STUDY TITLE

Spinal Cord Stimulation in the Treatment of Chronic, Intractable Pain using the Nalu™ Neurostimulation System (nPower™- US)

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Spinal Cord Stimulation in the treatment of Chronic, Intractable Pain using the Nalu™ Neurostimulation System (nPower™-US)

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Study Sponsor:	CRO Performing Site Management: NA
Nalu Medical, Inc. 2320 Faraday Ave Ste 100 Carlsbad, CA 92008 USA	

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Clinical site list, including investigators, sites, and institutions, to be kept separately from this protocol.

Approval Signatures

	Name	Signature	Date
VP Clinical Affairs	Patrick Martin	DocuSigned by: Patrick Martin 6DA282CA10844F3...	7/9/2021

1 Protocol Signature Page

Investigator's statement

I agree to conduct this clinical investigation in accordance with the design and specific provisions of this protocol; modifications to the study are acceptable only with a mutually agreed upon protocol amendment as approved by the sponsor and ethics review board. I agree to await ethics review board approval of the protocol and informed consent before initiating the study, obtain consent from subjects prior to their enrollment in the study, collect and record data as required by the protocol and case report forms and maintain study documents for the required period of time.

Confidentiality Statement

The confidential information in the following document is provided to you as an Investigator or Consultant for review by you and your staff. An Independent Ethics Committee or Institutional Review Board may also review the document. By accepting the document, you agree that the information contained herein will not be disclosed to others without written authorization from Nalu Medical except to the extent necessary to obtain subject/patient informed consent.

Investigator's Name: Date of Signature:

Investigator's Title:

Investigator's Signature:

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2 Protocol Synopsis

Title	Spinal Cord Stimulation in the treatment of Chronic, Intractable Pain using the Nalu™ Neurostimulation System (nPower™-US)
Protocol Number	NAL-01-2020-US
Study Device	Nalu™ Neurostimulation System
Intended Use	The Nalu Neurostimualtion System is indicated as the sole mitigating agent or as an adjunct to other modes of therapy used in a multidisciplinary approach for chronic, intractable pain of the trunk and/or limbs, including unilateral and bilateral pain. The trial devices are solely used for trial stimulation (no longer than 30 days) to determine efficacy before recommendation for a permanent (long term) device.
Study Population	Adults with chronic intractable pain in the legs and back, who meet the inclusion/exclusion criteria of the study.
Study Objectives	The primary objective of this study is to confirm the safety, comfort, and efficacy with the Nalu Neurostimulation System. Additional objectives include evaluation of responder rate and patient satisfaction with the various therapy options in subjects with chronic pain. Patient reported secondary outcomes (ODI, BDI, PGIC, EQ-5D, PROMIS sleep disturbance SF etc.) will be captured to assess patient response.
Study Design	Prospective, multi-center, open-label, clinical study. The study will include 3 phases: Screening/baseline, SCS Trial Phase, and Permanent Implant phase (Figure 2). Study subjects will be followed for up to 3-months after device activation. The study is expected to take 2.5 years from first enrollment to last follow up of last subject and subsequent study closure.
Population Size	Up to 250 subjects will be implanted at up to 25 centers in the United States. It is expected that up to 500 subjects will be consented and about 50% of these subjects will be screen or trial failures.
Inclusion Criteria	Inclusion criteria for subjects: 1. Subject is between 21 and 80 years of age at enrollment. 2. Subject has chronic (defined as at least 6 months duration), intractable neuropathic pain of back and/or leg(s); any nociceptive pain must be less prominent than the neuropathic pain. 3. Subject's pain is unresponsive to conservative treatment options for a minimum of 3-months. 4. Subject has a VAS score of at least 6 in the back and/or leg at screening. 5. Subject is able to distinguish between leg pain and back pain. 6. Subject is considered by the Investigator as a candidate for implantation of a spinal cord stimulator system. 7. Subject is willing to cooperate with the study requirements including compliance with the study procedures and completion of all study visits. 8. Pain Symptoms should be predominantly neuropathic in nature. 9. Subject reported stable pain (non-escalating) for 30 days prior to signing informed consent. 10. Subject has had stable pain medication use and dosage for 30 days prior to signing informed consent.

