CLINICAL STUDY PLAN

A Post-Market, Observational Clinical Study to Evaluate the Effects of DTM™ SCS programming in treating Intractable Chronic Upper Extremity Limb Pain

Protocol Number: DTM-PROC-2020PM3

NCT Number: 04466111

Protocol Reference: DTM SCS ULP

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Revision History:

Revision	Description	Date
1.0	Initial Release of Clinical Study Plan	20APR2020
2.0	Amendment of the Clinical Study Plan Addition of 6-month visit	02FEB2021
3.0	Amendment of the Clinical Study Plan Addition of 12-month visit	30JUL2021

PROTOCOL SYNOPSIS

Study Title	A Post-Market, Observational Clinical Study to Evaluate the Effects of DTM™ SCS programming in treating Intractable Chronic Upper Limb Pain
Protocol Number	DTM-PROC-2020PM3
Study Device	Intellis™ neurostimulator, a Spinal Cord Stimulation (SCS) device system manufactured and commercialized by Medtronic (Minneapolis, MN)
Study Purpose	The purpose of this observational clinical study is to evaluate the effectiveness and to collect safety data of DTM™ SCS programming on subjects with chronic, unilateral or bilateral upper limb pain.
Study Design	This is a post-market, open-label, prospective, multi-center, observational study evaluating upper limb pain relief with the DTM SCS programming approach. Data at follow-up visits will be compared to baseline assessments collected at the beginning of the study.
Study Size	Up to 90 subjects may be consented and screened in clinical sites in the United States. This would allow approximately 45 subjects to be implanted.
Study Duration	The expected total duration of this study is approximately 26months. Enrollment of subjects is expected to last 20 months. Subjects that have received the permanent implant will be followed up for 12 months after their device has been activated. A subject will likely be committed to the study for about 14 months. This consists of Baseline assessments, up to 10 days of trial stimulation and 12months of treatment following implantation and activation of the device. All current subjects or those who have completed their 6-month visit will be offered to return for an additional 12-month visit. This would increase their commitment to the study to 14 months.
Study Objective	The ***primary objective*** of this study is to evaluate the effectiveness of DTM SCS programming as a treatment for reducing intractable chronic pain of the upper limbs.

	The ***secondary objectives*** of this study are to further characterize the effectiveness of DTM SCS programming for the treatment of chronic pain of the upper limb and to collect safety data of DTM SCS programming.
Inclusion Criteria	A subject must MEET ALL of the following inclusion criteria: 1. Be diagnosed with chronic, intractable pain of the upper limb related to the cervical spine and/or neuropathic arm pain. 2. Be a candidate for SCS system (trial and implant) per labeled indication (upper limb pain due to one of the conditions listed in indications statement) 3. Considering daily activity and rest, has average upper limb pain intensity of ≥ 5 out of 10 cm on the Visual Analog Scale (VAS) at 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, including not increasing pain medications through the three month visit 9. Has adequate cognitive ability to use a patient programmer and recharger as determined by the Investigator
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. Have a medical condition or pain in other area(s), not intended to be treated with SCS, that could interfere with study procedures, as determined by the Investigator 3. Currently enrolled or planning to enroll in an interventional clinical study that could potentially confound the study results (co-enrollment in an interventional study is only allowed when documented pre-approval is obtained from the study manager or designee) 4. Has an existing active implanted device such as a pacemaker, another SCS unit, peripheral nerve stimulator, and/or drug delivery pump. 5. 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 6. Has significant cervical stenosis, as determined by the Investigator 7. Has facet spondylosis, as determined by the Investigator 8. Has mechanical spine instability, as determined by the Investigator 9. Has undergone, within 30 days prior to enrollment, an interventional procedure and/or surgery to treat upper limb pain, which is providing significant pain relief 10. Has unresolved major issues of secondary gain (e.g., social, financial, legal, such as worker compensation matters) 11. Be pregnant as 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. 12. Have evidence of an active disruptive psychological or psychiatric disorder as determined by a psychologist 13. Have a current diagnosis of a progressive neurological disease as determined by the Investigator 14. Have a current diagnosis of a coagulation disorder, bleeding diathesis, progressive peripheral vascular disease or uncontrolled diabetes mellitus 15. Have a condition that the Investigator determines would significantly increase perioperative risk 16. Any previous history of surgery on the posterior elements (laminectomy, posterior fusion) of the cervical spine 17. Have metastatic malignant disease or active local malignant disease 18. Have a life expectancy of less than 1 year 19. Have an active systemic or local infection 20. Have within 6 months of enrollment a significant untreated addiction to dependency producing medications or have been a substance abuser (including alcohol and illicit drugs)
Primary Endpoint	The primary efficacy endpoint is the percentage of implanted subjects who respond to DTM SCS therapy at 3-months after device activation. An individual responder is a subject that experiences at least a 50% decrease in upper limb pain relative to baseline assessment.

