulator site
- Placement of the epidural lead-extension is a surgical procedure that may expose patients to risks of epidural hemorrhage, hematoma, or paralysis
- Radicular chest wall stimulation
- Seroma or hematoma at the neurostimulator site
- Change in stimulation, possibly related to cellular changes around the electrode(s), shifts in electrode position, loose electrical connections, lead or extension fractures, which has been described by some patients as uncomfortable stimulation (jolting or shocking sensation).
- Formation of reactive tissue around the lead in the epidural space can result in delayed spinal cord compression and paralysis, requiring surgical intervention. Time to onset can range from weeks to many years after implant.
- Stimulation-dependent gastrointestinal symptoms such as diarrhea, incontinence, or constipation
- Stimulation-dependent bladder symptoms such as urinary retention, incontinence, or frequency

The safety and effectiveness of this therapy has not been established for pregnancy, unborn fetus, or delivery. The study procedures may involve unknown risks for female subjects, their embryo or fetus (unborn child), or delivery if they become pregnant. For this reason, pregnant females have been

excluded from participating in this study. Female subjects must agree to not become pregnant during the study by using a medically acceptable method of birth control; an identified pregnancy will result in immediate study withdrawal.

11.1.1.3 System Revision Risk

The Intellis neurostimulators will provide at least 9 years of operation before replacement is recommended. It is possible that the system will need to be revised (explanted, replaced, or repositioned) earlier than 9 years. Possible reasons for revision/explant may include infection, malfunction, and migration of the system components. The risks associated with system revision are equivalent to the commercially available systems.

11.1.1.4 Risks Associated with the Recharging System

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

11.1.1.5 Study-Specific Risks

Parameters used during the study may not be effective, which could result in an increased level of pain.

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.

11.2 Risk Minimization

The potential risks associated with the study were assessed, identified, and have been mitigated as far as possible. Any potential risks associated with this study are further minimized by selecting qualified investigators with proper SCS therapy and device implantation experience and training study personnel on the CIP. Instructions will be given to the study participants to ensure they can properly use the patient programmer/recharger system and at any time during the study, subjects will be able to turn their device “OFF”. Furthermore, a subject has the right to withdraw from the study at any time and for any reason (e.g., due to insufficient pain relief). Labeling that contains precautions, warnings, and contraindications, as well as instructions on the use of the devices are available to investigators who may provide this information to subjects.

Further mitigations reside in careful construction of the study. This includes selecting an appropriate patient population via inclusion/exclusion screening and closely monitoring subject progress and events reported for the study. Data will be anonymized, and secure electronic systems will be used for data transfer. In addition, investigators will be actively involved in the implantation and follow-up of the subjects in the study.

11.3 Potential Benefits

There may be no direct medical benefit to subjects participating in the study. During the study, subjects will have increased interaction with physicians or medical staff compared to routine clinical care, which may provide some indirect health benefits. Spinal cord stimulation and the settings used during this study may reduce pain intensity, return the patient to a more fully functional status, and/or improve quality of life. These benefits cannot be guaranteed due to the investigational nature of this study.

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

11.4 Risk-Benefit Rationale

Subjects participating in this study will be exposed to risks from commercial SCS therapy that have been deemed, through existing pre-market application approval, to be outweighed by the benefits of treating chronic, intractable pain within approved indications. Additional risks that exist due to participation in the study, including reduced efficacy and uncomfortable stimulation, are low severity, have been minimized by mitigations within the study design, and will be properly communicated to potential subjects. Based on the risk acceptance criteria for the DTM-LE SCS Study laid out in the Study Risk Management Plan, the study-specific residual risk is determined to be acceptable given the expected benefits of furthering the understanding of SCS therapy to inform future studies and product improvements outweigh these additional risks and support the conduct of this study.