	11. Subject is psychologically qualified to receive a spinal cord stimulator as per the clinician's standard clinical practice and does not have clinically relevant psychological condition(s) that would interfere with ability to accurately report outcomes or complete study procedures. 12. Subject is able to independently complete the pain diary and subject questionnaires. 13. Subject has demonstrated the ability to appropriately place the adhesive clip on the low back.
Exclusion Criteria	1. Subject currently has an active implantable medical device such as a drug pump, spinal cord stimulator, sacral nerve stimulator, deep brain stimulator, and/or cardiac pacemaker. 2. Subject has previously failed SCS therapy (either trial system evaluation or permanent implant). 3. Subject has had an ablative procedure directed at the spinal cord including the dorsal root entry zone (DREZ) or dorsal root ganglion (DRG). 4. Subject has pain in another anatomic region besides the leg(s) and back that would interfere with their ability to accurately report pain (e.g. hip joint pain). 5. Subject has mechanical spine instability detected by > 4 mm translational movement or excessive angular movement manifested by 20 degrees greater angular movement than in an adjacent segment based on flexion/extension films of lumbar spine (imaging is required for this determination and must have been done within the past 6 months or during screening). 6. Pain is absent at rest. 7. Subject has a medical condition that would prevent them from participating in the current study per investigator's or medical monitor's judgment. 8. Subject has had a successful interventional procedure within the past 3 months to treat the same pain condition(s) being examined in this study. 9. Subject is currently participating in another clinical investigation with an active treatment arm. 10. Subject is allergic to materials used in the device components including skin adhesives. 11. Subject is sensitive to skin adhesives used in the system or does not tolerate the wearable aspect of the device. 12. Subject has pending or ongoing legal issues (including unresolved worker's compensation claims or equivalent) or other conflicting secondary gain issues related to their chronic pain condition. 13. Subject has a current diagnosis of a coagulation disorder, bleeding diathesis, progressive peripheral vascular disease or uncontrolled diabetes mellitus that have not been medically corrected. 14. Subject has an active systemic infection. 15. Subject is unable to read and/or write or give informed consent. 16. Subject has a life expectancy of less than 1 year. 17. Subject has evidence of diabetic neuropathic pain on clinical exam 18. Subject has evidence of an alcohol or drug dependency within the last 6 months of enrollment.

	19. Subject is pregnant (if female and sexually active, subject must be using a reliable form of birth control, be surgically sterile or be at least 1 year post-menopausal). 20. Subject is nursing/breastfeeding. 21. Subject is on >90 mg-morphine equivalents per 24 hours.
Safety Measures	All adverse events will be recorded. The following types of events will be tabulated: • Serious adverse device effect • Adverse events • Adverse device effects • Serious adverse events
Performance Measures	• Wearable components ease of use, compliance and comfort questionnaires • Wearable usability diary • Pain scores (Visual Analogue Score (VAS), in office; Numeric Rating Scale (NRS), in office; NRS at- home diary) • Responder rates, defined as percentage of subjects with ≥50% reduction in pain score at 3 months compared to baseline • Quality of life (EQ5D) • Activities of Daily Living (Oswestry Disability Index, ODI) • Pain and paresthesia maps • Pain medication use • Procedure information, including surgical approaches, epidural lead placement locations, and surgical times • device performance information, including stimulation parameters, impedance measurements • Patient-reported questionnaire on device use • Physician Implantation Procedure questionnaire on device use • Beck Depression Inventory (BDI) • PROMIS Sleep Disturbance SF
Statistical Considerations	This study will not be formally powered, as it is a post-market data collection study. Basic statistical analyses will be completed on all endpoints including computation of average, variance, standard deviations, and trend analysis. Parametric and non-parametric statistics may be employed, as appropriate, to test for statistical significance or for trends in the data. Secondary objective data may be qualitative only and primarily will be used to guide further product design refinement.