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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. 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 the commercially available Intellis™ neurostimulator and compatible SCS system components from Medtronic using stimulation parameters within the specifications approved for use in the approved indications. The study will stimulate the cervical dorsal columns of the spinal cord. Section D of this Clinical Study Plan provides detailed description of Intellis™ neurostimulator.

A.2. PURPOSE OF THE INVESTIGATION

The purpose of this post-market, observation study is to characterize the effectiveness and collect safety data of DTM SCS programming on subjects with chronic, intractable unilateral or bilateral pain of the upper limbs. This study is an observational, open-label, multi-center, prospective evaluation of treatment outcomes resulting from the DTM SCS programming approach relative to pretreatment measurements. The DTM SCS programming approach will be discussed in section B.1 of this Clinical Study Plan.

This investigation will utilize a commercially available SCS system (Intellis™ neurostimulator and compatible SCS components) as is, without any modification, and using FDA-approved parameters. Outcomes will be assessed via standardized tests.

A.3. STUDY SIZE

Approximately 45 subjects are expected to complete the 3-month endpoint of the study. Up to 90 subjects may be consented to participate at clinical sites in the United States. A sample size estimate is discussed further in section B.5.5 of this Clinical Study Plan.

A.4. DURATION OF THE INVESTIGATION

The expected total duration of this study is approximately 26 months. Enrollment of subjects is expected to last 20 months. Subjects that have received the permanent implant will be followed up for 12 months after their device has been activated. A subject will likely be committed to the study for about 14 months. This consists of Baseline assessments, up to 10 days of trial stimulation, and 12 months of treatment following implantation and activation of the device. All current subjects or those who have completed their 6-month visit will be offered to return for an additional 12-month visit. This would increase their commitment to the study to 14 months.

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]. Low back pain, neck pain and limb pain are among the most prevalent pain conditions worldwide, all of them ranked in the top 10 for the most disabling conditions.[3]

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[4]. Furthermore, surgical interventions have also failed to remediate severe cases of neuropathies and intractable 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. It is currently indicated for the treatment of intractable chronic pain of the trunk and/or limbs. 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[5,6,7,8]. 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.

The conventional programming approach in SCS utilizes pulsed electric fields oscillating in the 40-250 Hz frequency range. The electric field induces a stimulation pattern (paresthesia), which is steered by the clinician and patient to overlay with the targeted pain location by modifying the duration (pulse width) and intensity of the applied electric field. The concept behind this programming approach is that the stimulation pattern induced by the electric field masks pain signals travelling to the brain. Although proven effective for the treatment of intractable chronic pain of the upper limbs by some practitioners, the variability of the paresthesia sensation, including uncomfortable sensations, due to the motion of the neck

have limited the utilization of the conventional SCS programming approach.

The DTM SCS programming approach relies on stimulation parameters that can be set by the clinician and patient to levels that avoid uncomfortable stimulation upon motion of the neck, while providing pain relief on the affected limb(s). DTM SCS programming will use stimulation parameters that are currently available in the device to be used in this study.

In a given therapy group, DTM SCS will provide programs with different pulse rates, pulse widths and intensities for the goal of better pain relief. For example, starting parameters may be a combination of a program with 50 Hz pulses with a duration of up to 200 microseconds and a program with 300 Hz pulsed with a pulse duration of up to 200 microseconds, while intensities will be custom adjusted by the patient for optimal pain relief and therapy comfort. It is anticipated that the low pulse amplitudes used in the DTM SCS programming approach would result in patients experiencing less uncomfortable stimulation events with the motion of the neck and upper limbs than what they might experience with a conventional SCS programming approach while providing effective pain relief. Should DTM SCS programming be shown to be effective and safe in this observational study, DTM SCS may offer an alternative approach that will help thousands of chronic pain sufferers make substantial improvement in pain relief, reduction in disabilities, and reduce the likelihood of uncomfortable paresthesia.

The study design is a post-market, open-label, prospective, observational multi-center study that will evaluate DTM SCS for chronic upper limb pain sufferers. Subjects participating in the study will trial SCS according to standard practice. Those who experience a successful trial will be eligible to get a permanently implanted device and evaluate the primary effectiveness point.

B.2. STUDY OBJECTIVES

The ***primary objective*** of this study is to characterize the application of DTM SCS programming as a treatment for reducing intractable chronic pain of the upper limbs.

The ***secondary objectives*** of this study are to further characterize the effectiveness of DTM SCS programming for the treatment of chronic pain of the upper limbs and to collect safety data of DTM SCS programming.

B.3. SELECTION OF STUDY POPULATION

B.3.1. STUDY POPULATION

The intended study population is individuals who have been diagnosed with chronic, intractable pain of the upper limbs associated with a number of conditions, and who the Principal Investigator deems is an appropriate candidate for SCS therapy as required for this study in this Clinical Study Plan.

