INVESTIGATIONAL PLAN

A Post-Market, Multicenter, Prospective, Randomized Clinical Trial Comparing 10 kHz Spinal Cord Stimulation (HF10™ Therapy) Combined with Conventional Medical Management to Conventional Medical Management Alone in the Treatment of Chronic, Intractable, Neuropathic Limb Pain

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Revision History:

Revision	Description	Date
A	Initial Release of Investigational Plan	26MAY2017
B	Protocol enhancements and clarifications	14MAR2018
C	Protocol clarifications	28MAR2018
D	Protocol clarifications, revision of enrollment estimate	19MAR2019

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List of Abbreviations

Abbreviation	Definition
6MWT	6-Minute Walk Test
AE	Adverse Event
BPI-DPN	Brief Pain Inventory for Diabetic Peripheral Neuropathy
CE	Conformité Européene (European Conformity)
cGCP	Current Good Clinical Practice
CGIC	Clinician Global Impression of Change
cm	Centimeter
CMM	Conventional Medical Management
CT	Computed Tomography
d	Day
DA	Device Activation
DN4	Douleur Neuropathique 4
DQOL	Diabetes Quality of Life Measure
DRG	Dorsal Root Ganglion
eCRF	Electronic Case Report Form
EMI	Electromagnetic Interference
EoT	End of Trial
EQ-5D-5L	EuroQol Five Dimensions Questionnaire
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric Acid
GAF	Global Assessment of Functioning
GCP	Good Clinical Practice
GIC	Global Impression of Change
HbA1c	Hemoglobin A1c
HF10™ therapy	Nevro Senza® 10 kHz Spinal Cord Stimulation
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
kHz	Kilohertz
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram
MHz	Megahertz
min	Minute
mL	Milliliter
mm	Millimeter
MRI	Magnetic Resonance Imaging
NNH	Numbers Needed to Harm
NNT	Numbers Needed to Treat
NSS	Modified Neuropathy Symptom Score
OR	Operating Room

PDN	Painful Diabetic Neuropathy
PGIC	Patient Global Impression of Change
PMA	Premarket Approval
PNS	Peripheral Nerve Stimulation
PSQ-3	Pain and Sleep Questionnaire Three-Item Index
SAE	Serious Adverse Event
SCS	Spinal Cord Stimulation
SF-12	12-Item Short Form Survey
SF-MPQ-2	Short Form McGill Pain Questionnaire
TGA	Therapeutic Goods Administration
TSM	Trial Stimulator
UADE	Unanticipated Adverse Device Effect
VAS	10 cm Visual Analog Scale
wks	Weeks

A. Purpose

A.1. Name and Intended Use of the Study Interventions

The Senza® Spinal Cord Stimulation (SCS) system (manufactured by Nevro Corp., Redwood City, CA) is a Food and Drug Administration (FDA) approved device system (PMA P130022) indicated as an aid in the management of chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with failed back surgery syndrome, intractable low back pain and leg pain. The system is designed to deliver electrical stimulation to the spinal cord using electrodes (also referred to as leads) and implantable pulse generators (IPGs) as described in this investigational plan. Conventional medical management (CMM) may include a variety of non-invasive or minimally invasive treatments that comprise the standard of care for neuropathic limb pain. The study interventions are to be used in accordance with Institutional Review Board (IRB) approval and require informed consent from study subjects.

A.2. Purpose of the Investigation

The purpose of this post-market study is to document comparative safety, clinical effectiveness, and cost-effectiveness of the addition of HF10™ therapy to CMM compared with CMM alone in subjects with chronic, intractable, neuropathic lower limb pain due to diabetic neuropathy (Painful Diabetic Neuropathy or PDN). This study is a multi-center, prospective, randomized comparison of the two treatments.

A.3. Study Size

Up to 432 subjects will be enrolled at multiple sites in the United States in order to obtain an estimated total of 216 randomized subjects (108 HF10 therapy plus CMM and 108 CMM alone) in the study.

A.4. Duration of the Investigation

The expected duration of this study is approximately 52 months. Enrollment is expected to last 20 months, with subjects followed up to a 24 month period following permanent implant [HF10 therapy plus CMM] or baseline visit [CMM alone], with safety and effectiveness assessments at 3 months post-intervention. Due to the crossover option included in the study design, the time commitment for an individual subject to complete the study will vary from approximately 26 months to 32 months, consisting of Baseline assessments, up to 14 days of HF10 therapy trial stimulation followed by permanent device implant for subjects randomized to the device, and last follow-up at 24 months post-intervention.

B. Protocol

B.1. Rationale for Study

Peripheral neuropathy is caused by damage to peripheral nerves, thereby causing pain, numbness, and/or weakness. Damage may affect small (myelinated Aδ and unmyelinated C) fibers along with injury to large myelinated fibers. One of the classifications is based on whether the damage is to a single nerve (mononeuropathy) or multiple nerves (polyneuropathy). Some of the causes include metabolic or endocrine disorders (e.g., painful diabetic neuropathy or PDN), treatment induced toxicity (radiation or chemo-therapy induced neuropathy), alcohol (alcoholic neuropathy), infection (post-herpetic neuralgia caused by Herpes Zoster virus, Lyme disease), autoimmune disorders (Guillain-Barre' syndrome, Charcot-Marie-Tooth neuropathy), stress (carpal tunnel syndrome, ulnar neuropathy, radial neuropathy, peroneal neuropathy) and trauma (trauma-induced neuropathy). Nearly half of these patients are diagnosed as idiopathic (Hsieh, 2010).

The American Chronic Pain Association estimates that more than 15 million people in the U.S. and Europe have some degree of neuropathic pain. More than two out of every 100 persons are estimated to have peripheral neuropathy; the incidence rises to eight in every 100 for people aged 55 or older (Azhary, Farooq, Bhanushali, Majid, & Kassab, 2010). In Europe, the prevalence of PDN ranged from 5.8–34% (Alleman, et al., 2015). The incidence rate of PDN was reported to be 0.72 per 1000 persons per year for the Netherlands (Dieleman, Kerklaan, Huygen, Bouma, & Sturkenboom, 2008), and 0.64–0.69 per 1000 persons per year in the UK (Hall, Carroll, & McQuay, 2008). Patients with PDN result in significant workforce and healthcare costs (Cole, 2007) (daCosta DiBonaventura, 2011). In addition, patients with PDN suffer diminished quality of life and increased disability (Dulipsingh, 2013) (Deli, 2013).

Anticonvulsants, including gabapentin and pregabalin, are among the most commonly prescribed medications for neuropathic pain due to PDN (Yang, 2015). Pregabalin, or (*S*)-3-(aminomethyl)-5-methylhexanoic acid, is an analog of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). It is a compound with analgesic, anticonvulsant, and anxiolytic properties active in the central nervous system (CNS). The drug binds potently to the α_2-δ subunit of voltage-gated calcium channels, thereby reducing calcium influx at nerve terminals (Gee, et al., 1996). This in turn reduces the release of neurotransmitters like glutamate, noradrenaline, and substance P (Dooley, Mieske, & Borosky, 2000) (Dooley, Donovan, & Pugsley, 2000) (Fink, et al., 2002) (Maneuf, Hughes, & McKnight, 2001). Clinical studies have demonstrated the effectiveness of this drug in treating intractable limb pain from PDN resulting from both type 1 and 2 diabetes (Rosenstock, Tuchman, LaMoreaux, & Sharma, 2004) (Boyle, et al., 2012) (Arezzo, Rosenstock, LaMoreaux, & Pauer, 2008). A review of 7 randomized controlled trials comparing pregabalin with placebo summarized the following average changes in pain scores: 1.47 cm (placebo), 1.98 cm (150 mg pregabalin), 2.44 cm (300 mg pregabalin) and 2.75 cm (600 mg pregabalin) (Freeman, Durso-DeCruz, & Emir, 2008). Mean follow-up was 4-12 weeks. Responder rates, representing the percent of subjects with at least 50% improvement from baseline, varied from 40-49% (placebo responder rates: 14.5-23.0%). Adverse events reported include dizziness, peripheral edema, somnolence, infection and weight gain. Approximately 77% of patients prescribed pregabalin for PDN will discontinue the treatment within one year due to intolerable side effects or lack of efficacy (Yang, 2015). In addition, a recent meta-analysis of RCTs with pregabalin treatment of neuropathic pain calculated the Numbers Needed to Treat (NNT) to achieve 50% pain reduction is 7.7; however, the safety profile for this medication is poor as the Number Needed to Harm (NNH) is 13.9 (Finnerup, 2015).

Low-frequency, paresthesia-based spinal cord stimulation (SCS) has also been shown to be effective in treating intractable pain associated with many peripheral neuropathies, including several studies on PDN (Kumar, Toth, & Nath, 1996) (Kumar, Toth, Nath, & Laing, 1998) (Pluijms, et al., 2012) (Slangen, et al., 2013) (Tesfaye, et al., 1996). In a single center, observational study, Pluijms et al. reported that the median pain score of subjects treated with SCS decreased from 6 cm at baseline to 1.8 cm at 3 months on the visual analog scale (VAS, range: 0-10 cm). However, at 12 months the median pain score increased up to 2.9 cm with slightly over half the subjects (8/15 or 53%) still responding to the therapy with at least 50% improvement in pain. In another study comparing SCS with best medical treatment, pain scores measured with the numerical rating scale (NRS, range: 0-10) decreased from 7.3 and 6.7 (day and night, respectively) at baseline to 4 and 3.5 at 24 months (van Beek, et al., 2015). Responder rates (subjects with ≥ 50% pain reduction) ranged from 47% (8/17, day) to 35% (6/17, night). Changes in pain scores in these studies were deemed both clinically and statistically significant.

Unlike traditional low-frequency, paresthesia-based SCS that seeks to induce paresthesias in the affected distribution, HF10 therapy delivers paresthesia-independent, high frequency (10 kHz) stimulation, by use of a unique waveform and uniform pulse width. The therapy has demonstrated safety and superior effectiveness for the treatment of back and leg pain (Kapural L. , et al., 2016) (Kapural L. , et al., 2015) (Al-Kaisy, et al., 2014). HF10 therapy has also been studied for the treatment of migraine headaches (Arcioni, et al., 2015) and upper and lower limb neuropathic pain (Al-Kaisy, Palmisani, Smith, Harris, & Pang, 2015). In a prospective, multicenter study treating chronic intractable pain of the limbs from peripheral polyneuropathy using HF10 therapy, subjects reported a decrease in mean pain score from 7.6 cm (±0.3, standard error of the mean [SEM]) at baseline (N=26) to 2.1 cm (±0.5, SEM) at 1 month post-implant (N=16), with 81% of subjects deemed responders (presented at NANS 2017, data on file). While these results are preliminary, they are nonetheless promising.

The current treatments for neuropathic pain secondary to PDN are suboptimal with substantial room for improvement. In the proposed post-market study, HF10 therapy plus CMM will be compared with CMM alone for safety, clinical effectiveness, and cost-effectiveness in treating subjects diagnosed with chronic, neuropathic limb pain resulting from diabetic neuropathy.

B.2. Study Objectives

The ***primary objective*** of this post-market study is:

> To compare the safety, clinical effectiveness, and cost-effectiveness of HF10 therapy plus CMM to CMM alone for the treatment of chronic, intractable, neuropathic lower limb pain resulting from diabetic neuropathy.

B.3. Subject Population

B.3.1. Indications for Use

HF10 therapy (Senza System PMA P130022) has been approved by the FDA with Indications for Use including the management of neuropathic pain of the limbs as described in this Investigational Plan. Treatment of subjects with peripheral neuropathies that result in limb pain is therefore an on-label use of the Senza System. CMM will follow the Investigators' standard of care and/or published clinical guidelines (Dworkin, 2010). Treatments include, but are not

limited to, pharmacological agents, physical therapy, cognitive therapy, chiropractic care, nerve blocks, and other non-invasive or minimally invasive therapies.

B.3.2. Inclusion Criteria

To participate in the study, subjects must meet all of the following inclusion criteria:

1. Have been clinically diagnosed with diabetes, according to the American Diabetes Association guidelines, as well as painful diabetic neuropathy (PDN) of the lower limbs, and:
    a. are symptomatic despite conservative therapy for a minimum of 12 months
    b. have tried pregabalin (Lyrica®) OR gabapentin (Neurontin®, Gralise®, etc.) administered at an adequate dose and for an appropriate duration, in the Investigator's judgement
    c. have tried at least one other class of analgesic medication in addition to pregabalin/gabapentin
    d. are on a stable dosage of analgesic medications for at least 30 days
2. Average pain intensity of ≥ 5 out of 10 cm on the VAS in the lower extremities at enrollment.
3. Have stable neurological status measured by motor, sensory and reflex function as determined by the investigator.
4. Be on a stable analgesic regimen, as determined by the Investigator, for at least 30 days prior to assessing pain intensity as described in inclusion criterion #2, and be willing to stay on those medications with no dose adjustments until activation of the permanently implanted SCS device (HF10 therapy group) or baseline assessment (CMM only group).
5. Be 22 years of age or older at the time of enrollment.
6. Be an appropriate candidate for the surgical procedures required in this study based on the clinical judgment of the implanting physician.
7. Be capable of subjective evaluation, able to read and understand English-written questionnaires, and able to read, understand and sign the written informed consent in English.
8. Be willing and capable of giving informed consent.
9. Be willing and able to comply with study-related requirements, procedures, and scheduled visits.
10. Have adequate cognitive ability to use a patient programmer and recharger as determined by the Investigator.