3 Abbreviations and Definitions

Term	Definition
ADE	Adverse Device Effect
AE	Adverse Event
AP	Advanced Programming
BDI	Beck Depression Inventory
Clinic	Investigator's consulting rooms where all non-surgical research visits will be performed
Clinical Research Personnel	Nalu Medical employee or contractor responsible for planning and execution of the clinical trial
Clinical Site Staff	Member of Investigators site responsible for managing the clinical trial
CMM	Conventional Medical Management
CP	Clinician Programmer
CRF	Case Report Form
eCRF	Electronic Case Report Form
DCF	Data Clarification Form
DREZ	Dorsal Root Entry Zone
EC	Ethics Committee
EDC	Electronic Data Capture
EQ-5D	EuroQol-5D questionnaire
FBSS	Failed Back Surgery Syndrome
FCE	Field Clinical Engineer – Sponsor representative who operates stimulation equipment
IFU	Instructions for Use
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
NRS	Numeric Rating Scale
ODI	Oswestry Disability Index questionnaire
PC	Personal Computer
PGIC	Patient Global Impression of Change
PROMIS	Patient Reported Outcomes Measurement Information System
QoL	Quality of Life questionnaire
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SCS	Spinal Cord Stimulation
SF	Short Form
Sponsor	Nalu Medical: the Sponsor initiates, organizes and supports the clinical study and takes responsibility for the overall conduct of the trial

Study Monitor	Nalu Medical employee or contractor responsible for execution of the monitoring plan to oversee the progress of the study at the investigational site
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analogue Scale
WDR	Wide Dynamic Range

4 Introduction

Nalu Medical (the sponsor) has developed a small, implantable spinal cord stimulation (SCS) system that is designed as an aid in the management of chronic intractable pain. The implanted device is externally powered and is approximately 1.5 cc in volume. The Nalu Neurostimulation System is capable of delivering multiple therapy options to address patient needs. The primary objective of this study is to confirm the safety, efficacy, comfort and compliance with the Nalu Neurostimulation system. Additional objectives include evaluation of responder rate and patient satisfaction with the various therapy options, in subjects with chronic pain. Patient reported secondary outcomes (ODI, BDI, PGIC, EQ-5D, PROMIS sleep disturbance SF etc.) will be captured to assess patient response.

5 Clinical Background

5.1 Chronic Pain

Chronic pain can be defined as pain lasting more than 6 months (Bonica, 1990), and it is often neuropathic in nature. Neuropathic pain differs from nociceptive pain in that it may be idiopathic in origin or arises following focal damage to the nervous system. With nociceptive pain, the painful sensation typically subsides with healing; whereas in the case of neuropathic pain, it may last months or years, and may never subside in some patients (Bennett, 1994).

One common cause of neuropathic pain is failed back surgery syndrome (FBSS) or post-lumbar laminectomy syndrome, which manifests after one or more surgical interventions in the lumbar or sacral spine (Van Buyten and Linderoth, 2010). FBSS is often associated with intractable neuropathic low back and leg pain; meaning significant pain persists, hindering the patient's function, activities of daily living and quality of life even after multiple potential interventions including injections, nerve blocks and pain medications. The causes of FBSS can include surgical damage to spinal nerves or joints, nerve roots, dura or even the spinal cord itself. Post-operative fibrosis and arachnoiditis may also be contributing factors (North et al. 1993, 1995; Rainov et al. 1996; Devulder et al. 1997; Wetzel et al. 2000).

