Open-Label, Post Market Study: A Clinical Trial to Study the Effects of DTM Spinal Cord Stimulation (DTM™SCS) programs in treating Intractable Chronic Back Pain in Subjects without prior history of Spine Surgery

Protocol Number: DTM-NOVA-2020PM1

NCT Number: NCT04571242

Study Reference: DTM-SCS RCT DDD

Sponsor: SGX Nova
2406 E. Empire St.
Bloomington, IL 61704

Study Responsibility: Wesley Park
Vice President, Clinical Affairs
SGX Nova

Date of Issue: April 21, 2020

Revision: 3.0

Revision History:

Revision	Description	Date
1.0	Initial Release of Investigational Plan	21 Feb 2020
2.0	Remote Visits	19 Mar 2020
3.0	Remote Programming	21 Apr 2020

Study Synopsis

Study Title	Open-Label, Post Market Study: A Clinical Trial to Study the Effects of Differential Target Multiplexed Spinal Cord Stimulation (DTM™SCS) programs in treating Intractable Chronic Back Pain in Subjects without prior history of spine surgery
Protocol Number	DTM-NOVA-2020PM1
Study Device	The Intellis™ neurostimulator, a Spinal Cord Stimulation (SCS) device system manufactured and commercialized by Medtronic (Minneapolis, MN)
Study Purpose	The purpose of this investigational study is to study the effects of Differential Target Multiplexed Spinal Cord Stimulation (DTM-SCS) in subjects with chronic, intractable pain of the trunk with or without lower limb pain, including unilateral or bilateral pain without prior history of spine surgery and refractory to conservative and surgical interventions
Study Design	This is an open-label prospective, randomized, controlled, multi-center study comparing DTM-SCS programming approach to Conventional SCS programming approach. Subjects meeting study entrance criteria will be randomized in a 1:1 ratio to one of two study treatment groups: • Test treatment group with DTM-SCS programming approach • Control treatment group with Conventional SCS programming approach Data at follow-up visits will be compared between the two treatment groups, and in reference to baseline assessments collected at the beginning of the study. There is an optional two-way crossover to the other treatment group available for all subjects who remain implanted at 6 month visit.
Study Size	Up to 250 subjects may be enrolled at up to 20 clinical sites in the United States in order to include an estimated 135 subjects to the point of randomization. This would allow a minimum of 100 subjects (50% in each treatment arm) to complete the 3-month endpoint.
Study Duration	The expected total duration of this study is approximately 32 months. Enrollment of subjects is expected to last 18 months. Subjects who have received the permanent implant will be followed up for approximately 14 months. This consists of Baseline assessments, up to 10 days of trial stimulation, and 12 months of treatment following implantation and activation of the device.

Study Objective	The ***primary objective*** of this study is to evaluate the effectiveness of DTM-SCS in reducing back pain as compared to Conventional SCS for the treatment of intractable chronic back pain.
Inclusion Criteria	A subject must MEET ALL of the following inclusion criteria: 1. Be a candidate for SCS system (trial and implant) per labeled indication (back pain with or without leg pain) 2. Have been diagnosed with chronic, refractory axial low back pain with a neuropathic component and are not eligible for spine surgery (e.g., lumbar fusion, discectomy, laminectomy, laminotomy) at the time of enrollment 3. Has an average *back* pain intensity ≥ 6.0 cm on the 10.0 cm Visual Analog Scale (VAS) at the time of enrollment 4. Be willing and capable of giving written informed consent to participate in this clinical study based on voluntary agreement after a thorough explanation of the subject's participation has been provided. 5. Be willing and capable of subjective evaluation, read and understand written questionnaires, and read, understand and sign the written inform consent. 6. Be 18 years of age or older at the time of enrollment 7. Be on a stable pain medication regimen, as determined by the study investigator, for at least 30 days prior to enrolling in this study 8. Be willing to not increase pain medications from baseline through the 3-Month Visit 9. Be willing and able to comply with study-related requirements, procedures, and visits
Exclusion Criteria	A subject must *NOT* MEET ANY of the following exclusion criteria: 1. Had previous lumbar spinal surgery (e.g., lumbar fusion, discectomy, laminectomy, laminotomy) 2. Has a medical, anatomical, and/or psychosocial condition that is contraindicated for commercially available Intellis™ SCS systems as determined by the Investigator 3. Has a diagnosed back condition with inflammatory causes of back pain (e.g., onset of severe pain with activity), serious spinal pathology and or neurological disorders, as determined by the Investigator 4. Be concurrently participating in another clinical study 5. Has an existing active implanted device such as a pacemaker, another SCS unit, peripheral nerve stimulator, and/or drug delivery pump, etc. 6. Has a pain in other area(s) and/or medical condition requiring the regular use of significant pain medications that could interfere with accurate pain reporting, and/or confound evaluation of study endpoints, as determined by the Investigator 7. Has mechanical spine instability as determined by the Investigator 8. Has undergone, within 30 days prior to enrollment, an interventional procedure and/or surgery to treat back and/or leg pain, which is providing significant pain relief 9. Has unresolved major issues of secondary gain (e.g., social, financial, legal), as determined by the investigator

	10. Be involved in an injury claim under current litigation or has a pending or approved worker's compensation claim 11. Be pregnant (determined by urine testing unless female subject is surgically sterile or post-menopausal. If female, sexually active, and childbearing age, subject must be willing to use a reliable form of birth control.)
Primary Endpoint	The primary efficacy endpoint is the percentage of randomized subjects who respond (a decrease in back pain VAS by at least 50% compared to baseline) to SCS therapy at 3 months (non-inferiority analysis). Subjects who do not have a successful Trial Phase are considered failures (non-responders) toward the primary endpoint.

Table of Contents

A. Purpose

A.1. Study Device

The Intellis™ neurostimulator is a commercially available implantable component of a Spinal Cord Stimulation (SCS) device system manufactured by Medtronic (Minneapolis, MN). The system is indicated for spinal cord stimulation (SCS) as an aid in the management of chronic, intractable pain of the trunk and/or limbs-including unilateral or bilateral pain associated with conditions, including Degenerative Disk Disease (DDD)/herniated disk pain refractory to surgical and conservative interventions. It is designed to deliver electrical stimulation to the spinal cord using arrays of electrodes (also called leads) placed in the dorsal epidural space. The study will use commercially available Intellis™ neurostimulator and compatible SCS system components from Medtronic in accordance to the approved FDA indications and labeling. Section D of this Investigational Plan provides detailed description of Intellis™ neurostimulator.

A.2. Purpose of the Investigation

The purpose of this post-market study is to evaluate the effects of Differential Target Multiplex SCS (DTM™SCS) programs in subjects with chronic, intractable pain of the trunk with or without lower limb pain associated with the following conditions: Degenerative Disk Disease (DDD)/herniated disk refractory to conservative and not a candidate for surgical interventions, in the abscense of previous back surgery. Differential Target Multiplexed SCS (DTM-SCS) programming approach relies on stimulation parameters that will be set to levels that span above the perception threshold, yet well below the levels that could cause uncomfortable paresthesia. This study is a post market, open-label, multi-center, prospective, randomized, controlled clinical trial that evaluates the treatment outcomes resulting from DTM-SCS programming approach and Conventional SCS programming approach. Both programming approaches will be discussed in section B.1 of this Investigational Plan.

This investigation is <u>not</u> comparing two different Spinal Cord Stimulation systems and their compatible device components. Both DTM-SCS and Conventional SCS programs will utilize an FDA-approved and commercially available SCS system (Intellis™ neurostimulator and compatible SCS components) as is, without any modification using approved parameters under approved labeling for indicated population. Outcomes will be assessed via standardized tests.

A.3. Study Size

Up to 250 subjects may be enrolled at up to 20 clinical sites in the United States in order to include an estimated 135 subjects to the point of randomization and trial phase. This would allow a minimum of 100 subjects (50% in each treatment arm) to complete the 3-month endpoint. Sample size estimates are discussed further in section B.5.5 of this Investigational Plan.

A.4. Duration of the Investigation

The expected total duration of this study is approximately 32 months. Enrollment of subjects is expected to last 18 months. Subjects that have received the permanent implant will be followed up for approximately 14 months. This consists of Baseline assessments, up to 10 days of trial stimulation, and 12 months of treatment following implantation and activation of the device.

B. Protocol

B.1. Rationale for Study

It is estimated that about 20% percent of the population worldwide is affected by moderate to severe chronic pain[1]. Chronic pain becomes a burden to the individual as this affects a person's ability to carry out many daily life activities, such as exercising, walking, driving a car, attending social events, or performing household chores. In the United States, chronic pain is considered one of the most pervasive and intractable conditions affecting at least one third of the population at an estimated cost of five hundred billion dollars per year, when combining health-related expenditure and the cost-impact on loss of productivity and income[2].

Conventional medical management, including medication and physical therapy, is often not adequate for treating chronic pain. Medication therapy based on opioids may also lead to addiction. Extensive use of opioid medications in the United States has led to the declaration of an epidemic crisis[3]. When these treatments fail to provide pain relief, imaging is performed to assess candidacy for back surgery[4]. However, surgery is only indicated for those patients with mechanical instability or pinched nerves[5]. For the many patients for whom imaging does not clearly show a cause of chronic back pain, or for the patients that have confounding medical issues precluding an invasive surgical procedure, there are few alternative treatment options[6]. Furthermore, surgical interventions have also failed to remediate severe cases of neuropathies and intractable back pain for many patients. Yoshihara et al. evaluated the surgical trends for lumbar degenerative disc disease in the US from 2000 to 2009[7]. They reported a 2.4-fold population-adjusted increase. Bae et al. reported an increase in the number of lumbar surgical fusion for spinal stenosis from 21.5% to 31.2% between 2004 and 2009[8]. Reoperation rate for disc herniation and spinal stenosis varied between 10 to 23%[9]. Overall, 40% of patients developed post-laminectomy syndrome or failed back surgery syndrome, requiring further treatment, with an estimated incidence of 80,000 cases per year[10]. Spinal cord stimulation (SCS) is a proven therapy that has been in use for about 50 years for various types of chronic pain. SCS is a reversible therapy that allows patients to evaluate the therapy for several days using an external neurostimulator (ENS) prior to receiving an implantable neurostimulator (INS) system[11,12,13,14]. Taylor et al, showed the cost effectiveness of SCS versus surgery and other interventions at $7,058 USD per quality adjusted life year[15].

Spinal Cord Stimulation (SCS) utilizes pulsed electric fields that are applied to the dorsal section of the spinal cord via electrode arrays, called leads, implanted in the epidural space.

