# Comparison of DTM™ SCS Therapy Combined with CMM to CMM Alone in the Treatment of Intractable Back Pain Subjects without previous history of Lumbar Spine Surgery

Clinical Investigational Plan, Revision B, 21 Aug 2020

NCT06442410

**CLINICAL INVESTIGATIONAL PLAN**

***Comparison of DTM™ SCS Therapy Combined with CMM to CMM Alone in the Treatment of Intractable Back Pain Subjects without previous history of Lumbar Spine Surgery***

Protocol Number: DTM-INT-2020PM2

Study Reference: EU RCT DTM™ SCS vs CMM

Sponsor: SGX International
2406 E. Empire St.
Bloomington, IL 61704
United States of America

Study Responsibility: [redacted]
SGX International

Date of Issue: 21 Aug 2020

Revision: B

Revision History:

| Revision | Description | Date |
|---|---|---|
| A | Initial Release of Clinical Investigational Plan | 01 Apr 2020 |

| | | |
|---|---|---|
| B | Clarifications:<br>- Section 3.2: Inclusion criterion nr. 2<br>- Section B.4 & B.6.16: Definition CMM<br>- Section B.6.16: CMM treatment at the 1 month visit.<br>- Section B.6.19: Medication usage<br>Corrections:<br>- Section B.5.5.1: test basis statistical power<br>- Section B.7.1: definition modified intent-to-treat<br>- Section B.9.2: corrections statistical analyses<br>Request Ethics Committee (Spain):<br>- Section B.9.1: EU GDPR reference<br>Administrative changes:<br>- Section B.9.1: Added text regarding remote data collection (due to a formatting issue with Rev A this text was accidently removed)<br>- Section B.9.1: Table 1a & 1b (corrections in the Schedules of Study Activities) | 21-Aug-2020 |

**Study Synopsis**

| | |
|---|---|
| **Study Title** | Comparison of Differential Target Multiplexed Spinal Cord Stimulation (DTM™ SCS) Therapy Combined with CMM to CMM Alone in the Treatment of Intractable Back Pain Subjects without previous history of Lumbar Surgery |
| **Protocol Number** | DTM-INT-2020PM2 |
| **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 document the safety, clinical effectiveness and health economic analytics of DTM™ SCS programming delivered through the Intellis™ neurostimulator 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 treatment and are not candidates for lumbar spinal surgery. |
| **Study Design** | This is a post-market, open-label, prospective, randomized, controlled, multi-center study comparing DTM™ SCS programming approach, delivered through the CE marked Intellis™ neurostimulator, to Conventional Medical Management (CMM).<br><br>Subjects meeting study entrance criteria will be randomized in a 1:1 ratio to one of two study treatment groups:<br>• Test treatment group with DTM™ SCS programming approach with CMM<br>• Control treatment group with CMM alone<br><br>Data at follow-up visits will be compared between the two treatment groups, and compared to baseline assessments collected at the beginning of the study.<br><br>There is an optional two-way crossover to the other treatment group available for all subjects who remain in the study at the 6-months visit. |
| **Study Size** | Up to 300 subjects may be enrolled at up to 15 clinical sites in Europe in order to include an estimated 150 subjects to the point of randomization.<br><br>This would allow minimum 100 subjects (50% in each treatment arm) to complete the 6-month primary endpoint. |
| **Study Duration** | The expected total duration of this study is approximately 44 months.<br>Enrollment of subjects is expected to last 18 months.<br>Subjects who have received the permanent implant will be followed up for approximately 26 months. This consists of Baseline assessments, up to 7 to 30 days (depending on the practice) of trial stimulation, and 24 months of treatment following implantation and activation of the device or 24 months of study visits for those in the CMM arm. |
| **Study Objective** | The ***primary objective*** of this study is to evaluate the effectiveness of DTM™ SCS in reducing back pain as compared to CMM for the treatment of intractable chronic low back pain. |

| | |
|---|---|
| | Other objectives of this study are to document the safety, clinical effectiveness and health economic analytics of DTM™ SCS in subjects with intractable chronic low back pain. |
| **Inclusion Criteria** | A subject must MEET ALL of the following inclusion criteria:<br>1. Be a candidate for SCS system (trial and implant)<br>2. Have been diagnosed with chronic, refractory axial low back pain with or without lower limb pain, with a neuropathic component as assessed by the investigator, 6 months refractory to conventional therapy and are not eligible for spine surgery (e.g., lumbar fusion, discectomy, laminectomy, laminotomy) at the time of enrollment<br>3. Has an average *back* pain intensity ≥ 6.0 cm on the 10.0 cm Visual Analog Scale (VAS) at the time of enrollment<br>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.<br>5. Be willing and capable of subjective evaluation, read and understand written questionnaires, and read, understand and sign the written inform consent.<br>6. Be 18 years of age or older at the time of enrollment<br>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<br>8. 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:<br>1. Had previous lumbar spinal surgery (e.g., lumbar fusion, discectomy, laminectomy, laminotomy)<br>2. Has a medical, anatomical, and/or psychosocial condition that is contraindicated for commercially available Intellis™ SCS systems as determined by the Investigator<br>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<br>4. Be concurrently participating in another clinical study<br>5. Has an existing active implanted device such as a pacemaker, another SCS unit, peripheral nerve stimulator, and/or drug delivery pump, etc.<br>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<br>7. Has mechanical spine instability as determined by the Investigator<br>8. Has undergone, within 30 days prior to enrollment, an interventional procedure to treat back and/or leg pain, which is providing significant pain relief<br>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<br>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 6 months (superiority analysis). Subjects who do not have a successful Trial Phase are considered failures (non-responders) toward the primary endpoint. |
| **Secondary Endpoints & Additional Measures** | Secondary endpoints of this study are to further document the safety, clinical effectiveness and health economic analytics of the DTM™ SCS delivered through Intellis™ system when compared to CMM alone for the treatment of chronic pain of the back and limbs. |

**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, stable intractable peripheral vascular disease, or stable intractable angina pectoris. It is designed to deliver electrical stimulation to the spinal cord using an array of electrodes (also called leads) placed in the dorsal epidural space. The study will use the commercially available Intellis™ neurostimulator and compatible SCS system components from Medtronic in accordance to the approved CE mark labeling (i.e. on-label use). Section D of this Investigational Plan provides a detailed description of the Intellis™ neurostimulator. The study devices will be used in accordance with the Intellis™ Manual.