5.2 Chronic Pain Treatments

Conservative therapies are the first line of treatment for chronic pain syndromes. These include exercise, physical, occupational and massage therapy. Biofeedback, TENS, behavioral and cognitive therapy may also be employed. Over-the-counter pain medications round out the first line treatments. The second line of treatment include nerve blocks through injection of steroids or local anesthetics. Prescription medications such as opioids and/or membrane stabilizers may also be indicated at this stage. Additionally, systemic infusion trials (Ketamine) may be of benefit. The last line, and more invasive of treatment include neurostimulation, intrathecal drug infusion, and neuroablation. Neurostimulation may include SCS, deep brain stimulation or peripheral nerve stimulation. Intrathecal or epidural spinal infusion may consist of opiates, local anesthetics, alpha-adrenergic agonists, and novel neuromodulators as

therapeutic options. Neuroablation of the central nervous system is another therapeutic option, which may include severing the dorsal roots of the afferent innervation into the spinal cord or lesioning a relevant section of the spinal cord. It can also include creating small lesions in the thalamus.

5.3 Spinal Cord Stimulation (SCS)

Spinal cord stimulation is an effective method of pain relief when conservative measures have been unsuccessful (Kumar et al. 2007; 2008; North et al. 2005). Kumar et al. (2007, PROCESS Study) randomized 100 FBSS subjects with neuropathic pain of the legs into one of two groups: 1) SCS plus conventional medical management (CMM), and 2) CMM alone. At 6 months 48% of the SCS and 9% of CMM showed a >50% reduction in pain ratings ($p<0.001$). Between 6 and 12 months, subjects were given the option to cross over into the other group. Only 5 SCS subjects crossed into the CMM group, whereas 32 CMM subjects crossed into the SCS group. The SCS subjects also improved in all quality of life and functional capacity measures ($p<0.05$ for all comparisons). At 24 months (Kumar et al. 2008) 42 of the 52 subjects randomized to SCS reported significant improvement in leg pain ($p<0.0001$), quality of life ($p<0.01$) and functional capacity ($p<0.0002$).

North et al (2005) compared spinal cord stimulation to repeat back surgery in subjects who had undergone at least one previous surgery. In this study, subjects with FBSS and primary leg pain were randomized to either repeat back surgery or SCS therapy. Of the 60 subjects randomized, 45 were available for long-term (3-year average) follow up. SCS was more successful than reoperation (9/19 for SCS vs 3/26 for reoperation; $p<0.01$). In addition, subjects randomized to SCS were significantly less likely to cross over to reoperation, than those who were randomized to reoperation (5/24 for SCS vs 14/26 for reoperation; $p<0.02$). Subjects randomized to reoperation required increased opiate analgesics significantly more often than those randomized to SCS ($p<0.025$). Other measures of activities of daily living and work status did not differ significantly.

When conservative treatment options have failed, spinal cord stimulation has been found to be an effective treatment for relieving pain in subjects with a variety of chronic pain conditions (Cameron, 2004; Turner et al. 2004; Taylor et al. 2005; Kumar et al. 2006; Frey et al. 2009). These studies concluded that SCS provided significant long-term pain relief and improved quality of life. In addition, they found that subjects also reported increases in social interactions, mood elevation, and improvements activities of daily living.

More recently, Kapural et al. (2015) conducted a randomized, controlled, trial of SCS for the treatment of chronic back and leg pain comparing tonic SCS (Boston Scientific Precision) to high-frequency (Nevro Senza, 10 kHz pulse rate, “HF10”) SCS. 81 subjects received traditional SCS. At the 3-month assessment, 43.8% of traditional subjects were responders for back pain, compared to 84.5% for HF10. In terms of leg pain at the 3-month follow-up, 83.1% of HF10 subjects were leg pain responders, compared with 55.5% for traditional SCS. Back and leg pain responder rates were sustained through the 12-months for both treatment groups. Subject’s

level of disability as measured by ODI improved for both treatment groups by an average of 16.5 for HF10 therapy and 13.0 for traditional SCS. Kapural et al. (2016) reported on the long-term results (24-month follow-up) from the randomized, controlled, trial of tonic vs. high-frequency SCS for the treatment of chronic back and leg pain conducted by Kapural et al. (2015). Back pain responder rates for HF10 and traditional SCS were 76.5% and 49.3%, respectively. Leg pain responder rates for HF10 and traditional SCS were 72.9% and 49.3%, respectively.