Conventional SCS programming approach utilizes pulsed electric fields oscillating in the 40-250 Hz frequency range. The electric field creates a stimulation pattern (paresthesia) that overlays with the targeted pain location. The concept behind Conventional SCS is that the stimulation pattern masks pain signals travelling to the brain. Conventional SCS programming

typically involves giving patients a few program groups, allowing patients to select the program group that suits them best. Each program group contains multiple programs that deliver, for a given pulse rate, different stimulation parameters (e.g. pulse width, amplitude) to same or different electrodes. This approach has been used to create better stimulation patterns for the given patient's pain locations or more tolerable stimulation depending on patient's different positions or postures.

Historically, Conventional SCS has not had high success for back pain patients due to the challenge of having the stimulation pattern overlap the back-pain region without causing uncomfortable paresthesia. Although different approaches to SCS exist, Conventional SCS still remains the most used SCS programming approach in treating chronic back and leg pain.

DTM-SCS programming approach relies on stimulation parameters that will be set to levels that span above the perception threshold, yet well below the levels that could cause uncomfortable paresthesia, which may result in greater pain relief. This can be done with programming parameters that are currently available on the device.

In a given program group, DTM-SCS will provide programs with different pulse rates and pulse widths for the goal of better pain relief. For example, starting parameters may be a combination of a program with 50 Hz pulses with duration of up to 200 microseconds setting and a program with 300 Hz with a pulse duration of up to 200 microseconds. This programming approach could result in patients experiencing less uncomfortable stimulation than with the Conventional SCS programming approach. This is possible because an DTM-SCS program group contains programs that allow subjects to access amplitudes below ones that could cause uncomfortable paresthesia and make more adjustments to the amplitude..

There is an ongoing post-market, open-label, prospective, randomized controlled study (NCT03606187) evaluating the DTM-SCS programming approach versus the Conventional one. The study includes more than 100 subjects randomized in 12 sites in the U.S. At the 3-month primary endpoint, the responder rate (percentage of subjects with ≥50% pain relief) for DTM-SCS programming was 80% vs 51% for the active control arm. Thus, the study met the primary objective for non-inferiority. A secondary objective of superiority of DTM-SCS was also met for the primary outcome. In addition, the mean percent of back pain relief relative to baseline at the 3-months follow up for DTM-SCS was 74% vs. 46% for conventional programming.

Thus, the ongoing study has shown that DTM-SCS is more effective than conventional SCS at the 3-month primary endpoint of the study. Results also show that DTM-SCS shows a risk profile in line with that widely documented for conventional SCS.

Therefore, DTM-SCS offers an alternative approach that might help thousands of chronic pain sufferers make substantial improvement in pain relief, reduction in disabilities, and reduce the likelihood of uncomfortable paresthesia.

A multicenter feasibility study (NCT03110601) has also been completed in which DTM-SCS programming approach was evaluated during the required period for trialing SCS therapy. In this acute study 20 subjects completed a trial with DTM-SCS and Conventional SCS programming approaches. In terms of back pain relief, DTM-SCS programming approach provided a mean of 68% pain relief and Conventional SCS programming approach provided a mean of 43% pain relief, which translates to DTM-SCS achieving 25% greater reduction than

Conventional SCS. Notably with DTM-SCS, 80% of subjects experienced 50% or better back pain relief, and 85% of the subjects preferred therapy received through DTM-SCS programming approach. The safety results were in line with expectations of previous SCS studies and were mostly resolved within a few days with minimal interventions. There was one serious adverse event, epidural abscess, which although uncommon, is well established as a potential risk in SCS trial and was not related to either programming approach. There were no unanticipated adverse events.

The study is a post market, open-label, prospective, randomized, controlled multi-center study that will evaluate DTM-SCS programming and Conventional SCS programming for chronic back with or without leg pain sufferers without previous back surgery. There is an optional two-way crossover to the other treatment group available for all subjects who remain implanted at the 6 month visit. This scientifically sound study will provide more information on the effectiveness of DTM-SCS programming approach.

B.2. Study Objectives

The ***primary objective*** of this study is to evaluate the effectiveness of DTM-SCS in reducing back pain as compared to Conventional SCS for the treatment of intractable chronic back pain in subjects without prior history of spine surgery.

The ***secondary objectives*** of this study are to further demonstrate the effectiveness of the DTM-SCS when compared to Conventional SCS for the treatment of chronic pain of the trunk and limbs. This study will also include the characterization of the safety of DTM-SCS.

B.3. Selection of Study Population

B.3.1. Study Population

The intended study population is individuals suffering from chronic, intractable pain of the trunk and/or limbs who are not considered candidates for spine surgery and are candidates for commercially available SCS device systems.

B.3.2. Inclusion Criteria

In order to participate in the study, a subject must MEET ALL of the following inclusion criteria:

1. Be a candidate for SCS system (trial and implant) per labeled indication (back with or without leg pain)
2. Have been diagnosed with chronic, refractory axial low back pain with a neuropathic component and are not eligible for spine surgery (e.g., lumbar fusion, discectomy, laminectomy, laminotomy) at the time of enrollment
3. Has an average *back* pain intensity ≥ 6.0 cm on the 10.0 cm Visual Analog Scale (VAS) at the time of enrollment

4. Be willing and capable of giving written informed consent to participate in this clinical study based on voluntary agreement after a thorough explanation of the subject's participation has been provided.
5. Be willing and capable of subjective evaluation, read and understand written questionnaires, and read, understand and sign the written inform consent
6. Be 18 years of age or older at the time of enrollment
7. Be on a stable pain medication regime, as determined by the study investigator, for at least 30 days prior to enrolling in this study
8. Be willing to not increase pain medications from baseline through the 3-Month Visit
9. Be willing and able to comply with study-related requirements, procedures, and visits

B.3.3. Exclusion Criteria

In order to participate in the study, a subject must *NOT* MEET ANY of the following exclusion criteria:

1. Had a previous spinal surgery (e.g., lumbar fusion, discectomy, laminectomy, laminotomy)
2. Has a medical, anatomical, and/or psychosocial condition that is contraindicated for commercially available Intellis™ SCS systems as determined by the Investigator
3. Has a diagnosed back condition with inflammatory causes of back pain (e.g., onset of severe pain with activity), serious spinal pathology and or neurological disorders as determined by the Investigator
4. Be concurrently participating in another clinical study
5. Has an existing active implanted device such as a pacemaker, another SCS unit, peripheral nerve stimulator, and/or drug delivery pump, etc.
6. Has pain in other area(s) and/or medical condition requiring the regular use of significant pain medications that could interfere with accurate pain reporting, study procedures, and/or confound evaluation of study endpoints, as determined by the Investigator
7. Has mechanical spine instability as determined by the Investigator
8. Has undergone, within 30 days prior to enrollment, an interventional procedure and/or surgery to treat back and/or leg pain, which is providing significant pain relief
9. Has unresolved major issues of secondary gain (e.g., social, financial, legal), as determined by the investigator
10. Be involved in an injury claim under current litigation or has a pending or approved worker's compensation claim
11. Be pregnant (determined by urine testing unless female subject is surgically sterile or post-menopausal. If female, sexually active, and childbearing age, subject must be willing to use a reliable form of birth control.)

B.4. Treatment Groups

Subjects meeting the study entrance criteria will be randomized to one of two study treatment groups in a 1:1 ratio:

- Control Treatment Group: Conventional SCS programming approach
  - Stimulation parameters in the 40-250 Hz frequency range will be trialed according to standard practice as described in the Intellis™ labeling/manuals
    - If frequency parameter above 250 Hz is used during the study, the subject will be counted as failure towards Coventional SCS programming approach but will continue to permanent implant.
- Test Treatment Group: DTM-SCS programming approach
  - As with Conventional SCS programming, stimulation parameters will be trialed according to standard practice as described in the Intellis™ labeling/manuals. Subjects will be given multiple program groups to try. Each DTM-SCS program group will have multiple parameters. The stimulation parameters will be within the specifications described in the Intellis™ labeling/manuals. Each DTM-SCS program group has at least two programs with different pulse rate in the 50 to 1,000 Hz range and each having a maximum pulse width of 1 ms. The subject will progress through each of the program groups until satisfactory pain relief has been reached. The subject will be able to adjust the amplitude of the signals as deemed needed to obtain pain relief. If sufficient pain relief is not achieved with the initial program group, the subject will be instructed to trial another DTM-SCS program group.

B.5. Study Design

B.5.1. Overall Design

This is a post market, open-label, multi-center, prospective, randomized, controlled study to evaluate DTM-SCS in subjects with chronic, intractable pain of the lower back. Data at follow-up visits will be compared between the two treatment groups, and in reference to baseline assessments collected at the beginning of the study.

B.5.2. Bias Minimization

This Investigational Plan and its associated documentation have been designed to minimize potential sources of bias. Each Investigator's qualification for meeting the requirements of this investigational plan will be reviewed prior to their participation in this investigation. Randomization of subjects to one of the two treatment groups will occur after the subject completes Baseline assessments in order to minimize selection bias.

Each therapy, DTM-SCS programs and Conventional SCS programs, will be programmed by clinical representatives of SGX and Medtronic respectively, and in accordance with their Conventional therapy algorithms for optimal pain relief. This will minimize bias related to potential preference by a given clinical representative to a particular SCS therapy.

B.5.3. Comparison Groups

Both groups in the study are active treatment groups. Treatment outcomes from subjects in the DTM-SCS group will be compared to those of the Conventional SCS group.

B.5.4. Blinding

Due to the nature of the programs, it is not feasible to blind the subjects, implanting physicians or the clinical site personnel to the DTM-SCS programming and Conventional programming SCS group assignments. Each SCS group will be programmed under the direction of physicians with support of clinical representatives of the Test and Control treatments, which may identify the type of treatment to study participants. Also, open communication about sensation of paresthesia and pain relief is important in adjusting program parameters to provide optimal pain relief for subjects. The assessments of device performance are done by the subjects and not by the site personnel so the lack of blinding of site personnel should not affect results as pain is the major assessment and subjects tend to describe pain truthfully since it affects their everyday life dramatically and not be influenced by knowledge of the device programming. Despite the inability to blind the study, past SCS studies indicate that there is no reason to believe that subjects and Investigators/clinical staff will be influenced one way or another by the knowledge that a particular SCS program has been used. Best efforts will be made to limit bias by training investigators, clinical site personnel, and all clinical representatives on the relevant areas of the study protocol to limit their influence.