### A.2. Purpose of the Investigation

The purpose of this post-market study using the CE marked Intellis™ neurostimulator is to evaluate the effects of Differential Target Multiplexed SCS (DTM™ SCS) programs in subjects with chronic, intractable pain of the trunk with or without lower limb pain. The DTM™ SCS programming approach uses on-label SCS programming parameters [redacted] This therapy is CE-marked, commercially available and the related procedures (trial and permanent implant) are part of the standard practice and are not investigational. The pain symptoms of the study population are commonly associated with degenerative spine conditions such as Degenerative Disk Disease (DDD) or herniated intervertebral disks, which are refractory to conservative treatments, and do not indicate the need for surgical interventions of the lumbar spine. This study is a post-market, open-label, multi-center, prospective, randomized, controlled clinical trial that evaluates the treatment outcomes resulting from the DTM™ SCS programming approach with Conventional Medical Management (CMM) versus CMM alone. The DTM™ SCS programming approach with CMM will be discussed more in section B.1 of this Investigational Plan.

### A.3. Study Size

Up to 300 subjects may be enrolled at up to 15 clinical sites in Europe in order to include an estimated 150 subjects to the point of randomization. This would allow a minimum of 100 subjects (50% in each treatment arm) to complete the 6-month primary 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 44 months. Enrollment of subjects is expected to last 18 months. Subjects that have received the permanent implant will be followed up for approximately 26 months. This consists of Baseline assessments, duration of trial stimulation (up to 7 to 30 days depending on the practice), implantation and activation of the device and 24 months of study visits for those in the CMM arm.

## 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 (CMM), including medication and physical therapy, is often not adequate for treating chronic pain. Medication therapy based on opioids may also lead to addiction. Indeed, 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]. Re-operation 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].

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.

The Differential Target Multiplexed SCS (DTM™ SCS) programming approach [redacted] This can be done with programming parameters that are currently available on the Intellis™ neurostimulator device.

In a given program group, DTM™ SCS will provide programs [redacted]

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 compared 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 of the widely documented profile for conventional SCS. Therefore, DTM™ SCS programming approach offers an alternative programming approach to SCS that might help thousands of chronic pain sufferers make substantial improvements 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, the DTM™ SCS programming approach provided a mean of 68% pain relief and the 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 the DTM™ SCS programming approach. The safety results were in line with expectations of previous SCS studies and the adverse events 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 trials and was not related to either programming approach. There were no unanticipated adverse events.

The current study is a post-market, open-label, prospective, randomized, controlled multi-center study that will evaluate DTM™ SCS programming with CMM in comparison to CMM alone for chronic back pain sufferers with or without leg pain. This scientifically sound study will provide more information on safety, efficacy and health economic analytics for the DTM™ SCS programming approach.

## B.2. Study Objectives

The ***primary objective*** of this study is to evaluate the clinical effectiveness of DTM™ SCS with CMM in reducing back pain as compared to CMM alone for the treatment of intractable chronic back pain.

*The* ***secondary objectives*** of this study are to further document the safety, clinical effectiveness and health economic analytics of the DTM™ SCS delivered through Intellis™ system when compared to CMM alone, for the treatment of chronic pain of the trunk and limbs.

## B.3. Selection of Study Population

### B.3.1. Study Population

The intended study population are individuals suffering from chronic, intractable pain of the back 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)
2. Have been diagnosed with chronic, refractory axial low back pain with or without lower limb pain, with a neuropathic component as assessed by the investigator, 6 months refractory to conventional therapy 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 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 Medical Management (CMM)**

- The choice of appropriate Conventional Medical Management will be **made by the Investigator as determined to be the best standard of care** for each individual subject i.e. optimized individual conventional therapy. These treatments would be generally consistent with the American College of Physicians and the American Pain Society Guidelines as published in the Annals of Internal Medicine (http://annals.org/article.aspx?articleid=736814) and European/UK guidelines[1,2,3]. The CMM treatment can be modified at any moment by the investigators based on their clinical evaluation and local standard of care. They may also consists of one or more of the following treatments:
    - Medications: Over-the-counter analgesic medications, opioid medications, nonsterioidal anti-inflammatory drugs (NSAIDs), anticonvulsants, antidepressants, topical analgesics
    - Combined physical and psychological management (CPPM)
    - Physical therapy
    - Back rehabilitation program
    - Spinal manipulation and spinal mobilization
    - Traction
    - Acupuncture
    - Cognitive behavioral therapy (CBT)
    - Biofeedback
    - Nerve blocks
    - Radio frequency ablation
    - Epidural steroid injections
    - Transcutaneous electrical nerve stimulation (TENS)
    - Intradiscal electrothermal therapy (IDET)
    - Nucleoplasty, also called plasma disc decompression (PDD) or similar

**Test treatment group: DTM™ SCS programming approach with CMM**

- Along with the appropriate CMM treatment made by the Investigator, the subject will be trialed and implanted with an Intellis™ neurostimulator system using DTM™ SCS programming parameters. [redacted]

[1] Clinical guidelines for the management of low back pain in primary care: an international comparison; Spine. 26(22):2504-2513, November 15th, 2001. Koes et al

[2] Clinical guidelines for the management of non-specific low back pain in primary care: an updated overview; European Spine Journal 27, 2791-2803(2018).Oliveira et al

[3] Low back pain and sciatica in over 16s: assessment and management. NICE guideline. Published 30 November 2016. www.nice.org.uk/guidance/ng59

## 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 with CMM in comparison to CMM alone, in subjects with chronic, intractable back pain, who have not received lumbar spine surgery and are not candidates for back surgery. Data at follow-up visits will be compared between the two treatment groups, and compared 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 and will be performed by an electronic system. Regular follow-up visits and phone calls from the site personnel either as part of the study protocol or routine clinical practice should minimize attrition.

### B.5.3. Comparison Groups

Both groups in the study are treatment groups. Treatment outcomes from subjects in the DTM™ SCS with CMM group (test treatment) will be compared to those of the CMM alone group (control treatment).

### B.5.4. Blinding

Due to the nature of the treatment groups, comparing an implantable medical device with conventional medical management that may involve multiple different treatments, it is not feasible to blind the subjects, implanting physicians or the clinical site personnel to the group assignments. The assessment of treatments 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 which treatment arm

they are assigned to. In order to minimize potential assessment bias, the subjects will receive the standard instructions for completing the questionnaires.

### B.5.5. Sample Size

Primary Endpoint Assessment occurs at the follow up visit 6 months after Device Activation for subjects randomized in the DTM™ SCS with CMM group, or 6 months after randomization for those in the CMM alone group. Based on the primary endpoint requirement, the estimated sample size of this study is 100 total subjects (approximately 50 subjects in the DTM™ SCS with CMM group and approximately 50 subjects in CMM alone group) who have passed screening requirements and have been randomized.

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 150 subjects to the point of randomization, up to 300 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 superiority of the test group to the control group. Established methods were followed in determining the superiority criteria and the related sample size estimate

- Test basis: Pearson Chi-square binomial test for superiority
- Estimated responder rate of 60% in the test group and 30% in the control group
- Significance level, alpha, of 0.05 two-sided
- Randomization: 1:1
- A sample size of 50 subjects in each group will result in greater than 85% power for the study

Based on these assumptions, a minimum of 50 randomized 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 33% for subjects that do not complete the Trial Phase, and subjects that exit study before the 6-month primary endpoint visit, approximately 150 subjects would need to be randomized.

