CLINICAL INVESTIGATIONAL PLAN

Stimgenics Open-Label, Post Market Study: A Clinical Trial to Study the Effects of Stimgenics Spinal Cord Stimulation (SGX-SCS) programs in treating Intractable Chronic Back Pain

Protocol Number:	SGEN-2018PM2
NCT Number	NCT03606187
Study Reference:	SGX-SCS RCT
Sponsor:	Stimgenics 2406 E. Empire St. Bloomington, IL 61704

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Date of Issue: Jan 2, 2019

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Study Synopsis

Study Title	Stimgenics Open-Label, Post Market Study: A Clinical Trial to Study the Effects of Stimgenics Spinal Cord Stimulation (SGX-SCS) programs in treating Intractable Chronic Back Pain
Protocol Number	SGEN-2018PM2
Study Device	The Intellis™ neurostimulator, a Spinal Cord Stimulation (SCS) device system manufactured and commercialized by Medtronic (Minneapolis, MN)
Study Purpose	The purpose of this investigational study is to study the effects of Stimgenics Spinal Cord Stimulation (SGX-SCS) in subjects with chronic, intractable pain of the trunk with lower limb pain, including unilateral or bilateral pain associated with the following conditions: failed back surgery syndrome, intractable low back pain and leg pain.
Study Design	This is an open-label prospective, randomized, controlled, multi-center study comparing SGX-SCS programming approach to Standard SCS programming approach. Subjects meeting study entrance criteria will be randomized in a 1:1 ratio to one of two study treatment groups: • Test treatment group with SGX-SCS programming approach • Control treatment group with Standard SCS programming approach Data at follow-up visits will be compared between the two treatment groups, and in reference to baseline assessments collected at the beginning of the study.
Study Size	Approximately 250 subjects will be enrolled at up to 15 clinical sites in the United States in order to include an estimated 125 subjects to the point of randomization and trial phase. This would allow at least 100 subjects (approximately 50% in each treatment arm) to complete the 3-month endpoint.
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Study Objective	The ***primary objective*** of this study is to evaluate the effectiveness of SGX-SCS in reducing back pain as compared to Standard SCS for the treatment of intractable chronic back pain.
Inclusion Criteria	A subject must MEET ALL of the following inclusion criteria: 1. Be a candidate for SCS system (trial and implant) per labeled indication (back and leg pain) 2. Has an average *back* pain intensity ≥ 5.0 cm on the 10.0 cm Visual Analog Scale (VAS) at the time of enrollment with moderate to severe chronic leg pain 3. 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. 4. Be willing and capable of subjective evaluation, read and understand English-written questionnaires, and read, understand and sign the written inform consent in English. 5. Be 18 years of age or older at the time of enrollment 6. Be on a stable pain medication regime, as determined by the study investigator, for at least 30 days prior to enrolling in this study 7. Be willing to not increase pain medications from baseline through the 3-Month Visit 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: 1. Has a medical, anatomical, and/or psychosocial condition that is contraindicated for commercially available Intellis™ SCS systems as determined by the Investigator 2. Be concurrently participating in another clinical study 3. Has an existing active implanted device such as a pacemaker, another SCS unit, peripheral nerve stimulator, and/or drug delivery pump, etc. 4. 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 5. Has mechanical spine instability as determined by the Investigator 6. 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 7. Has unresolved major issues of secondary gain (e.g., social, financial, legal), as determined by the investigator 8. Be pregnant (determined by urine testing unless female subject is surgically sterile or post-menopausal. If female, sexually active, and childbearing age, subject must be willing to use a reliable form of birth control.)
Primary Endpoint	The primary efficacy endpoint is the percentage of randomized subjects who respond (a decrease in back pain VAS by at least 50% compared to baseline) to SCS therapy at 3 months (non-inferiority analysis). Subjects who do not have a

	successful Trial Phase are considered failures (non-responders) toward the primary endpoint.

A. Purpose

A.1. Study Device

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

A.2. Purpose of the Investigation

The purpose of this investigational study is to study the effects of Stimgenics spinal cord stimulation (SGX-SCS) programs in subjects with chronic, intractable pain of the trunk with lower limb pain, including unilateral or bilateral pain associated with the following conditions: failed back syndrome, intractable low back pain and leg pain. This study is a post market, open-label, multi-center, prospective, randomized, controlled clinical trial that evaluates the treatment outcomes resulting from SGX-SCS programming approach and Standard SCS programming approach. Both programming approaches will be discussed in section B.1 of this Investigational Plan.