B.5.5. Sample Size

Primary Endpoint Assessment occurs at the follow up visit 3 months after Device Activation. Based on the primary endpoint requirement, the estimated sample size of this study is 100 total subjects (approximately 50 subjects in the DTM-SCS group and approximately 50 subjects in Conventional SCS group) who have passed screening requirements, have been randomized, and have completed the primary endpoint assessment. Randomization of approximately 135 subjects is planned to maintain power in the event of attrition.

The clinical investigational plan requires a screening process for all subjects that provide written informed consent. These subjects will undergo screening to assess eligibility. Subjects may be excluded for various reasons during screening. Accordingly, in order to include an estimated 135 subjects to the point of randomization and trial phase, up to 250 subjects may need to be consented and enrolled to account for exclusions prior to randomization.

B.5.5.1 Sample size rationale and statistical power

The sample size estimate to determine primary endpoint is based on the primary objective of demonstrating non-inferiority of the test group to the control group at 3

months. Established methods were followed in determining the non-inferiority criteria and the related sample size estimate

- Test basis: Farrington-Manning binomial test for non-inferiority
- Estimated responder rate of 70% in the test group and 50% in the control group
- Significance level, alpha, of 0.05 one-sided
- Statistical power = approximately 90% or greater
- Non-inferiority margin of 10%
- Randomization: 1:1

Based on these assumptions, a minimum of 50 randomized and trialed subjects per treatment group (100 total) are required.

B.5.5.2 Overall Sample Size and Enrollment

Based on the primary endpoint requirement, a minimum of 50 subjects per treatment group are required (100 total). To account for a combined estimated attrition of 25% for subjects that do not complete the Trial Phase, and subjects that exit study before the 3-month primary endpoint visit, approximately 135 subjects would need to be randomized and trialed.

To account for 46% attrition prior to randomization (including subject ineligibility after signing the informed consent and subject dropout), it is estimated that a total of up to 250 subjects would need to be enrolled in the study.

B.5.6. Study Duration

This study is expected to last approximately 32 months. Enrollment of subjects is expected to last 18 months. Subjects who are expected to complete the study will commit to it for approximately 14 months. This consists of Baseline assessments, up to 10 days of trial stimulation, and 12 months of treatment following implantation and activation of the device.

B.5.7. Interim Administrative Analyses

For the purposes of business decisions and planning purposes (e.g., to provide an update to third-party investors), administrative analyses may be performed. The results of the analyses will not be widely distributed, and access will be limited to those persons with a "need to know". Access will be restricted from those involved directly with the study conduct or management to prevent the introduction of bias. The administrative analysis will not be used to modify the trial or stop early for potential benefit. As there is no chance of early stopping, the type I error rate is not affected. Limiting changes to the protocol and access to the interim administrative analysis also prevents operational bias due to knowledge of interim results.

B.6. Enrollment, Assessments, Randomization, and Clinical Procedure

Enrollment of subjects will occur at the clinical sites after Institutional Review Board (IRB) approvals, and when written informed consent from subjects has been obtained. Prior to enrollment, Investigators and clinical site staff will approach subjects, who have been determined to be candidates for SCS therapy and talk about potential participation in the study. Following informed consent, the eligibility of subjects to participate in the study will be assessed according to inclusion and exclusion criteria outlined in this Investigational Plan. Various assessments including pain intensity, evaluation of medical history and records, and the Investigator's clinical judgment will be used in the selection process.

B.6.1. Summary of Study Protocol

Potential study subjects will be identified from a pool of candidates for SCS therapy that are either affiliated with or referred to the clinical sites. Notice of availability of the study may be used for recruitment purposes, upon approval of the patient recruitment materials by the study IRB(s). An informed consent form (ICF) will be given to the potential subject for private evaluation. The Investigator or Study Clinical Staff will be available to respond to any questions the potential subject may have during evaluation of the ICF. Potential study subjects willing to participate in the study will visit the study site for providing written consent and for evaluation of eligibility based on inclusion and exclusion criteria. Subjects may also be consented via a combination of mail and telephone calls. The RC will document the telephone calls and follow-up by signing the consent once the subject returns the signed consent. The RC will then provide a photo copy to the subject. Once a consented subject is deemed qualified to participate in the study, baseline assessments and randomization will occur followed by scheduling of the trial stimulation phase with the assigned treatment group. Subjects who complete a successful SCS trial phase will be scheduled to receive a permanent implant of leads and the implanted neurostimulator (INS) and will undergo 12 months of stimulation delivery with assessments at 1, 3, 6, 9, and 12 months after the activation of the therapy.

All subjects who remain implanted at or after the 6 month visit, but are not getting sufficient pain relief and would like to try the other treatment arm's parameters will have the option to cross over to the other treatment group (this is an optional two-way crossover). X-ray may be required to determine lead locations. Crossover must be completed within 30 days of the 6 month visit.

Baseline assessments will include measures for pain intensity, use of medication, extent of disability, and quality of life.

Following completion of the baseline assessment, study subjects will be randomized in a 1:1 ratio to either the DTM-SCS programming group or the Conventional SCS programming group.

After randomization, subjects will undergo a Trial Phase lasting up to 10 days to determine subject's response to assigned treatment group. Temporary or permanent leads and an external neurostimulator (ENS) will be used during the Trial Phase. Subjects will evaluate the assigned treatment group based on pain intensity under optimal parameters. Those who have a "successful Trial Phase" (defined as a 40% or greater pain reduction from Baseline

in their back pain) will proceed to permanent implantation of a SCS system to evaluate the assigned treatment group.

The implanted neurostimulator (INS) will be activated within 14 days after surgical procedure and SCS therapy will be delivered for the next 12 months. Activation of the device marks the initial time point for effectiveness evaluation of the study therapies after implantation. Assessments of pain intensity, use of medication and adverse events will be made at 1 month following Device Activation. At 3, 6, 9, and 12 months after Device Activation, subjects will be assessed for pain intensity, adverse events, extent of disability, use of medication, and quality of life (EuroQol EQ-5D-5L). Patient Global Impression of Change, and subject satisfaction will also be recorded at 3, 6, 9 and 12 months after Device Activation. Subjects have the option to crossover to the other arm after completing the 6 months visit (up to 30 days after completing the 6 month visit).

Figure 1 summarizes the sequence of study-related assessments, procedures, and activities.

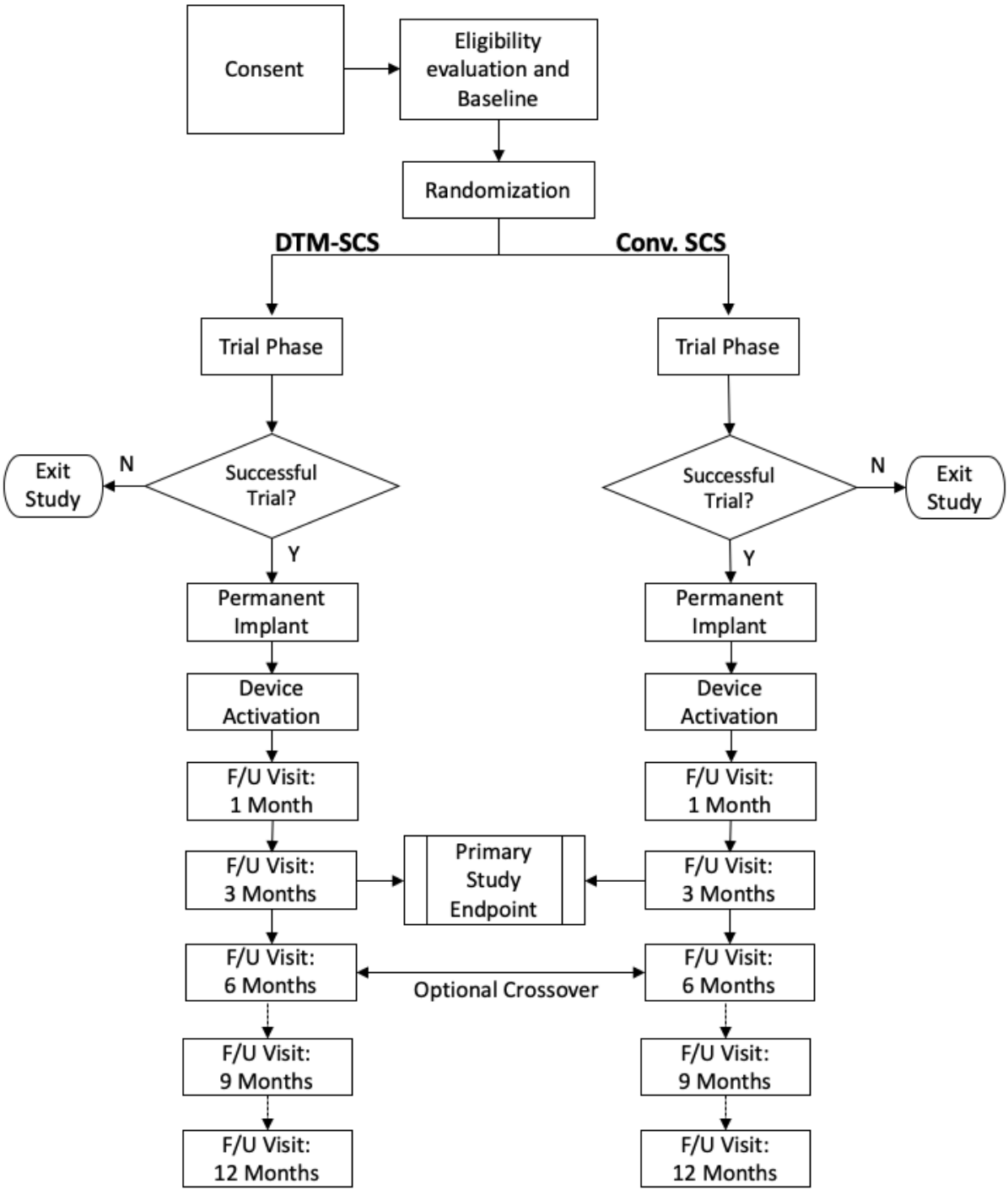

Figure 1. Study Flowchart

B.6.2. Consent/Enrollment

Medical records of all subjects deemed by the Investigator to be potential candidates for the study will be de-identified and sent to a sponsor designated physician for pre-screening. De-identified medical records should include detailed medical and surgical history of the pain condition under study as well any information about comorbidities. Any imaging studies (such as MRI, CT, X-ray) should be included for evaluation of the study candidate. Once the site has received confirmation that subject may be an appropriate candidate for this study, the site may proceed with the eligibility process. This de-identified pre-screening process assists in reducing unnecessary visits for subjects that would not be eligible for this study.