B.3.3. Exclusion Criteria

To participate in the study, subjects must *not* meet any of the following exclusion criteria:

1. Have a diagnosis of a lower limb mononeuropathy (e.g., causalgia and tibial or peroneal neuropathies), have had a lower limb amputation other than toes due to diabetes, or have large (≥3 cm) and/or gangrenous ulcers of the lower limbs.
2. Have an average pain intensity of ≥ 3 out of 10 cm on the VAS in the upper extremities due to diabetic neuropathy at enrollment.
3. Currently have a hemoglobin A1c (HbA1c) > 10%.
4. Have a BMI > 45.
5. Currently prescribed a daily opioid dosage > 120 mg morphine equivalents.
6. Have a medical condition or pain in other area(s), not intended to be treated in this study, that could interfere with study procedures, accurate pain reporting, and/or confound evaluation of study endpoints, as determined by the Investigator (such as primary headache, fibromyalgia, post-herpetic neuralgia, osteoarthritis, peripheral vascular disease, or small vessel disease).
7. Have a current diagnosis of a progressive neurological disease such a multiple sclerosis, chronic inflammatory demyelinating polyneuropathy, rapidly progressive arachnoiditis, brain or spinal cord tumor, central deafferentation syndrome, Complex Regional Pain Syndrome, acute herniating disc, severe spinal stenosis and brachial plexus injury, as determined by the Investigator.
8. Have a current diagnosis or condition such as a coagulation disorder, bleeding diathesis, platelet dysfunction, low platelet count, severely diminished functional capacity due to underlying cardiac/pulmonary disease, symptomatic uncontrolled hypertension, progressive peripheral vascular disease or uncontrolled diabetes mellitus that presents excess risk for performing the procedure, as determined clinically by the Investigator.
9. Have prior experience with SCS, dorsal root ganglion (DRG) stimulation, peripheral nerve field stimulation (PNfS), or peripheral nerve stimulation (PNS) for chronic intractable pain.
10. Have significant spinal stenosis, objective evidence of epidural scarring and/or any signs or symptoms of myelopathy as determined by the Investigator based on MRI conducted within the past 12 months.
11. Any previous history of surgery on the posterior elements (laminectomy, posterior fusion) resulting in a compromised epidural space, as determined by the Investigator.
12. Be benefitting from an interventional procedure and/or surgery to treat lower limb pain (Subjects should be enrolled at least 30 days from last benefit).
13. Have an existing drug pump and/or another active implantable device such as a pacemaker.
14. Have a condition currently requiring or likely to require the use of diathermy or MRI that is inconsistent with Senza system guidelines in the Physician's Manual.
15. Have either a metastatic malignant neoplasm or untreated local malignant neoplasm.
16. Have a life expectancy of less than one year.

17. Have a local infection at the anticipated surgical entry site or an active systemic infection.
18. Be pregnant or plan to become pregnant during the study. Women of childbearing potential who are sexually active must use a reliable form of birth control, be surgically sterile, or be at least 2 years post-menopausal.
19. Have within 6 months of enrollment a significant untreated addiction to dependency producing medications, alcohol or illicit drugs.
20. Be concomitantly participating in another clinical study.
21. Be involved in an injury claim under current litigation.
22. Be a recipient of temporary Social Security Disability Insurance (SSDI) benefits due to chronic pain.
23. Have a pending or approved worker's compensation claim.
24. Have evidence of an active disruptive psychological or psychiatric disorder or other known condition significant enough to impact perception of pain, compliance with intervention and/or ability to evaluate treatment outcome, as determined by a psychologist in the last 12 months.

B.4. Study Design

B.4.1. Overall Design

This is a post-market, multi-center, prospective, randomized clinical study to document the comparative safety, clinical effectiveness, and cost-effectiveness of the addition of HF10 therapy to CMM compared with CMM alone in subjects with chronic, intractable, neuropathic lower limb pain. Data from follow-up visits will be compared to baseline data for each treatment group. Comparisons will also be made between the treatment groups.

B.4.2. Bias

In preparing the investigational plan and associated documentation, an attempt has been made to anticipate and minimize potential sources of bias. The qualifications of each Investigator and his/her ability to appropriately screen and treat subjects from his/her caseloads and to comply with investigational plan requirements will be reviewed before their participation in the trial.

B.4.3. Randomization/Comparison Groups

Subjects meeting inclusion and exclusion criteria will be randomized 1:1 to HF10 therapy delivered by the Senza System plus CMM or to CMM alone.

B.4.4. Crossover

Subjects randomized to either treatment group will have the potential to crossover to the alternative treatment arm at the 6-month visit if they meet all of the following criteria:

- < 50% lower limb pain relief from baseline. For pain relief calculations, a subject's right and left lower limb VAS scores collected during a single visit will be averaged together to generate a lower limb pain score.

- Documented subject dissatisfaction with the treatment ("dissatisfied" or "very dissatisfied" on subject satisfaction measure).
- Investigator agreement with crossover.

B.4.5. Blinding

This study is not blinded. Due to the nature of the treatments, specifically an implanted medical device compared with CMM, it is not feasible to blind either the subjects or the clinical site personnel to the treatment group assignments. This factor aside, there is little reason to believe that responses provided by subjects or Investigators/clinical staff will be influenced by the knowledge of which treatment is received.

B.4.6. Sample Size

Up to 432 subjects will be enrolled at multiple sites in the United States in order to obtain an estimated total of 108 subjects randomized to HF10 plus CMM and 108 subjects randomized to CMM alone.

B.4.6.1. Sample Size Rationale

Up to 432 subjects will be provisionally enrolled at multiple clinical sites in the United States. Assuming a 50% screen failure rate,[1] an estimated total of 216 subjects will be randomized, resulting in 108 subjects assigned to each treatment group. The subjects will continue with their respective treatments through the 3 month primary endpoint with an expected 10% attrition rate, resulting in approximately 97 subjects in each group at the primary endpoint. This is the sample size required based on the following assumptions: a 60% responder rate for the HF10 therapy group (80% trial success rate and 75% responders at 3 months among permanent implant subjects), a 36% responder rate for the CMM only group, 90% power, and two-sided type I error of 0.05.

B.4.7. Study Duration

The expected duration of this study is approximately 52 months. Enrollment is expected to last 20 months, with subjects followed up to a 24 month period following permanent implant (HF10 therapy plus CMM group) or baseline assessment (CMM only group), with a composite of effectiveness and safety assessed at 3 months post-intervention. Due to the crossover option included in the study design, the time commitment for an individual subject to complete the study will vary from approximately 26 months to 32 months, consisting of Baseline assessments, up to 14 days of trial stimulation followed by permanent device implant for subjects randomized to the device arm, and last follow-up at 24 months post-intervention.

B.4.8. Interim Analysis

Interim analysis will be performed to reassess sample size assumptions when 25% of the subjects reach the 3 month primary endpoint.

[1] This study includes an exclusion criterion for HbA1c in excess of 10% at enrollment. This threshold is approximately one standard deviation above the average HbA1c values found in prior studies in this population. Assuming a normal distribution, this criterion may result in excluding approximately 16% of enrolled subjects. An additional 34% of enrolled subjects may screen fail due to failure to meet other inclusion/exclusion criteria.

B.5. Enrollment, Assessments, and Clinical Procedure

Enrollment of subjects will occur at the clinical sites only after IRB approval and written informed consent from subjects have been obtained. Subjects who have been determined to be candidates for SCS therapy will be approached by Investigators/clinical site staff about potential participation in the study. Following consent, subjects will be selected to participate in the study based upon inclusion and exclusion criteria defined in this investigational plan. Inclusion and exclusion criteria will be assessed based on pain assessments, MRI, pregnancy test (if needed), psychological evaluation, laboratory tests, including measure of HbA1c, subject medical records and history, assessment tools, subject interviews, and the Investigator's clinical judgment.

B.5.1. Summary of Study Protocol

Study subjects will be identified from the pool of candidates for SCS therapy affiliated with, or referred to, the clinical sites. Advertisements may be distributed, as approved by local IRBs. Subjects will participate in this investigational plan that includes entry criteria evaluation, baseline assessments, trial stimulation (HF10 therapy subjects), and post-trial assessments (HF10 therapy subjects). Subjects randomized to the HF10 therapy plus CMM arm with a successful trial phase will be eligible to receive a permanent implant of an IPG and leads. Subjects randomized to the CMM only arm will be optimized according to the Investigator's standard of care and/or clinical treatment guidelines (Dworkin, 2010). Subjects will receive their assigned treatment for 24 months with assessments at 1, 3, 6, 9, 12, 18, and 24 months Post-Intervention.

Subjects who sign the informed consent will undergo evaluations to determine eligibility for the study based on the inclusion and exclusion criteria. Baseline assessments will include measures for pain, disability, functioning, neurological function, work status, weight, healthcare utilization (including medication usage for pain and diabetes management, as well as office and hospital visits), health-related quality of life, sleep, assessment of adverse events and collection of third-party payer data. The presence of any lower limb wounds will be documented by measuring the greatest diameter and taking a photograph.

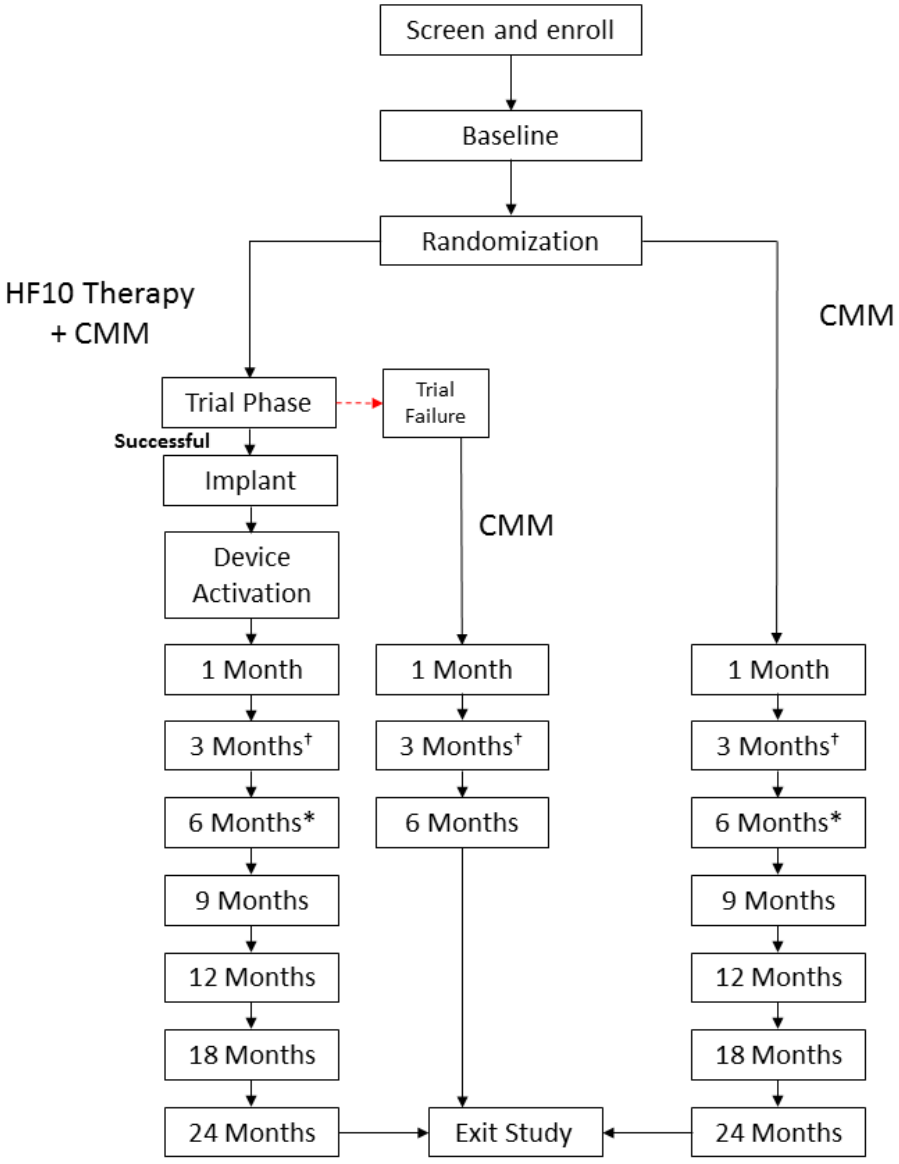
Implantation and use of the Senza System will follow the Nevro Physician's Implant Manual and other supporting manuals. It is recommended that subjects maintain blood glucose levels less than 200 mg/dL during the perioperative period. Subjects will undergo a Trial Phase lasting up to 14 days to determine his/her response to SCS therapy. Following the Trial Phase with external device stimulation, subjects will be assessed for their pain. Those who have an "unsuccessful" trial with less than 50% lower limb pain reduction from baseline will be followed on CMM for 6 months prior to study completion. Those who have a "successful" Trial Phase (defined as a 50% or greater pain reduction in lower limb pain from Baseline) will be eligible to proceed to permanent implantation of a Senza system. Following permanent device implant, the IPG will be activated and stimulation will be delivered on an ongoing basis for the entirety of the patient's participation in the study, up to 24 months. At the 6 month assessment, subjects may opt to crossover to the CMM only treatment arm if they meet the criteria for crossover. Subjects who crossover will complete the remainder of the scheduled 24 months of follow-up.