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

A.3. Study Size

Approximately 250 subjects will be enrolled at up to 15 clinical sites in the United States in order to include an estimated 125 subjects to the point of randomization and trial phase. This would allow at least 100 subjects (approximately 50% in each treatment arm) to complete the 3-month endpoint. Sample size estimates are discussed further in section B.5.5 of this Investigational Plan.

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B. Protocol

B.1. Rationale for Study

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

Conventional medical management, including medication and physical therapy, is often not adequate for treating chronic pain. Medication therapy based on opioids may also lead to addiction. Extensive use of opioid medications in the United States has led to the declaration of an epidemic crisis[3]. Furthermore, surgical interventions have also failed to remediate severe cases of neuropathies and intractable back pain for many patients. 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[4,5,6,7].

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

Standard SCS programming approach utilizes pulsed electric fields oscillating in the 40-250 Hz frequency range although up to 1,200 Hz is approved for use. The electric field stimulates neurons that induce a tingling sensation (paresthesia) that is steered by the clinician and patient to overlay with the targeted pain location by modifying the applied electric field. The concept behind Standard SCS is that the paresthesia induced by the applied oscillating electric field masks pain signals travelling to the brain. Standard SCS programming typically involves giving patients a few program groups, allowing patients to select the program group that suits them best. Each program group contains multiple programs that deliver, for a given pulse rate, different stimulation parameters (e.g. pulse width, amplitude) to same or different electrodes. This approach has been used to create better paresthesia patterns for the given patient's pain patterns or more tolerable paresthesia depending on patient's different positions or postures.

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

Stimgenics SCS (SGX-SCS) programming approach relies less on paresthesia pattern and programmed stimulation parameters will be set to levels that span above the perception threshold, yet well below the levels that could cause uncomfortable paresthesia. **SGX-SCS will use only programming parameters that are currently available on the device.**

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Stimgenics has completed a multicenter feasibility study (NCT03110601) in which SGX-SCS programming approach was evaluated during the required period for trialing SCS therapy. In this acute study 20 subjects were trialed with SGX-SCS and Standard SCS programming approaches. In terms of back pain relief, SGX-SCS programming approach provided a mean of 68% pain relief and Standard SCS programming approach provided a mean of 43% pain relief, which translates to SGX-SCS achieving 25% greater reduction than Standard SCS. Notably with SGX-SCS, 80% of subjects experienced 50% or better back pain relief, and 85% of the subjects preferred therapy received through SGX-SCS programming approach. The safety results were in line with expectations of previous SCS studies and were mostly resolved within a few days with minimal interventions. There was one serious adverse event, epidural abscess, which although uncommon, is well established as a potential risk in SCS trial and was not related to either programming approach. There were no unanticipated adverse events.

For this study, the study design is a post market, open-label, prospective, randomized, controlled multi-center study that will again evaluate SGX-SCS programming and Standard SCS programming for chronic back and leg pain sufferers. This scientifically sound study will provide more information on effectiveness of SGX-SCS programming approach.

B.2. Study Objectives

The ***primary objective*** of this study is to evaluate the effectiveness of SGX-SCS in reducing back pain as compared to Standard SCS for the treatment of intractable chronic back pain.

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

B.3. Selection of Study Population

B.3.1. Study Population

The intended study population is individuals suffering from chronic, intractable pain of the trunk and/or limbs associated with a number of conditions, including Failed Back Syndrome (FBS) and are candidates for commercially available SCS device systems.