Written informed consent for participation in the study must be obtained from subjects before initiation of any study-related activities. Following informed consent, subjects will be assigned a unique subject identification number and will be considered to be enrolled in the study. Eligibility for advancing to the next stage of the study will be evaluated by the Investigator based on the defined inclusion and exclusion criteria. Subjects will be assessed for pain intensity and disability.

B.6.3. Entry Criteria Evaluation

The eligibility of subjects who have consented participation will be assessed based on the inclusion and exclusion criteria. Study subjects must meet all of the study inclusion criteria and none of the study exclusion criteria to be eligible. Assessments for eligibility include average pain intensity (which will be used as Baseline pain intensity), medication usage, medical records and history, and the Investigator's clinical judgment. Subjects with confirmed eligibility will proceed to Baseline assessment, while subjects who do not will be discontinued from the study.

B.6.4. Baseline

Before a subject is randomized, a subject will be requested to fill out standard questionnaires that will assess extent of disability, use of medications, and quality of life. The medical and surgical history of the subject will be collected. At this visit and subsequent visits, the subject will be assessed for adverse events, medication usage and be reminded to not increase pain medications from baseline through the 3-Month Visit.

Pre-operative assessments will follow the standard of care for SCS therapy and be determined by the site Investigator.

B.6.5. Randomization

Subsequent to completing Baseline assessments, qualifying subjects will be randomly assigned to either one of the two study treatment groups: DTM-SCS programming or Conventional SCS programming (active comparator). Randomization will be stratified by gender and whether the subject has leg pain or no leg pain at Baseline. Randomization will be done at each study site by randomly permuted blocks.

B.6.6. SCS Trial Phase

Subjects will undergo a Trial Phase with the randomly assigned treatment group. The Trial Phase will last up to 10 days and in accordance to approved labeling. Percutaneous leads will be placed in the epidural space at a vertebral level based on the subject's pain condition and pain pattern as described in the Physician Implant Manual. Stimulation will be delivered from an external neurostimulator (ENS).

Anterior-posterior (AP) and lateral X-ray imaging will be done following lead implantation at the beginning of the Trial Phase. The subject should flex forward prior to the final AP and lateral X-ray imaging. Imaging may also be done when lead migration is suspected.

Stimulation therapy will be as follows for each study arm:

- For Conventional SCS: stimulation parameters in the 40-250 Hz frequency range will be trialed according to standard practice as described in the Intellis™ labeling/manuals
- For DTM-SCS: As with Conventional SCS programming stimulation parameters will be trialed according to standard practice as described in the Intellis™ labeling/manuals. Subjects will be given multiple program groups to try. Each DTM-SCS program group will have multiple parameters. The stimulation parameters will be within the specifications described in the Intellis™ labeling/manuals. Each DTM-SCS program group has at least two programs with different pulse rate in the 50 to 1,000 Hz range and each having a maximum pulse width of 1 ms. The subject will progress through each of the program groups until satisfactory pain relief has been reached. The subject will be able to adjust the amplitude of the signals as deemed needed to obtain pain relief. If sufficient pain relief is not achieved with the initial program group, the subject will be instructed to trial another DTM-SCS program group.

Adjustments to a program group may be made based on patient feedback following the trialing of a particular program group or set of stimulation parameters. The primary factor for assessing response to a given program group or stimulation parameters is the subject's self-reported pain relief. Adjustments to therapy will be attempted until at least 50% self-reported back pain reduction from baseline is achieved or until conclusion of the trial phase (no more than 10 days). Subjects will be assessed for adverse events and medication usage.

B.6.7. End of Trial Assessment

At the end of the Trial Phase, subjects will be assessed for pain intensity under optimal therapy parameters. Anterior-posterior (AP) and lateral X-ray imaging may be done at the end of the Trial Phase. The subject will be assessed for adverse events and medication usage.

Those who have a "successful Trial Phase" (defined as a 40% or greater pain reduction from Baseline in their back pain) will proceed to permanent implantation of a SCS system to evaluate the assigned therapy, and permanent implantation of the Intellis™ SCS system will be scheduled. A threshold of 40% for the Trial Phase was predetermined as the minimum pain reduction that warrants consideration of a permanent implant and an

opportunity to achieve a 50% pain reduction as defined in the Individual Subject Success criterion (see Section B.7.3).)

Data from subjects who did not achieve 40% or greater pain reduction in back and do not receive permanent implantation will be carried forward toward the primary and secondary endpoints. These subjects will exit the study after being followed up for two weeks after explant of the leads to assess adverse events.

B.6.8. Permanent Device Implant (0-60 days from end of successful Trial Phase)

As described in section B.6.7, subjects who underwent a successful trial of the assigned SCS therapy and who agreed to continue into the next stage of the study will proceed to permanent implantation stage.

Permanent percutaneous leads will be placed in the epidural space at a vertebral level based on the subject's pain condition and pain pattern as described in the Intellis™ Physician Implant Manual. The INS will be implanted by a trained physician according to standard practice and following the Physician Implant Manual for the device. Anterior-posterior (AP) and lateral X-ray imaging will be obtained. Standard practice of a study site for prophylactic pre-surgery antibiotics and post-surgery pain medications will be followed). Subjects will be assessed for adverse events and medication usage.

B.6.9. Device Activation (0-14 days following Permanent Implant)

Clinical site personnel will assess if healing of surgical wounds is sufficiently appropriate to start charging and programming of the INS. The INS will be initially programmed to the group therapy or set of stimulation parameters that provided adequate pain relief during the Trial Phase. Adjustments to therapy may be made based on patient response to a program group or set of stimulation parameters. The subject will be provided with instructions on how to operate the charger and patient remote control at this visit. Subjects will be assessed for adverse events and medication usage.

B.6.10. Unscheduled Visits

Unscheduled visits may occur at any time during the study for the assessment of possible adverse events, changes in pain medication, and programming adjustments. Each unscheduled visit will be documented and recorded on an eCRF.

B.6.11. Telephone Calls

Subjects will be contacted by the study coordinator, via a telephone call, before each study visit. The study coordinator will check on the well-being of the subject, remind the subject of the upcoming scheduled visit, remind the subject not to change pain medication usage at least two weeks prior to the scheduled visit, remind the subject not to start any new strenuous activity prior to the visit, and remind the subject to contact the Investigator/study staff should he/she have any concerns or questions. The telephone calls should be made two to three weeks *before* the scheduled visit.

B.6.12. 1 Month After Device Activation (± 15 days)

Subjects will visit the study site where they will be assessed for pain intensity. Programming adjustments may be made, as needed. Anterior-posterior (AP) and lateral X-ray imaging may be done if significant lead migration is suspected. Subjects will be assessed for adverse events and medication usage.

B.6.13. 3 Months After Device Activation (± 21 days)

Subjects will visit the study site where they will be assessed for pain intensity, extent of disability, use of medication, quality of life, Patient Global Impression of Change, and subject satisfaction. Paresthesia generated by the stimulator will be assessed. Programming adjustments may be made, as needed. Anterior-posterior (AP) and lateral X-ray imaging will be done. Subjects will also be assessed for possible adverse events and medication usage.

B.6.14. 6 Months After Device Activation (± 31 days)

Subjects will visit the study site where they will be assessed for pain, extent of disability, quality of life, Patient Global Impression of Change, and subject satisfaction. Paresthesia generated by the stimulator will be assessed. Programming adjustments may be made, as needed. Anterior-posterior (AP) and lateral X-ray imaging may be done if significant lead migration is suspected. Subjects will also be assessed for possible adverse events and medication usage.

After the 6 month assessment is completed, subjects in both arms will have an option to change to the other arm if the subject is not receiving sufficient pain relief and desires to try the the other arm's parameters. The subject can crossover immediately after completing the 6 month assessment or within 30 days after completing the 6 month assessment. At the time of crossover, imaging may be required to confirm lead location before programming. If the subject has gross lead migration and is not a candidate for a lead revision, the subject may have to be withdrawn due to the inability to program effectively. If withdrawn, the subject would be continued to be followed by their pain physician as a non-study, commercial patient.

B.6.15. 9 Months After Device Activation (± 31 days)

Subjects will visit the study site where they will be assessed for pain, extent of disability, quality of life, Patient Global Impression of Change, and subject satisfaction. Paresthesia generated by the stimulator will be assessed. Programming adjustments may be made, as needed. Subjects will also be assessed for possible adverse events and medication usage.

B.6.16. 12 Months After Device Activation (± 45 days)

The follow-up visit 12 Months after Device activaction is the final scheduled study visit. Subjects will visit the study site where they will be assessed for pain, extent of disability, quality of life, Patient Global Impression of Change, and subject satisfaction. Paresthesia generated by the stimulator will be assessed. Programming adjustments may be made, as

needed. Subjects will also be assessed for possible adverse events and medication usage.

If there are no ongoing study related adverse events, the subject will complete the study at this visit. In situations where there is an ongoing study related adverse event, subjects will be followed until resolution of that adverse event or determination that the subject's condition is stable, at which point the Study Completion Clinical Research Form (eCRF) should be completed.

Beyond the 12 month visit, there will be no additional scheduled follow-up visits in the study. Following the last scheduled study visit, subjects will be followed by the Investigator at regular intervals, as dictated by standard of care at each site, in order to facilitate pain management, stimulation adjustments, possible revisions and/or replacements of neurostimulation components. Any additional non-study related monitoring of the subject will be the responsibility of the subject's personal physician, as dictated by reasonable medical care.

B.6.17 Other Assessments and Information

At any time during the study, if lead migration is suspected, the subject may have additional AP and lateral X-rays taken to confirm the new lead position in order to aid the Investigator in determining a course of action.

Paresthesia testing may also be performed to assess lead location and therapy coverage of pain areas. Programming adjustments may be made based on patient feedback following assessment.

Additional information on Medication Usage:

- The investigator will instruct all subjects to take the Baseline doses of pain medication until the 3-Month Visit. However, after Device Activation Visit, the Investigator may reduce the dose of pain medication if the subject is benefitting greatly from SCS and not benefitting from Baseline dose pain medication.
    - Subjects should not fluctuate medication usage nor dosages even if the dose is at or below Baseline doses. The research coordinator or investigator should instruct all subjects to maintain stable dosing of medication for at least two weeks prior to scheduled follow-up visits.
- Acetaminophen, NSAIDs or other pain medications (new prescriptions or greater than Baseline doses) may only be taken for an acute condition and for a limited duration. For each type of pain medication, dosing should not exceed the maximum daily dosage recommended by the manufacturer and usage should not continue beyond 5 days. Should acute pain medication usage coincide with a follow-up visit, the visit will be postponed until two weeks after acute pain medication usage has been stopped.
- Following trial and permanent implants, the clinical site's standard practice for prophylactic pre-surgery antibiotics and post-surgery pain medications will be followed. Investigators will instruct subjects not to change usage of any other concomitant pain medications.