B.3.2. INCLUSION CRITERIA

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

1. Be diagnosed with chronic, intractable pain of the upper limbs related to the cervical spine and/or neuropathic arm pain.
2. Be a candidate for SCS system (trial and implant) per labeled indication (upper limb pain due to one of the conditions listed in indications statement)
3. Considering daily activity and rest, has average upper limb pain intensity of ≥ 5 out of 10 cm on the Visual Analog Scale (VAS) at 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, including not increasing pain medications through the three months visit
9. Has adequate cognitive ability to use a patient programmer and recharger as determined by the Investigator

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. Have a medical condition or pain in other area(s), not intended to be treated with SCS, that could interfere with study procedures, as determined by the Investigator
3. Currently enrolled or planning to enroll in an interventional clinical study that could potentially confound the study results (co-enrollment in an interventional

study is only allowed when documented pre-approval is obtained from the study manager or designee)

4. Has an existing active implanted device such as a pacemaker, another SCS unit, peripheral nerve stimulator, and/or drug delivery pump.
5. 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
6. Has significant cervical stenosis, as determined by the Investigator
7. Has facet spondylosis, as determined by the Investigator
8. Has mechanical spine instability, as determined by the Investigator
9. Has undergone, within 30 days prior to enrollment, an interventional procedure and/or surgery to treat upper limb pain, which is providing significant pain relief
10. Has unresolved major issues of secondary gain (e.g., social, financial, legal, such as worker compensation matters)
11. Be pregnant as 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.
12. Have evidence of an active disruptive psychological or psychiatric disorder as determined by a psychologist
13. Have a current diagnosis of a progressive neurological disease as determined by the Investigator
14. Have a current diagnosis of a coagulation disorder, bleeding diathesis, progressive peripheral vascular disease or uncontrolled diabetes mellitus
15. Have a condition that the Investigator determines would significantly increase perioperative risk
16. Any previous history of surgery on the posterior elements (laminectomy, posterior fusion) of the cervical spine
17. Have metastatic malignant disease or active local malignant disease
18. Have a life expectancy of less than 1 year
19. Have an active systemic or local infection
20. Have within 6 months of enrollment a significant untreated addiction to dependency producing medications or have been a substance abuser (including alcohol and illicit drugs)

B.4. TREATMENT GROUPS

Subjects meeting the study eligibility criteria will be treated with DTM SCS programming approach. A trial period of up to ten days, which is the standard of care in SCS, will serve to determine if a subject is eligible to undergo permanent implantation of the SCS system.

B.5. STUDY DESIGN

B.5.1. OVERALL DESIGN

This is a post-market, prospective, open-label, observational, multi-center study designed to evaluate the effectiveness and to collect safety data of the DTM SCS programming approach in subjects with chronic, intractable pain of the upper limbs. Data at follow-up visits will be compared to baseline data collected at the beginning of the study.

B.5.2. BIAS MINIMIZATION

This Clinical Study Plan and its associated documentation have been designed to minimize potential sources of bias. Each Investigator's qualification for meeting the requirements of this Clinical Study plan will be reviewed prior to their participation in this investigation.

B.5.3. BLINDING

This open label, single-arm study is not blinded. All subjects eligible to participate will be trialed with commercially available Intellis trialing SCS system. Those who successfully trial DTM SCS programming may be implanted with a commercially available Intellis SCS system.

B.5.4. SAMPLE SIZE

Primary Endpoint Assessment occurs at the 3-months follow up visit after activation of the implanted device. There is no statistical hypothesis to be evaluated in this study, but it is believed that approximately 45 subjects will be required to evaluate the effectiveness and to collect additional safety data of DTM SCS programming at the primary endpoint. Based on this requirement, the estimated sample size of this study is up to 90 consented subjects.,

B.5.4.1 SAMPLE SIZE RATIONALE

There is no statistical hypothesis to be evaluated in this study. It is believed that approximately 45 subjects permanently implanted subjects will be sufficient to evaluate the effectiveness and to collect additional safety data of the DTM SCS programming in the target population at the primary endpoint.

Up to 90 subjects will be consented to participate in the eligibility screening process. Those who do not meet all the inclusion criteria and none of the exclusion criteria will be considered screen failures and will not move into the trialing phase. It is estimated that approximately 55 subjects will be trialed. Only subjects with a successful trial phase will be eligible to move into permanent implantation of the device.

B.5.5. STUDY DURATION

The expected total duration of this study is approximately 26 months. Enrollment of subjects is expected to last 20 months. Subjects that have received the permanent implant will be followed up for 12 months after their device has been activated. A subject will likely be committed to the study for about 14 months. This consists of Baseline assessments, up to 10 days of trial stimulation, and 12 months of treatment following implantation and activation of the device. All current subjects or those who have completed their 6-month visit will be offered to return for an additional 12-month visit. This would increase their commitment to the study to 14 months

B.6. ENROLLMENT, ASSESSMENTS, 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 Clinical Study 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. Advertisements of the study may be used for recruitment purposes, upon approval of the patient recruitment materials by the study IRB(s). An informed consent form (ICF) will be given to the potential subject for private evaluation. The Investigator or Study Clinical Staff will be available to respond to

any questions the potential subject may have during evaluation of the ICF. Potential study subjects willing to participate in the study will visit the study site for providing written consent and for evaluation of eligibility to participate based on inclusion and exclusion criteria. Once a consented subject is deemed qualified to participate in the study, baseline assessments will occur followed by scheduling of the trial stimulation phase.