To account for 50% attrition prior to randomization (including subject ineligibility after signing the informed consent and subject dropout), it is estimated that a total of up to 300 subjects would need to be enrolled in the study.

### B.5.6. Study Duration

This study is expected to last approximately 44 months. Enrollment of subjects is expected to last 18 months. Subjects who are expected to complete the study will commit to it for approximately 26 months. This consists of Baseline assessments, trial stimulation phase for those randomized to DTM™ SCS, and 24 months of treatment following implantation and activation of the device or 24 months after randomization for those subjects randomized to CMM alone.

### B.5.7. Interim Administrative Analyses

In order to monitor data on patient safety and to help ensure accuracy of data collection, administrative analyses may be performed. The results of the analyses will not be widely distributed, and access will be limited to those persons on a "need to know" basis. Administrative analyses 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 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 Ethics Committee (EC) 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 EC(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 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. Once a consented subject is deemed qualified to participate in the study, baseline assessments and randomization will occur. Baseline assessments will include measures for pain intensity,

use of medication, extent of disability, health care utilization, work status 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 + CMM or the CMM alone group.

- **Subjects randomized in the test group (DTM™ SCS with CMM)** will be scheduled for the trial stimulation phase, lasting approximately up to 30 days based on typical clinical practice of the site, to determine the subject's response to DTM™ SCS. Temporary or permanent leads and an external neurostimulator (ENS) will be used during this Trial Phase. Subjects will evaluate the therapy based on pain intensity under optimal DTM™ SCS parameters. Those who have a "successful Trial Phase" (defined as a 50% or greater pain reduction from Baseline in their back pain) will proceed to receive a permanent implant of leads and the internal neurostimulator (INS) and will undergo up to 24 months of stimulation delivery with assessments at 1, 3, 6, 9, 12, 18 and 24 months after the activation of the therapy. The implanted INS will be activated within 14 days after surgical procedure and DTM™ SCS therapy will be delivered for the next 24 months. Activation of the device marks the initial time point for effectiveness evaluation of the test study therapy after implantation. If needed, the investigator may attempt other SCS programming parameters available on Intellis™ neurostimulator to provide pain relief. If other parameters are effective, the parameters should be noted and analyzed. Assessments for pain intensity, use of medication and adverse events will be made at 1 month following Device Activation. At 3, 6, 9, 12, 18 and 24 months after Device Activation, subjects will be assessed for pain intensity, adverse events, extent of disability, use of medication, quality of life , health care utilization, Patient Global Impression of Change, and subject satisfaction. In addition, work status will be evaluated at 6, 12 and 24 months.
- **Subjects randomized in the control group (CMM alone)** will follow the best standard of care under CMM as prescribed by the Investigator i.e. optimized individual conventional therapy (see Section B.6.16). Randomization into the control group marks the initial time point for evaluation of the control study therapy. Subjects in the control group will also undergo up to 24 months of CMM with the same assessments as the test group at 1, 3, 6, 9, 12, 18 and 24 months after randomization.
- **Crossover**: Subjects randomized to either treatment group will have the possibility to crossover to the alternative treatment arm after the 6-month visit, if they meet all of the following criteria:
  - < 50% back pain relief from baseline;
  - Documented subject dissatisfaction with the treatment ("dissatisfied" or "very dissatisfied" on subject satisfaction measure);
  - Investigator agreement with crossover

  Crossover from DTM™ SCS + CMM to CMM: will occur following completion of the 6 month follow-up visit. If the subject and investigator believe that the DTM™ SCS + CMM treatment has not generated sufficient pain relief to warrant

continued treatment, then the subject will be provided with the option to crossover to the CMM group. If all SCS programming attempts fail, then DTM™ SCS therapy will be switched off and the subject will continue with their CMM treatment and will visit the clinic at the 9, 12 and 18 month visits (approximately a total of 18 months follow-up in the study i.e. 6 months DTM™ SCS and 12 months CMM). The subjects will be indicated as a 'crossover to CMM'. The subject can exit the study at any time to try other therapies not falling under CMM or not available in this study. This will be based on the investigator's assessment and will be documented in the CRF and source notes.

Crossover from CMM to DTM™ SCS + CMM: will occur following completion of the 6 month follow-up visit. If the subject and investigator believe that the CMM treatment has not generated sufficient pain relief to warrant continued treatment, then the subject will be provided with the option to crossover to the DTM™ SCS therapy group. The subject will be indicated as a 'crossover to DTM™ SCS'. The subject will then undergo a trial phase with DTM™ SCS therapy. If the trial phase is successful (i.e. at least 50% pain relief compared to the baseline VAS score), the subject will proceed to a permanent device implantation. Following their device activation, they will attend visits starting at 1 month after device activation and continue the study visits until 12 months post-device activation (approximately a total of 18 months follow-up in the study i.e. 6 months CMM and 12 months DTM™ SCS).