12. Adverse Events and Device Deficiencies

12.1 Adverse Events

AE definitions are provided in Table 12-1. All device-related, therapy-related, and procedure-related adverse event information will be collected throughout the study duration, starting at the time of signing the IC. Each event will be classified according to 5 different levels of causality using the following terms:

- Not related
- Unlikely
- Possible
- Probable
- Causal

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

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. Unavoidable Adverse Events (UAE), listed in Table 12-1, need not be reported unless the adverse event worsens or is present outside the stated timeframe post-implant.

For AEs that require immediate reporting (see Table 12-3), initial reporting may be done by phone, email, or on the CRF completing as much information as possible. The completed AE CRF must be submitted to Medtronic as soon as possible. Any medication/treatment associated with the treatment of an AE must be reported

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

12.2 Device Deficiency

The DD definition is provided in Table 12-1. DD information will be collected throughout the study and reported to Medtronic. Note that DD that result in an AE to the subject should be captured as an AE only.

12.3 Processing Updates and Resolution

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

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

12.4 Definitions/Classifications

Where the definition indicates “device”, it refers to any device used in the study.

Table 12-1: AE and DD Definitions

General	
Adverse Event (AE)	Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices. (ISO 14155:2020, 3.2)
Adverse Device Effect (ADE)	AE related to the use of an investigational medical device NOTE 1: This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device. NOTE 3: this includes 'comparator' if the comparator is a medical device. (ISO 14155:2020, 3.1)
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. NOTE 1: DD include malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labeling. NOTE2: This definition includes device deficiencies related to the investigational medical device or the comparator. (ISO 14155:2020, 3.19)

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

Seriousness	
Serious Adverse Event (SAE)	AE that led to any of the following a) death, b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic disease, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE. (ISO 14155:2020, 3.45)
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2020, 3.44)

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

Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
Casual Relationship	The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: – the event is a known side effect of the product category the device belongs to or of similar devices and procedures; – the event has a temporal relationship with investigational device use/application or procedures; – the event involves a body-site or organ that – the investigational device or procedures are applied to; – the investigational device or procedures have an effect on; – the serious event follows a known response pattern to the medical device (if the response pattern is previously known); – the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); – other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; – harm to the subject is due to error in use; – the event depends on a false result given by the investigational device used for diagnosis[1], when applicable; – In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event. [1] If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition.

<table>
<tr><th colspan="2">Other</th></tr>
<tr><td>Unavoidable Adverse Event (UAE)</td><td>An AE inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the Investigator's opinion, including, but not limited to:
<table>
<tr><th>Event Description</th><th>Timeframe from Surgical Procedure</th></tr>
<tr><td>Anesthesia related nausea / vomiting</td><td>24 hours</td></tr>
<tr><td>Low-grade fever (<100°F or 37.8°C)</td><td>48 hours</td></tr>
<tr><td>Seroma</td><td>72 hours</td></tr>
<tr><td>Sleep problems (insomnia)</td><td>72 hours</td></tr>
<tr><td>Back pain/discomfort/stiffness related to laying on table</td><td>72 hours</td></tr>
<tr><td>Mild to moderate bruising / ecchymosis</td><td>7 days</td></tr>
<tr><td>Pocket site / Incisional pain</td><td>7 days</td></tr>
</table></td></tr>
</table>

12.5 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).

12.5.1 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 12-3 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 12-2: Adverse Event Classification Responsibilities

What is classified	Who Classifies	Classification Parameters
Relatedness	• Investigator • Sponsor	• Device related • Therapy related • Procedure related Only events that are classified as possible, probable or causal are considered to be related.
Seriousness	• Investigator • Sponsor	SAE
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator

12.5.2 Adverse Event and Device Deficiency Reporting Requirements

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 12-3: 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.
All Other Reportable AEs	
Investigator shall submit to:	
Medtronic	Submit in a timely manner (within 5 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 5 weeks) after the investigator first learns of the deficiency.
IRB	Submit to IRB per local reporting requirement.