Subjects who complete a successful DTM SCS trial phase will be scheduled to receive a permanent implant of the SCS system and will undergo 3 months of therapy with assessments at 1, 3, 6 and 12 months after the activation of the implanted device. All current subjects or those who have completed their 6-month visit will be offered to return for an additional 12-month visit. This would increase their commitment to the study to 14 months Baseline assessments will include measures for pain intensity, use of medication, and extent of disability.

Subjects will undergo a Trial Phase lasting up to 10 days to determine subject's response to DTM SCS. Commercially available stimulation leads and a commercially available external neurostimulator (ENS) will be used during the Trial Phase. Subjects will evaluate DTM SCS therapy based on pain intensity under optimal stimulation parameters within the specifications of the device. Subjects who have a "successful Trial Phase" (defined as a 40% or greater pain reduction from Baseline in their upper limb pain) will proceed to permanent implantation of a SCS system.

The implanted INS will be activated within 14 days after surgical procedure and SCS therapy will be evaluated for the next 12 months. Activation of the device marks the initial time point for effectiveness evaluation of the study therapy after implantation. Assessments of pain intensity, use of medication and study-related adverse events will be made through the 12 month following Device Activation. Additionally, a 3, 6 and 12months after Device Activation, subjects will also be assessed for extent of disability, Patient Global Impression of Change, subject satisfaction and paresthesia. All current subjects or those who have completed their 6-month visit will be offered to return for an additional 12-month visit. This would increase their commitment to the study to 14 months Figure 1 summarizes the sequence of study-related assessments, procedures, and activities.

B.6.2. PRE-SCREENING/CONSENT/ENROLLMENT

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

Written informed consent for participation in the study must be obtained from subjects

before initiation of any study-related activities, 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. ELIGIBILITY CRITERIA EVALUATION

The eligibility of subjects who have consented participation will be assessed based on the inclusion and exclusion criteria. Study subjects must meet all of the study inclusion criteria and none of the study exclusion criteria to be eligible. Assessments for eligibility include average pain intensity (which will be used as Baseline pain intensity), other pain intensity (such as secondary pain or related pain), 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 considered screen failures and discontinued from the study.