B.3.2. Inclusion Criteria

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

1. Be a candidate for SCS system (trial and implant) per labeled indication (back and leg pain)
2. Has an average *back* pain intensity ≥ 5.0 cm on the 10.0 cm Visual Analog Scale (VAS) at the time of enrollment with moderate to severe chronic leg pain
3. 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.
4. Be willing and capable of subjective evaluation, read and understand English-written questionnaires, and read, understand and sign the written inform consent in English.
5. Be 18 years of age or older at the time of enrollment
6. Be on a stable pain medication regime, as determined by the study investigator, for at least 30 days prior to enrolling in this study
7. Be willing to not increase pain medications from baseline through the 3-Month Visit
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. Has a medical, anatomical, and/or psychosocial condition that is contraindicated for commercially available Intellis™ SCS systems as determined by the Investigator
2. Be concurrently participating in another clinical study
3. Has an existing active implanted device such as a pacemaker, another SCS unit, peripheral nerve stimulator, and/or drug delivery pump, etc.
4. 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
5. Has mechanical spine instability as determined by the Investigator

6. 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
7. Has unresolved major issues of secondary gain (e.g., social, financial, legal), as determined by the investigator
8. 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:

- Test treatment group with SGX-SCS programming approach
- Control treatment group with Standard SCS programming approach

B.5. Study Design

B.5.1. Overall Design

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

B.5.2. Bias Minimization

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

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

B.5.3. Comparison Groups

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

B.5.4. Blinding

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

B.5.5. Sample Size

Primary Endpoint Assessment occurs at the follow up visit 3 months after Device Activation. Based on the primary endpoint requirement, the estimated sample size of this study is at least 100 total subjects (at least 50 subjects in the SGX-SCS group and at least 50 subjects in Standard SCS group) who have passed screening requirements, have been randomized, and have completed the primary endpoint assessment.

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 125 subjects to the point of randomization and trial phase, approximately 250 subjects may need to be consented and enrolled to account for exclusions prior to randomization.

B.5.5.1 Sample size rationale and statistical power

The sample size estimate to determine primary endpoint is based on the primary objective of demonstrating non-inferiority of the test group to the control group. Established methods were followed in determining the non-inferiority criteria and the related sample size estimate

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

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

B.5.5.2 Overall Sample Size and Enrollment

Based on the primary endpoint requirement, a minimum of 50 subjects per treatment group are required (100 total). To account for a combined estimated attrition of 20% for subjects that do not complete the Trial Phase, and subjects that exit study before the 3-month primary endpoint visit, a total of 125 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 250 subjects would need to be enrolled in the study.

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

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

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B.6.2. Consent/Enrollment

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. Subjects will be assessed for pain intensity and disability.

B.6.3. Entry Criteria Evaluation (0-14 days from Enrollment)

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

B.6.4. Baseline

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

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

B.6.5. Randomization

Subsequent to completing Baseline assessments, qualifying subjects will be randomly assigned to either one of the two study treatment groups: SGX-SCS programming or Standard SCS programming (active comparator). Randomization will be stratified by gender and whether the subject has bilateral or unilateral leg pain at Baseline. Randomization will be done at each study site by randomly permuted blocks.

B.6.6. SCS Trial Phase

Subjects will undergo a Trial Phase with the randomly assigned treatment group. The Trial Phase will last up to 10 days. Percutaneous leads will be placed in the epidural space at a

vertebral level based on the subject's pain condition and pain pattern as described in the Physician Implant Manual. Stimulation will be delivered from an external neurostimulator (ENS).

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

Stimulation therapy will be as follows for each study arm:

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

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

B.6.7. End of Trial Assessment

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

Those who have a "successful Trial Phase" (defined as a 40% or greater pain reduction from Baseline in their back pain) will proceed to permanent implantation of a SCS system to evaluate the assigned therapy, and permanent implantation of the Intellis™ SCS system will be scheduled. A threshold of 40% for the Trial Phase was predetermined as the minimum pain reduction that warrants consideration of a permanent implant and an opportunity to achieve a 50% pain reduction as defined in the Individual Subject Success criterion (see Section B.7.3).)

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

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

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

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

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

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

B.6.10. Unscheduled Visits

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

B.6.11. Telephone Calls

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

B.6.12. 1 Month After Device Activation (± 10 days)

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

B.6.13. 3 Months After Device Activation (± 15 days)

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

B.6.14. 6 Months After Device Activation (± 30 days)

The follow-up visit 6 Months after Device Activation is the final scheduled study visit. Subjects will visit the study site where they will be assessed for pain, extent of disability, quality of life, Patient Global Impression of Change, and subject satisfaction. Paresthesia generated by the stimulator will be assessed. Programming adjustments may be made, as needed. Subjects will also be assessed for possible adverse events and medication usage. If there are no ongoing study related adverse events, the subject will complete the study at this visit. In situations where there is an ongoing study related adverse event, subjects will be followed until resolution of that adverse event or determination that the subject's condition is stable, at which point the Study Completion Clinical Research Form (eCRF) should be completed.