12.6 Subject Death

The investigator must notify Medtronic immediately and the IRB, as required, after learning of a subject's death, regardless of whether or not the death is related to the device system, therapy or procedure. In case of death that is device-related, therapy-related, or procedure-related, there should be one AE with the outcome of death. All other deaths will be recorded on a study exit CRF.

In the event of a subject's death, it is recommended that the implanted system be explanted and returned to Medtronic for analysis whenever possible per local process. Local laws and procedures must be followed where applicable. If any system component is returned to Medtronic, internal return

product reporting systems may be used to gather additional information about the returned device/component.

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

In summary, the following data will be collected:

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

12.7 Product Complaint Reporting

Product complaint reporting and vigilance reporting are applicable and AEs related to any market-released device during the study must be reported. The reporting of product complaints is not part of the study and should be done in addition to the AE reporting requirements. Refer to local regulations for reporting requirements.

Product Complaint: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.

- Abuse: Abnormal use (definition acc. #4.1 of Meddev 2.12-1
- Misuse: Use error (definition acc. #4.20 of Meddev 2.12-1)

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

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

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

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

13. Data Review Committees

This study will not use a Clinical Events Committee (CEC), Adverse Events Advisory Committee (AEAC), or an independent Data Monitoring Committee (DMC). Instead, regular meetings will be held by sponsor personnel, including the Medical Advisor, to review adverse events and device deficiencies, identify potential trends in safety data during the clinical study, and ensure consistent reporting.

14. Statistical Design and Methods

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

14.1 General Aspects of Analysis

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

General descriptive statistics for categorical and continuous variables will be used: categorical variables will be summarized as counts and percentages; continuous variables will be presented using mean, standard deviation, median, quartiles and range as applicable.

[redacted]

14.1.2 Handling Missing Data

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

The primary analysis of the primary and secondary objectives will include subjects who follow DTM-LE SCS programming and provide data (Per-protocol Analysis Set). Sensitivity analyses will be performed for the primary objective using Completer Analysis Set, as well as Implanted Analysis Set with the Multiple Imputation (MI) methodology for missing data. Details of the imputation method are described in Section 14.4.

14.1.3 Multiplicity

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

14.1.4 Investigation Site Pooling

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

There is no a priori provision to exclude any sites from the analysis. The data from all sites will be pooled for analysis. To reduce the possibility of atypical results from a site overly influencing the combined results, no more than 10 subjects will be enrolled at each site. The per-study site enrollment cap may be increased upon Sponsor approval.

14.2 Analysis Execution

A formal analysis for the DTM-LE SCS study will occur after all subjects complete 3-Month visit. Analysis will include both primary and secondary objectives at 3-Month visit. Additional objectives will be addressed based on available data. A final report will be prepared once all data collection has ended and all subjects have completed the 12-Month visit and have been exited. The analysis for the primary and secondary objectives may be updated for the final report if the analysis is performed before final report. Additional objectives will be addressed based on complete data.

14.3 Interim Analysis

No interim analyses are planned for this study.

14.4 Primary Objective

The primary objective is to characterize changes in overall (back and leg) pain intensity, as measured by visual analog scale (VAS), from Baseline to 3-Month visit in subjects with devices programmed to DTM-LE SCS.

14.4.1 Hypothesis

There is no hypothesis testing for the primary objective. The primary objective is to characterize the overall pain relief from baseline to 3-Month visit in subjects with DTM-LE SCS.

14.4.2 Endpoint definition and derivation

The measurements of pain intensity using VAS is described in Section 10.17.1. The overall pain intensity as measured by VAS will be collected at both baseline and 3-Month visit. The primary endpoint of change in overall pain VAS is calculated using VAS at the 3-Month visit minus VAS at the baseline visit. A negative change is an improvement.

14.4.3 Analysis Methods

The change in overall pain VAS as well as overall pain VAS at both baseline and the 3-Month visit will be summarized using descriptive statistics, (e.g., mean, standard deviations, etc.). The 95% CI of the mean change will be calculated.