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

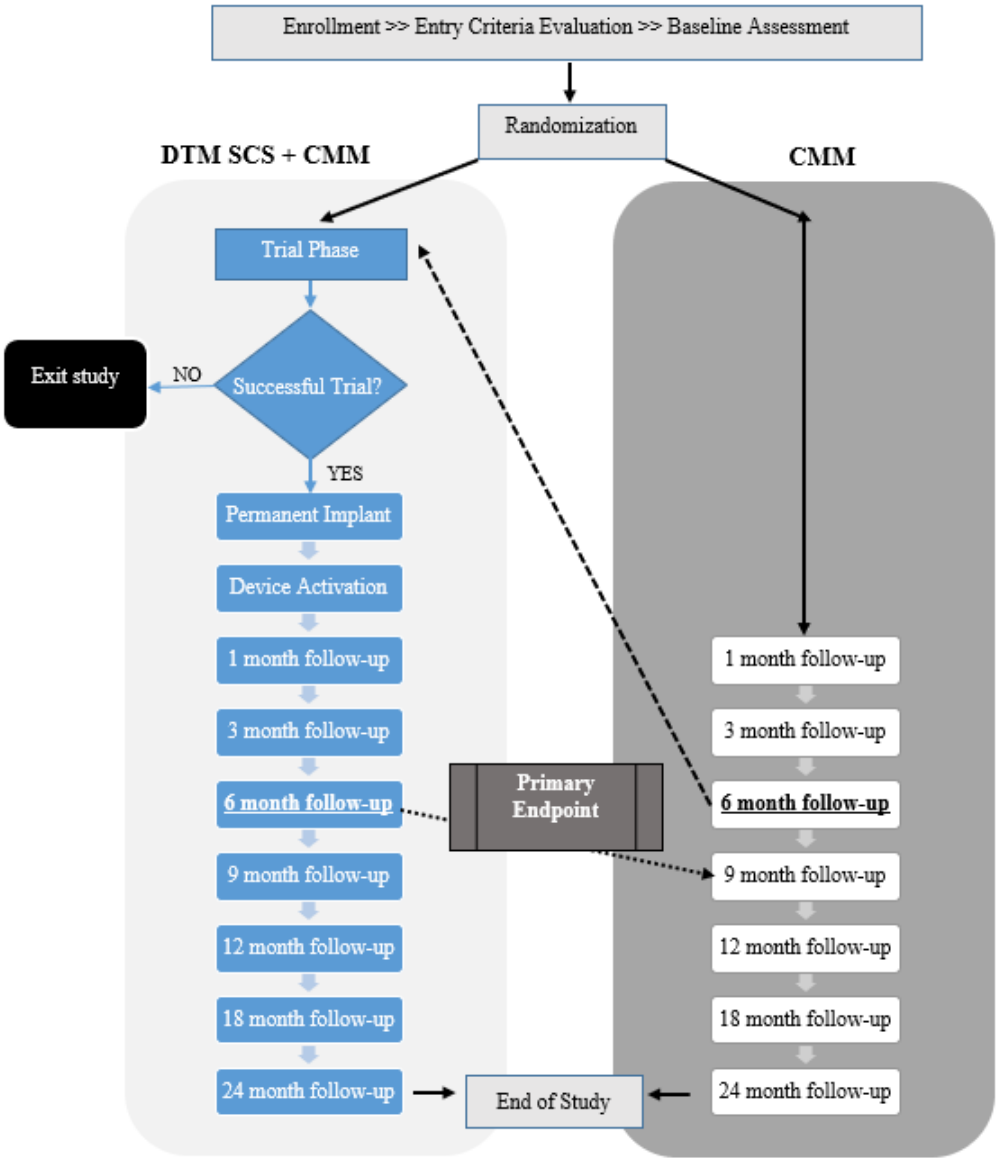


**Figure 1. Study Flowchart**

Crossover to DTM SCS (following CMM 6 month visit this will include DTM SCS Trial phase and follow-up until 12 month; a total of 18 months in the study)

Crossover to CMM (following DTM SCS 6 month visit this will include a 9, 12 and 18 month follow visit; a total of 18 months in the study)

Both crossovers are optional and pending the subject's and investigator's assessments.

### B.6.2. Enrollment/Entry Criteria Evaluation

Written informed consent for participation in the study must be obtained from subjects before initiation of any study-related activities, including those that assess eligibility. 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 site Investigator based on the defined inclusion and exclusion criteria.

The eligibility of subjects who have consented 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. Pregnancy tests will be conducted for participants of child bearing potential; pregnant women will not be allowed to participate (see also Section B.6.6 - Note). Subjects with confirmed eligibility will proceed to Baseline assessment, while subjects who do not will be discontinued from the study.

It is recommended that all above assessments are performed in 1 day; a 14 day window to collect the appropriate data for eligibility assessment is allowed.

### B.6.3. Baseline

Before a subject is randomized, a subject will be requested to fill out standard questionnaires that will assess [redacted] use of medications, healthcare utilization, [redacted] The medical and surgical history of the subject will be collected.

Only applicable for the DTM™ SCS arm: Pre-operative assessments will follow the standard of care for SCS therapy and be determined by the site Investigator.

Note: the enrollment, entry criteria evaluation and baseline visit might be combined in one visit, if all enrollment and entry criteria fulfilled at time of the baseline visit.

### B.6.4. Randomization

Subsequent to completing Baseline assessments, qualifying subjects will be randomly assigned to either one of the two study treatment groups: DTM™ SCS programming with CMM or CMM alone. 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. Randomization assignments will be computer-generated and allocated via the Electronic Data Capturing (EDC) system.

### B.6.5. Test Arm: DTM™ SCS Trial Phase

Subjects will undergo a Trial Phase with DTM™ SCS programming. The Trial Phase will last up to 30 days depending on the typical clinical practice of the site. As part of the standard SCS practice, 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. Stimulation will be delivered from an external neurostimulator (ENS).

As per standard SCS practice anterior-posterior (AP) and lateral X-ray imaging will be done following lead implantation at the beginning of the Trial Phase and when significant lead migration is suspected.

*Note: Depending on the standard of care for SCS practice at the participating site and if the time window is ≥28 days between criteria evaluation and trial implant, for participants of child bearing potential a pregnancy test will be repeated at the pre-assessment for the trial implant.

### B.6.6. Test Arm: 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 will 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 50% or greater pain reduction from Baseline in their back pain) will proceed to permanent implantation of the SCS system to evaluate DTM™ SCS therapy, and permanent implantation of the Intellis™ SCS system will be scheduled. A threshold of 50% 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 50% or greater pain reduction in back pain will not receive permanent implantation and will be carried forward toward the primary endpoint. These subjects will have the leads explanted and will exit the study. Following this exit, 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. 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.6.7. Test Arm: Permanent Device Implant (0-90 days from end of successful Trial Phase)

As described in section B.6.6, subjects who underwent a successful trial of DTM™ SCS programming and who agreed to continue into the next stage of the study will proceed to permanent implantation stage.

As per standard SCS practice, 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. As per standard practice anterior-posterior (AP) and lateral X-ray imaging will be obtained. Standard practice of the 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.6.8. Test Arm: Device Activation (0-14 days following Permanent Implant)

Clinical personnel at the site will assess if healing of surgical wounds is sufficiently appropriate to start charging and programming 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.6.9. Test Arm: 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. As per standard practice, anterior-posterior (AP) and lateral X-ray imaging may be done if significant lead migration is suspected. Subjects will be assessed for adverse events, healthcare utilization and medication usage.

### B.6.10. Test Arm: 3 Months After Device Activation (± 21 days)

Subjects will visit the study site where they will be assessed for pain intensity, [redacted] Programming adjustments may be made, as needed. As per standard practice, 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, healthcare utilization and medication usage.

### B.6.11. Test Arm: 6 Months After Device Activation (± 31 days)

Subjects will visit the study site where they will be assessed for pain, [redacted] Programming adjustments may be made, as needed. As per standard practice, 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, healthcare utilization, [redacted] and medication usage.

Each subject and the Investigator will evaluate whether or not there has been sufficient pain relief to continue stimulation. If the subject and Investigator agree that pain relief has been sufficient to continue therapy, the DTM™ SCS system will remain active. If the subject and Investigator believe that the treatment has not generated sufficient pain relief to warrant continued treatment, then the device will be given the option to switch the device off and remain in the study. Those subjects will be followed up for an additional 12 months using CMM only and continue the study follow-up until the 18 month visit. They will be indicated as 'crossover to CMM'. See Section B.6.1 – Crossover.

### B.6.12. Test Arm: 9 Months After Device Activation (± 31 days)

Subjects will visit the study site where they will be assessed for pain, [redacted] Programming adjustments may be made, as needed. As per standard practice, 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, healthcare utilization and medication usage.