B.6.15. 12 Months After Device Activation (± 30 days)

Subjects will be offered an additional visit at 12 months after device activation. The visit will consist of the same assessments as the 3 and 6 month visits. Subjects will visit the study site where they will be assessed for pain, extent of disability, quality of life, Patient Global Impression of Change, and subject satisfaction. Paresthesia generated by the stimulator will be assessed. Programming adjustments may be made, as needed. Subjects will also be assessed for possible adverse events and medication usage. 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.

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

monitoring of the subject will be the responsibility of the subject's personal physician, as dictated by reasonable medical care.

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B.6.17. Device Explant

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

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

B.6.18. 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.

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B.6.20. Study Suspension and Termination

Subjects will be considered to have completed all study requirements following the completion of the follow up visit 6 Months after Device Activation. Each clinical site will be considered to have completed study requirements at the end of the required monitored close out visit. The study will be considered 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 IRB.

Stimgenics, the Investigators, or the IRB(s) may suspend or terminate the study early at any time. If the study is suspended or terminated prematurely, all subjects that are still enrolled will be terminated from the study. A Study Completion eCRF will be completed

noting that the study has been terminated. If there is an ongoing adverse event related to the device or treatment, the subject will be followed until resolution of the adverse event or determination that the adverse event is not likely to change.

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

Stimgenics 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. Stimgenics will notify Investigators and IRBs in writing in the event of study termination.

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

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

B.7. Study Endpoints

B.7.1. Definition of Analysis Populations

- Intent to Treat (ITT): All randomized subjects.
- Modified Intent to Treat (mITT): All randomized subjects who complete the Trial Phase.

[redacted]

B.7.2. Effectiveness Assessment Definitions

- Primary Effectiveness Assessment: For subjects who have a successful Trial Phase and receive a permanent implant, the Primary Efficacy Assessment occurs at the follow up visit 3 months after Device Activation. For subjects who do not have a successful Trial Phase, the Primary Efficacy Assessment occurs at the end of the Trial Phase.

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B.7.3. Primary Endpoint

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

- ***Individual Responder*:** A decrease in back pain VAS by at least 50% at 3 months Post-Permanent Device Activation as compared with Baseline.