In addition, percentage of change in overall pain VAS will be calculated using change in overall pain VAS divided by overall pain VAS at baseline. A negative percentage of change in VAS is a percentage of reduction in VAS, thus an improvement. The percentage of change in overall pain VAS will be summarized using descriptive statistics, (e.g., median and inter-quartile range, etc.)

14.4.4 Determination of Subjects/Data for Analysis

The primary analysis will use subjects who are implanted with Intellis neurostimulator, follow DTM-LE SCS programming, and provide outcome measures at both baseline and 3-Month visit (Per-protocol Analysis set).

Two sensitivity analyses will be performed, one uses Completers Analysis Set and one uses Implanted Analysis Set. The sensitivity analysis of all implanted subjects will be performed using MI method for missing data at the 3-Month Visit. For scheduled 3-Month visit, if an Unscheduled Visit occurred within the 3-Month visit window, and the VAS is collected at the Unscheduled Visit, the VAS from the Unscheduled Visit will be used in the analysis of the 3-Month visit. Otherwise, the missing VAS will be imputed using 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. The model variables in MI will include study site, subject age, gender, primary diagnosis, VAS at baseline, 1-Month visit. The fully conditional specification method with 10 burn-in iterations within SAS and 10 repetitions (M = 10) will be used for imputation. Constraints will be set so that the imputed VAS are restricted to values ranging from 0-10. Following imputation, the objective will be evaluated using MI analysis method.

14.5 Secondary Objective

To characterize programming parameters associated with energy use from Device Trial through 12-Month visit.

14.5.1 Hypothesis

There is no hypothesis testing for the secondary objective. The secondary objective is to characterize programming parameters associated with energy use.

14.5.2 Endpoint Definition and derivation

Subject's programmed settings (frequency, pulse width, and amplitude) together with the impedance range measurements and cycling ON-OFF time will be summarized.

14.5.3 Analysis Methods:

The programming parameters associated with energy use will be summarized using descriptive statistics, (e.g., mean, standard deviations, etc.) from Device Trial through 12-Month visit. Where possible, the energy use may be summarized by average recharge interval.

14.5.4 Determination of Subjects/Data for Analysis

The analysis will use subjects who contribute to follow-up visits.

14.7 Safety assessment

To characterize all device-related, therapy-related, and procedure-related adverse events and device deficiencies from the Device Trial Start Visit until study exit. 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.

14.8 Sample Size Justification

The statistical software PASS 11 was used for sample size and precision calculation at 95% confidence level (2-sided) using the Confidence Intervals for One Mean module. The precision estimates (the distance from mean to limits) by sample size and standard deviation of VAS are provided in Table 14-1. Assuming a standard deviation of 2.6 based on internal historical studies, a sample size of 30 subjects provides an expected precision of 0.97.

Table 14-1: Precision by Sample Size and Standard Deviation of VAS

Sample size (N)	Standard deviation (S)			
	2.4	2.6	2.8	3.0
26	0.97	1.05	1.13	1.21
28	0.93	1.01	1.09	1.16
30	0.90	0.97	1.05	1.12
32	0.89	0.94	1.01	1.08

With estimated attrition of 40% between enrollment and implant and 10% between implant and 3-Month from historical internal and external pain studies, to achieve approximately 30 subjects at 3-Month visit, up to 56 subjects may be enrolled into the study.

14.9 Minimization of Bias

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

- 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.

15. Ethics

15.1 Statement(s) of Compliance

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

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

16. Study Administration

16.1 Monitoring

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

16.1.1 Monitoring Visits

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

16.2 Data Management

This study will use the Oracle Clinical Remote Data Capture (RDC) system, which allows the study sites to enter data directly to the eCRF in the sponsor's database over a secure internet connection. This system is fully validated and controls user access, ensures data integrity, and maintains audit trails. User access to the RDC system will be granted to each individual based on his or her delegation of authority. If a person only authorized to complete eCRFs makes changes to an already signed eCRF, the system will require the investigator, or authorized delegate, to re-sign the eCRF. The principal investigator will ensure that only appropriately delegated study personnel are given access to the electronic eCRF system; user IDs and passwords may not be shared.