Administration of CMM will follow the Investigator's standard of care and/or published clinical guidelines (Dworkin, 2010) in order to maximize pain relief with minimal side effects. Treatments include, but are not limited to, pharmacological agents, physical therapy, cognitive

therapy, chiropractic care, nerve blocks, and other non-invasive or minimally invasive therapies. The follow-up schedule for the CMM only group starts at the baseline assessment and will continue up to 24 months. Subjects may opt to crossover to the HF10 therapy plus CMM group at the 6 month assessment if they meet the criteria for crossover. These subjects will undergo trial stimulation with HF10 therapy with those who achieve at least 50% lower limb pain reduction from baseline eligible for a permanent device implant. Permanent implant subjects will receive 24 months of stimulation delivery with regularly scheduled assessments. Subjects who crossover to the HF10 therapy arm but fail trial stimulation with less than 50% lower limb pain reduction from baseline will be monitored for adverse events for 2 weeks before exiting the study.

At 1, 9, and 18 months Post-Intervention, subjects will be assessed for pain and adverse events as well as disability, functioning, healthcare utilization (including medication usage for pain and diabetes management, as well as office and hospital visits), weight, health-related quality of life, and sleep. The presence of any lower limb wounds will be documented by measuring the greatest diameter and taking a photograph. At 3, 6, 12, and 24 months Post-Intervention, subjects will be assessed for pain intensity, distribution of pain and other symptoms (HF10 therapy group only), adverse events, disability, functioning, health-related quality of life, healthcare utilization (including medication usage for pain and diabetes management, as well as office and hospital visits), neurological function, weight, sleep, clinician global impression of change, patient global impression of change, and subject satisfaction. The presence of any lower limb wounds will be documented by measuring the greatest diameter and taking a photograph. Subject HbA1c levels will be measured at 3, 6, 12, 18, and 24 months. At the 6, 12, and 24 month visits subjects will also be asked about their work status. Subjects in the HF10 therapy group will be assessed for pain intensity at the End of Trial as well as the distribution of pain at Trial and possibly the End of Trial and Permanent Implant visits. HF10 therapy subjects may be assessed for the distribution of additional symptoms (such as numbness, cold, tingling, or burning) at the Trial and Permanent Implant visits. HF10 therapy subjects will have paresthesia assessments with low frequency stimulation at 3 and 24 months and may have paresthesia assessments with low frequency stimulation at the Trial, End of Trial, Permanent Implant, Permanent Device Activation visit and at 1, 6, 9, 12, and 18 months Post-Permanent Device Activation. In addition, AP, lateral and/or oblique x-rays may be performed at follow-up to assess lead location in the stimulation group.

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



†Primary endpoint analysis
***Option to cross-over to other therapy arm**

B.5.2. Consent/Enrollment

Subjects will be consented for the study prior to the initiation of any study-related assessments, including those that might determine any remaining eligibility criteria, procedures, and/or activities. Subjects will be assigned a unique study identification number following consent.

B.5.3. Criteria Evaluation

Subjects will be assessed against the study inclusion and exclusion criteria. Subjects determined to be on stable pain medications (no change to analgesic medications for ≥ 30 days) will be initially assessed for pain using a 10 cm VAS. To be eligible to participate, the subject must mark an average pain score ≥ 5 cm on the VAS for the lower limbs. Subjects who mark an average pain score ≥ 3 cm on the VAS for the upper limbs due to diabetic neuropathy will be excluded. Subjects with upper limb pain unrelated to diabetic neuropathy may be enrolled even if the upper limb pain VAS exceeds 3 cm if, in the Investigator's clinical judgement, the pain will not confound the subject's ability to accurately report lower limb pain. Throughout the study, appropriateness for advancement to the next stage of the study will be evaluated by a study site Investigator. Pregnancy tests will be conducted for participants of child bearing potential; pregnant women will not be allowed to participate. A psychological evaluation will be conducted by a site psychologist for subjects who did not have an evaluation conducted within 12 months prior to enrollment, or sooner, at the discretion of the Investigator. Subjects will be assessed for adverse events at all follow-up visits. Study subjects must meet all of the study inclusion criteria and none of the study exclusion criteria to be eligible for study participation. Inclusion and exclusion criteria will be evaluated with pain assessments, a pregnancy test, if necessary, psychological evaluation, subject medical records and history, MRI performed within the past 12 months, labwork for measure of HbA1c, subject interviews, recording dosages for all current medications, including those for pain relief as well as diabetes management, and the Investigator's clinical judgment. Those subjects who meet the entry criteria will proceed to Baseline assessment, and subjects who do not will be discontinued from the study. With the exception of lab measures of HbA1c, results of assessments from Entry Criteria Evaluation will not be included as a Baseline assessment; however, if entry criteria evaluation and baseline assessment occur on the same date, the subject will complete a single worksheet for lower limb pain VAS scores to satisfy the requirement for both visits. In this case, the site would document that a single VAS score worksheet was collected for both entry evaluation and baseline.

B.5.4. Baseline

At the Baseline visit, assessments will be performed and subjects will be asked to fill out standard questionnaires to assess their baseline pain severity and stability, pain experience, functioning, disability, healthcare utilization (including medication usage for pain [opioid intake expressed as morphine sulfate equivalents per day and any other analgesic medications], and diabetes management, as well as recent office and hospital visits), health-related quality of life, and sleep. The presence of any lower limb wounds will be documented by measuring the greatest diameter and taking a photograph. Medical and surgical histories will be collected. A walking assessment will be performed. A neurological assessment will be conducted. It is preferable that the healthcare provider who conducts the baseline neurological assessment conducts all future neurological assessments for that subject to minimize inter-rater variability.

Pre-operative assessments will follow the standard of care for SCS therapy and be determined by the site Investigator. Third party payer coverage data and work status will also be collected. In addition, subjects will be assessed for adverse events.

B.5.5. Randomization

Following completion of the Baseline procedures, eligible subjects will be randomized by the sites using a block technique in a 1:1 ratio to either the HF10 therapy plus CMM group or CMM alone. Those randomized to the stimulation group will receive HF10 therapy with the Senza System in addition to CMM. Implantation and use of the Senza System will follow the Nevro Physician's Implant Manual and other supporting Manuals. Those randomized to CMM only will be optimized according to the Investigator's standard of care and/or published clinical guidelines (Dworkin, 2010) in order to maximize pain relief with minimal side effects. CMM treatments include, but are not limited to, pharmacological agents, physical therapy, cognitive therapy, chiropractic care, nerve blocks, and other non-invasive or minimally invasive therapies.

B.5.6. Trial Phase (SCS group only)

Subjects randomized to the stimulation group will undergo a Trial Phase which may last up to 14 days. It is recommended that subjects maintain blood glucose levels less than 200 mg/dL during the perioperative period. Before the Trial begins, subjects will record the distribution of pain on a map and may also be asked to record additional symptoms, such as numbness, cold, tingling, or burning, on a map. 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. Subjects will be assessed for possible adverse events. Radiographic images of anterior-posterior, lateral and/or oblique views of the leads will be captured to ensure appropriate placement. Additional images may be captured as necessary. Any changes in medication intake, including medications for pain and diabetes management, will be recorded. Stimulation will be delivered from an external pulse generator.

Standard SCS practice will be followed to determine when stimulation parameters should be modified; however, it is recommended that stimulation parameters be trialed by a subject for at least 2 days prior to making programming changes in stimulation. The primary factor for determining stimulation parameters is subject self-reported pain relief. The stimulation parameters will be modified until at least 50% self-reported pain reduction from baseline is achieved or until conclusion of the trial phase. Paresthesia assessment (low-frequency SCS) may be performed to assess lead location. Programming adjustments for optimal pain relief may be made based on patient feedback.

B.5.7. End of Trial Assessment (SCS group only)

At the end of the Trial Phase, subjects will be assessed for pain and changes in medication intake, including medications for pain and diabetes management. At this visit, subjects will also be assessed for possible adverse events, neuropathic symptoms, and neurological function. Subjects may be asked to record the distribution of pain on a map. Radiographic images of anterior-posterior, lateral and/or oblique views of the leads will be captured. In the case of a permanent, buried lead trial, radiographic images of the leads will instead be captured after the

Permanent Implant procedure. Additional images may be captured as necessary for this treatment group.

The purpose of the Trial Phase is to determine whether subjects respond favorably to HF10 therapy and should be candidates to proceed to permanent implant of the device system. A 30% reduction in pain has been documented as being clinically meaningful (Farrar, Young Jr, LaMoreaux, Werth, & Poole, 2001) (Oakley, Krames, Stamatos, & Foster, 2008). A successful trial is defined as the subject experiencing 50% or greater pain reduction in the primary area of pain as compared to Baseline pain levels. A threshold of 50% for the Trial Phase exceeds the minimum threshold for being clinically meaningful and therefore indicates that the subject is likely to respond longer term to the therapy, potentially achieving at least a 50% pain reduction during the permanent implant phase as defined in the Individual Subject Success criterion.

Subjects who pass the Trial Phase will be scheduled for permanent implantation of the Senza System after the Investigator and subject agree that the subject should continue to the next phase. Subjects who have failed the Trial Phase will not receive a permanent SCS system as part of the study, but will receive CMM and continue to be followed for 6 months of data collection prior to exiting the study.

B.5.8. Permanent Device Implant (SCS group only, 0-60 days from end of Trial Phase)

As in the Trial Phase for stimulation group subjects, it is recommended that subjects maintain blood glucose levels less than 200 mg/dL during the perioperative period. Before the Permanent Implant procedure, subjects may record the distribution of pain and additional symptoms, such as numbness, cold, tingling, or burning, on a map. 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 (if permanent leads are placed for the Trial Phase, an IPG will be implanted and connected to the existing leads). It is suggested that the IPG be implanted approximately 1.5 cm below the surface of the skin in the buttock or abdomen. Radiographic images of anterior-posterior, lateral and/or oblique views of the leads will be captured as needed to insure appropriate placement. Additional images may be captured as necessary. The IPG will be programmed to provide adequate pain relief. The primary factor for determining stimulation parameters is the subject's self-reported pain relief. The amplitude of the stimulation range will be kept at a tolerable range and parameters will be modified until at least 50% self-reported pain reduction from baseline is achieved. The subject will be provided with instructions on how to operate the charger and remote control at this visit. Paresthesia assessment with low-frequency SCS may be performed to assess lead location. Following programming, the IPG will be left in the off position until the device activation visit, which may occur on the same day as the implant or up to 14 days later, at the discretion of the Investigator. Subjects will be assessed for changes in medication intake, including medications for pain and diabetes management, and possible adverse events during the device placement procedure, if any. The clinical site's standard practice for prophylactic pre-surgery antibiotics and post-surgery analgesic medications will be followed.

B.5.9. Device Activation (SCS group only, 0-14 days following Permanent Implant)

The IPG will be activated at this visit and the subject will be provided with a device charger and remote control. Changes in medication usage, including medications for pain and diabetes

management, will be assessed. Subjects will also be assessed for possible adverse events. The presence of any lower limb wounds will be documented by measuring the greatest diameter and taking a photograph.

B.5.10. Unscheduled Visits

Unscheduled visits may occur at any time during the study for the assessment of possible adverse events, medication changes and programming adjustments. Each unscheduled visit must be documented on the unscheduled visit electronic Case Report Form (eCRF).

B.5.11. Telephone Calls

The study site staff may contact subjects by telephone, per the site's standard of care, to check on the well-being of the subject, remind the subject of an upcoming scheduled visit, remind the subject to keep analgesic medication usage unchanged for two weeks prior to the scheduled visit, remind the subject to maintain normal activity levels prior to scheduled study visits, and to contact the Investigator/study staff with any questions or concerns. Participants with HF10 therapy may also be contacted by a Nevro representative to see if they are having problems with the equipment and answer questions related to the use of the device.