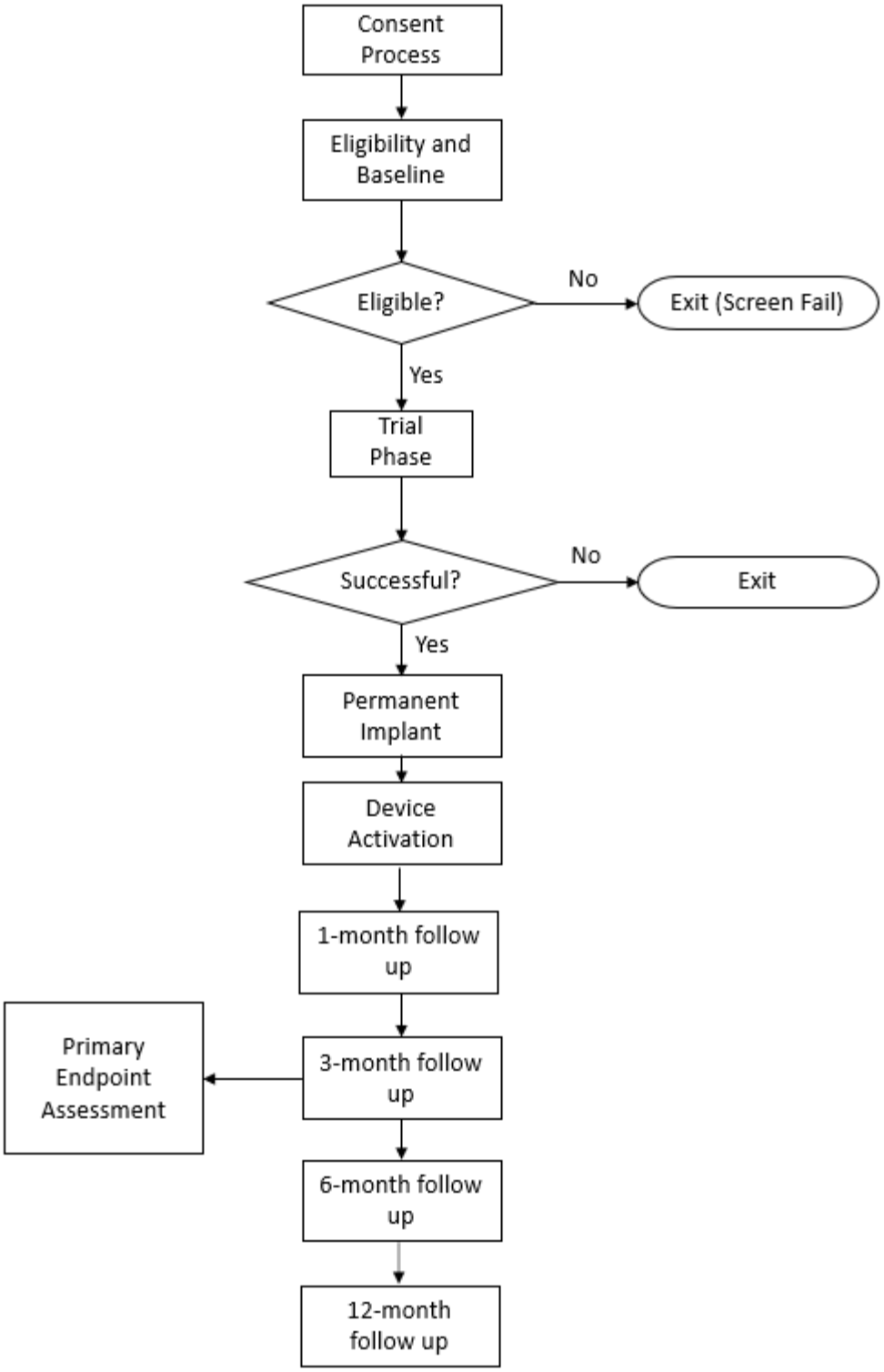

Figure 1. A flowchart of the study.

B.6.4. BASELINE

A subject that is eligible to continue into the trial phase according to the inclusion and exclusion criteria will be requested to fill out standard questionnaires that will assess extent of disability and use of medications. The medical and surgical history of the subject will also be collected. At this visit and subsequent visits, the subject will be assessed for study-related adverse events, medication usage and will 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. SCS TRIAL PHASE

Subjects will undergo a Trial Phase with DTM SCS programming. 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 Manuals. Stimulation will be delivered from an external neurostimulator (ENS).

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

Stimulation therapy will be as follows:

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

Following the standard of care of SCS, 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 40% self-reported pain reduction from baseline is achieved or until conclusion of the trial phase (no more than 10 days). Subjects will be assessed for study-related adverse events and medication usage during the duration of the Trial Phase.

B.6.6. 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 study-related adverse events and medication usage.

Subjects who have a "successful Trial Phase" (defined as a 40% or greater pain reduction from Baseline in the upper limbs pain and the subject would like to move forward to the implant phase) will proceed to permanent implantation of a SCS system to evaluate DTM SCS programming. 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).

Subjects who did not achieve 40% or greater pain reduction in upper limb and do not receive permanent implantation will exit the study after being followed up for two weeks after removal of the leads to assess study-related adverse events.

B.6.7. PERMANENT DEVICE IMPLANT (0-60 DAYS FROM END OF SUCCESSFUL TRIAL PHASE)

As described in section B.6.6, subjects who underwent a successful trial of DTM 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 Physician Implant Manuals. The implantable neurostimulator (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. The standard practice of the study site will be followed for prophylactic pre-surgery antibiotics. Subjects will be assessed for study-related adverse events and medication usage.

B.6.8. 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 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 study-related adverse events and medication usage.

B.6.9. UNSCHEDULED VISITS

Unscheduled visits may occur at any time during the study for the assessment of possible study-related adverse events, changes in pain medication, and programming adjustments. Each unscheduled visit will be documented and recorded in the corresponding case report form (CRF).

B.6.10. 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.6.11. 1 MONTH AFTER DEVICE ACTIVATION (± 15 DAYS)

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

B.6.12. 3 MONTHS AFTER DEVICE ACTIVATION (± 21 DAYS)

Subjects will visit the study site where they will be assessed for pain, other pain (if applicable), extent of disability, Patient Global Impression of Change, and subject satisfaction. Paresthesia generated by the stimulator will be assessed. Programming adjustments may be made, as needed. Anterior-posterior (AP) and lateral X-ray imaging will be done. Subjects will also be assessed for possible study-related 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 CRF should be completed.

B.6.13. 6 MONTHS AFTER DEVICE ACTIVATION (± 31 DAYS)

. The 6 Months visit will consist of the same assessments as the 3-month visit except the anterior-posterior (AP) and lateral X-ray imaging is optional. 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.

However, all subjects who remain implanted at the time of Study Completion will be offered to return for an additional visit 12-months after device activation.

Following the last scheduled study visit, subjects will be followed by their pain physician 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.6.14. 12 MONTHS AFTER DEVICE ACTIVATION (± 31 DAYS)

Subjects will be offered an optional visit at 12 months after device activation. This visit will consist of the same assessments as the 6-month 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. 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.