Additionally, Deer et al. (2018) reported the outcomes of a prospective, randomized, crossover, open-label clinical study of SCS (St. Jude Prodigy) using traditional tonic stimulation or burst stimulation among subjects with chronic, intractable pain of the trunk and/or limbs. 100 subjects experienced at least 50% pain relief with test stimulation and were sequentially implanted. Efficacy data was collected at 6, 12, 18, and 24 weeks. Subjects underwent 12 weeks of randomized burst or tonic stimulation followed by a crossover to the alternate modality for another 12 weeks; after 24 weeks, subjects could choose which waveform they preferred. The responder rates for burst and tonic stimulation was 60% and 51%, respectively. VAS scores decreased by at least 30% in 51 tonic subjects and 60 burst subjects. Greater than 50% drop in pain scores was observed in 39 burst subjects and 32 tonic subjects.

Although SCS involves the implantation of a medical device, it is a minimally invasive, reversible surgery. Complications are usually mild and resolve quickly. Additionally, multiple publications have shown it to be cost effective, particularly in the FBSS population (Bell et al. 1997; Budd, 2002; Taylor et al., 2010).

5.4 SCS Mechanisms of Action

Spinal cord stimulation has been used in humans since the late 1960's (Shealy et al., 1967; Shealy, 1969); however, the exact mechanism of action remains unclear. In 1965 Melzack and Wall proposed the gate theory of pain (Melzack and Wall, 1965), which was the original impetus for SCS therapy. More recently it has become increasingly clear that several physiologic mechanisms may be at play through a series of ascending and descending spinal pathways (Figure 1). The central target for the SCS effect is thought to be the wide-dynamic-range (WDR) neurons contained in the dorsal horn, which receive multiple inputs from a variety of pathways responsible for modulating pain in the central nervous system. In addition, a number of neurotransmitters are involved in pain processing, including GABAergic, cholinergic and adenosine containing cells.