B.6.18. Device Explant

At any time during the study, a subject may elect to withdraw from the study and have the SCS device system explanted. Additionally, an Investigator may elect to explant a device due to an adverse event.

The Investigator must follow the appropriate guidelines set forth by the Medtronic for returning the explanted device and/or lead(s) as well as the accessories (charger, patient remote control).

B.6.19. Early Subject Withdrawal

Although efforts will be made by Investigators and study staff to encourage subjects to remain enrolled in the study, subjects may withdraw early from the study for a number of reasons, including but not limited to:

- Failure of SCS Trial Phase
- Subject request
- Investigator request
- Subject lost to follow-up
- Subject's death
- Adverse events (e.g., intolerable adverse event occurrence that forces subject to stop participation in the study)

If a subject is considering withdrawing from the study due to unsatisfactory effectiveness of the assigned treatment, the Investigator will make attempts to improve therapy during a study visit. When a subject is withdrawn early from the study, a Study Termination eCRF will be completed describing the reason for discontinuation. Study staff will contact subjects to remind them about their scheduled visits and make sufficient efforts to locate a subject that is not responding to a contact call. In situations where study withdrawal is due to an adverse event, subjects will be followed until resolution of the adverse event or determination that the adverse event is not likely to change.

B.6.20. Study Completion

All subjects enrolled in the study are expected to complete all scheduled visits through the follow up visit 12 months after Device Activation. A Study Completion eCRF should be completed at the end of this visit. If there is an ongoing study related adverse event, subjects will be followed until resolution of that adverse event or determination that the adverse event is not expected to change.

B.6.21. Study Suspension and Termination

Subjects will be considered to have completed all study requirements following the completion of the follow up visit 12 Months after Device Activation. Each clinical site will be considered to have completed study requirements at the end of the required monitored close out visit. The study will be considered closed when all of the requirements of this Investigational Plan have been fulfilled, all close out visits have been completed and all Sponsor and Investigator reports have been issued and reported to the IRB.

SGX, the Investigators, or the IRB(s) may suspend or terminate the study early at any time. If the study is suspended or terminated prematurely, all subjects that are still enrolled will be terminated from the study. A Study Completion eCRF will be completed noting that the study has been terminated. If there is an ongoing adverse event related to the device or treatment, the subject will be followed until resolution of the adverse event or determination that the adverse event is not likely to change.

Subsequent follow-up of the subjects after study completion will be the responsibility of the subject's personal physician.

SGX reserves the right to terminate the study but intends only to exercise this right for reasons related to the protection of subjects or valid scientific or business reasons. SGX will notify Investigators and IRBs in writing in the event of study termination.

SGX reserves the right to stop the enrollment of subjects at any clinical site at any time after the clinical site initiation. Possible reasons for suspending or terminating a clinical site may include, but are not limited to:

- Non-compliance by Investigator
- Failure to obtain proper written informed consent
- Repeated failure to complete or submit eCRFs in a timely manner
- Failure to report SAEs to the Sponsor within 48 hours of knowledge of the event and to reviewing IRB in accordance with its policies
- Repeated failure to comply with clearance of queries generated during monitoring of the study
- Inactivity

B.7. Study Endpoints

B.7.1. Definition of Analysis Populations

- Modified Intent to Treat (mITT): All successfully randomized subjects who complete the Trial Phase.
- Intent-to-Treat (ITT): All successfully randomized subjects who met all the enrollment criteria.
- Per-Protocol (PP): All subjects who received a permanent device implant and contributed their data to the 3-month endpoint without any major protocol deviations or adverse events (that would render their data unevaluable).

  The primary analysis of the primary and secondary endpoints will be performed on the mITT population. Supportive analyses will be performed for the Intent-to-Treat and Per-Protocol population.

  For analyses incorporating crossover data (i.e. data gathered in the post 6-month periods), analyses will be based on the mITT population with treatment group defined by the treatment status at the corresponding time point to capture the impact of crossover. Additional sensitivity analyses censoring data post-crossover will be performed to examine the impact of crossover.

B.7.2. Effectiveness Assessment Definitions

- Primary Effectiveness Assessment: For subjects who have a successful Trial Phase and receive a permanent implant, the Primary Efficacy Assessment occurs at the follow up visit 3 months after Device Activation. For subjects who do not have a successful Trial Phase (based on subject's pain score) or subjects who do not want a permanent device implant due to insufficient pain relief (based on subject's discontinuation reason), the Primary Efficacy Assessment occurs at the end of the Trial Phase.

B.7.3. Primary Endpoint

Pain rating on the 10 cm Visual Analog Scale is considered the primary outcome measure. VAS is the most widely used outcome measure in assessing pain due to its documented reliability and validity, ease in administration, and minimal training requirements for the administrator.

- ***Individual Responder*:** A decrease in back pain VAS by at least 50% at 3 months after Permanent Device Activation as compared with Baseline. All subjects must be using the assigned programming parameters. If a subject is switched to a programming parameter that is not considered to be DTM-SCS nor Conventional SCS programming the subject will be counted as a non-responder for the following follow-up visit if one of the two following conditions exist:
    - If a subject is switched to a programming parameter that is not considered to be DTM-SCS nor Conventional SCS programming for a period over two weeks
    - If a subject is switched to a programming parameter that is not considered to be DTM-SCS nor Conventional SCS programming for any length of time within the 2 weeks prior to a follow-up visit.

***Overall Study Success*:** The percentage of Individual Responders in the test group is shown to be statistically non-inferior to the percentage in the control group.

B.7.4. Secondary Endpoints

The following secondary endpoints will be evaluated:

- Comparison of the percentage of Individual Responders between the test and control groups in a statistical test of superiority over time (i.e. based on repeated measures analysis). In addition, data will be summarized at the individual time points at 3 months, 6 months, 9 months, and 12 months. This will be performed based on all observed data with treatement defined as a time dependent covariate, and additionally based on censoring data post-crossover.

- Comparison of change from Baseline in back pain score (VAS) between test and control in statistical tests of non-inferiority and superiority. This is calculated as: Change from Baseline in Back Pain VAS = Follow-up Visit Pain VAS – Baseline Pain VAS. A negative result reflects a decrease in the Pain VAS, while a positive result reflects an increase in Pain VAS. All subjects must be using the assigned programming parameters. If a subject is switched to a programming parameter that is not considered to be DTM-SCS nor Conventional SCS programming, that subject's Baseline Back Pain VAS will used instead of Follow-up Visit VAS after the programming change has occurred for the following follow-up visit if one of the two following conditions exist:
    - If a subject is switched to a programming parameter that is not considered to be DTM-SCS nor Conventional SCS programming for a period over two weeks
    - If a subject is switched to a programming parameter that is not considered to be DTM-SCS nor Conventional SCS programming for any length of time within the 2 weeks prior to a follow-up visit.

Analysis of both secondary endpoints will be based on a repeated measures approach that accounts for within subject correlation. Treatment group status for the repeated measures models will be based on treatment status at the current time point (i.e. it will be based on treatment status incorporating potential crossover, not necessarily the original randomized assignment).

B.7.5. Additional Data Collection

These following data will be collected:

- Frequency of treatment emergent adverse events
- Comparison of opioid medication usage from baseline at 3, 6, 9 and 12 months after device activation between the two arms
- Comparison of mean change from Baseline in Leg Pain VAS, evaluated at 3, 6, 9 and 12 months after device activation for subjects with baseline leg pain VAS score ≥ 5 between test and control
- Comparison of Leg Pain Treatment Success, measured as at least a 50% reduction in Leg Pain VAS, evaluated at 3, 6, 9, and 12 months after device activation for subjects with baseline leg pain VAS score ≥ 5 between test and control
- Comparison of patient satisfaction between two arms
- Patient Global Impression of Change, evaluated at 3, 6, 9 and 12 months after device activation
- Comparison of Patient Global Impression of Change between two arms

- Comparison of ODI change from baseline at 3, 6, 9 and 12 months after device activation between the two arms
- Comparison of quality of life (QoL) change (from EuroQol EQ-5D-5L) from baseline at 3, 6, 9 and 12 months after device activation between the two arms
- Quality of paresthesia at 3, 6, 9 and 12 months, comparison between test and control
- Percentage of subjects that crossover
- Comparison of mean change from last visit prior to crossover to 12 months visit. This analysis censors data post-crossover.
- Activity level based on Intellis™ adaptive data log (when available)
- Analysis of additional evaluable data items will be based on treatment status at the current time point (i.e. it will be based on treatment status incorporating potential crossover, not necessarily the original randomized assignment).

B.8. Evaluation Criteria

B.8.1. Effectiveness

Results of the tests and standard questionnaires will be recorded in Case Report Forms at Baseline and during follow-up visits. Changes from Baseline will be calculated and compared between the two groups.

Effectiveness will be measured for each subject using the following tests:

- Pain
  - Visual Analog Scale (VAS, 10 cm) at Baseline, End of Trial Phase, Months 1, 3, 6, 9 and 12
- Disability
  - Oswestry Disability Index Questionnaire
- Quality of Life
  - EuroQol EQ-5D-5L
- Impression of Change in Quality of Life
  - Patient Global Impression of Change
- Satisfaction with Therapy
  - Subject Satisfaction Questionnaire

Study personnel will be appropriately trained for administration of each test.

B.8.2. Definition of Success

The subject's self-reported pain intensity score based on the 10 cm Visual Analog Scale (VAS) is considered the outcome measure for the efficacy component of the primary endpoint. VAS is a widely used outcome measure in assessing pain. It is a reliable and valid

method, which is easy to administer, and requires minimal training for the test administrator. VAS scores will be collected for both back and leg pain.

Study success will be declared if the non-inferiority test for the primary effectiveness endpoint is statistically significant.

There are no additional pre-specified subject or study-level success criteria for secondary and tertiary endpoints.

B.8.3. Safety

Safety will be assessed by characterizing adverse events at all study visits with descriptive statistics.

B.8.3.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a subject associated with the use of the therapy under the study whether or not related to Intellis™ SCS system or the study procedures. An AE is also any event related to any underlying medical condition, present at baseline, which increases in severity or frequency by a clinically meaningful amount during the study as determined by the Investigator.

For all adverse events, the Investigator will provide an assessment of the relationship to the study. If the adverse event is study-related, the following parameters will be assessed: its seriousness, severity, treatment/intervention provided, and resolution.