### B.6.13. Test Arm: 12 Months After Device Activation (± 45 days)

Subjects will visit the study site where they will be assessed for pain, [redacted] Programming adjustments may be made, as needed. As per standard practice, 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, healthcare utilization, [redacted] and medication usage.

### B.6.14. Test Arm: 18 Months After Device Activation (± 45 days)

Subjects will visit the study site where they will be assessed for pain, [redacted] Programming adjustments may be made, as needed. As per standard practice, 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, healthcare utilization, and medication usage.

### B.6.15. Test Arm: 24 Months After Device Activation (± 60 days)

The follow-up visit 24 Months after Device activaction is the final scheduled study visit. Subjects will visit the study site where they will be assessed for pain, [redacted] Programming adjustments may be made, as needed. As per standard practice, 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, healthcare utilization, [redacted] 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 it is determinated that the subject's condition is stable, at which point the Study Completion Clinical Research Form (eCRF) should be completed.

Beyond the 24 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.6.16 Control Arm: CMM**

The choice of appropriate Conventional Medical Management will be made **by the Investigator as determined to be the best standard of care** for each individual subject i.e. optimized individual conventional therapy. These treatments would be generally consistent with the American College of Physicians and the American Pain Society Guidelines as published in the Annals of Internal Medicine (http://annals.org/article.aspx?articleid=736814) and European/UK guidelines[4,5,6]. The CMM treatment can be modified at any moment by the investigators based on their clinical evaluation and local standard of care. They may also consists of one or more of the following treatments:

- Medications: Over-the-counter Analgesic medications, opioid medications, Nonsterioidal anti-inflammatory drugs (NSAIDs), Anticonvulsants, Antidepressants, topical analgesics
- Combined physical and psychological management (CPPM)
- Physical therapy
- Back rehabilitation program
- Spinal manipulation and spinal mobilization
- Traction
- Acupuncture
- Cognitive behavioral therapy (CBT)
- Biofeedback
- Nerve blocks
- Radio frequency ablation
- Epidural steroid injections
- Transcutaneous electrical nerve stimulation (TENS)
- Intradiscal electrothermal therapy (IDET)
- Nucleoplasty, also called plasma disc decompression (PDD) or similar

Subjects will continue under CMM therapy until the 24 month visit. No interventions (e.g., facet joint blocks) shall be performed during the 4 weeks leading up to a follow-up visit.

Note: except for the 1 month follow-up visit this is not applicable as the time interval between Randomization and 1 month visit may be too short due to organizational inconvenience. We recommend however to complete the CMM intervention after the Randomization or short after the Randomization and make use of the available time windows at the 1 month visit (i.e. 15 days) to make sure this intervention can be completed within the proposed time window.

[4] Clinical guidelines for the management of low back pain in primary care: an international comparison; Spine. 26(22):2504-2513, November 15th, 2001. Koes et al

[5] Clinical guidelines for the management of non-specific low back pain in primary care: an updated overview; European Spine Journal 27, 2791-2803(2018).Oliveira et al

[6] Low back pain and sciatica in over 16s: assessment and management. NICE guideline. Published 30 November 2016. www.nice.org.uk/guidance/ng59

**At the 1 month (±15 days)** follow up visit, subjects will be assessed for pain and for adverse events, medication usage, healthcare utilization and treatment usage.

**At the 3 month (±21 days)** follow up, subjects will visit the study site where they will be assessed for pain, [redacted] Subjects will also be assessed for possible adverse events, medication usage, healthcare utilization and treatment usage.

**At the 6 month (±31 days)** follow up visit, subjects will visit the study site where they will be assessed for pain, [redacted] Subjects will also be assessed for possible adverse events, medication usage, healthcare utilization, [redacted] and treatment usage. Subjects will have the option to crossover to the test treatment arm if the subject is not receiving sufficient pain relief from CMM alone and desires to try the other treatment arm. They will be indicated as 'crossover to DTM™ SCS'. See Section B.6.1 – Crossover.

Those subjects that switch to the test arm will be considered a failure in the control arm. Subjects that crossover to the test arm will follow the steps described in Sections B.6.5. to B.6.13, and the subjects will be followed for another 12 month which includes 1, 3, 6, 9 and 12 months visits post-device activation.

For those subjects that decide to crossover to the DTM™ SCS + CMM arm, there will be no additional scheduled follow-up visits in the study beyond the 12 month post-device activation visit. 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.

Subjects that continue with CMM and do not cross over, will visit the study site at the **9 month (±31 days), 12 month (±31 days), and 18 month (±31 days)** post-randomization for follow up visits, where they will be assessed for pain, [redacted] Subjects will also be assessed for possible adverse events, medication usage, healthcare utilization, [redacted] and treatment usage.

**At the 24 months (±60 days)** follow up visit (the final scheduled study visit), subjects will visit the study site where they will be assessed for pain, [redacted] Subjects will also be assessed for possible adverse events, medication usage, healthcare utilization, [redacted] and treatment usage. 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.

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.

### B.6.17. Unscheduled Visits

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

### B.6.18. 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 prior to the scheduled visit, and remind the subject to contact the Investigator/study staff should he/she have any concerns or questions. The study site may also call the subject periodically to answer subject questions and to check on their health. Participants may also be contacted by a representative of SGX to see if they are having problems with the equipment and answer questions related to the use of the device. The telephone calls should be made two to three weeks *before* every scheduled visit.

### B.6.19. Other Assessments and Information

At any time during the study, for those subjects implanted with SCS, 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.

As per the Intellis™ neurostimulator's instructions for use:

- 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 when allocated to the DTM™ SCS arm and crossover subjects (from CMM to DTM™ SCS):

- It is recommended that the investigator instructs all subjects to take the Baseline doses of pain medication until the 6 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. The investigator will instruct all subjects to maintain stable dosing of medication for at least two weeks prior to scheduled follow-up visits.
- For the 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.

Additional information on Medication Usage when allocated to the CMM arm and crossover subjects (from DTM™ SCS to CMM):

- Subjects should follow the investigator's instructions. The investigator will instruct all subjects to maintain stable dosing of medication for at least two weeks prior to scheduled follow-up visits.

### B.6.20. Device Explant

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

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

### B.6.21. 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. If a subject has withdrawn consent for the study, or is lost to follow-up, the completion of this visit is not required. 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.6.22. Study Completion

All subjects enrolled in the study are expected to complete all scheduled visits through the follow up visit 24 months after Device Activation for the test arm or 24 months after they are randomized to the control arm. If a control arm (CMM) subject crosses over to the test arm (DTM$^{TM}$ SCS), the subject will be followed for 12 months after device activation. If a test arm (DTM$^{TM}$ SCS) subject crosses over to the control arm (CMM), the subject will be followed until the 18 month follow-up visit. 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 (i.e. AE is stable).