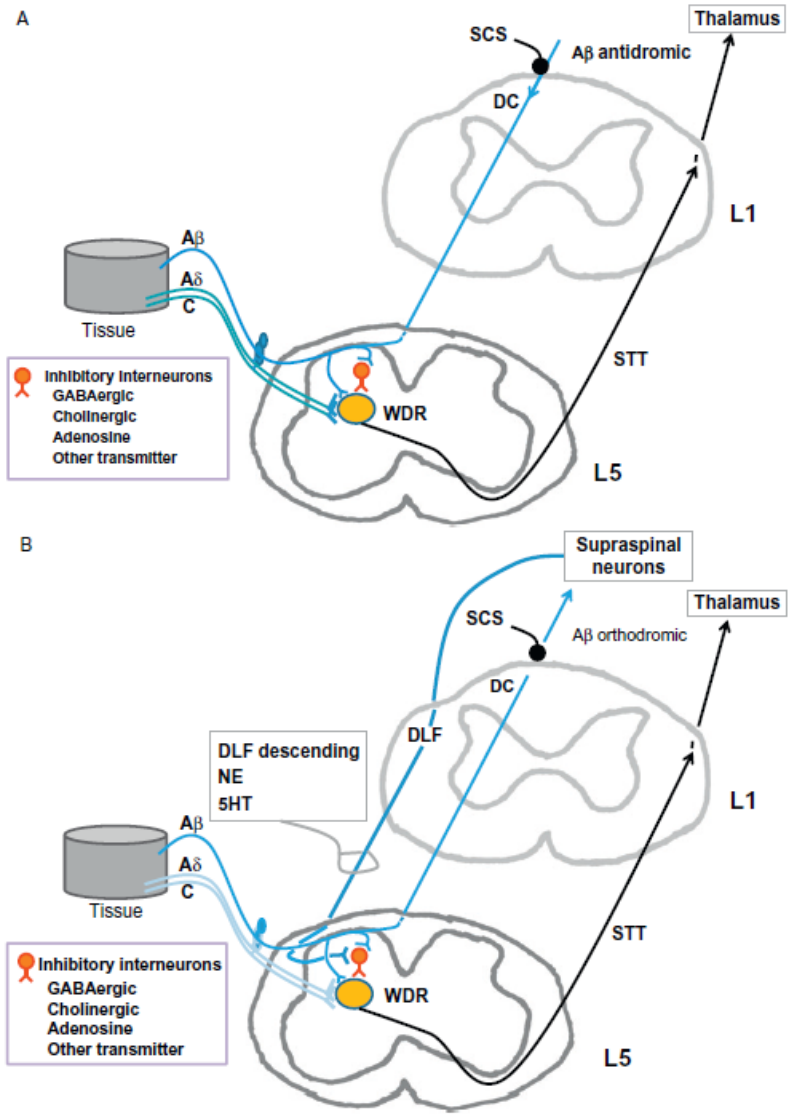


Figure 1. Possible mechanisms of SCS in treatment of neuropathic pain. The black dot on segment L1 represents an SCS electrode. Applied SCS activates dorsal column fibers both antidromically (descending; A) and orthodromically (ascending; B). Antidromically transmitted action potentials activate collaterals of the primary A-beta afferents that in turn excite the inhibitory interneurons (orange). Activation of the interneurons inhibits the activity of the WDR, which are key neurons in the propagation of pain information up the spinal cord to the brain. Orthodromic activation of the dorsal column fibers excites supra-spinal brain stem relays that transmit descending information, modulating the release of neurotransmitters in the spinal cord which modulate the WDR cells (from Foreman and Linderoth, 2014).

5.5 Current SCS Technology

The first SCS system was implanted for just a few days in a terminal cancer patient (Shealy et al., 1967). The implant contained only two electrode contacts (one cathode and one anode), and it was externally powered and controlled via a large RF coil placed outside the body. The

patient felt paresthesias and received some pain relief in his trunk and abdomen. Since this first highly experimental application of SCS, the field has evolved considerably.

To date, well over 200,000 patients worldwide have been treated with commercial SCS. The technology has undergone significant technological advancement. There are currently multiple available, fully implantable commercial systems ranging in size from 44cc down to 14cc. The leads also currently range from 4 to 16 electrode contacts on a single lead. Some of these SCS systems are rechargeable, which has paved the way to smaller sized batteries and implants. However, side effects such as lead migration, pocket pain, infection at the implant site, and uncomfortable paresthesias persist as issues faced by the implanted patient (Cameron, 2004). Consequently, device manufacturers continue to address such side effects through improvements in product configuration. For example, one of the latest Boston Scientific SCS systems has 16 electrode contacts on a single lead, which span a longer rostral-caudal range over the dorsal columns of the spinal cord. This new lead may help mitigate the risks associated with lead migration in a rostral-caudal axis. Some additional efforts to further mitigate SCS side effects include a small (less than 1 cc volume), externally powered implant (Stimwave) which may reduce pocket pain and infection risk. Other manufacturers offer SCS therapy without paresthesias (Nevro, Abbott, Boston Scientific, Stimwave).

Even a 14cc implantable pulse generator (IPG) is large enough to potentially cause significant pocket pain at the implant site. In addition to pocket pain, large IPGs increase the risk of skin erosion with exposure of the device to the outside milieu and subsequent infection, requiring system explant. The Nevro system, which provides the most widely adopted paresthesia-free therapy, is currently the largest IPG, at 33 cc, implanted for SCS therapy due to the need for a larger battery. Thus, there is a notable need for smaller implantable devices. Nalu Medical has designed an SCS therapy with an IPG less than 1.5cc.

6 Study Device

6.1 Summary description

The Nalu SCS system incorporates a battery-free, miniature implantable pulse generator (IPG), powered by an externally worn device (Therapy Disc). All SCS therapies, including the Nalu device, utilize mild electrical pulses to create an energy field that acts to modulate the transmission of pain signals to the brain.