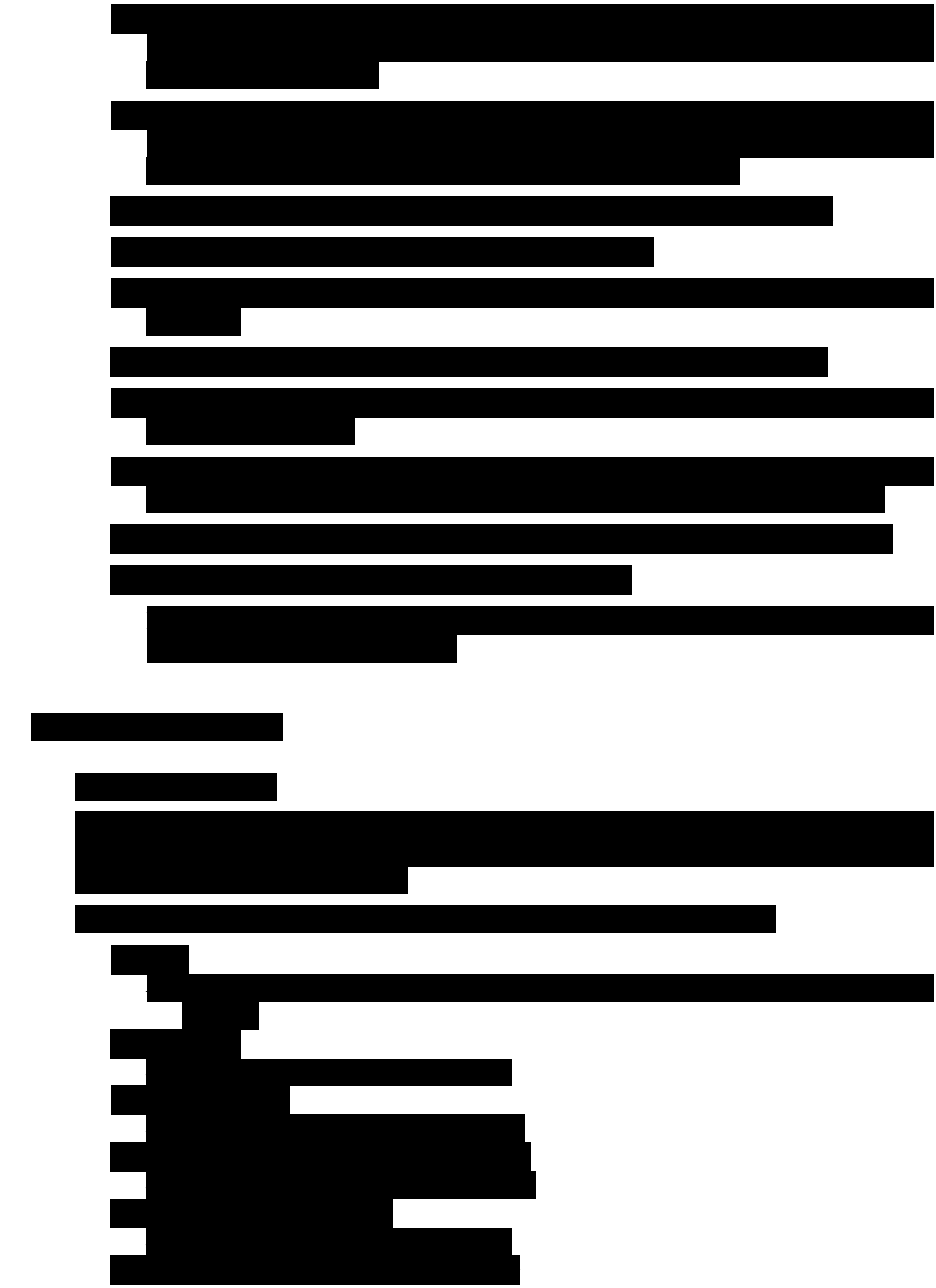
***Overall Study Success*:** The percentage of Individual Responders in the test group is shown to be statistically non-inferior to the percentage in the control group.

B.7.4. Secondary Endpoints

The following secondary endpoints will be evaluated:

- Comparison of the percentage of Individual Responders between the test and control groups in a statistical test of superiority
- Comparison of change from Baseline in back pain score (VAS) determined at the 3-month visit after device activation, between test and control in a statistical test of non-inferiority. This is calculated as: Change from Baseline in Back Pain VAS = 3-Month 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.
- Comparison of Back Pain Treatment Success (responder rate), measured as subjects with at least a 50% reduction in Back Pain VAS, evaluated at 6 months after device activation, between test and control
- Comparison of mean change from Baseline in Back Pain VAS, evaluated at 6 months after device activation, between test and control
- Comparison of mean change from Baseline in disability as measured by Oswestry Disability Index (ODI), evaluated at 3 months after device activation between test and control
- Frequency of treatment emergent adverse events

[redacted]



[redacted]

[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 non-inferiority test for the primary effectiveness endpoint is statistically significant.

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

B.8.3. Safety

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

B.8.3.1 Definitions

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

For all adverse events, the Investigator will provide an assessment of the adverse event, its seriousness, treatment/intervention provided, relationship to the device/procedure, and resolution.

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

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

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

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

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

B.8.3.2 Reporting

All AEs and SAEs will be assessed and captured from enrollment through the completion of the study on the Adverse Event Case Report Form (AE-eCRF). AEs and SAEs will be reported as required by the IRB. However, as would be the common practice when using commercial medical devices, device -related AEs may be reported by the site (per their institutional policy) to the Customer Service or Technical Support of Medtronic as specified in the manufacturer's labeling/manuals.