As the efficacy measures in this study are back and leg pain, back and leg pain do *not* need to be reported as an adverse event unless it meets the definition of a serious adverse event. Investigators may, however, report any other pain-related adverse events during the study.

Pre-existing conditions will not be reported as an adverse event unless there has been a substantial increase in the severity or frequency of the problem, which has not been attributed to its natural history.

A **serious adverse event** (SAE) is an adverse event that

- Leads to death
- Leads to serious deterioration in the health of the subject, that either results in
    - a life-threatening illness or injury (life-threatening is defined as at risk of death at the time of the event), or
    - a permanent impairment of a body structure or a body function, or
    - in-patient hospitalization or prolongation of existing hospitalization (in-patient hospitalization is defined as a hospital admission for a period of greater than 24 hours), or
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- Leads to fetal distress, fetal death, or a congenital abnormality or birth defect

Those known adverse events related to the device, procedure or therapy are listed in the section C. (Risk Analysis) of this Investigational Plan.

B.8.3.2 Reporting

All AEs and SAEs will be assessed and captured from enrollment through the completion of the study on the Adverse Event Source Worksheet. AEs and SAEs will be reported as required by the IRB.

All Adverse Events (see list in section C.1.) assessed/determined to be study-related study will document seriousness, severity, treatment/intervention provided, relationship to the device/procedure, and resolution.

Adverse events that are determined to be not study related by the investigator will not be reported in the EDC.

As would be the common practice when using commercial medical devices, device - related AEs may be reported by the site (per their institutional policy) to the Customer Service or Technical Support of Medtronic as specified in the manufacturer's labeling/manuals.

This is a post market, open-label study so Data Monitoring Committee will not be used.

B.9. Data Collection and Analysis

B.9.1. Data Collection

Study data will be collected using a secure Electronic Data Capture system meeting the requirements of 21 CFR part 11. Each data field completed via the EDC system is expected to have a verifiable source document. The clinical site will enter the data from the source documents directly into the EDC system. Subject confidentiality will be maintained, and each subject will be identified only by the assigned study subject number. Subject names will not be published. Data collection is summarized in Table 1.

Remote data collection from the subjects is allowed. This should be evaluated on a case by case basis, pending Investigator's approval based on safety and clinical condition. Subjects who are not demonstrating study compliance, e.g. not returning phone calls, not charging device or turning the device off should not be mailed the questionnaires until they demonstrate compliance with the study. The site should continue to contact the subject and ensure compliance before mailing the questionnaires. The communications will be documented in the source worksheets.

Visit windows remain in place and should be maintained as much as possible. Subjects should be contacted via phone to confirm AEs, medications and concurrent procedures. All questionnaires required at a visit should be obtained via phone, email or via mail based on site and/or subject preference.

If by phone: site staff will read each question to the subject an record their answers. The site staff should initial and date the bottom of each form and indicate that is was completed via phone.

If by email: the site staff should send the provided questionnaires . Subjects can either print and manually complete or complete the forms electronically.

If manually completed (printed): the subject will be instructed to initial and date each page and scan and email or mail the responses back to the sites.

If the forms are completed electronically: the subject will be instructed to complete the questionnaires and return the responses to the site. Ideally, questionnaires will be completed and returned to the site within 3 business days.

If the questionnaires are sent in hard copy by mail: the subjects should be instructed to complete the questionnaires and initial and date each page after completion and return to site as soon as possible. Ideally, within 3 business days of receipt.

Source documentation should clearly describe the process utilized for each subject at each visit when these alternative methods are utilized.

Remote data collection/remote visits would apply to any visit that could be conducted remotely without the subject being present on-site, including remote programming, if available. Procedural visits (trial and IPG) and any unscheduled visits required for adverse events obviously should continue to be performed on-site when possible.

Table 1. Schedule of Study Activities

Activity	Pre-Trial Phase			Trial Phase		Permanent Implant (up to 60 days after end of trial)	Permanent Implant Phase Follow-up					
	Enrollment	Baseline	Randomization	Start Trial Phase	End Trial Phase (up to10 days after start of trial)		Device Activation (0-14 days after implant)	1-month visit (±15 days after activation)	3 months visit (±21 days after activation)	6 months visit (±31 days after activation)	9 months visit (±31 days after activation)	12 months visit (±45 days after activation)
Informed Consent	X											
Pain Intensity Evaluation (VAS)	X				X			X	X	X	X	X
Medication Use	X	X		X	X	X	X	X	X	X	X	X
Medical/Surgical History	X	X										
Eligibility Criteria Evaluation	X											
Disability Assessment (ODI)		X							X	X	X	X
Quality of Life Assessment (EQ-5D-5L)		X							X	X	X	X
Randomization			X									
AP/Lateral x-ray imaging				X	[X]	X	[X]	[X]	X	[X]	[X]	[X]
Paresthesia Questionnaire									X	X	X	X
Patient Global Impression of Change									X	X	X	X
Subject Satisfaction									X	X	X	X
Adverse Event Monitoring		X		X	X	X	X	X	X	X	X	X
Device Programming				X			X	[X]	[X]	[X]	[X]	[X]
Device Log									[X]	[X]	[X]	[X]
Cross over										[X]		
Study Completion					X[a]							X

a For subjects that do not have a successful Trial Phase.
[X] Optional activity.

B.9.2. Statistical Analysis

Descriptive statistics will be used to summarize baseline and outcome data collected during the study. Continuous variables will be summarized using means, standard deviations, and ranges. Categorical variables will be summarized in frequency distributions. Repeated measures models will account for within subject correlation by use of a compound-symmetric covariance structure (based on logistic regression/generalized estimating equations for binary variables, and linear repeated measures models for continuous variables).

B.9.2.1 Primary Analyses

The *primary efficacy endpoint* will be evaluated with a Farrington-Manning binomial test for non-inferiority with a 10% margin at the one-sided 0.05 alpha level.

H_0: The percentage of subjects (P) who achieve a 50% improvement in their back VAS pain score at 3 months in the Test group is inferior to that in the Control group.

$P_{Test} \leq P_{Control} - 10\%$

H_1: The percentage of subjects (P) who achieve a 50% improvement in their back VAS pain score at 3 months in the Test group is not inferior to that in the Control group.

$P_{Test} > P_{Control} - 10\%$

A 10% margin has been previously used in a similar study.[16] Meeting the statistical threshold for this test based on a 10% margin should produce clinically acceptable results.

B.9.2.2 Secondary Analyses

The following *secondary endpoints* will be evaluated:

- If the primary efficacy endpoint in the test group is found to be non-inferior to that in the control group, then a secondary endpoint will evaluate whether the proportion of subjects who achieve a 50% improvement in their back pain VAS score at 3 months in the test group is superior to that in the control group. A superiority test based on the difference in proportions will be performed based on the following null hypothesis, with a one-sided p-value of 0.05 or less considered evidence of statistical significance.

  H_0: The proportion of subjects (P) who achieve a 50% improvement in their back pain VAS score at 3 months in the Test group is less than or equal to that in the Control group.

  $P_{Test} \leq P_{Control}$

  H_1: The proportion of subjects (P) who achieve a 50% improvement in their back pain VAS score at 3 months in the Test group is greater than that in the Control group.

$$P_{Test} > P_{Control}$$

- Change in mean VAS will be evaluated with two-sample t-test of non-inferiority in means with a 0.65 cm margin at 3 months.

H_0: The change (C) in subject's VAS pain intensity score relative to baseline at the Primary Efficacy Assessment in the Test group is inferior to that of subjects in the Control group (active control).

$$C_{Test} \geq C_{Control} - 0.65 \text{ cm}$$

H_1: The change (C) in subject's VAS pain intensity score relative to baseline at the Primary Efficacy Assessment in the Test group is not inferior to that of subjects in the Control group (active control).

$$C_{Test} < C_{Control} - 0.65 \text{ cm}$$

The non-inferiority margin of 0.65 cm was selected based on a previous study of a similar therapy against traditional SCS[16]. In that study, the experimental therapy showed a 4.9 point improvement while traditional SCS showed a 3.6 point improvement for a difference of 1.3 points. Taking 50% of this treatment effect yields the margin of 0.65.

The following secondary endpoints do not have an associated hypothesis, and no significance level will be assigned to statistical tests that may be performed. Analysis of these endpoints will be based on a repeated measures approach that accounts for within subject correlation. Treatment group status for the repeated measures models will be based on treatment status at the current time point (i.e. it will be based on treatment status incorporating potential crossover, not necessarily the original randomized assignment).

- Comparison of Back Pain Treatment Success (responder rate), measured as subjects with at least a 50% reduction in Back Pain VAS, between test and control
- Comparison of mean change from Baseline in Back Pain VAS, between test and control

B.9.2.3 Additional Data

- Comparison of Leg Pain Treatment Success (responder rate), measured as subjects with at least a 50% reduction in Leg Pain VAS, between test and control for subjects with baseline leg pain VAS score ≥ 5
- Comparison of mean change from Baseline in Leg Pain VAS, between test and control for subjects with baseline leg pain VAS score ≥ 5
- *Satisfaction with Therapy*: Subject Satisfaction will be compared between test and control
- *Patient Global Impression Change*: The Patient Global Impression of Change from Baseline to follow-ups at 3-, 6-, 9- and 12-month visits after device activation will be compared between the treatment groups.

- *Oswestry Disability Index (ODI)*: The changes in ODI from Baseline to 3-, 6-, 9- and 12-months will be summarized as continuous variables and compared between the treatment groups.
- *Quality of Life*: The changes in the EQ-5D-5L instrument from Baseline to follow-ups at 3-, 6-, 9- and 12-months will be summarized as continuous variables and compared between the treatment groups.
- *Paresthesia Questionnaire:* Questions about the paresthesia will be used at 3-, 6-, 9-and 12-month visits and compared between test and control

B.9.2.4 Handling of Missing Data

Missing data will be minimized by rigorous follow-up and investigator and site training. Additionally, for subjects who do not have a successful Trial Phase, results from the Trial Phase will be utilized for the primary endpoint as described in Section B.7.2. Effectiveness Assessment Definitions. Any other data will be imputed via Multiple Imputation. Additionally, sensitivity analyses for missing data will be performed. Unless otherwise specified, all other analyses will be based on the evaluable data with no imputation.

Details on imputation will be provided in a separate statistical analysis plan.

C. Risk Analysis

C.1. Description and Analysis of All Increased Risks to Subjects

Spinal Cord Stimulation (SCS) Risks:

DTM-SCS programming approach will be used with commercially available, FDA approved Intellis™ SCS system within approved indications for use. Anticipated potential adverse events resulting from the study are expected to be in line with adverse events already documented for SCS using a Standard programming approach.