B.5.12. 1 (± 7 days), 3 (± 14 days), 6 (± 30 days), 9 (± 30 days), 12 (± 30 days), 18 (± 30 days), and 24 (± 30 days) Months Post-Device Activation (SCS) or Baseline (CMM only)

Subjects will be assessed for pain, adverse events, disability, functioning, healthcare utilization (including medication usage for pain and diabetes management, as well as office and hospital visits), weight, and sleep at follow-up visits at 1, 3, 6, 9, 12, 18, and 24 months Post-Intervention. The presence of any lower limb wounds will be documented by measuring the greatest diameter and taking a photograph. HF10 therapy subjects may undergo device programming or have additional radiographic images taken at these visits, if necessary. Health-related quality of life, Patient Global Impression of Change, Clinician Global Impression of Change, subject satisfaction, and neurological assessment will be performed only at 3, 6, 12, and 24 months Post-Intervention. HF10 therapy subjects will be asked to record the distribution of pain and additional symptoms, such as numbness, cold, tingling, or burning, on a map at 3, 6, 12, and 24 months Post-Permanent Device Activation. Hemoglobin A1c measurements will be collected at 3, 6, 12, 18, and 24 months. In addition, information regarding work status will be collected at the 6, 12, and 24 month visits. A walking assessment will be performed at 3, 12, and 24 months. Paresthesia mapping in the stimulation group subjects will be performed at low frequency at 3 and 24 months Post-Permanent Device Activation. Paresthesia assessment with low-frequency SCS may be performed to assess lead location at 1, 6, 9, 12, and 18 months Post-Permanent Device Activation.

At the 6 Month Post-Intervention visit, the continued effect of treatment on achieving pain relief will be assessed. Each subject and the Investigator will evaluate whether or not there has been sufficient pain relief to continue treatment. If the subject and Investigator agree that pain relief has been sufficient to continue therapy, the SCS system will be left in place for the stimulation subjects or conventional therapies will continue to be administered for the CMM only subjects. If the subject and Investigator believe that the treatment has not generated sufficient pain relief to warrant continued treatment, then the IPG and leads will be removed for the stimulation

subjects or conventional therapies may be discontinued for the CMM only subjects. Subjects have the option to crossover to the alternate treatment arm at the 6 month visit if they experience insufficient pain relief, are not satisfied with their therapy, and the Investigator agrees with the decision.

A similar assessment will be performed at 24 Months Post-Intervention. Following this last study visit, subjects will be followed by the Investigator at regular intervals, as dictated by the standard of care at each site, in order to facilitate pain management, medication adjustments stimulation adjustments, and possible revisions and/or replacements of device components. These visits will occur until device explant or discontinuation of therapy. 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. If the subject and/or Investigator believe that the treatment has not generated sufficient pain relief to warrant continuation, then the IPG and leads will be removed for the stimulation subjects or conventional therapies will be discontinued for the CMM only subjects.

B.5.13. Other Assessments and Information

For stimulation group subjects, paresthesia assessment (low-frequency SCS) may be performed. Programming adjustments may be made based on patient feedback following testing. At any time during the study, if lead migration is suspected, the subject may have additional radiographic images taken to determine lead positioning. In the event the subject's lead locations are not adequate for pain relief, as determined by the Investigator, leads may be moved to a different vertebral location.

Medication Usage:

- All subjects will continue to take their stable, pre-study doses of analgesic medications until the device activation visit (HF10 plus CMM group) or baseline assessment (CMM only group), with the exception of procedure-related analgesics prescribed according to the Investigator's standard of care.
- Subjects will be required to maintain stable dosing of all analgesic medications for two weeks prior to scheduled follow-up visits.
- Changes to non-study medications shall be permitted as directed by the treating physician.
- Following SCS trials and permanent IPG implants, the clinical site's standard practice for prophylactic pre-surgery antibiotics and post-surgery analgesic medications will be followed. Investigators will instruct subjects not to change usage of any other concomitant analgesic medications.
- All prescription medications as well as over-the-counter analgesic medications taken by subjects will be recorded throughout the study.

B.5.14. Device Explant

At any time during the study, subjects in the stimulation group may elect to have the SCS system explanted. Additionally, an Investigator may elect to explant a device due to an adverse event.

If any serious adverse event(s) (e.g., subject injury) occurs that is believed to be related to the Senza device or there is a Senza device malfunction, it is requested that the device be explanted.

When the Senza IPG and/or the lead(s) is/are explanted from a subject for any reason, the Investigator is to contact Nevro prior to the procedure to arrange shipping of the explanted device(s) to Nevro. The explanted device(s) and all accessories (i.e., Charger, Remote Control) are to be returned to Nevro for device analysis.

B.5.15. Early Subject Withdrawal

Subjects may be withdrawn early from the study for a number of reasons, including but not limited to:

- Entry criteria failure (e.g., lower limb pain VAS score < 5 cm)
- Trial stimulation failure
- Subject request
- Investigator request
- Subject pregnancy
- Subject lost to follow-up
- Subject death
- Adverse events (e.g., intolerable adverse event occurrence or treatment forces subject to stop participation in the study)
- Lack of efficacy

If a study subject is discontinued from the study early, a Termination eCRF will be completed describing the reason for discontinuation. Subjects will be asked about adverse events or device/medication-related issues. In situations where study withdrawal is due to an adverse event, subjects will be followed until resolution of that adverse event or determination that the subject's condition is stable. If a subject has withdrawn consent for the study, the site should no longer collect any further data for that participant.

B.5.16. Study Completion

All subjects randomized in this study are expected to complete all scheduled visits through the 24 Month Post-Intervention Visit. A Study Completion eCRF should be completed at the last study 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 eCRF should be completed.

The study may be completed when all of the requirements of the investigational plan have been fulfilled. Subjects will be considered to have completed all study requirements following completion of the 24 Month Post-Intervention visit. The clinical site will be considered to have completed the study requirements at the end of the clinical site close out monitoring visit. The study will be considered completed when all close out visits have been completed and all Sponsor and Investigator reports have been issued.

B.5.17. Study Suspension and Termination

Nevro, the Investigators, or the IRB may suspend or terminate the study at any time. If the study is suspended or terminated prematurely, all currently randomized subjects will be withdrawn from the study and a Study Completion eCRF or Termination eCRF will be completed. If there

is an ongoing adverse event related to the device or therapy, the subject will be followed until resolution of that adverse event or determination that the subject's condition is stable.

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

Nevro reserves the right to terminate the study, but intends only to exercise this right for valid scientific or business reasons, or reasons related to the protections of subjects. Investigators and IRBs will be notified in writing in the event of study termination. Possible reasons for study termination include, but are not limited to:

- The discovery of unexpected, significant, or unacceptable risk to subjects enrolled in the study.
- A decision on the part of Nevro to suspend or discontinue development of the Senza device.

This study will be in compliance with the requirements of the clinical trial registration and results submission described in Section 801 of the Food and Drug Administration Amendments Act, known as FDAAA 801 and will hasten the posting of the results if the study is terminated early.

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

- Investigator non-compliance
- Repeated failure to complete or submit eCRFs in a timely manner
- Failure to obtain written informed consent
- Failure to report SAEs or UADEs to the Sponsor and/or IRB within 48 hours of knowledge
- Multiple or severe protocol deviations without justification
- Failure to control or account for study products used
- Lack of patient accrual/enrollment

B.6. Study Endpoints

B.6.1. Outcome Measures

The primary endpoint of this study is a composite of safety and effectiveness, specifically the difference between treatment groups in responder rates at 3 month follow-up in subjects without a clinically meaningful neurological deficit compared with baseline. A responder is defined as a subject with ≥ 50% lower limb pain reduction from baseline. For each subject, the right and left lower limb VAS scores collected during a single visit will be averaged together to generate a lower limb pain score.

In addition to the primary endpoint, several secondary endpoints will be evaluated. For all analyses, right and left lower limb VAS scores collected on a single visit will be averaged together to generate a lower limb pain score for each subject. The secondary endpoints will include:

- Difference between the treatment groups in proportion of remitters (remission is defined as having a lower limb pain VAS score ≤ 2.5 cm) at 3 months.
- Difference between the treatment groups in crossover rates.
- Within group evaluation of responder rates at 12 months.
- Within group evaluation of proportion of remitters at 12 months.
- Within group evaluation of changes in health-related quality of life as assessed by the EuroQol Five Dimensions questionnaire (EQ-5D-5L) at 12 months.
- Difference between the treatment groups in proportion of subjects with improvement from baseline in neurological assessment (motor, sensory or reflex) at 3 months.
- Within group evaluation of the proportion of subjects with improvement from baseline in neurological assessment (motor, sensory or reflex) at 12 months.
- Within group evaluation of the average percentage change from baseline in HbA1c levels at 12 months.

Tertiary endpoints:

- Difference between the treatment groups in the average percentage change from baseline in lower limb pain VAS scores at 3 and 6 months. Within group evaluations will be done at 12 and 24 months.
- Difference between the treatment groups in proportion of subjects with ≥ 30% improvement in lower limb pain VAS at 3 and 6 months. Within group evaluations will be done at 12 and 24 months.
- Difference between the treatment groups in proportion of remitters at 6 months. Within group evaluation will be done at 24 months.
- Difference between the treatment groups in responder rates at 6 months. Within group evaluation at 24 months.
- Difference between the treatment groups in proportion of subjects with improvement from baseline in neurological assessment (motor, sensory or reflex) at 6 months. Within group evaluation will be done at 24 months.
- Difference between the treatment groups in Numbers Needed to Treat (NNT) based on responder rates at 3 and 6 months. Within group evaluations will be done at 12 and 24 months.
- Difference between the treatment groups in average percentage change from baseline in opioid dosage at 3 and 6 months. Within group evaluations will be done at 12 and 24 months.
- Difference between the treatment groups in average percentage change from baseline in PDN-specific analgesic dosages at 3 and 6 months. Within group evaluations will be done at 12 and 24 months.

- Difference between the treatment groups in average percentage change from baseline in HbA1c, levels at 3 and 6 months. Within group evaluation will be done at 24 months.
- Difference between the treatment groups in average percentage change from baseline in diabetic control medication dosages at 3 and 6 months. Within group evaluations will be done at 12 and 24 months.
- Difference between the treatment groups in average percentage change from baseline in BMI at 3 and 6 months. Within group evaluations will be done at 12 and 24 months.
- Difference between the treatment groups in the average percentage change from baseline on distance covered during the 6MWT at 3 months. Within group evaluations will be done at 12 and 24 months.
- Difference between the treatment groups in the change over time in size of lower limb wounds at 3 and 6 months. Within group evaluations will be done at 12 and 24 months.
- Difference between the treatment groups at 3 and 6 months in health economic outcomes, including: 1) healthcare utilization [i.e. medications, office visits, ER visits, hospital admissions, medical tests, etc.]; 2) employment status; and 3) health-related quality of life as assessed by the EuroQol Five Dimensions questionnaire (EQ-5D-5L) and the Diabetes Quality of Life measure (DQOL). Within group evaluations will be done at 12 and 24 months.

All other outcome measures will be quantified and reported as mean ± standard deviation (where applicable). Descriptive and non-descriptive statistics will also be reported.

B.6.2. Definition of Success

Individual subject success encompasses clinical effectiveness and safety at the 3 month follow-up:

- Effectiveness: A responder is defined as a subject with ≥ 50% improvement from baseline lower limb pain score, as measured by the 10 cm VAS. For each subject, the right and left lower limb VAS scores collected during a single visit will be averaged together to generate a lower limb pain score.
- Safety: A subject without a clinically meaningful decrease from baseline in neurological status.

Study success is assessed by comparing responder and safety rates between treatment groups at 3 months.

B.6.3. Safety

Safety will be assessed by characterizing clinically meaningful deficits in neurological status (primary) and adverse events (secondary) at all study visits.

Neurologic status includes motor, sensory and reflex functions, which will be characterized as improved, maintained, or a deficit as compared with baseline status as follows:

A clinically meaningful neurological improvement is defined as a significant persistent improvement in neurological function that impacts subject's well-being and is attributable to a neurological finding; and is new or improved as compared with the baseline assessment.

A clinically meaningful neurological deficit is defined as a treatment-related significant persistent abnormality in neurological function that impacts subject's well-being and is attributable to a neurological finding; and is new or worsened as compared with the baseline assessment.

If neither a clinically meaningful neurological improvement nor a clinically meaningful neurological deficit is observed, then neurologic status is maintained.

For a clinically meaningful neurological deficit from Baseline, persistent is defined as lasting beyond what would be expected for a transient event in this population and unable to be resolved through device reprogramming.

Definitions

An **adverse event** (AE) is any untoward medical occurrence defined as an unintended disease or injury or untoward clinical signs (including abnormal laboratory findings deemed clinically significant as determined by the Investigator) in a subject whether or not related to the medical device or medication. This definition includes events related to the study treatments and events related to the study procedures. An AE is also any event related to any underlying medical condition, present at Baseline, which increases in severity by a clinically meaningful amount during the study as determined by the Investigator.

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

As the primary efficacy measure in this study is pain, lower limb peripheral neuropathic pain does *not* need to be reported as an adverse event unless it meets the definition of a serious adverse event. However, Investigators may, at their discretion, report any pain-related adverse events during the study.

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

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

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

An **unanticipated adverse device effect** (UADE) is a serious adverse device effect that was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

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

Reporting

All AEs, SAEs, and UADEs (see list in section C.1) occurring during the study will be collected. The site will document onset, severity, treatment/intervention provided, relationship to the treatment/procedure, and resolution and record the data on the Adverse Event eCRF. Any UADEs and/or deaths occurring during the study procedures will also be evaluated to determine whether the SCS system or medication might have caused or contributed to the event.