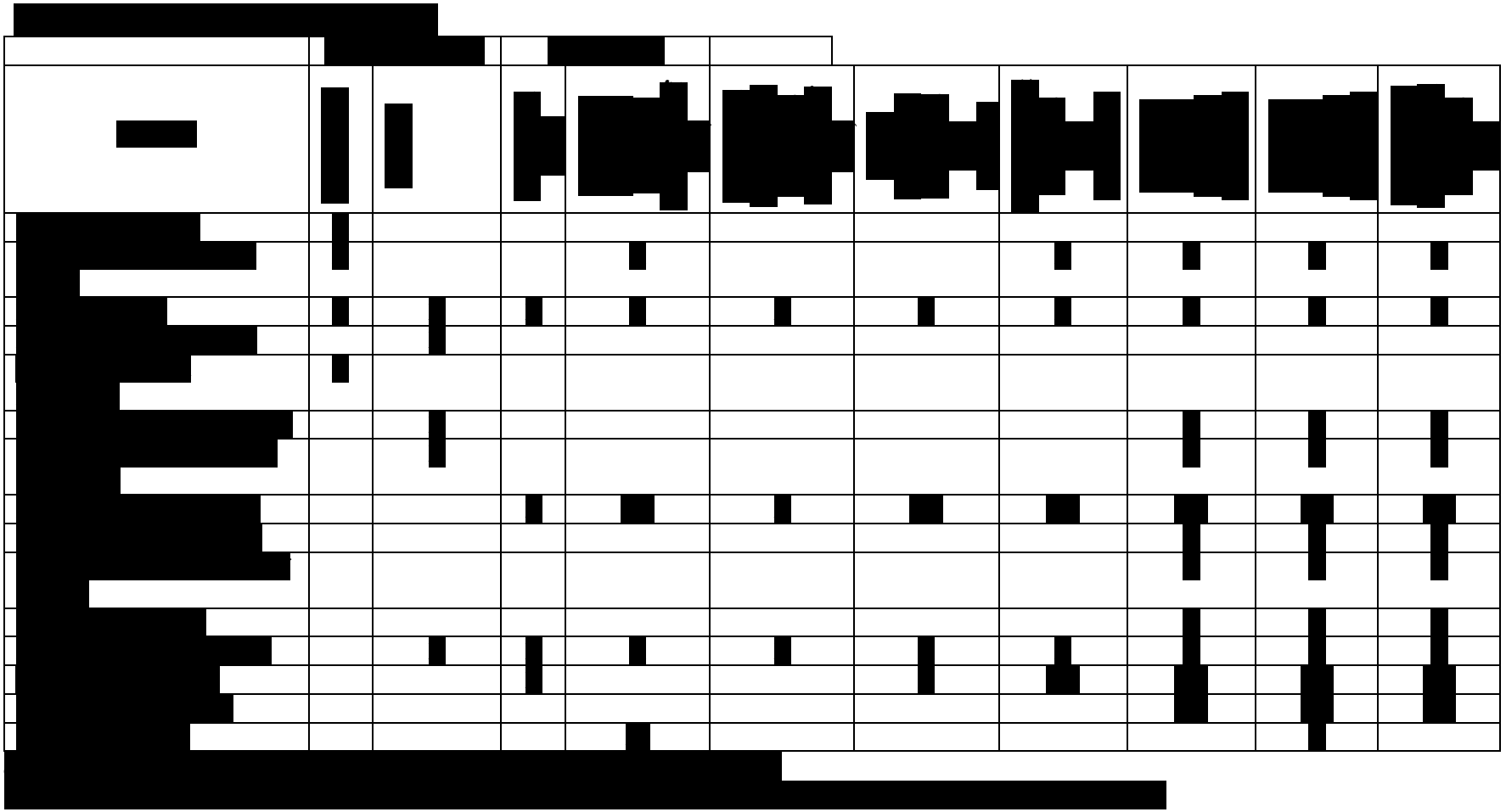
All Adverse Events (see list in section C.1.) reported during the study will document seriousness, treatment/intervention provided, relationship to the device/procedure, and resolution.

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

B.9. Data Collection and Analysis

B.9.1. Data Collection

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



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 Farrington-Manning binomial test for non-inferiority at the one-sided 0.05 alpha level.

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

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

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

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

A 10% margin has been previously used in a similar study.[8] Meeting the statistical threshold for this test based on a 10% margin should produce clinically acceptable results.

B.9.2.2 Secondary Analyses

The following *secondary endpoints* will be evaluated:

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

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

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

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

  $P_{Test} > P_{Control}$

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

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

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

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

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

The non-inferiority margin of 0.65 cm was selected based on a previous study of a similar therapy against traditional SCS.8 In that study, the experimental therapy showed a 4.9 point improvement while traditional SCS showed a 3.6 point improvement for a difference of 1.3 points. Taking 50% of this treatment effect yields the margin of 0.65.