There are known risks associated with the use of any SCS system. Known risks are associated with the implant procedure, the stimulation, the implanted device (not associated with stimulation) and external devices such as the charger and remote control. These are typical of commercial SCS systems. Subjects will be informed of these anticipated risks in the study consent process.

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.

Spinal Cord Stimulation Risks

The implantation of a spinal cord stimulation system involves risks that are similar to other spinal procedures. In addition to those normally associated with surgery, implantation or use of a neurostimulation system includes, but is not limited to the following risks:

- Allergic or immune system response to the implanted materials
- Infection
- Lead or neurostimulator erosion through the skin or migration
- Leakage of cerebrospinal fluid
- Loss of pain relief may return patients to their underlying pain condition
- Persistent pain at the neurostimulator site
- Placement of the epidural lead is a surgical procedure that may expose patients to risks of epidural hemorrhage (bleeding), hematoma, or paralysis
- Radicular chest wall stimulation
- Seroma (fluid collection in pocket where stimulator is placed) 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 fractures, which has been described by some patients as uncomfortable stimulation (jolting or shocking sensation)
- Over time there could be changes in the level of symptom control. In most cases, the physician can correct these changes without surgery.
- Formation of excessive tissue around the lead in the epidural space can result in delayed spinal cord compression and paralysis, requiring surgical intervention. Time to onset can range from weeks to many years after implant.
- The safety of this therapy is unknown for pregnancy, unborn fetus, or delivery
- Stimulation-dependent gastrointestinal symptoms such as diarrhea, incontinence or constipation
- Stimulation-dependent bladder symptoms such as urinary retention, incontinence or frequency
- Unexpected changes in stimulation - Electromagnetic interference, changes in posture, and other activities can cause a perceived increase in stimulation

System Revision Risk

The Intellis AdaptiveStim Neurostimulator may require replacement in 9 years or earlier, regardless of the number of times the neurostimulator is recharged. 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.

Pregnancy Risks

Pregnant women are not able to take part in this study. Female subjects must agree to not become pregnant during the study by using a medically acceptable method of birth control. If a

subject becomes pregnant during this study, there may be risks to the unborn child that are not yet known. Subjects will be advised and encouraged to notify the study doctor immediately if they think they are or have become pregnant. Subjects that become pregnant during the study will be instructed to turn the neurostimulator "OFF" and will be exited from the study.

Radiographic Imaging

As part of the study, subjects may be required to have fluoroscopic or X-ray images taken of their thoracic spine in addition to the imaging conducted to implant the leads. This may be beyond what is standard of care. The risk associated with these additional images has been considered and determined to be minimal since the total radiation dose will be approximately the same as one CT scan of the abdomen.

Study Risk Control Measures

The following will be done to mitigate risks associated with the implanted system:

- Investigators who are experienced with spinal cord stimulation implantation techniques will be utilized
- Instructions will be given to the study participants to ensure they can properly use the patient programmer and recharger system
- Subjects can turn off stimulation at any time during the study with the patient programmer or recharger
- Periodic monitoring of the study participants
- Written materials that contain precautions, warnings, and contraindications, as well as instructions on the use of the devices will be available and/or provided to the clinicians and subjects

Since the efficacy measure in this study is intensity of pain in the back and legs, pain in these areas does not need to be reported as an adverse event unless it meets the definition of a serious adverse event. However, Investigators may, at their discretion, report any other pain-related adverse events during the study.

C2. Minimization of Risks

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

Medtronic has carefully designed and tested the Intellis AdaptiveStim Neurostimulation Systems to ensure the safety and performance for the treatment of chronic, intractable pain. Medtronic has completed an extensive risk analysis to ensure the identification of potential hazards and subsequent mitigation of these hazards to eliminate them entirely or reduce them to an acceptable level.

The risks associated with the surgical implantation of the device, device use, and device failures are the same as those observed for commercially available SCS devices. With an existing pre-market application approval for the commercially available Intellis AdaptiveStim Neurostimulation Systems, an established safety profile of probable benefit outweighing risk already exists for SCS Therapy for chronic back and/or leg pain. In most cases implantation of SCS is a reversible procedure and the system can be turned off or removed. Moreover,

stimulation parameters are adjustable to minimize or reverse complications and maximize therapeutic effects. System output and programming parameters used with the proposed stimulation parameters are within the range of the commercially available Intellis AdaptiveStim Neurostimulation Systems. The anticipated benefits of the clinical outcomes of SCS therapy per the study design outweigh the overall risk.

Study Investigators are experienced in the diagnosis and treatment of chronic pain, have proper surgical and clinical training and will take adequate steps to ensure subject safety throughout the entire study.

Investigators and study personnel will receive product training to become familiar with the components of the Intellis™ SCS systems and their functions. They will also receive training on assessment tools. All Investigators and study personnel must provide evidence of training in Good Clinical Practice (GCP) in the conduct of clinical trials with human participants.

D. Description of the Device

D.1. Each Important Component, Ingredient, and Property of the Device

D.1.1. Device System Overview

The Intellis™ system is a totally implantable spinal cord stimulation system that is indicated to aid in the management of chronic intractable pain of the trunk and/or limbs. The system has been approved by the FDA and is available for commercial use.

The Intellis system system consists of a rechargeable implantable neurostimulator (INS) with 16 output channels. The INS is implanted in a subcutaneous pocket and is capable of stimulating the dorsal aspect of the spinal cord when used with one or two 8-contact percutaneous leads located in the epidural space. The INS can be controlled by a Patient Programmer and/or a Clinician Programmer.

Before permanent implantation, a trial phase of therapy lasting up to 10 days is required. Components of the system during trial include an External Neurostimulator (ENS) capable of delivering the same stimulation as the INS, and Stimulation Leads. Other components of the system include Clinician Programmer, Communicator, Patient Programmer, Extensions, Charger and charging system, and surgical accessories.

D.1.2. Device System Details

Only FDA approved, commercially available components will be used for the study and used in a maner that is consistent with approved labeling.

D.1.2.1 Major Components

Implantable Neurostimulator: Intellis neurostimulator (Model 97715, Medtronic, Minneapolis MN) will be used for the study. The INS is a multi-programmable, rechargeable device that delivers stimulation through one or two 8-electrode percutaneous leads. The stimulation settings are stored in programs. A program is a specific combination of pulse width, rate, and amplitude settings acting on a specific electrode combination (up to 16 electrodes per program). Each of the 16 electrodes in

the leads can be set to be a cathode, an anode, or to remain off. The INS is powered by a Li-Ion rechargeable battery. The INS is capable of stimulating the dorsal aspect of the spinal cord through the electrodes in the leads that are connected to the output terminals of the INS. The electrical pulses used for stimulation are generated using a single current source. The INS is designed to produce charge-balanced, biphasic rectangular pulses.

The battery is recharged using an external charger that uses transcutaneous RF energy transmission. The INS is capable of communicating with the Charger to control the recharging function.

The INS communicates with the Clinician Programmer and Patient Programmer (also called Patient Remote Controller). Clinician Programmer is used to program the INS and the ENS. The Patient Programmer is used by the subject to control some of the therapy parameters, change therapy programs, and turn stimulation on and off.

External Neurostimulator (ENS) for Trial Phase: The Medtronic Model 97725 Wireless External Neurostimulator (ENS) is part of a neurostimulation system used for trial stimulation outside of the operating room. The ENS is powered by two standard alkaline AAA batteries. The ENS is connected to leads implanted in the subject. The subject uses the ENS during the Trial Phase to evaluate the effectiveness of SCS therapy prior to receiving a permanent implant. The ENS also communicates with the Clinician Programmer system and Patient Remote Controller, similar to the INS.

Clinician Programmer System: The Medtronic Model A710 Intellis™ clinician programmer application resides on a tablet and is intended to be used by healthcare professionals to program the ENS (Model 97725) and Intellis™ INS (Model 97715 and 97716) for pain therapy. The Clinician Programmer requires the use of the Communicator (Model 8880T2) to communicate with the INS.

Patient Programmer: The Patient Programmer (Model 97745), also called Patient Remote Controller, is a handheld unit able to communicate with the INS or ENS. The Patient Programmer is powered by two standard AA alkaline batteries (during trial) or a rechargeable battery (after permanent implantation). The Patient Programmer is used by subjects to select the SCS therapy program to be applied, to turn on or off the INS or ENS, and to change some of therapy parameters such as stimulation amplitude.

Charging System: The Charging system (Model 97755) is used by the subject to transcutaneously charge the INS battery. It is a portable device powered by a rechargeable battery and can be held in one hand. The charging system used in this study is a commercially available charging system manufactured by Medtronic (Minneapolis, MN) and fully compatible with the study INS.

Stimulation Leads and Lead Extensions: The study will use commercially available percutaneous eight-electrode leads manufactured by Medtronic (Minneapolis, MN) and compatible with the INS and ENS to be used in this study. The leads are positioned percutaneously in the epidural space of the subject and are used for delivering the stimulation field to the dorsal aspect of the spinal cord. The percutaneous leads are intended to be single use. Temporary or permanent percutaneous leads may be used during the Trial Phase of the study. The proximal end of these leads connect directly to

the ENS. Permanent leads will be used during the Permanent Phase of the study. These may be connected to a Lead Extension. The leads or lead extensions are tunneled subcutaneously to connect to the INS. Commercially available lead extensions (Medtronic, Minneapolis, MN) compatible with the percutaneous leads and INS may be used in this study.

D.1.2.2. Surgical Accessories

The surgical accessories that will be used in the study will be commercially available devices.

Torque Wrench: A commercially available Torque Wrench is used to tighten the screws that lock a percutaneous lead into the INS and/or a lead extension. It also tighten the screws that lock the lead extension into the INS when this is used.

Lead anchors: Lead anchors may be used to possibly prevent lead migration and/or lead strain. These are used to anchor the percutaneous leads to the supraspinous ligament or fascia. Lead anchors used in this study are commercially available (Medtronic, Minneapolis, MN) and designed to slide freely over the lead length to the required fixation position. Surgical sutures are then tied around the anchor clamping the sleeve in place on the lead.

Insertion Needle: Percutaneous leads are implanted in the dorsal epidural space using insertion needles. An insertion needle contains a cannula and stylet that facilitate access to the spinal canal for lead placement. The insertion needle is a 14G epidural needle with a thin wall and a modified Touhy non-coring tip. The cannula and stylet are designed to lock together and maintain the orientation of the tip of each component. The hub of the insertion needle has a standard luer fitting.