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.6.15 OTHER ASSESSMENTS AND INFORMATION

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

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

Additional information on Medication Usage:

- The Investigator will instruct all subjects to take the Baseline doses of pain medication until the 3-Month Visit. However, after Device Activation Visit, the Investigator may reduce the dose of pain medication if the subject is benefitting greatly from DTM SCS therapy and not benefitting from Baseline dose pain medication.
    - Subjects should not fluctuate medication usage nor dosages even if the dose is at or below Baseline doses. The Investigator/Study staffwill instruct all subjects to maintain stable dosing of medication for at least two weeks prior to scheduled follow-up visits.
- Following trial and permanent implants, the clinical site's standard practice for prophylactic pre-surgery antibiotics and post-surgery pain medications will be followed. Investigators/Study staff will instruct subjects not to change usage of any other concomitant pain medications.

Remote data collection from the subjects is allowed. This should be evaluated on a case by case basis, pending Investigator's approval based on safety and clinical condition. Subjects who are not demonstrating study compliance, e.g. not returning phone calls, not charging device or turning the device off should not be mailed study questionnaires until they demonstrate compliance with the study. The site should continue to contact the subject and ensure compliance before mailing the questionnaires. The communications will be documented in the source worksheets. Remote visits would apply to any visit that could be conducted remotely without the subject being present, including remote programming, if available. Procedural visits (trial and IPG) and any unscheduled visits required for study-related adverse events would continue to be performed in office where possible.

- Visit windows remain in place and should be maintained as much as possible. Subjects should be contacted via phone to collect 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 is was completed via phone.
- If by email: the site staff should send the study questionnaires. Subjects can either print and manually complete or complete the forms electronically.
- If manually completed (printed): the subject will be instructed to initial and date each page and scan and email or mail the responses back to the site.
- If the forms are completed electronically: the subject will be instructed to complete the questionnaires and return the responses to the site as soon as possible, ideally, within 3 business days.

- If the questionnaires are sent in hard copy by mail: the subject 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.

B.6.16. 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 manufacturer of the device for returning the explanted device and/or lead(s) as well as the accessories (charger, patient remote control).

B.6.17. EARLY SUBJECT WITHDRAWAL

Although efforts will be made by Investigators and study staff to encourage eligible 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 DTM SCS programming, the Investigator will attempt to improve therapy during a study visit. When a subject is withdrawn early from the study, a Study Termination CRF 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 a study-related adverse event, subjects will be followed until resolution of the adverse event or determination that the adverse event is not likely to change.

B.6.18. STUDY COMPLETION

All subjects enrolled in the study are expected to complete all scheduled visits through the

follow up visit 12 Months after Device Activation. However, all subjects who remain implanted at the time of Study Completion will be offered to return for an additional visit 12-months after device activation. A Study Completion CRF should be completed at the end of this visit unless they decide to remain in the study. If the subject decides to decline the additional 12-month visit and 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.

Subjects who decide to complete the 12-month visit would also be followed equivalently in cases of ongoing study related adverse events.

B.6.19. STUDY SUSPENSION AND TERMINATION

Subjects will be considered to have completed all study requirements following the completion of the follow up visit 3 Months after Device Activation. All subjects who remain implanted at the time of Study Completion will be offered to return for an additional 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 Clinical Study 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.

The Sponsor, 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 CRF will be completed noting that the study has been terminated. If there is an ongoing study-related adverse event, 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.

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 IRBs 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 CRFs in a timely manner
- Failure to report study-related serious adverse events (SAEs) or unanticipated adverse device events (UADEs) 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

All subjects who receive a permanent SCS system implant and complete the study without any major protocol deviations (that would render their data unevaluable).

B.7.2. EFFECTIVENESS ASSESSMENT DEFINITIONS

Primary Effectiveness Assessment: For subjects who have a successful Trial Phase and receive a permanent implant, the Primary Effectiveness Assessment occurs at the follow up visit 3 months after Device Activation.

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.

The primary effectiveness endpoint is the percentage of implanted subjects who respond to DTM SCS therapy at 3-months after device activation.

An Individual Responder is a subject that reports a decrease in upper limb pain VAS score by at least 50% at 3 months after activation of the permanent SCS system (Device Activation) as compared with Baseline measurement.

B.7.4. SECONDARY ENDPOINTS

The following secondary endpoints will be evaluated:

- Change from Baseline in upper limb pain mean VAS score determined at the 3-month visit after device activation. This is calculated as: Change from Baseline in Upper Extremities Pain VAS = 3-Month Visit Pain VAS – Baseline Pain VAS. A negative result reflects a decrease in Pain VAS score, while a positive result reflects an increase in Pain VAS score.
- Change from Baseline in extend of disability as measured by mean Pain Disability Index (PDI), evaluated at 3 months after device activation.
- Frequency of treatment emergent adverse events.