### B.6.23. Study Suspension and Termination

Test subjects will be considered to have completed all study requirements following the completion of the follow up visit 24 Months after Device Activation and control subjects will be considered to have completed all study requirements following the completion of the 24 month follow up visit after randomization. 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 terminated 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 EC.

The Sponsor, the Investigators, or the EC(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.

In the event of suspension or termination of the study, subjects may be explanted according to Device Explant procedures. Subjects may choose to retain the implant and receive ongoing stimulation. Subsequent follow-up of the subjects after study completion will be the responsibility of the subject's personal physician.

The Sponsor 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. The Sponsor will notify Investigators and ECs in writing in the event of study termination.

The Sponsor 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 24 hours of knowledge of the event and to reviewing EC 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 randomized subjects to the test arms who successfully complete the Trial Phase and all successfully randomized subjects to the control arm.
- Intent-to-Treat (ITT): All successfully randomized subjects who met all the enrollment criteria.
- Per-Protocol (PP): All test subjects who received a permanent device implant and all control subjects who contributed their data to the primary and secondary endpoint without any major protocol deviations (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 secondary endpoint analyses incorporating crossover data (i.e. data gathered in the post 6-month periods), sensitivity analyses will be performed to examine the impact of crossover.

### B.7.2. Effectiveness Assessment Definitions

- Primary Effectiveness Assessment: For test subjects who have a successful Trial Phase and receive a permanent implant, the Primary Efficacy Assessment occurs at the follow up visit 6 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. For control arm subjects, the Primary Efficacy Assessment occurs at the 6 months follow up visit post-randomization.

### B.7.3. Primary Endpoint

Pain rating on the 10 cm Visual Analog Scale (VAS) 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 6 months Post-Permanent Device Activation (Test group) or 6 months post-randomization (Control group) as compared with Baseline.

***Overall Study Success*:** The percentage of Individual Responders in the test group is shown to be statistically superior to the percentage of Individual Responders 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. In addition, data will be summarized at the individual time points at 1 month, 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months.
- Comparison of change from Baseline in VAS back pain score between test and control in statistical tests of non-inferiority and superiority at 1 month, 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months . 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.

Analysis of results through 6 months will be based on the mITT population. Sensitivity analysis of both secondary endpoints will also be performed to assess the impact of crossover.

### B.7.6. Safety

Safety will be assessed by characterizing clinically meaningful change in adverse events at all study visits.

**Definitions**

An **Adverse Event** (AE) is any untoward medical occurrence defined as an unintended disease or injury or untoward clinical signs (including abnormal laboratory findings deemed clinically significant as determined by the investigator) in a subject whether or not related to the investigational or commercial medical device. This definition includes events related to the study medical devices and events related to the study procedures. An AE is also any event related to any underlying medical condition, present at Baseline, which increases in severity 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 adverse event, its severity, treatment/intervention provided, relationship to the device/procedure, and resolution.

As the primary efficacy measure in this study is pain, back or leg pain 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 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 natural history.

A **Serious Adverse Event** (SAE) is an adverse event that

- Led to death
- Led to serious deterioration in the health of the subject, that either resulted 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,
- Led 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 Risk Analysis Section C.

A **Serious Adverse Device Effect** (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

An **Unanticipated Serious Adverse Device Effect** (USADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. Additionally, an **Anticipated Serious Adverse Device Effect** (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

Those known adverse events related to the device, procedure or therapy are listed in the Risk Analysis Section C.

An anticipated serious adverse device effect (ASADE) is a serious adverse device effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report. Untoward medical occurrences that are not unanticipated, i.e. are unsurprising, are identified in the Physician Manual or Protocol and ICF.

Those known adverse events related to the device, procedure or therapy are listed in Section C.

Device deficiencies will be handled under the post-market surveillance/vigilance system from the manufacturer (i.e. Medtronic) as the Intellis system is a CE marked device which meets vigilance reporting criteria.

**Reporting**

All device or procedure-related adverse events will be captured from enrollment through the completion of the study on the Adverse Event Case Report Form (CRF). However, in accordance with ISO 14155 latest version when using commercial medical devices, device deficiencies, SAEs, SADEs and USADEs must be reported per the post-market surveillance/vigilance system of the manufacturer as specified in the manufacturer's labeling/manuals.

All AEs, Device Deficiencies, SAEs, SADEs and USADEs (see list in section C) reported during the study will document severity, treatment/intervention provided, relationship to the device/procedure, and resolution. Any USADEs and/or deaths occurring during the study procedures will also be evaluated to determine whether the SCS system might have malfunctioned, or caused or contributed to the event.

All SAEs/SADEs/USADEs will be documented and reported to SGX as soon as possible, but no later than 24 hours after becoming aware of the SAE.

The SGX contact information for these events is or reporting through eCRF:

| E-mail: sae@sgx-international.com |
|---|

The Investigator or site staff may report an event to the sponsor by email, telephone or fax initially, but must follow-up by completing an Adverse Event CRF. The monitored CRF should be sent to SGX and, if possible, be accompanied by copies of source documentation regarding the event (e.g., physician / nurse notes or summaries / hospitalizations records). The Investigator must also report the SAE to the EC according to their local regulations.
An attempt must be made by the Investigator/site staff to schedule a subject visit as soon as feasible following the report of the SAE. In the event of a subject death, all available information (e.g. autopsy or other post-mortem findings) should be provided on the CRF.
An Investigator shall submit a report to the sponsor of any USADE occurring during the study as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect. SGX will conduct an evaluation of the event to determine whether the event is an anticipated event based on labeling and risk analysis. The Investigator must also report the event to the EC if it is determined to be unanticipated.
All AEs will be followed until the event is resolved (with or without sequelae). If a device-related event is ongoing at the time of study completion or termination, the subject will be followed until resolution or the Investigator determines that the subject's condition is stable.

## B.8. Evaluation Criteria

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

### 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** The 10 cm visual analog scale (VAS) is a well validated and widely used scaled psychometric instrument to report pain severity. Subjects will score the severity of pain on a 10 cm line, with 0 indicating no pain and 10 indicating the worst pain imaginable. Subjects will complete a chronic back pain VAS in the clinic during scheduled study visits. Subjects will serve as their own control for the pain relief endpoint. Each subject's baseline pain score will be compared to the score at follow-up visits. Mean changes from baseline will be calculated for the entire cohort. The percentage of subjects who achieved ≥ 50% (back) pain relief will also be calculated based on VAS changes from baseline. VAS scores collected during the study visits will be used for the primary endpoint.

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

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

**B.8.2. Safety Measurements**

**Adverse Events:** Subjects will be assessed for adverse events starting at enrollment and continuing through to study completion. If an adverse event occurs, an adverse event CRF will be completed. The event will be followed until resolution or determination that the subject's condition is stable.

The Investigators shall categorize all adverse events for seriousness, severity, and relationship. All determinations of severity, device relation, and resolution are made by the Investigator and not by the Sponsor.