All SAEs/UADEs will be documented and reported to Nevro as soon as possible, but:

- no later than 48 hours after becoming aware of the SAE (US);

The Nevro contact information for these events is:

E-mail: sae@nevro.com
Tel: +1.650.251.0005
*Press 2 for Product Support
Fax: +1.650.251.9415

The Investigator or site staff may report an event to the sponsor by email, telephone or fax initially, but must follow-up by completing an Adverse Event eCRF. The eCRF should be accompanied by copies of source documentation regarding the event (e.g., physician/nurse notes or summaries/hospitalizations records; including hospital admission reports, progress notes and hospital discharge notes). The Investigator must also report the SAE to the IRB according to their local regulations. In the event of a subject death, all available information (e.g. autopsy or other post-mortem findings) should be provided with or on the eCRF.

An Investigator shall submit a report to the sponsor of any UADE occurring during the study as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect. Nevro will conduct an evaluation of the event to determine whether the event is an anticipated event based on labeling and risk analysis. The Investigator must also report the event to the IRB if it is determined to be unanticipated.

All AEs will be followed until the event is resolved (with or without sequelae). If a device-related event is ongoing at the time of study completion or termination, the subject will be followed until resolution or the Investigator determines that the subject's condition is stable.

In addition to the above reporting and in accordance with Medical Device Reporting requirements of 21 CFR 803, when using commercial medical devices, device related SAEs and UADEs must be reported to Nevro's Product Support Department at the above email, phone

number, or fax number, as specified in the manufacturer's labeling/manuals. If the "study related" box is checked on the AE eCRF, this reporting applies.

For all treatments administered as CMM, the Investigator shall report suspected medication-related or treatment-related AEs to the FDA or manufacturer according the site's usual practice and/or the manufacturer's label. The FDA contact information for these events is:

FDA: (800) FDA-1088 www.fda.gov/medwatch

Nevro will convene a Clinical Events Safety Committee with outside physician members to review SAEs, unanticipated device or medication-related AEs or SAEs, cases of persistent neurological deficits, and overall trends in AE frequencies throughout the course of the study.

B.7. Data Collection and Analysis

B.7.1. Data Collection

Data will be collected using eCRFs via an Electronic Data Capture (EDC) system (M-Core, Medrio Inc.). Data will be entered directly into eCRFs in the EDC system at the sites. The clinical site will record data on outcome variables as well as adverse events should they occur. Subject confidentiality will be maintained and each subject will be identified by his or her subject number. Subject names will not be published. Data collection is summarized in Table 1.

B.7.2. Data Handling

The Sponsor is responsible for data analyses. The sponsor and/or its affiliates will be responsible for compiling and submitting all required reports to governmental agencies.

Nevro personnel will follow Nevro's Standard Operating Procedures and supporting study-specific documentation when handling data.

B.7.3. Record Keeping

Source documents will be maintained by the Investigator and made available to the Sponsor for the purpose of monitoring the study. Investigators will be required to keep study records for a period of two (2) years or as defined by the local law and regulations where the study is conducted.

Passwords will be issued to appropriate personnel to insure confidentiality and protection of data.

The Investigator must contact the sponsor prior to destroying or archiving at an off-site facility any records, reports or study materials pertaining to this investigation to ensure that they no longer need to be retained on-site.

All original patient files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or medical practice or at a secure off-site facility. If archiving can no longer be maintained by the site, the investigator will notify the sponsor.

All data and documents shall be made available on request of the relevant authorities in case of an audit and/or inspection.

The sponsor will archive and retain all essential clinical investigation documents from prior, during and (as specified) after the clinical investigation as per requirements.

Table 1. Schedule of Events – Enrollment through 24 Month Visit

Assessment	Enrollment			Trial & Permanent Phase (SCS only)				Follow-up Phase						
Visit	Consent	Entry Criteria[a]	Baseline Assessment	Trial Implant	End of Trial (EoT)	Permanent Implant	Device Activation (DA)	1 Month Visit	3 Month Visit	6 Month Visit	9 Month Visit	12 Month Visit	18 Month Visit	24 Month Visit
Window	-			-	0-14 d from Trial Implant	0-60 d from EoT	0-14 d from Perm. Implant	4 wks ± 7 d from DA (SCS) or baseline (CMM)	12 wks ± 14 d from DA (SCS) or baseline (CMM)	24 wks ± 30 d from DA (SCS) or baseline (CMM)	36 wks ± 30 d from DA (SCS) or baseline (CMM)	52 wks ± 30 d from DA (SCS) or baseline (CMM)	78 wks ± 30 d from DA (SCS) or baseline (CMM)	104 wks ± 30 d from DA (SCS) or baseline (CMM)
Informed Consent	X													
Medication Usage		X[b]	X	X	X	X	X	X	X	X	X	X	X	X
Diabetes Medication Usage			X	X	X	X	X	X	X	X	X	X	X	X
Healthcare Utilization			X					X	X	X	X	X	X	X
Pain Assessment (VAS)		X	X		X			X	X	X	X	X	X	X
Weight		X	X						X	X		X		X
Pregnancy Test		X[c]												
Psychological Evaluation		X[d]												
Medical/Surgical History		X												
MRI		X[e]												
AP/Lateral and/or Oblique X-Rays[f]				X	X	X		[X]	[X]	[X]	[X]	[X]	[X]	[X]
Neuropathic Pain Assessment (DN4)			X		X			X	X	X		X		X
Modified Neuropathy Symptom Score (NSS)			X		X			X	X	X		X		X
Brief Pain Inventory (BPI-DPN)			X					X	X	X	X	X	X	X
Pain Experience (SF-MPQ-2)			X						X	X		X		X
Diabetes Quality of Life (DQOL)			X						X	X		X		X
Quality of Life Assessment (EQ-5D-5L)			X						X	X		X		X
Pain and Sleep Assessment (PSQ-3)			X					X	X	X	X	X	X	X
Pt Global Impression of Change (PGIC)									X	X		X		X
Clin Global Impression of Change (CGIC)									X	X		X		X
Assessment of Functioning (GAF)			X					X	X	X	X	X	X	X
6-Minute Walk Test (6MWT)			X						X			X		X
Labwork		X							X	X		X	X	X
Subject Satisfaction									X	X		X		X
Neurological Assessment			X		X				X	X		X		X
Work Status & Disability			X							X		X		X
Third-Party Payer Data			X											
Adverse Event Monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X
Wound Assessment			X				X	X	X	X	X	X	X	X
Device Programming[f]				X		X	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]
Paresthesia Assessment[f, g]				[X]	[X]	[X]	[X]	[X]	X	[X]	[X]	[X]	[X]	X
Pain Map[f]				X	[X]	[X]			X	X		X		X
Additional Symptom Map[f]				[X]		[X]			X	X		X		X
Crossover										[X]				
Study Completion[h]				[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	[X]	X

[a]All Entry Criteria to be completed before the Baseline Assessment. [b]Pain medications must be stable for ≥30 days before VAS may be completed. [c]To be completed for participants of child bearing potential. [d]Psychological evaluation to be completed for subjects who did not have an evaluation performed within the last 12 months. [e]MRI to be completed for subjects who did not have one within the last 12 months. [f]For SCS subjects only. [g]May be performed as appropriate, as determined by the field clinical engineer. [h]To be completed for all subjects upon completion of the study, including those who withdraw early or do not pass the Trial Phase. Trial failure subjects who were initially randomized to SCS will be followed for 6 months while subjects who fail trial after crossover will be followed for a minimum of 2 weeks or until resolution of an ongoing adverse event, if applicable, prior to completing this form. Wks = weeks, d = days, [X] = optional

B.8. Outcome Measurements

B.8.1. Effectiveness Measurements

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

Pain Visual Analog Scales: The visual analog scale (VAS) is a well validated and widely used scaled psychometric instrument to report pain severity. Subjects will score the severity of pain on a 10 cm line, with 0 indicating no pain and 10 indicating the worst pain imaginable.

Subjects will complete a chronic upper or lower limb pain VAS worksheet (either a questionnaire or CRF) in the clinic during scheduled study visits. Subjects will serve as their own control for the pain relief endpoint. Each subject's baseline pain score will be compared to the score at follow-up visits. Mean changes from baseline will be calculated for the entire cohort. The percentage of subjects who achieved ≥ 50% pain relief in their primary area of pain will also be calculated based on changes from baseline. VAS scores collected during the study visits will be used for the primary endpoint.

Douleur Neuropathique 4 (DN4): DN4 is a well validated survey to help identify subjects with neuropathic pain. The questionnaire has 10 yes/no items that describe qualities of pain as well as assess the presence of sensory nerve phenomena such as hypoesthesia and allodynia.

Modified Neuropathy Symptom Score (NSS): The modified NSS is a 5-item questionnaire with a maximum score of 9 that evaluates symptoms of neuropathy in the lower limbs.

Paresthesia assessment: Representatives of Nevro may record where subjects experience paresthesia with the SCS system at low (non-therapeutic) frequency. Summary results, if available, will be presented.

Brief Pain Inventory for Diabetic Peripheral Neuropathy (BPI-DPN): The BPI-DPN is a modified version of the Short Form BPI, a brief survey that assesses the severity of the subject's pain and the level of interference with typical life activities, such as sleeping, walking, and working. The BPI-DPN has been validated in patients with PDN.

McGill Pain Questionnaire: The Short Form McGill Pain Questionnaire version 2 (SF-MPQ-2, hereafter referred to as MPQ) is a well validated and widely used questionnaire used to measure the major symptoms of pain. Subjects will be asked to rate the intensity of each of 22 pain descriptors from 0 (do not experience, or none) to 10 (worst possible) at follow-up visits outlined in the schedule of events.

Four subscale scores (continuous pain, intermittent pain, predominantly neuropathic pain, and affective descriptors) and a total score will be calculated. Each subject's baseline scores will be compared to the scores at study visits. Mean change from baseline will be calculated for the entire cohort.

Diabetes Quality of Life Measure (DQOL): The DQOL is a patient-completed questionnaire with 46 items that ask the respondent to select a value of 1 to 5, with 1 representing "no impact," "no worries," and "always satisfied," while a score of 5 represents "always affected," "always worried," and "never satisfied." The measure was specifically developed and validated in diabetic patient populations. The total score can be broken down into four subscales:

satisfaction, impact, diabetes worry, and social worry. A lower score indicates a better quality of life.

EuroQol Five Dimensions Questionnaire (EQ-5D-5L): The EQ-5D-5L is a standardized quality of life questionnaire applicable to a wide range of health conditions. The questionnaire consists of 5 items as well as a health-related VAS and is completed by the subject.

Pain and Sleep Questionnaire Three-Item Index (PSQ-3): Pain and Sleep Questionnaire (PSQ), an eight-item questionnaire developed to assess the impact of pain on sleep. PSQ-3 is a subset of PSQ, consisting of questions 1, 4 and 5 and has been validated to assess impact of chronic pain on sleep.

Medication usage: Medication usage will be recorded at all study visits. Changes of usage for subjects will be summarized.

Healthcare Utilization: Doctors' office visits, ER visits, medical tests, and hospital admissions will be recorded at all follow-up visits.

Global Assessment of Functioning: Investigators will complete a Global Assessment of Functioning (GAF) scale to rate subjectively the social, occupational, and psychological functioning of subjects. This is a numeric scale, with scores of 0 through 100, with 100 being the highest functioning. Mean scores and changes from baseline will be calculated. A higher score indicates an improvement.

6-Minute Walk Test (6MWT): The 6MWT is an easily administered objective test of functional exercise capacity that measures the total distance a subject can walk during a finite time period.

Global Impression of Change: Both the subject and clinician will complete a global impression of change scale. This 7-point scale is used to assess the subject's global change in activity, limitations, symptoms, emotions and overall quality of life since the beginning of the study. Responses range from "no change (or condition has got worse)" to "a great deal better". Summary results will be presented for both the subject and clinician completed scales.

Subject Satisfaction Questionnaire: Subject satisfaction will be assessed using a 5 point scale. Responses range from "very satisfied" to "very dissatisfied." Summary results will be presented.

B.8.2. Safety Measurements

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

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

For purposes of consistent adverse event reporting and analysis, adverse events will be categorized using the Medical Dictionary for Regulatory Activities (MedDRA®) terminology, consistent with the *MedDRA® Term Selection: Points to Consider* document. Events are

grouped by System Organ Classification (SOC) and Preferred Term (PT), according to diagnosis and/or event description as provided by the Investigator on the eCRF.

Neurological Assessments: Neurological examinations include assessment of motor, sensory and reflex functions. Clinicians shall characterize the findings as improved, maintained, or a deficit as compared with baseline status, based on the following pre-specified definitions:

- A clinically meaningful neurological improvement is defined as a significant persistent improvement in neurological function that impacts subject's well-being, is attributable to a neurological finding, and is new or improved as compared with the baseline assessment.
- A clinically meaningful neurological deficit is defined as a treatment-related significant persistent abnormality in neurological function that impacts subject's well-being, is attributable to a neurological finding, and is new or worsened as compared with the baseline assessment.
- If neither a clinically meaningful neurological improvement nor a clinically meaningful neurological deficit is observed, then neurologic status is maintained.