B.7.5. ADDITIONAL DATA COLLECTION

The following will also be collected:

- Comparison of mean change from Baseline in upper limb pain mean VAS score evaluated at 1, 3, 6 & 12months after device activation.
- Subject Satisfaction, evaluated at 3, 6 & 12months after device activation.
- Patient Global Impression of Change, evaluated at 3, 6 & 12 months after device activation.
- Quality of paresthesia at 3, 6 & 12 months.
- Comparison of mean change from baseline in other pain mean VAS score evaluated at 3, 6 & 12- months after device activation (if available)
- Activity level based on Intellis^{TM} Adaptive-Stim data log.

B.8. EVALUATION CRITERIA

B.8.1. EFFECTIVENESS

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

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

- Pain
- Visual Analog Scale (VAS, 10 cm) at Baseline, End of Trial Phase, Months 1, 3, 6 and12 monthsDisability
  Pain Disability Questionnaire at 3, 6 and 12 months
- Impression of Change in Quality of Life
  Patient Global Impression of Change at 3, 6 and 12 months
- Satisfaction with Therapy
  Subject Satisfaction Questionnaire at 3, 6 and 12 months
- Paresthesia generated by the stimulation
  Paresthesia Questionnaire at 3, 6 and 12 months

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

B.8.3. SAFETY

Safety will be assessed by characterizing study-related 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 the 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. Study-related is defined as relating to device, procedure or therapy.

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

As the effectiveness measure in this study is upper limb pain, upper limb 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 study pain-related adverse events during the study.

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

An **unanticipated adverse device event** (UADE) is a serious adverse event that was not previously identified in nature, severity, or degree of incidence in the Clinical Study Plan, or any unanticipated serious problem associated with a device that related to the rights, safety, or welfare of subjects.

Known adverse events related to the device, procedure or therapy are listed in the section C. (Risk Analysis) of this Clinical Study Plan.

B.8.3.2 REPORTING

Reported AEs, SAEs and UADEs will be assessed and captured from enrollment through the completion of the study on the Adverse Event Source Worksheet. Study-related is defined as relating to the device, procedure or therapy. The assessment/evaluation can be performed initially by a designee, but the Investigator will make the final determination.

Only adverse events that are evaluated by the Investigator to be study-related will be captured on the CRF.

All study-related adverse events will document seriousness, severity, treatment/intervention provided, relationship to the device/procedure/therapy, and resolution.

AEs and SAEs will be reported as required by the IRB.

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.

Data Monitoring Committee will not be used as this is a post-market open label study and will adhere to all IRB reporting requirements and the device manufacturer’s reporting requirements.

B.9. DATA COLLECTION AND ANALYSIS

B.9.1. DATA COLLECTION

Study data will be collected using paper CRFs. Each data field is expected to have a verifiable source document. Subject confidentiality will be maintained, and each subject will be identified by the assigned study subject number. Subject names will not be published. Data collection is summarized in Table 1.

B.9.2. STATISTICAL ANALYSIS

There are no formal hypotheses evaluated in this study. All baseline and outcome data will be reported using summary statistical methods. 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.

Table 1. Schedule of Study Activities

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

[X] Optional activity.

a) For subjects that do not have a successful Trial Phase.

b) Some subjects may need to be reconsented to complete these visits.

c) Some subjects were originally consented to complete the study at the 3 or 6 month visit and may not consent for additional visit.

C. RISK ANALYSIS

C.1. DESCRIPTION AND ANALYSIS OF ALL INCREASED RISKS TO SUBJECTS

DTM SCS programming approach will be used with a commercially available, FDA approved, Intellis™ SCS system, with parameters within the specifications for the indicated use. Anticipated potential adverse events resulting from the study are expected to be in line with adverse events already documented for SCS using a conventional 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 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 maybe 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 upper limbs, pain in these areas does not need to be reported as an adverse event unless it meets the definition of a serious adverse event. However, Investigators may, at their discretion, report any other pain-related adverse events during the study.

C2. MINIMIZATION OF RISKS

Neurostimulation therapies, such as SCS, are used as an aid in the management of chronic, intractable pain that cannot be effectively managed with medications and/or other conservative treatments alone. Patients considered for neurostimulation therapy have typically had pain of long duration and have failed multiple therapeutic paths.
Medtronic has carefully designed and tested the Intellis™ AdaptiveStim Neurostimulation Systems to ensure the safety and performance for the treatment of chronic, intractable pain. Medtronic has completed an extensive risk analysis to ensure the identification of potential hazards and subsequent mitigation of these hazards to eliminate them entirely or reduce them to an acceptable level.
The risks associated with the surgical implantation of the device, device use, and device failures are the same as those observed for commercially available SCS devices. With an existing pre-market application approval for the commercially available Intellis™ AdaptiveStim Neurostimulation Systems, an established safety profile of probable benefit outweighing risk already exists for SCS Therapy for chronic back and/or leg pain. In most cases implantation of SCS is a reversible procedure and the system can be turned off or removed. Moreover, stimulation parameters are adjustable to minimize or reverse complications and maximize therapeutic effects. System output and programming parameters used with the proposed stimulation parameters are within the range of the commercially available Intellis AdaptiveStim Neurostimulation Systems. The anticipated benefits of the clinical outcomes of SCS therapy per the study design outweigh the overall risk.