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

The principal investigator is responsible for the overall quality (completeness and accuracy) of the data entered on the eCRFs and in all other required reports. The data reported on the CRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. See Section 10.19 for CRFs and data collection elements that may be considered source.

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

16.3 Direct Access to Source Data/Documents

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

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

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

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

16.4 Confidentiality

All 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.

16.5 Liability

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

16.6 CIP Amendments

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

16.7 Record Retention

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.

16.7.1 Investigator Records

The investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator) or Subject Study Binder. CRFs must be maintained and signed electronically within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of 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.

16.7.2 Sponsor Records

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

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

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

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

16.8 Reporting Requirements

16.8.1 Investigator Reports

The 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 12. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 16-1: Investigator Reports

Report	Submit to	Description/Constraints
Withdrawal of IRB approval (either suspension or termination)	Sponsor and Relevant Authorities	The investigator must report a withdrawal of approval by the reviewing IRB of the investigator's part of the investigation within 5 working days.
Study Deviations	Sponsor and IRB	Any deviation from the clinical investigation plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being 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.
Other	IRB and Relevant Authorities	An investigator shall, upon request by a reviewing IRB, FDA or any other RA, provide accurate, complete, and current information about any aspect of the investigation.
Final Report	IRB and Relevant Authorities	This report must be submitted within 6 months of study completion or termination.

16.8.2 Sponsor Reports

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

16.9 Publication and Use of Information

Medtronic may publish the results from the DTM-LE SCS 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.

16.9.1 Criteria for Determining Authorship

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

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

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

Lead authorship will be given to the principal investigator who meets the criteria listed above and has the highest number of evaluable subjects. If there is a tie for lead authorship, the authors will be listed in alphabetical order. Medtronic personnel who meet the criteria for authorship will have the right to be listed as an author. Other significant contributors to the study who do not meet the criteria for authorship will be listed in the acknowledgement section of the publication.

16.9.2 Transparency

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

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

16.10 Suspension or Early Termination

16.10.1 Planned Study Closure

Study Closure is a process initiated by distribution of a study closure letter. Study closure is defined as closure of a study that occurs when Medtronic and/or regulatory requirements have been satisfied per the CIP and/or by a decision by Medtronic or RA), whichever occurs first. The study closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing IRB oversight is required until the overall study closure process is complete. Refer to Section 10.21 for additional information regarding study exit procedures.

16.10.2 Early Termination or Suspension

Early Termination is the closure of a study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single study site. Suspension is a temporary postponement of study activities related to enrollment and distribution of the product. This is possible for the whole study or a single study site.

16.10.2.1 Study-wide termination or suspension

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

- AEs associated with the 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

16.10.2.2 Investigator/study site termination or suspension

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

- Failure to obtain initial 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)

16.10.3 Procedures for Termination or Suspension

16.10.3.1 Medtronic-initiated and regulatory authority-initiated

- Medtronic will promptly inform the clinical investigators of the termination or suspension and the reasons and inform the 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

16.10.3.2 Investigator-initiated

- The investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension
- The investigator will promptly inform the institution (where required per regulatory requirements)
- The investigator will promptly inform the 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

16.10.3.3 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, or legally-authorized designees or guardians and/or the personal physician of the subjects, with the rationale for the study termination or suspension

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[redacted]

18. Appendices

There are no appendices within this clinical investigational plan.

19. Version History

Version	Summary of changes	Author(s)/Title
1.0	• Not Applicable, New Document	[redacted]

2.0	[redacted]	[redacted]