  For clinically meaningful neurological change from baseline, *persistent* is defined as lasting beyond what would be expected for a transient event in this population and unable to be resolved through device reprogramming.

B.8.3. Statistical Analysis

Descriptive statistics will be used to summarize all subject 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. The statistical analysis plan (SAP) will be described in detail elsewhere.

C. Risk Analysis

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

Risks Associated with Study Assessments and Questionnaires:

The Senza System has received PMA approval and CE Mark for use of the device in the treatment of chronic intractable pain. Compared with standard practice, subjects who participate in this study will undergo medical assessments and complete questionnaires at scheduled intervals. There are no risks associated with completion of these assessments and questionnaires. Blood will also be drawn at various points in the study for laboratory tests and this procedure carries a risk of infection.

Risks Associated with Conventional Medical Management (CMM):

Investigators will follow their standard of care and/or published clinical guidelines (Dworkin, 2010) to administer CMM to both treatment groups. Treatments include, but are not limited to, pharmacological agents, physical therapy, cognitive therapy, chiropractic care, nerve blocks, and other non-invasive or minimally invasive therapies. The risks associated with these treatments are typical of routine medical care.

Spinal Cord Stimulation (SCS) Risks:

A risk analysis was completed in accordance with ISO 14971 – Application of Risk Management for Medical Devices. This analysis showed that the Senza System exhibits a safety profile equivalent to the other commercially available SCS stimulators.

There are known risks associated with the use of any SCS system. These risks include those related to the implant procedure, those related to stimulation, those related to the device (not associated with stimulation) and those related to the external devices such as the charger and remote control. Table 3 lists the type and level of risk associated with the use of SCS systems. These anticipated risks are typical of all SCS systems and are presented in the study informed consent, Patient Manual and Physician Implant Manual.

Table 3: Type and Level of Risk Associated with the Use of SCS Systems

Type of Risk	Level of Risk	Description of Risk
Implant Procedure	Possible	Surgical complications, infection, cellulitis, abscess, fever, sepsis
		Suboptimal lead/IPG placement or migration requiring explant, revision
		Bleeding
		Cerebrospinal fluid leak
		Epidural hemorrhage
		Temporary pain or persistent tenderness/pain at implant site
		Inadequate wound healing
		Hematoma, seroma or thrombosis
		Risks associated with anesthesia

	Unlikely	Nerve/nerve root/spinal cord injury
	Very Unlikely	Death Paralysis
Stimulation	Possible	Increased pain (other than at implant site or areas being treated) Increased pain (higher than before device implant) in the areas being treated Loss of pain relief Undesirable sensation, unpleasant paresthesia Undesirable/unwanted stimulation due to cellular changes around electrodes, changes in electrode position, loose electrical connections, or lead failure Uncomfortable stimulation of tissue around the leads including skin and muscle Intermittent stimulation Tingling, prickling or numbness in pain area
	Unlikely	Malfunction
	Very Unlikely	Seizure
Implanted Device	Possible	Tissue reaction or allergy to implanted materials External sources of electromagnetic interference that cause the device to malfunction and could affect stimulation
	Unlikely	Persistent pain at implant site (electrode or IPG) Failure of device components or the battery including lead breakage or movement (migration), hardware malfunctions, loose connections, electrical shorts or open circuits and lead insulation breaches Failure or malfunction requiring explant and re-implantation
	Very Unlikely	Skin erosion over lead or IPG site Pressure sores
External Device	Unlikely	Malfunction Uncomfortable heating effects, discomfort or burns

Other Risks – These warnings and precautions are discussed in the Patient Manual and Physician Implant Manual.

***SCS Warnings*:**

Other Active Implanted Devices – The Senza system may interfere with other implanted stimulators, such as cardiac pacemakers and defibrillators which have sensing features, and may result in sensing problems or inappropriate responses. The effect of other implanted devices, including deep brain stimulators, peripheral nerve stimulators, implanted drug delivery pumps, and cochlear implants on the Senza system are unknown.

Sleep – Patients using therapy that generates paresthesia (tingling sensations caused by stimulation) may choose to turn stimulation off to avoid uncomfortable sensations during sleep. Therapy at 10 kHz does not generate paresthesia and therefore stimulation can remain on during sleep.

Operation of Vehicles (e.g., driving) or Machinery – Patients using therapy that generates paresthesia should not operate motorized vehicles such as automobiles or potentially dangerous machinery and equipment with the stimulation on. Stimulation must be turned off first in such

cases. For these patients, any sudden stimulation changes may distract patients from proper operation of the vehicle, machinery, or equipment.

Therapy at 10 kHz does not generate paresthesia and it is less likely that sudden stimulation changes resulting in distraction could occur while having stimulation on when operating moving vehicles, machinery, and equipment.

Heat From Charging – The charging coil may become warm while charging. Patients may experience discomfort or burn if they charge while sleeping or do not use the provided charging belt. Additionally, the charger should not be placed over insensate skin.

Diathermy Therapy – Do not use shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy on patients implanted with a neuromodulation system. Energy from diathermy can be transferred through the implanted system and can cause tissue damage at the location of the implanted electrodes, resulting in severe injury or death. The neuromodulation system, whether it is turned on or off, may be damaged.

Computed Tomography (CT) – Before beginning a CT scan, the operator should use CT scout views to determine if implanted or externally worn electronic medical devices are present and if so, their location relative to the programmed scan range.

For CT procedures in which the medical device is in or immediately adjacent to the programmed scan range, the operator should:

- Determine the device type;
- If practical, try to move external devices out of the scan range;
- Ask patients with neurostimulators to shut off the device temporarily while the scan is performed;
- Minimize x-ray exposure to the implanted or externally worn electronic medical device by:
    - Using the lowest possible x-ray tube current consistent with obtaining the required image quality; and
    - Making sure that the x-ray beam does not dwell over the device for more than a few seconds;

Important note: For CT procedures that require scanning over the medical device continuously for more than a few seconds, as with CT perfusion or interventional exams, attending staff should be ready to take emergency measures to treat adverse reactions if they occur.

After CT scanning directly over the implanted or externally worn electronic medical device:

- Have the patient turn the device back on if it had been turned off prior to scanning.
- Have the patient check the device for proper functioning, even if the device was turned off.
- Advise patients to contact their healthcare provider as soon as possible if they suspect their device is not functioning properly after a CT scan.

Magnetic Resonance Imaging (MRI) – The Senza system is MR Conditional which means that safety has been demonstrated only within specifically defined conditions. Scanning under different conditions may result in severe patient injury or device malfunction. Refer to the Senza system 1.5T and 3T MRI Guidelines (US) manual for MRI-specific warnings and precautions on conducting a MRI scan on a patient with the Senza system.

Devices in Hospital/Medical Environments – The use of following medical devices or procedures may damage the SCS system or turn the stimulation off. After usage of these devices or procedures, the IPG may need to be explanted as a result of permanent damage.

- Electrocautery: The IPG should not be exposed to electrocautery. If electrocautery is necessary with the IPG implanted, use bipolar electrocautery. Do not use monopolar electrocautery.
- External defibrillation: The safety of discharge of an external defibrillator on patients implanted with an SCS system has not been established.
- Lithotripsy or high-output ultrasonics: Do not use these devices in patients with an implanted IPG.
- Radiation therapy: If radiation therapy is needed near the IPG, shield the area over the IPG.
- Ultrasonic scanning: Do not use it over the IPG.

If a patient is required to undergo lithotripsy, high-output ultrasound, electrocautery, external defibrillation, radiation therapy, or ultrasonic scanning, follow these precautions.

- Turn off the IPG before the procedure.
- Use the equipment as far away from the IPG as possible.
- Keep fields, such as current, radiation, or high-output ultrasonic beams, away from the IPG.
- Equipment should be set to the lowest energy setting possible.
- After the therapy or procedure, check to see that the IPG is functioning properly by gradually increasing the IPG's stimulation to the desired level.
- If the patient suspects that the device is not functioning properly after the use of these therapies or procedures, advise the patient to contact his or her healthcare provider.

Electromagnetic Interference (EMI) – Electromagnetic energy is generated by equipment found in the home, work, medical or public environments. Electromagnetic interference may occur when the energy is strong enough to interfere with neurostimulator function. Most electrical devices and magnets that patients will encounter in a normal day are unlikely to affect the operation of the SCS system. However, some equipment may generate strong electromagnetic fields that can turn the stimulator (IPG or trial stimulator [TSM]) off or cause shocks or jolts (see below). Patients should keep away from areas of EMI and turn off the stimulator if they are in such an area. The following are examples of sources that can potentially generate strong EMI.

- Theft detection systems or security screening devices (scanners and wands) such as those found in airport security screenings, retail stores, and libraries.

Note: It is recommended that patients request assistance to bypass the theft detector or security screener. If they must go through a screening device, the patient should turn off the stimulator and go through the area as quickly as possible and as far away from the theft detector or security screener as possible.

- Power lines and power generators
- Arc welders
- Large, magnetized stereo speakers
- Radio frequency identification devices (RFID)

If EMI is suspected or encountered, patients will need to turn off the stimulator. Then, the patients will need to move away from the EMI area and check whether the therapy is on or off. Before therapy can be turned off, the batteries may need to be replaced in the TSM or recharged in the IPG.

Strong electromagnetic interference can result in the following:

- **Serious patient injury,** resulting from heating of the implanted components of the neurostimulation system and damage to surrounding tissue.
- **System damage,** resulting in a loss of or change in symptom control and requiring surgical replacement.
- **Operational changes to the neurostimulator,** causing it to turn on or off
- **Unexpected changes in stimulation,** causing a momentary increase in stimulation or intermittent stimulation, which some patients have described as a jolting or shocking sensation. Although the unexpected change in stimulation may feel uncomfortable, it does not damage the device or injure the patient directly. In rare cases, as a result of the unexpected change in stimulation, patients have fallen down and been injured.

Strong electromagnetic fields arising from closeness to electrical equipment such as mobile phones, satellite phones and radio systems may interfere with the radio communication between the Remote Control and IPG. As described in the Troubleshooting section of the Patient Manual, communication failure is indicated by three beeps. Communication can be restored by moving away from the interfering electrical equipment and retrying the operation.

Electrostatic Discharge (ESD) is a common source of electromagnetic interference that can occur when a person or object accumulates a static charge. ESD is made worse by low humidity and synthetic materials.

- If the battery terminals of the Trial Simulator are exposed to ESD, the device may reset and stop stimulation. Stimulation can be restarted by following the instructions in the "How to Turn ON Stimulation" section of the Patient Manual. To avoid unintentionally stopping stimulation, do not open the battery compartment while stimulation is ongoing.
- ESD may cause the Charger to stop charging the IPG. If this happens, charging can be resumed by repeating the steps in the "How to Charge the IPG" section of the Patient Manual. ESD events can be minimized by keeping the charger in the Charger Holster while recharging the IPG.

Radio-frequency or microwave ablation – Safety has not been established for radiofrequency (RF) or microwave ablation in patients who have an implanted neurostimulation system. Induced electrical currents may cause heating, especially at the lead electrode site, resulting in tissue damage.

***SCS Precautions*:**

Patients Who Are Poor Surgical Candidates – Do not implant an SCS system if a patient is considered a poor surgical candidate. Implanting an SCS system has risks similar to surgical procedures of the spine, including spinal fluid leak, headaches, swelling, bruising, bleeding, infection, or paralysis.

Pregnancy – The safety and effectiveness of spinal cord stimulation has not been established for use during pregnancy and nursing.

Patient Activities – Patients using therapy that generates paresthesia (see Warning regarding Stimulation Frequencies) may experience increased paresthesia when changing posture or making abrupt movements. Such patients should lower the amplitude or turn off the stimulation before making posture changes, such as stretching and moving their arms over their head. If unpleasant sensations occur, the IPG should be turned off.

Stimulation at 10 kHz does not generate paresthesia, so patients should not experience unpleasant sensations caused by posture changes or movement. As such, patients would not need to change amplitudes in their programs in response to posture changes or movement.

Patient Activities Related to Lead Movement – Advise patients to not make sudden and excessive bending, stretching, or twisting movements, particularly within the first weeks after the surgery. An implanted lead can move from its original location during such movements, which might affect delivery of therapy. In such cases, the patient may need to be reprogrammed or the lead may need to be repositioned through another operation.

Scuba Diving and Hyperbaric Chambers – Patients with IPGs should avoid scuba diving to depths greater than 35 meters and hyperbaric chambers with pressure greater than 4.5 ATM. Pressure greater than 35 meters or 4.5 ATM may damage the Senza system.

Storage – Store the system components and accessories between the prescribed temperatures. Excessively hot or cold temperatures may damage the components, particularly high heat. Devices should be kept in temperature regulated areas within the acceptable temperature range. Do not expose the components to liquids or excessive moisture.

- The storage temperature for the IPG, Lead, Lead Extension, and Charger should not exceed the range of 0° C to 45° C (32° F to 113° F).
- The storage temperature for the Trial Stimulator and the Patient Remote Control should not exceed the range of -20 to 60 °C (-4 to 140 °F).
- The storage temperature for the Charger should not exceed 0 to 45°C (32 to 113 °F).