For purposes of consistent adverse event reporting and analysis, adverse events will categorized using the Medical Dictionary for Regulatory Activities (MedDRA®) terminology, consistent with the *MedDRA® Term Selection: Points to Consider* document. Events are grouped by System Organ Classification (SOC) and Preferred Term (PT), according to diagnosis and/or event description as provided by the Investigator on the case report form.

**B.8.3. Health Economic Measures**

Costs and health outcomes (in terms of life-years and quality-adjusted life-years [QALYs]) associated will be captured from healthcare utilization data [redacted]

**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 superiority 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.9. Data Collection and Analysis

### B.9.1. Data Collection

Study data will be collected using a secure Electronic Data Capture (EDC) system. 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 document 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 collected.
Data collection is summarized in Table 1a (DTM™ SCS test arm) & 1b (CMM control arm).
The study data collection from the subjects (which are European citizens) will be processed in accordance with the provisions of Regulation 2016/679 of the European Parliament and the Council of April 27, 2016 on the protection of natural persons in regarding the processing of personal data.

**Exceptional procedure - in case of exceptional circumstances** (e.g. Covid-19 pandemic)
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, follow-up visits may be temporarily completed by alternative means.

- Visit windows remain in place as described by the Clinical Investigation Plan (CIP) 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 and record their answers. The site staff should initial and date the bottom of each form and indicate that this was completed via phone.
- If by email: the site staff should send the provided pdf questionnaires and certification statement to the subjects to complete and return. 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 certification statement 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.

Enrolment/Entry criteria visits, procedural visits (trial and IPG) and any unscheduled visits required for adverse events obviously should continue to be performed in office when possible. If feasible, remote programming ( DTM™ SCS arm) and/or remote treatment consultation (CMM arm) can be performed.
The preferred method of data collection for this study is an in-office visit, however; until such a time as deemed safe to return to normal operations, we do not want to place the patients and study partners at undue risk.

## Table 1a - Schedule of Study Activities for the Test arm (DTM™ SCS)

| Assessment | Pre-Trial | | Trial Phase | | Permanent Implant Phase | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | Enrollment /Entry Criteria | Baseline | Trial Implant | End of Trial (EoT) | Permanent Implant | Device Activation (DA) | Phone Call | 1 Month Visit | Phone Call | 3 Month Visit | Phone Call | 6 Month Visit | Phone Call | 9 Month Visit | Phone Call | 12 Month Visit | Phone Call | 18 Month Visit | Phone Call | 24 Month Visit |
| Window | Might be combined into one visit, if all enrollment and entry criteria are fulfilled at time of baseline assessment | | - | 0-30 d from Trial Implant | 0-90 d from EoT | 0-14 d from Perm Implant | | ± 15 d from DA | | ± 21 d from DA | | ± 31 d from DA | | ± 31 d from DA | | ± 45 d from DA | | ± 45 d from DA | | ± 60 d from DA |
| Informed Consent* | X | | | | | | 2-3 Weeks before 1 Month Visit | | 2-3 Weeks before 3 Month Visit | | 2-3 Weeks before 6 Month Visit | | 2-3 Weeks before 9 Month Visit | | 2-3 Weeks before 12 Month Visit | | 2-3 Weeks before 18 Month Visit | | 2-3 Weeks before 24 Month Visit | |
| Medication Usage | X | X | X | X | X | X | | X | | X | | X | | X | | X | | X | | X |
| Pain Intensity (VAS) | X | | | X | | | | X | | X | | X | | X | | X | | X | | X |
| Eligibility criteria | X | | | | | | | | | | | | | | | | | | | |
| Pregnancy Test | [X] | | [X] | | | | | | | | | | | | | | | | | |
| Medical/Surgical History | X | | | | | | | | | | | | | | | | | | | |
| AP/Lateral X-Rays | | | X | X | X | | | [X] | | [X] | | [X] | | [X] | | [X] | | [X] | | [X] |
| [redacted] | | | | | | | | | | | | | | | | | | | | |
| Healthcare Utilization | | X | | | | | | X | | X | | X | | X | | X | | X | | X |
| Adverse Event Monitoring | | X | X | X | X | X | | X | | X | | X | | X | | X | | X | | X |
| Device Programming§ | | | X | | | X | | [X] | | [X] | | [X] | | [X] | | [X] | | [X] | | [X] |
| Cross over | | | | | | | | | | | | [X] | | | | | | | | |
| Study Completion | | | [X] | [X] | [X] | [X] | | [X] | | [X] | | [X] | | [X] | | [X] | | [X] | | X |

[X] Optional activity.

*For subjects consented prior to the EC approval of the revised consent, they may be reconsented at any study visit.

§As per the Intellis™ neurostimulator instructions for use. This may also include paresthesia testing.

Unscheduled visit: VAS, Adverse Event monitoring and medication to be collected

## Table 1b - Schedule of Study Activities for the Control arm (CMM)

| Assessment | Evaluation phase | | CMM Phase | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | Enrollment /Entry Criteria | Baseline | Phone Call | 1 Month Visit | Phone Call | 3 Month Visit | Phone Call | 6 Month Visit | Phone Call | 9 Month Visit | Phone Call | 12 Month Visit | Phone Call | 18 Month Visit | Phone Call | 24 Month Visit |
| Window | Might be combined into one visit, if all enrollment and entry criteria are fulfilled at time of baseline assessment | | 2-3 Weeks before 1 Month Visit | ± 15 d from Baseline | 2-3 Weeks before 3 Month Visit | ± 21 d from Baseline | 2-3 Weeks before 6 Month Visit | ± 31 d from Baseline | 2-3 Weeks before 9 Month Visit | ± 31 d from Baseline | 2-3 Weeks before 12 Month Visit | ± 45 d from Baseline | 2-3 Weeks before 18 Month Visit | ± 45 d from Baseline | 2-3 Weeks before 24 Month Visit | ± 60 d from Baseline |
| Informed Consent* | X | | | | | | | | | | | | | | | |
| Medication Usage | X | X | | X | | X | | X | | X | | X | | X | | X |
| Pain Intensity (VAS) | X | | | X | | X | | X | | X | | X | | X | | X |
| Eligibility criteria | X | | | | | | | | | | | | | | | |
| Pregnancy Test | [X] | | | | | | | | | | | | | | | |
| Medical/Surgical History | X | | | | | | | | | | | | | | | |
| [redacted] | | | | | | | | | | | | | | | | |
| Healthcare Utilization | | X | | X | | X | | X | | X | | X | | X | | X |
| Adverse Event Monitoring | X | X | | X | | X | | X | | X | | X | | X | | X |
| Cross over | | | | | | | | [X] | | | | | | | | |
| Study Completion | | | | [X] | | [X] | | [X] | | [X] | | [X] | | [X] | | X |

[X] Optional activity.
*For subjects consented prior to the EC approval of the revised consent, they may be reconsented at any study visit.
Unscheduled visit: VAS, Adverse Event monitoring and medication to be collected

### 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.

#### B.9.2.1 Primary Analyses

The *primary efficacy endpoint* will be evaluated with a Pearson Chi-square binomial test for superiority at the two-sided 0.05 alpha level.