Stylets: Stylets are used to push and "steer" a percutaneous lead into the desired place within the epidural space. The distal end of the stylet could be straight or curved. The implanter is able to use either one in order to comfortably maneuver a percutaneous lead through the epidural space until it reaches the desired implant location.

Tunneling Tool: A Tunneling Tool is used to create a subcutaneous tunnel that directs the percutaneous leads or lead extensions from the midline incision to the leads from the INS implant site. This is a single use tool.

INS Template: The INS Template is an aid to be used for the implanter intended for proper sizing of the INS pocket within each subject.

INS Port Plug: An INS Port Plug is used to seal the port of the INS that is not in use when only one percutaneous lead is implanted.

Lead Blank: A Lead Blank is an optional aid made out of flexible stainless steel that has an outer diameter similar in size to the percutaneous lead. A lead blank can be optionally used to clear a path for the introduction of a percutaneous lead into the epidural space.

D.2. Principle of Operation of the Device

Only commercially approved Intellis™ SCS system will be used according to its indications for use. Spinal cord stimulation therapy for pain management has been used for more than four decades. Its efficacy and safety has been widely documented.

D.3. Labeling

Instructions for Use: The study devices will be used in accordance with Intellis™ Manual.

D.4. Any Anticipated Changes in the Device

There are no anticipated changes at this time.

E. Administrative Procedures

E.1. Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), and with applicable regulatory requirement(s).

E.1.1. Study Clinical Monitor

SGX Nova (sponsor) will assign a Clinical Monitor(s) in order to fulfill the required Sponsor and monitoring responsibilities according to the Study Monitoring Plan. The Study Monitoring Plan describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, the distribution of monitoring reports, and key monitoring activities and specifies the data to be reviewed over the course of the clinical study. The monitoring plan will facilitate compliance with Good Clinical Practices (GCP) and other relevant guidelines. The clinical study monitors will conduct monitoring visits in accordance with this plan.

E.1.2. Monitoring Procedures

Monitoring visits to the clinical investigational sites will be made on-site periodically and according to the monitoring Plan. These visits will ensure that Investigators and their staff understand and accept their defined responsibilities, assess compliance with current GCP guidelines, evaluate clinical trial progress, assess the continued acceptability of the site facilities, evaluate compliance with this investigational plan, and verify the data entered on the eCRFs. Remote monitoring visits may also be made periodically.

Investigators are to maintain, in an appropriate secure location, all source documents as required by the investigational plan. Source documents include signed informed consents. subject completed questionnaires, laboratory results, supporting medical records, supporting study worksheets and any applicable electronic files. These source documents will be used by the Clinical Monitor at the scheduled monitoring visits to verify information entered into the EDC System. Clinical monitoring activities will include review and resolution of missing or inconsistent results to assure the accuracy of the reported data. Where any discrepancies are noted, the Clinical Monitor will generate queries. Discrepancies will be resolved with the Investigator and/or an individual designated by the Investigator. If data is incomplete, the Investigator will attempt to obtain the missing data. The original source documents will remain stored in a secure location at the clinical sites as designated by the Investigator.

The safety and welfare of study subjects will be ensured by following the appropriate GCP guidelines for informed consent, including proper documentation (Informed Consent Form) by following the investigational plan, and by reporting and following up study-related adverse events as appropriate.

The Clinical Monitor will summarize the evaluation and assessment of each monitoring visit in written reports. These reports will identify any issues with repeated data recording or reporting and will specify clear recommendations for resolution of noted deficiencies.

The conduct and monitoring of the clinical investigation will be conducted in accordance with sponsor's internal procedures.

E.2. Data Quality Assurance

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. The subject data will be entered into an electronic data capture system (EDC) system following the study visits. Paper copies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Data recorded in the electronic case report form (eCRF) should be consistent with the data recorded on the source documents. Data will be reviewed to identify inconsistent or missing data as well as potential study-related adverse events. Data discrepancies will be addressed by written communication or by telephone with the clinical site and/or during clinical site monitoring visits. The sponsor and representatives of regulatory authorities are permitted to access study documents (e.g. investigational plan, eCRFs, medical records/files) as needed. All attempts will be made to preserve the privacy and confidentiality of subjects.

E.3. Study Conduct

The Investigator agrees that the study will be conducted according to this investigation plan, the principles of GCPs as outlined in the United States Code of Federal Regulations (CFR) - 21 CFR Parts 50, 56 and 812, and the Sponsor internal standard operating procedures. The

Investigator will conduct all aspects of the study in accordance with all Federal and local laws of pertinent regulatory authorities.

The Investigator will assure correct implementation and conduct of the trial including those study related duties delegated to other appropriately qualified individuals and designated in the delegation of authority documentation. The Investigator will assure that study staff cooperates with monitoring and audits, and will demonstrate due diligence in recruiting, screening, and retaining study subjects.

The Investigator will also be responsible for filing an annual study progress report to the IRB as per IRB guidelines. The Investigator and/or Sponsor, as required by local regulations, are required to report in writing to the IRB, notice of completion, termination, or discontinuation of the study. If the study is discontinued for safety concerns, the Investigator and/or Sponsor will notify the IRB immediately.

The Investigator is also responsible for recording and assessing the relationship to the study and the seriousness of Adverse Events. Investigators must report any study related serious adverse event (SAE) to the sponsor within 48 hours of knowledge of the event and to the IRB as per their regulations.

The Investigator is also responsible for promptly reporting to the Sponsor any deviations and exceptions to this investigational plan and to the IRB per their requirements.

E.4. Informed Consent Materials

Informed consent must be obtained from all subjects prior to study participation. Informed consent will be obtained by the Investigator or an Investigator-designated healthcare professional as per GCP guidelines. An informed consent form (ICF) will be provided to potential subjects for their private evaluation. If a subject consents to participate, the ICF must be signed by the subject or a legally authorized representative of the subject. Study ICF must be approved by the IRB. Signed ICFs will be retained in the subject's study records at the clinical site. Subjects may be consented via a combination of mail and telephone calls. The RC will document the telephone calls and follow-up by signing the consent once the subject returns the signed consent. The RC will then provide a photo copy to the subject.

The ICF will be in compliance with the requirements set forth in 21 CFR 50, Protection of Human Subjects.

E.5 Investigators and Institutions

The clinical Investigators participating in this study will be chosen based on their qualifications and experience.

E.6. Amendments and Deviations

This investigational plan is to be followed by Investigators and all personnel involved in the clinical study. Any changes to the study covered by this investigational plan must be documented on a formal investigational plan amendment *prior to* implementation in the study.

Changes to the investigational plan may be initiated by the sponsor or at the request of an Investigator. A formal change to this study under this investigational plan cannot be initiated by Investigator or clinical site personnel without sponsor's approval, IRB approval, and the Investigator's approval.

> *Exception for Emergency Deviation*: An exception to the policy noted above is an emergency deviation to the investigational plan which may be initiated by the Investigator *without* prior approval from sponsor only in cases where a change is necessary to eliminate any immediate apparent hazard to subjects. Emergency deviations must be reported to the Sponsor and the IRB no later than 24 hours following the emergency.

Deviations from the investigational plan and study requirements (including GCP guidelines) will be reviewed by the sponsor and will be evaluated on an ongoing basis. Appropriate corrective actions will be implemented as necessary.

E.7. Additional Record and Reports

This study will be registered on clinicaltrials.gov. Sponsor/Investigator Records and Reports will be maintained and provided in accordance to 21 CFR 812.140 and 812.150. No additional records or reports will be maintained.

F. Appendices

A. Informed Consent Form

B. Subject Questionnaires

G. References

[1] The Global Pain Therapeutics Market Analysis, R&D Pipelines and Competitive Landscape, Arrowhead Publishers, 2007, pp. 408.

[2] Institute of Medicine (US) Committee on Advancing Pain Research C, and Education. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington (DC): National Academies Press (US), 2011, pp. 2.

[3] https://www.hhs.gov/opioids/about-the-epidemic/index.html

[4] Weinstein, J.N., et al., Surgical versus nonoperative treatment for lumbar spinal stenosis four-year results of the Spine Patient Outcomes Research Trial. Spine (Phila Pa 1976), 2010. 35(14): p. 1329-38.

[5] Chen, E., K.B. Tong, and M. Laouri, Surgical treatment patterns among Medicare beneficiaries newly diagnosed with lumbar spinal stenosis. Spine J, 2010. 10(7): p. 588-94.

[6] Ragab, A. and R.D. Deshazo, Management of back pain in patients with previous back surgery. Am J Med, 2008. 121(4): p. 272-8

[7] Yoshihara H, Yoneoka D. National trends in the surgical treatment for lumbar degenerative disc disease: United States, 2000-2009. Spine J 2015;15:265-271.

[8] Bae HW, Rajaee SS, Kanin LE. Nation-wide trends in the surgical management of lumbar spinal stenosis. Spine (Phil Pa 1976). 2013;38:916-926.

[9] Lad SP, Babu R, Ugiliweneza B, Patil CG, Boakye M. Surgery for spinal stenosis: Long-term reoperation rates, health case cost, and impact of instrumentation. Spine (Phila Pa 1976) 2014;39:978-987.

[10] Amirdelfan K, Webster L, Poree L, Sukul V, McRoberts P. Treatment options for fail back surgery syndrome patients with refractory chronic pain. An evidence based approach. Spine (Phila Pa 1976)2017;42:S41-S52.

[11] Smits H, van Kleef M, Holsheimer J, et al. Experimental spinal cord stimulation and neuropathic pain: mechanism of action, technical aspects, and effectiveness. Pain Practice 2013; 13:154-168.

[12] Deer TR, Mekhail N, Provenzano D, et al. The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the neuromodulation appropriateness consensus committee. Neuromodulation 2014; 17:515-550.

[13] Deer TR, Mekhail N, Provenzano D, et al. The appropriate use of neurostimulation: avoidance and treatment of complications of neurostimulation therapies for the treatment of chronic pain. Neuromodulation. 2014; 17:571-597.

[14] Taylor RS, Van Buyten JP, Buchser E. Spinal cord stimulation for chronic back and leg pain and failed back surgery syndrome: a systematic review and analysis of prognostic factors. Spine (Phila Pa 1976) 2005; 30:152-160.

[15] Taylor RS, Ryan J, O'Donell R, Eldabe S, Kumar K, North RB. The cost-effectiveness of spinal cord stimulation in the treatment of fail back surgery syndrome. Clin J Pain 2010;26:463-469.

[16] Kapural L, Yu C, Doust MW, et al. Novel 10-kHz high-frequency therapy (HF10 Therapy) is superior to traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg Pain: The SENZA-RCT randomized controlled trial. Anesthesiology 2015; 123:851-860.