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

Investigators and study personnel will receive product training to become familiar with the components of the Intellis™ SCS systems and their functions. They will also receive training on assessment tools. Investigators will also be reminded that the risk of serious injury to the patient increases as location of the selected needle insertion site progresses up the vertebral column—from a lower risk at a lumbar location to a higher risk at a cervical location. Therefore, they should select a vertebral location that provides the widest and easiest access to the epidural space during needle insertion to reduce the risk of serious patient injury resulting from direct trauma to the spinal cord. All Investigators and study personnel must provide evidence of training in Good Clinical Practice (GCP) in the conduct of clinical trials with human participants.

C3. POTENTIAL BENEFITS

It is possible that an individual subject will experience no direct benefit from participating in the study. However, if a subject is benefiting from therapy, he/she will be allowed to keep the implanted device and accessories after completion of the study, with post-study care conducted by the subject's personal physician.

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. The system has been approved by the FDA and is available for commercial use.

The Intellis 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: The Intellis neurostimulator (INS, 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). The 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 a Communicator (Model 8880T2) to communicate with the INS.

Patient Programmer: The Patient Programmer (Model 97745), also called Patient Remote Controller, is a handheld unit able to communicate with the INS or ENS. The Patient Programmer is powered by two standard AA alkaline batteries during the Trial Phase and a rechargeable battery after implant of the INS. 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 (Vectris, 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. As with any spinal procedure, the risk of serious injury to the patient (e.g, hemorrhage, hematoma, or paralysis) increases as location of the selected needle insertion site progresses up the vertebral column—from a lower risk at a lumbar location to a higher risk at a cervical location. Select a vertebral location that provides the widest and easiest access to the epidural space during needle insertion to reduce the risk of serious patient injury resulting from direct trauma to the spinal cord.

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 tightens 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

A commercially approved Intellis™ SCS system approved by the FDA for the treatment of intractable chronic pain of the trunk and limbs. The study will utilize this device within the approved specified parameters. 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 to their Physician Manual.

D.4. ANY ANTICIPATED CHANGES IN THE DEVICE

There are no anticipated changes at this time.

E. ADMINISTRATIVE PROCEDURES

E.1. MONITORING

Clinical site monitoring is conducted to ensure compliance with Good Clinical Practice (GCP) guidelines to protect the rights and well-being of trial participants, 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. Monitoring may be conducted on-site or remotely.

E.1.2. MONITORING PROCEDURES

Monitoring visits to the clinical study sites will be made either remotely or on-site periodically and according to the monitoring Plan. These visits will ensure that Investigators and their staff understand and accept their defined responsibilities, assess compliance with current GCP guidelines, evaluate clinical trial progress, assess the continued acceptability of the site facilities, evaluate compliance with this Clinical Study plan, and verify the data entered on the CRFs.

Investigators are to maintain, in an appropriate secure location, all source documents as required by the Clinical Study 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 onto the CRFs. 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 Clinical Study 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 on paper CRFs following the study visits. 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 on the CRFs should be consistent with the data recorded on the source documents. Data will be reviewed to identify inconsistent or missing data as well as 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. Clinical Study plan, CRFs, medical records/files) as needed. All attempts will be made to preserve the privacy and confidentiality of subjects.

E.3. STUDY CONDUCT

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

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

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

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

The Investigator is also responsible for promptly reporting to the Sponsor any deviations and exceptions to this Clinical Study 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. Study ICF must be approved by the IRB. Signed ICFs will be retained in the subject's study records at the clinical site. Subjects may also be consented via a combination of mail and telephone calls. The Investigator or delegate will document the telephone calls and follow-up by signing the consent once the subject returns the signed consent. Study staff will then provide a photocopy to the subject.

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

E.5 INVESTIGATORS AND INSTITUTIONS

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

E.6. AMENDMENTS AND DEVIATIONS

This Clinical Study plan is to be followed by Investigators and all personnel involved in the clinical study. Any changes to the study covered by this Clinical Study plan must be documented on a formal Clinical Study plan amendment *prior to* implementation in the study. Changes to the Clinical Study plan may be initiated by the Sponsor or at the request of an Investigator. A formal change to this study under this Clinical Study plan cannot be initiated by Investigator or clinical site personnel without sponsor's approval, IRB approval, and the Investigator's approval.

> *Exception for Emergency Deviation*: An exception to the policy noted above is an emergency deviation to the Clinical Study plan that 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 IRB no later than 24 hours following the emergency.

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

E.7. ADDITIONAL RECORD AND REPORTS

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

9. 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] Vos T, Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015; 386: 743–800

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

[5] 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.

[6] 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.

[7] 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.

[8] 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.

F. APPENDICES

A. Informed Consent Form

B. Subject Questionnaires