Sterilization – This device is for single use only and is not intended to be re-sterilized.

- Prior to opening the sterile package, inspect the sterilization indicator and the sterile package.
- Do not use the contents if the package is broken or torn, or if contamination is suspected because of a defective sterile package seal.
- Do not use any component that shows signs of damage.
- Do not re-sterilize the package or the contents. There is risk of infection and device malfunction.
- Do not use if "Use by" date has passed.
- All implanted components are intended for single use only. Do not re-use.

Handling – Use care when handling the system components and accessories. Do not drop them or submerge them in water. Do not impact the system components against hard surfaces and avoid rough handling. Although reliability testing has been performed to ensure quality manufacturing and performance, dropping the devices on hard surfaces or in water or other rough handling, can permanently damage the components and accessories. Do not plug the charger into a power source near water.

Handling the Leads and Lead Extensions - Follow these guidelines when handling the Leads or Lead Extensions:

- Lead and lead extension should be handled with care at all times.
- Do not make sharp bends to the lead or lead extension.
- Do not severely kink, crush or stretch the lead or lead extension.
- Do not apply severe torque (twist) to the lead or lead extension. Do not tie suture directly to the lead or the lead extension.
- When placing a suture around the lead, use the provided lead anchors.
- Do not force the lead into the epidural space. Use the lead blank prior to inserting the lead.
- Create a stress relief loop to minimize tension on the lead.
- Do not stretch the lead.
- Do not use sharp instruments to handle the lead or lead extension.
- Wipe off any bodily fluids (e.g. blood) from the lead's proximal end before connecting it to any other component.
- Wipe off any bodily fluids (e.g. blood) from the lead stylet before inserting or reinserting it into the lead.
- When inserting the stylet into the lead, do not use excessive force.

Handling the IPG - Follow these guidelines when handling the IPG:

- Avoid rough handling of the IPG.
- Take care not to drop the IPG. If it has been dropped on a hard surface, do not use the device and send it back to Nevro Corp.

System Compatibility – Do not use any cables or adaptors unless they are explicitly approved by Nevro Corp.

Transcranial Magnetic Stimulation (TMS) and Electroconvulsive Therapy (ECT) – Safety has not been established for TMS or ECT in patients who have an implanted neurostimulation system. Induced electrical currents may cause heating, especially at the lead electrode site, resulting in tissue damage.

Transcutaneous Electrical Nerve Stimulation – Do not place transcutaneous electrical nerve stimulation (TENS) electrodes so that the TENS current passes over any part of the neurostimulation system. If patients feel that the TENS may be interfering with the implanted neurostimulator, patients should discontinue using the TENS until they talk with their doctor.

Post-Operative Pain – In the days after the surgery, the patient may experience pain in the implant area, which is typical in SCS surgeries.

IPG Location and Patient Manipulation – Advise patients not to twist or rotate the IPG. If the IPG flips over in the body, the charger may not be able to charge the IPG. The patient's manipulation of the IPG in his or her body may cause the skin over the IPG to become thinner over time.

Infection – Use proper infection control procedures. If a patient experiences persistent discomfort or excessive redness around the wound areas, the patient may need to be checked for infection. Infections related to the SCS may require the implanted components to be explanted. Do not use the charger if the incision is not sufficiently healed. The charger and the charging belt are not sterile and should not be in contact with the incision.

Operating Temperature – The operating temperature range for the Patient Remote Control is 10 to 40 °C (50 to 104 °F). The operating temperature range for the Trial Stimulator is 10 to 38 °C (50 to 100 °F). While the Charger is plugged into the wall and charging itself, the operating temperature range for the Charging System is 10 to 40 °C (50 to 104 °F). While the Charger is charging the IPG, the operating temperature for the Charging System is 10 to 30 °C (50 to 86 °F).

Caring for the Trial Stimulator, Remote Control, and Charging System – These components can be cleaned by rubbing all surfaces without undue pressure with soft cloth damped with water, isopropyl alcohol or mild detergent. The remaining residue should be removed by wiping the surfaces with a dry cloth. Do not use abrasive cleansers for cleaning. Do not allow moisture to get inside the components.

Cell Phones – The impact of cell phones on the neuromodulation system is unknown at this time.

IPG Failure – If the patient's IPG does not provide stimulation even after complete charging of the IPG or replacement of the batteries in the Patient Remote Control, turn off the IPG and contact Nevro Corp. When frequency of recharging becomes too inconvenient for your patient, the IPG may need to be replaced. Contact Nevro Corp.

Device Disposal – Do not dispose the IPG, Patient Remote Control or Charger in fire. The battery in these devices can explode in fire. The IPG should be explanted in the case of cremation. All explanted IPGs should be returned to Nevro Corp. Do not dispose of electrical components, including batteries, in the unsorted municipal waste stream. Dispose of electrical components, including batteries, according to local regulations.

Risk Mitigation **-** The design of this study minimizes the potential for serious risk to the health, safety or welfare of the subject. At all times during this study, all subjects are under a physician's supervision and care. SCS implantation, the delivery of electrical stimulation, and CMM are also under the supervision and care of a physician.

The treatments used in this study involve routine medical procedures using standard products/technology (e.g., implantable pulse generator (IPG), electrodes, etc.) and CMM, in conjunction with known medical skills (e.g., surgical placement of IPGs and electrodes, imaging techniques, dosage titration, etc.). Examples include:

- Imaging of lead placement by fluoroscopy
- Surgical procedure for placement of the electrodes in the spinal epidural space, tunneling of the lead/electrode, and placement of the IPG
- Use of stimulation electrodes
- Setting of stimulation parameters and threshold levels
- Stimulation system removal
- Medication prescribing and titration to effect
- Administration of appropriate adjunctive therapies such as physical therapy, cognitive therapy, and chiropractic care.
- Pain, functional and quality of life measures

Overall, the potential risks associated with this study are identical to those of commercially available medical treatments, including the use of the Senza System or other commercially available SCS systems as well as CMM.

C.2. Potential Benefits to the Subject

It is possible that individual subjects will experience no benefit from participation in this study. Additionally, if the subject receives a reduction in pain from study treatments, it is not known how long the benefit will last.

C.3. Minimization of Risks

The Senza System used in this study is identical to the commercially available Senza System and is designed to operate in a similar fashion as other commercially available SCS devices. 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 drugs used to treat chronic pain conditions. Additionally, the treatment is reversible in that the SCS device may be turned off and/or explanted at any time for any reason. CMM as defined in this study is identical to routine, commercially available medical care for patients with neuropathic limb pain.

Investigators will be experienced in the diagnosis and treatment of chronic pain, including prescribing medications, proper surgical and clinical training, and will take adequate steps to ensure subject safety during implant procedures and throughout the study. As is done with commercial SCS device systems, Investigators and study personnel will receive product training to become familiar with the components of the Senza System and their functions.

C.4. Justification for the Investigation

A justification for the study is provided in the rationale section (section B.1). In brief, if HF10 therapy proves safe and effective in reducing pain and disability associated with chronic neuropathic pain of the lower limbs due to painful diabetic peripheral neuropathy it would have important health, quality of life, and economic benefits for many thousands of people. This potential benefit outweighs the potential risk of harm to the subjects in this study.

C.5. Description of the Subject Population

Subjects participating in the study will be subjects who have been clinically diagnosed with chronic neuropathic pain of the lower limbs as a result of painful diabetic peripheral neuropathy.

In the study, up to 432 subjects will be enrolled in order to obtain 108 subjects randomized to each of two treatment groups: HF10 therapy plus CMM subjects and CMM only subjects.

Standardized, validated, and reliable tests of pain, disability, functioning, healthcare utilization (including medications, office visits, and hospital admissions), health-related quality of life, and sleep will be administered to each subject at Baseline, and followed through the course of treatment and follow-up.

After patient enrollment, patient demographic and third party payer coverage data will be collected. This will allow an understanding of the third party payer coverage landscape for the study patients, including the percentage of Medicare-eligible patients. This information is not for the purpose of assessing safety and effectiveness, but is expected to help determine the degree to which beneficiaries may be affected by the device under investigation and how the generalizability of the study results to the Medicare beneficiary population in relation to age, disability, or other eligibility status.

D. Description of the Study Interventions

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

D.1.1. Device System Overview

The Senza System is a totally implantable spinal cord stimulation system that is intended to aid in the management of chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: failed back surgery syndrome, intractable low back pain, and leg pain, and received CE Mark in May 2010, Therapeutic Goods Administration (TGA) approval in Australia in June 2011, and FDA PMA approval in May 2015. The Senza System is similar to other commercially available SCS systems in design and function.

The Senza System consists of a rechargeable implantable pulse generator (IPG) with 16 output channels. The IPG is implanted in a subcutaneous pocket and is capable of stimulating the spinal cord nerves when used with one or two 8-contact percutaneous leads. The IPG is controlled by a Patient Remote and/or the Programmer.

Other components of the system include an external Trial Stimulator capable of delivering the same stimulation as the IPG, Lead, Extensions, Charger and charging system, operating room (OR) cables and surgical accessories.

D.1.2. Device System Details

D.1.2.1. Major Components

Implantable Pulse Generator (Figure 2): The Implantable Pulse Generator (IPG) is a rechargeable implantable device with 16 output channels. Each of the 16 outputs can be programmed as a cathode or an anode. The IPG is powered by a nominal Li-Ion rechargeable battery (single cell). It is capable of stimulating the spinal cord nerves through the electrodes of the leads connected to any combination of the output terminals, using a single current source. The IPG is designed to produce a charge-balanced, biphasic capacitively-coupled rectangular output pulse. The IPG is current-regulated and capable of delivering an output energy level between 0-15 μC/per phase. This is equivalent to the commercially available SCS devices.

The hermetic IPG enclosure is made of Titanium Grade 1 or 2, with the dimensions of 54.5 mm (height without header, with header 72.5 mm), 47.5 mm (width) and 11.5 mm (thickness). The epoxy header contains the charging coil, feed thru, RF antenna, and two ports to allow the insertion of two 8-contact leads. The battery housing is hermetically sealed and fits inside the hermetic IPG enclosure. Currently FDA-approved IPG models, including Senza® and Senza II®, as well as future FDA-approved IPG models with similar capabilities may be incorporated into this clinical study.

Figure 2. Implantable Pulse Generator

IPG/Trial Stimulator interface with other Senza components (Figure 3): A bi-directional communication link exists between the IPG and the Charger. Similar to other commercial SCS systems, the Charger uses transcutaneous RF energy transmission in order to recharge the IPG battery. Energy is transmitted from the Charger to the IPG using a frequency between 410 kHz and 485 kHz. The IPG is capable of communicating with the Charger to control the recharging function.

The IPG/Trial Stimulator uses the MedRadio band frequency between 402 MHz and 405 MHz (RF) in order to communicate with the Patient Remote or Programmer (a personal computer, PC) via the Programmer Wand. The Programmer Wand is used to program the IPG/Trial Stimulator and retrieves diagnostic information from either the IPG/Trial Stimulator. The RF antenna is located in the header of the IPG.

The subject is also able to send commands to the IPG/Trial Stimulator directly using the Patient Remote. The wireless telemetry technology in the Senza System allows communication between the IPG/Trial Stimulator and Patient Remote of greater than 2 feet. The IPG also includes a magnetic switch for turning the therapy off by using an external magnet.

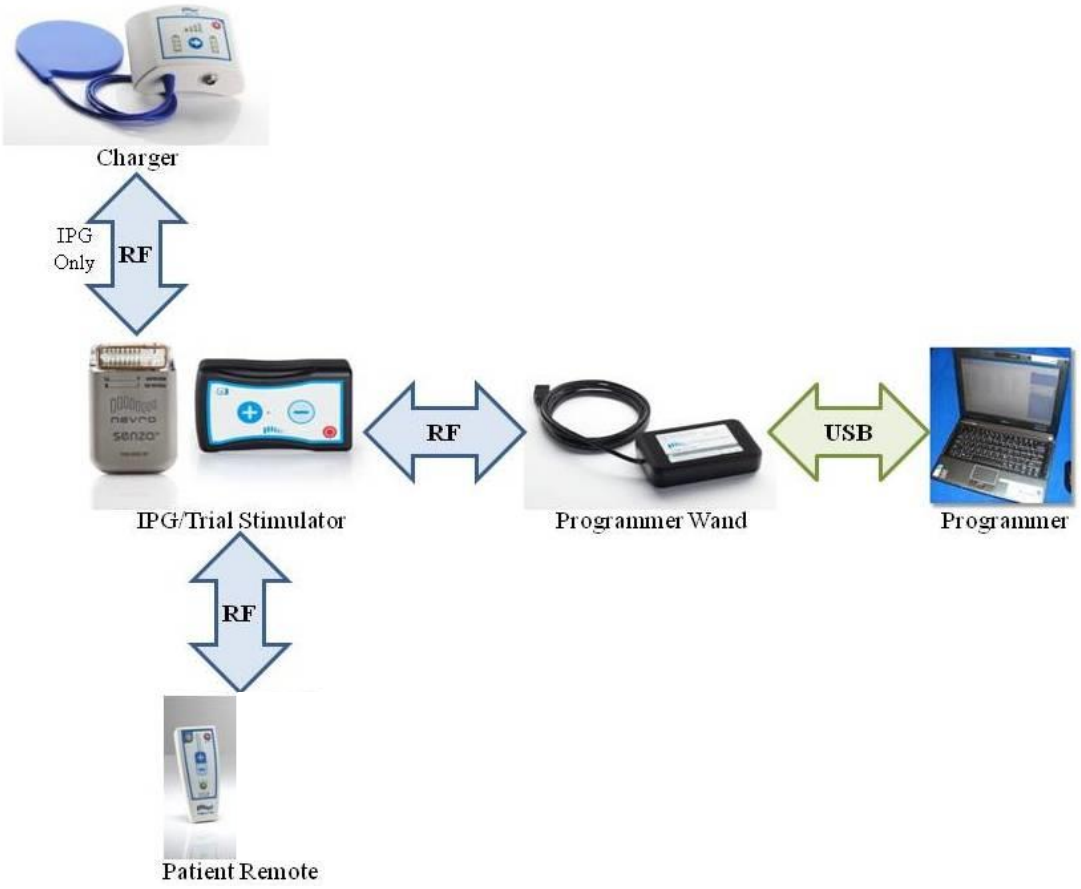


Figure 3. Graphical Representation of the Senza System

Trial Stimulator (Figure 4): The Trial Stimulator is a handheld device powered by 2 lithium 3.6V AA batteries and is capable of providing the same stimulation as the IPG. During the Trial Phase of SCS, the subject wears this external Trial Stimulator for a period of time to evaluate the effectiveness of the stimulation prior to receiving a permanent implant. The Trial Stimulator is connected to the subject's implanted leads by the use of OR cables.