The following secondary endpoints do not have an associated hypothesis, and no significance level will be assigned to statistical tests that may be performed.

- Comparison of Back Pain Treatment Success (responder rate), measured as subjects with at least a 50% reduction in Back Pain VAS, evaluated at 6-months after device activation, between test and control:
- Comparison of mean change from Baseline in Back Pain VAS, evaluated at 6-months after device activation, between test and control
- Comparison of mean change from Baseline in disability as measured by Oswestry Disability Index (ODI), evaluated at 3- months after device activation between test and controlFrequency of treatment emergent adverse events

  Data will be summarized in frequency distributions by study group of each adverse event (AE) type and by the percentages of subjects with one or more of each AE type.

[redacted]

[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 who do not have a successful Trial Phase, results from the Trial Phase will be utilized for the primary endpoint as described in Section B.7.2. Effectiveness Assessment Definitions. Any other data will be imputed via Multiple Imputation. Additionally, sensitivity analyses for missing data will be performed. [redacted]

C. Risk Analysis

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

Spinal Cord Stimulation (SCS) Risks:

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

There are known risks associated with the use of any SCS system. Known risks are associated with the implant procedure, the stimulation, the implanted device (not associated with

stimulation) and external devices such as the charger and remote control. These are typical of commercial SCS systems. Subjects will be informed of these anticipated risks in the study consent process.

Risks of Surgery

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

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

Spinal Cord Stimulation Risks

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

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

System Revision Risk

The Intellis AdaptiveStim Neurostimulator may require replacement in 9 years or earlier, regardless of the number of times the neurostimulator is recharged. It is possible that the system will need to be revised (explanted, replaced, or repositioned) earlier than 9 years. Possible reasons for revision/explant may include infection, malfunction, and migration of the system components. The risks associated with system revision are equivalent to the commercially available systems.

Pregnancy Risks

Pregnant women are not able to take part in this study. Female subjects must agree to not become pregnant during the study by using a medically acceptable method of birth control. If a subject becomes pregnant during this study, there may be risks to the unborn child that are not yet known. Subjects will be advised and encouraged to notify the study doctor immediately if they think they are or have become pregnant. Subjects that become pregnant during the study will be instructed to turn the neurostimulator "OFF" and will be exited from the study.

Radiographic Imaging

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

Study Risk Control Measures

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

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

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

C2. Minimization of Risks

The study will use commercially available Intellis™ SCS system within the approved indications for use. The risks associated with the use of SCS systems have been well characterized and are minimal compared to the side effects associated with most surgical procedures or the use of many medications used to treat chronic pain conditions. Additionally, SCS therapy is reversible since the SCS device may be turned off and the SCS system may be explanted at any time for any reason.

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 and Good Clinical Practice (GCP) in the conduct of clinical trials with human participants.

D. Description of the Device

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

D.1.1. Device System Overview

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

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

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

D.1.2. Device System Details

Only FDA approved, commercially available components will be used for the study.

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.

D.4. Any Anticipated Changes in the Device

There are no anticipated changes at this time.

E. Administrative Procedures

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

E.3. Study Conduct

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

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

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

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

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

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

E.4. Informed Consent Materials

Informed consent must be obtained from all subjects prior to study participation. Informed consent will be obtained by the Investigator or an Investigator-designated healthcare professional as per GCP guidelines. An informed consent form (ICF) will be provided to potential subjects for their private evaluation. If a subject consents to participate, the ICF must be signed by the subject or a legally authorized representative of the subject. Study ICF must be approved by the IRB. Signed ICFs will be retained in the subject's study records at the clinical site.

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

E.5 Investigators and Institutions

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

E.6. Amendments and Deviations

This investigational plan is to be followed by Investigators and all personnel involved in the clinical study. Any changes to the study covered by this investigational plan must be documented on a formal investigational plan amendment *prior to* implementation in the study. Changes to the investigational plan may be initiated by Stimgenics 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 Stimgenics' approval, IRB approval, and the Investigator's approval.

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

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

E.7. Additional Record and Reports

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

F. Appendices

A. Informed Consent Form

B. Case Report Forms

G. References

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[5] 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.

[6] 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.

[7] 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.

[8] 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.