$H_0$: The percentage of subjects (P) who achieve a 50% improvement in their back VAS pain score at 6 months in the Test group is the same as in the Control group.

$P_{Test} = P_{Control}$

$H_1$: The percentage of subjects (P) who achieve a 50% improvement in their back VAS pain score at 6 months in the Test group is superior to that in the Control group.

$P_{Test} \neq P_{Control}$

#### 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 superior 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 1, 3, 9, 12, 18 or 24 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 two-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 1, 3, 9, 12, 18, or 24 months in the Test group is less than or equal to that in the Control group.

  $P_{Test} = P_{Control}$

  $H_1$: 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.

  $P_{Test} \neq P_{Control}$

- Change in mean VAS will be evaluated with two-sample t-test of non-inferiority in means with a 0.65 cm non-inferiority margin at 6 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 worse than that of subjects in the Control group by more than 0.65 cm.

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

$H_1$: The change (C) in subject's VAS pain intensity score relative to baseline at the Primary Efficacy Assessment in the Test group is no more than 0.65 cm worse than the mean change from baseline in the control group.

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

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 cm. If the null hypothesis is successfully rejected for the non-inferiority test, a test for superiority of treatment to control will be performed based on a two-sided 0.05 alpha level.

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 results through 6 months will be based on the mITT population. For time points after 6 months where crossover is allowed, crossover subjects will be counted as failures (i.e. non-responders) for endpoints defined in terms of responders, carrying forward the baseline (pre-treatment). Sensitivity analysis of both secondary endpoints will also be performed to where crossover subjects are censored at the point of crossover.

- 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
    - Repeated measures models will be used to produce estimates for these two secondary endpoints, with graphical presentation of the responder rates and mean changes from baseline.

[redacted]

### 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 in the DTM™ SCS arm 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. In case of missing data Mixed Model for Repeated Measures (MMRM) will be used to produce estimates. 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 these analyses 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:***

The DTM™ SCS programming approach will be used with commercially available, US FDA approved, CE marked 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™ 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 other 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™ 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™ 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™ 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 as an aid in the management of chronic intractable pain of the trunk and/or limbs, stable intractable peripheral vascular disease, or stable intractable angina pectoris. The system has been approved by the US FDA, has CE mark certification, 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 30 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 US FDA approved, CE mark certified commercially available components will be used for the study and used in a maner that is consistent with the 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 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. 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.

*Labeling:* For this study, the Intellis™ System labeling will be consistent with CE marked labeling for commercial distribution in Europe.

### D.4. Any Anticipated Changes in the Device

There are no anticipated changes at this time.

### D.5. Device Accountability

No device accountability log will be used as this is a commercially available product.

## 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

The 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 (per latest ISO 141155 version), 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.

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, 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 the 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 ISO 14155 latest version, and the recommendations guiding physicians in biomedical research involving humans adopted by the 18$^{th}$ World Medical Assembly, Helsinki, Finland (1964 and later versions). The Investigator will conduct all aspects

of the study in accordance with all national, European Union 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 (or more if required) to their EC as per EC guidelines. The Investigator and/or Sponsor, as required by local regulations, are required to report in writing to the EC, 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 EC 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 severe adverse event (SAE) to the sponsor immediately of knowledge of the event and to the EC 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 EC 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 EC. Signed ICFs will be retained in the subject's study records at the clinical site.

The ICF will be in compliance with the requirements set forth in the Declaration of Helsinki and ISO 14155 latest version.

Subjects may be reimbursed for their participation in this study as referenced in the informed consent form (ICF) as per the applicable local regulations.

### 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 the Sponsor's approval, EC 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 the 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 EC **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 publicly registered in an ICMJE accredited register. Sponsor/Investigator Records and Reports will be maintained and provided in accordance to ISO 14155 latest version. No additional records or reports will be maintained.

### E. 8 Publication Policy

See site's clinical trial agreement (CTA) for the agreed publication policies.

## F. Appendices

### F. 1 Appendix I – Clinical Investigation Plan Signature Page

**Signature Page**

***Comparison of DTM™ SCS Therapy Combined with CMM to CMM Alone in the Treatment of Intractable Back Pain Subjects without previous history of Lumbar Spine Surgery***

DTM INT-2020PM2

**Principal Investigator Signature**

I have read this clinical investigation plan and agree to participate in the clinical investigation sponsored by SGX International. I agree to conduct this investigation according to the requirements of the clinical investigation plan and in accordance with the Declaration of Helsinki, ISO 14155 latest version, European and/or local regulations and conditions imposed by the reviewing Ethics Committee. I agree to supervise all Sub-Investigators at my site as well as the use of all of the devices at my institution and to ensure appropriate informed consent is obtained from all subjects prior to inclusion in this study.

| | |
|---|---|
| *Signature* | *Date* |
| *Printed name* | Principal Investigator<br>*Title* |

**Sponsor Signature**

**Confidentiality Statement**

All information concerning the study device supplied by SGX International in connection with this study, and not previously published, is considered confidential and proprietary information. This information includes the clinical investigation plan, subject informed consent and case report forms. This confidential information shall remain the sole property of SGX International, shall not be disclosed to others without prior written consent from SGX International and shall not be used except in the performance of this study.

The information developed during the conduct of this clinical study is also considered confidential and will be used by SGX International in connection with the development of the study device. This information may be disclosed as deemed necessary by SGX International.

The below-named individuals are authorized to sign this clinical investigation plan and its amendments.

| | |
|---|---|
| Signature | Date |
| Printed name | Vice President, Clinical<br>Title |

## F. 2 Appendix II – List of Abbreviations

| | |
|---|---|
| ADE | Adverse Device Effect |
| AE | Adverse Event |
| ASADE | Anticipated Serious Adverse Device Effect |
| CA | Competent Authorities |
| CIP | Clinical Investigation Plan |
| CRF | Case Report Form |
| DD | Device Deficiency |
| DMP | Data Management Plan |
| DTM | Differential Target Multiplexed |
| EC | Ethics Committee |
| EQ-5D-5L | European Quality of Life-5 Dimensions |
| ICF | Informed Consent Form |
| ID | Identification |
| ISO | International Organization for Standardization |
| MMRM | Mixed Model Repeated Measures |
| MP | Monitoring Plan |
| ODI | Oswestry Disability Index |
| PGIC | Patient Global Impression of Change |
| PI | Principal Investigator |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SCS | Spinal Cord Stimulation or Spinal Cord Stimulator |
| SD | Standard Deviation |
| SF-12 | Short-Form Health Survey |
| USADE | Unanticipated Serious Adverse Device Effect |
| VAS | Visual Analog Scale |
| WMA | World Medical Association |

## 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.