Figure 4. Trial Stimulator

Patient Remote (Figure 5): The Patient Remote is a handheld battery operated unit able to communicate via RF with the IPG/Trial Stimulator. It is used by the subject to select the stimulation program to be applied, to activate and deactivate the IPG/Trial Stimulator and change stimulation amplitude.

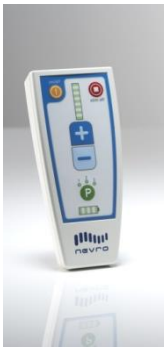


Figure 5. Patient Remote

Charger (Figure 6): This Charger is used by the subject to transcutaneously charge the IPG battery. It is a portable device powered by a rechargeable battery and can be held in one hand.

Figure 6. Charger

Programmer: The Programmer is an off-the-shelf laptop installed with proprietary Nevro software to allow the programming of the IPG/Trial Stimulator and Patient Remote via the Programmer Wand.

Programmer Wand (Figure 7): The Programmer Wand is the Programmer interface that allows the communication with an IPG or Trial Stimulator. The Programmer Wand connects to the Programmer laptop through a USB port and communicates via RF with the IPG or Trial Stimulator.

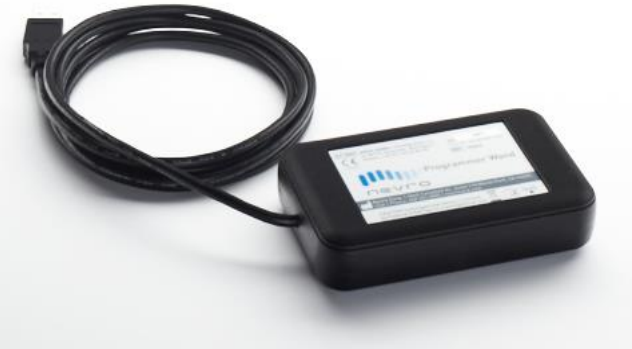


Figure 7. Programmer Wand

Percutaneous Leads (Figure 8) and Lead Extensions (Figure 9): Similar to available commercial SCS systems, the Nevro Lead is intended to be used with the IPG or Trial Stimulator for use in delivering stimulation in the spinal cord. The Percutaneous Lead is intended to be single use and interfaces with the IPG, Lead Extensions, OR Cable, and lead accessories.

The Percutaneous Lead has an isodiametric body made out of Pellathane 55D, which carries eight low impedance cables that conduct signals from the contact rings on the proximal end of the lead to the distal electrodes. The proximal connector end has eight (8) individual contacts which interface with the Nevro IPG and Lead Extensions. The Lead proximal end also has an electrically isolated retention ring to reversibly anchor the Lead in the IPG or Lead Extension using a set screw.

Figure 8. Percutaneous Lead

The Lead Extension is intended to be used when the implant site for the IPG is located too far from the stimulation site to directly connect to the Percutaneous Lead. The design, material and construction methods on the proximal end and lead body of the Lead Extension are identical to the Percutaneous Lead. The distal end of the Lead Extension is designed to accept the proximal end of the Percutaneous Lead. The Lead Extension is the same size and diameter as the Percutaneous Lead except at the distal end where the Extension has a larger diameter to accept the proximal portion of the Percutaneous Lead.

The construction of the Lead Extension is identical along its length to the Percutaneous Lead.

Figure 9. Lead Extension

D.1.2.2. Surgical Accessories

Torque Wrench: The Torque Wrench is used to tighten the set screws that lock the Percutaneous Lead into the IPG or to lock the Percutaneous Lead into a Lead Extension.

Lead anchors: The Lead Anchors are used to anchor the Percutaneous Lead to the fascia or supraspinous ligament. Lead Anchors are designed to slide freely over the lead length to

the required fixation position and sutures are then tied around the anchor clamping the sleeve in place on the lead. Lead anchors may be used to possibly prevent lead migration and/or lead strain.

Insertion Needle: The Insertion Needle is used during implant surgery to introduce the Percutaneous Lead between the vertebrae into the epidural space. The Insertion Needle is a two part needle that contains a cannula and Stylet to facilitate access to the spinal canal for lead placement. This Insertion Needle is a 14GA epidural needle with thin wall and a Touhy non-coring tip. The Stylet and cannula are designed to lock together to maintain the orientation of the tip of each component, and the hub has a standard luer fitting.

Coiled Lead Blank: The Coiled Lead Blank made out of stainless steel is optionally used during surgery to clear a path for the introduction of the Percutaneous Lead into the epidural space. The Lead Blank has an outer diameter similar in size to the Lead and is designed to be flexible.

Stylets: The Stylets are used to push and "steer" the Lead into place. There are two different configurations of the Stylet's distal end, "straight" and "curved". These are standard commercial configurations offering the implanter the flexibility to choose the configuration to best maneuver the Leads through the epidural space to the desired implant location.

IPG Port Plug: The IPG Port Plug is provided to seal the port of the IPG that is not in use when only one Lead is implanted.

OR Cables: The OR Cables with extension and connector are used during the Percutaneous Lead implant procedure and subject Trial Phase to make electrical and mechanical connections between the Trial Stimulator and the Percutaneous Leads or Lead Extensions.

Tunneling Tool: The Tunneling Tool creates a subcutaneous tunnel for the leads from the IPG site to the midline incision. This single use tool is provided with two versions of tunneling tips; one (1) trocar tip and one (1) blunt tip.

IPG Template: The IPG Template acts as an aid for the physician in proper sizing of the pocket for the IPG within each subject.

D.2. Principle of Operation of the Device

The Senza System works on the same basic principle as commercially marketed spinal cord/electrical stimulators/IPGs and epidural electrodes. Spinal cord stimulation has been used for decades and studied extensively.

Manufacturing and quality testing is performed to verify the proper functionality of the Senza System prior to device shipment. Additional testing is performed at the clinical site to verify Senza System function prior to implantation - refer to the Senza Physician's Implant Manual.

D.3. Description of Conventional Medical Management (CMM)

CMM may include a variety of non-invasive or minimally invasive treatments that comprise the standard of care for neuropathic limb pain. Investigators will follow their standard of care and/or published clinical guidelines (Dworkin, 2010) to administer CMM to both treatment groups. Treatments include, but are not limited to, pharmacological agents, physical therapy, cognitive therapy, chiropractic care, nerve blocks, and other non-invasive or minimally invasive therapies.

D.4. Labeling, Supply and Storage of Device

Instructions for Use: The Senza System will be used in accordance to the Physician Implant Manual.

Labeling: For this study, the Senza System labeling will be consistent with the FDA-approved labeling for commercial distribution in the U.S.

The clinical sites will be responsible for safely storing components of the Senza System. All study supplies will be maintained in a locked, limited access area and stored at room temperature.

D.5. Any Anticipated Changes in the Device

For any changes to the device, Nevro will comply with the regulations for modifications to a PMA-approved device.

D.6. Device Accountability

Investigators or designees are responsible for maintaining accurate accountability records of the study products throughout the clinical study. Device accountability will be recorded on a Device Billing and Registration Form.

E. Administrative Procedures

E.1. Monitoring

E.1.1. Study Monitor

The Clinical Monitor(s) assigned to the study will fulfill the required Sponsor and monitor responsibilities. He/she will be responsible for monitoring subject eCRF data, reviewing the regulatory documentation, ensuring that the investigational plan has been approved by the IRB and assuring compliance with this investigational plan.

E.1.2. Monitoring Procedures

Monitoring visits to the clinical sites will be made periodically for the purpose of ensuring that Investigators and their staff understand and accept their defined responsibilities, assessing compliance with current Good Clinical Practices (GCP) guidelines, evaluating clinical trial progress, assessing the continued acceptability of the clinical site facilities, assessing compliance with this investigational plan, and verifying the data recorded on the eCRFs.

eCRFs, designed by Nevro, will be used for the collection and recording of data at the clinical site. Investigators will be responsible for the timely completion of these forms to Nevro.

- Investigators are to maintain all source documents as required by the investigational plan, including laboratory results, supporting medical records, informed consents and applicable electronic files. The source documents will be used at the regular monitoring visits to verify information submitted on the eCRFs. Clinical monitoring will include review and resolution of missing or inconsistent results to assure the accuracy of the reported data. Where any discrepancies are noted, they will be resolved with the Investigator and/or an individual designated by the Investigator. Where the data are incomplete, attempts will be made to obtain the missing data. The source documents will remain at the clinical sites.

Subject safety will be ensured by noting that the consent was properly documented, the investigational plan was followed, and that adverse events were reported and followed-up as appropriate.

The Clinical Monitor will evaluate and summarize the results of each clinical site visit in written reports, identifying any repeated data problems with any Investigator and specifying recommendations for resolution of noted deficiencies.

The conduct and monitoring of the clinical investigation will be conducted in accordance with Nevro's internal procedures (including the Monitoring Plan) as required by the regulations.

E.2. Data Quality Assurance

The eCRF data will be entered into an EDC (M-Core, Medrio Inc.) at the sites. The data will be reviewed to identify inconsistent or missing data and potential 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 data management department at Nevro will ensure that all hard copy forms and data files are secured in order to maintain confidentiality.

E.3. Study Conduct

The Investigator agrees that the study will be conducted according to this investigation plan and the ICH guidelines on GCP and principles of cGCPs as outlined in the United States Code of Federal Regulations (CFR) - 21 CFR Parts 50, 56, and 812, the Declaration of Helsinki (version 2013) and other applicable regulatory requirements. The Investigator will conduct all aspects of the study in accordance with all Federal and local laws of pertinent regulatory authorities. All clinical data will be recorded promptly, accurately, legibly, directly and indelibly manually on appropriate sheets/forms or eCRFs.

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.

All clinical study findings and documents will be regarded as confidential. Investigators and designees will not disclose such information without prior written approval from the sponsor as spelled out in the clinical trial agreement (CTA).

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

E.4. Informed Consent Materials

Written informed consent must be obtained from all subjects prior to study participation. Consent will be obtained by the Investigator or an Investigator-designated healthcare professional. The original signed consent, as approved by the respective clinical site Institutional Review Board (IRB), will be retained in the subject's study records at the clinical site. The informed consent is in compliance with the requirements set forth in 21 CFR 50, Protection of Human Subjects.

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

E.5. IRB Information

IRB approval is required prior to initiation of the study at the clinical site. Approval will be obtained by the clinical Investigator who will submit the investigational plan and supportive information for IRB review and approval.

E.6. Investigators and Institutions

This is a multicenter study. The clinical Investigators participating in this study will be chosen based on their qualifications and experience. All sites will obtain IRB approval prior to enrolling subjects in the study.

E.7. Amendments and Deviations

The investigational plan is to be followed by Investigators and all personnel involved in the clinical study. Changes to the study covered by this investigational plan must be documented on a formal investigational plan amendment *prior to* implementation in the study. Amendments to the investigational plan may be initiated by Nevro or at the request of the Investigator. A formal

amendment cannot be initiated by an Investigator or clinical site personnel without Nevro's approval or IRB approval (if applicable), and Investigator approval.

- *Exception for Emergency Deviation*: The 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 Nevro only in cases where a change is necessary to eliminate immediate apparent hazard to subjects. Emergency deviations must be reported to Nevro and the IRB no later than 24 hours following the emergency.

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

E.8. Additional Record and Reports

Sponsor/Investigator Records and Reports will be maintained and provided in accordance to 21 CFR 312.50-312.68, 812.140 and 812.150. No additional records or reports will be maintained.

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