This system including its therapy options was cleared for commercial use in the US through the 510(k) review process on 22 March 2019 (K183047).

For the Nalu SCS system, neurostimulation signals are generated through internal and external components. The IPG provides the electrical stimulation pulses that are transmitted through the leads to the desired epidural spinal cord site. The IPG receives radio frequency (RF) power and control data from the Therapy Disc worn over the IPG site with an adhesive clip applied to the skin or with a custom belt positioned appropriately.

The Nalu SCS system is capable of delivering multiple therapy options to ensure treatment optimization based on patient needs.

The Nalu SCS System comprises (please refer to Surgical Manual for more detail):

- Implantable Pulse Generator (IPG)
- Implantable leads and lead extensions
- Implantable anchor(s)
- Surgical tools
- A trial system, which includes leads, Electrode Interface Cable, Electrode Interface Cable extension cable and Trial Therapy Discs
- Externally worn rechargeable battery powered Therapy Discs to power and control the implant
- Clinician Programmer
- Patient remote control
- Therapy Disc Charger
- Wearable accessories (adhesive clips and belts)

Nalu offers advanced programming (AP) settings that operate within the established safe parameter range for electrical stimulation of the spinal cord. Additional details regarding stimulation parameters can be found in the system manuals.

Stimulation Parameters available with this device:

- Amplitude: 0-10.2 mA
- Pulse Width: 12us-1ms
- Pulse Rate: 1 Hz to 1500 Hz
- Pulse Pattern On: 12us-1000us
- Pulse Pattern Off: 12us-1000us
- Dosage On: 1ms-25ms
- Dosage Off: 1ms-25ms
- Charge Recovery: Passive or Active
- Electrode Configuration: Industry standard

6.2 Manufacturer of the Study Device

Nalu Medical, Inc. is a privately held medical device company located in Carlsbad, CA.

6.3 Traceability

The IPG, Therapy Disc, and Trial Therapy Disc have unique Nalu designated models and serial numbers for traceability. The Clinician Programmer and any Nalu Patient remote control, if provided, will be physically identified by a unique identifier linked directly to their commercial

product labeling and by version control of the software deployed onto them. The remaining items will be traced by lot number.

6.4 Intended Indications and Population of the Study Device

The Nalu Neurostimualtion System is indicated as the sole mitigating agent or as an adjunct to other modes of therapy used in a multidisciplinary approach for chronic, intractable pain of the trunk and/or limbs, including unilateral and bilateral pain. The trial devices are solely used for trial stimulation (no longer than 30 days) to determine efficacy before recommendation for a permanent (long term) device. The device will be studied in adults with chronic intractable pain in the legs and back, and who meet the inclusion/exclusion criteria of the study.

6.5 Training and Experience Needed to Use the Study Device.

The Nalu SCS System will be implanted by experienced and licensed physicians who have been trained in the implant of SCS devices and on the Nalu system in particular. Training will take place prior to participation in the clinical investigation. Training will be documented for each Investigator on an appropriate training log, that is to be filed in the investigator's site binder.

6.6 Description of the Specific Medical or Surgical Procedures Involved in the Use of the Study Device.

The implant procedure for the Nalu SCS system is very similar to other SCS systems that have long been used in medical practice. As is the case with commercially available systems, the Nalu SCS system allows for a trial period, to provide the subjects with the opportunity to experience the therapy for a short period of time (commonly 3-30 days) before committing to a long-term implant. During such trials, stimulation contacts on a lead are deployed into the epidural space using minimally invasive techniques. Two methods are available for the trial phase with the Nalu SCS system in this study, given that different physicians have different clinical practices with currently available commercial systems. The intent is to allow physicians to choose the method that most closely mirrors their current practice. The decision as to which will be used for each particular study participant will be based upon the Investigator's standard clinical practice and preferred choice for that subject:

1) Temporary trials: During the trial phase, each lead is percutaneously externalized and connected to the Trial Therapy Disc directly to deliver therapy. After a successful trial phase (defined as ≥50% pain relief in average NRS diary scores for the subject's back pain), the trial leads are removed, and new leads are permanently implanted with the IPG. The implantation of the IPG may occur within a few days or weeks of the lead removal.
2) Permanent trials: During the trial phase, the lead is anchored under the skin, and connected to a lead extension. The lead extension is percutaneously externalized and connected to the Trial Therapy Disc to deliver therapy. After a successful trial phase (defined as ≥50% pain relief in average NRS diary scores for the subject's back

pain), the extension is removed, but the leads remain in place, and the IPG is implanted and connected to the implanted leads. The implantation of the IPG may occur on the same day of the lead extension removal.

As with standard SCS procedures, the epidural leads are placed in a minimally invasive manner, and the IPG is placed in the subcutaneous tissue in the back. For additional details on the implantation procedure, refer to the Nalu SCS surgical manuals.

6.7 Justification for the Design of the Clinical Investigation

The Nalu Neurostimulation device is capable of providing several types of stimulation paradigms, within the approved parameter space, with expected outcomes comparable to historical outcomes with other SCS systems. The clinical study will formally gather feedback from subjects and physicians on their experience with the device. The study is designed as a prospective, multi-center, single-arm study that will confirm device safety, efficacy and performance. Study bias will be reduced by including multiple centers and by prospectively collecting data.

6.8 Risks and Benefits of the Study Device and Clinical Investigation

6.8.1 Anticipated Clinical Benefits.

Spinal cord stimulation has been used for over 50 years to aid in the management of chronic pain. It has been shown to reduce the severity of pain and improve the quality of life in patients who have tried and failed conventional treatment options (Cameron, 2004; Turner et al. 2004; Kumar et al. 2006; Taylor et al. 2005). Patients may reduce medications as a result of successful SCS therapy, which reduces the many potential risks of long-term use of opioids and other pain medications (North et al. 2005; Kumar et al. 2007). The cost effectiveness of SCS therapy over several years has also been clearly demonstrated (Bell et al. 1997; Budd, 2002). Because the Nalu SCS System is designed to provide therapy similar to commercially available systems, but in a smaller device, these benefits are expected to remain unchanged, while some risks associated with discomfort, pain, and skin erosion may be lowered when compared to commercially available devices due to the device's small size.

6.8.2 Anticipated Adverse Device Effects.

Despite all such benefits, some risks remain. The implantation of an SCS device is a surgical procedure, and thus involves risks commonly associated with surgery such as: infection, epidural hematoma, seroma, pain, and neurological deficit. However, these risks are extremely small, with infection being the highest at around 3% (Kumar et al. 2007). Serious complications such as permanent neurological deficit have been documented to occur in less than 0.056% of patients (Levy et al. 2011). In addition to the known surgical complications, reoperation may be required due to complications with the device itself. These complications may include: hardware malfunction, lead breakage, and lead migration; with lead migration being the

highest reported at around 13% (Cameron, 2004). In the past, lead migration has often required a revision re-operation, but the advent of multi-contact leads, reprogramming and better surgical techniques may compensate for the adverse effects of such complications.

A list of adverse side effects, though not exhaustive, that may occur during surgery and/or during standard spinal cord stimulation:

0.5% or less

- Spinal cord injury and or compression with subsequent neurological deficits - permanent or temporary.
- Stroke.
- Allergic or rejection reaction to the anesthesia, implanted components, or external components
- Cerebral spinal fluid (CSF) leak inclusive of those requiring active medical intervention.
- Death and/or catastrophic neurological complications.
- Weakness.
- Numbness.
- Clumsiness.
- Tissue damage.
- Nerve damage.
- Paralysis.
- Skin erosion around the Nalu Implantable system.
- Formation of reactive tissue in the epidural space around the lead can result in delayed spinal cord compression and paralysis, requiring surgical intervention. Time to onset can range from weeks to many years after implant.
- Arrythmia
- Cardiac arrest
- Intracranial hypotension

2% or less

- Sensory loss.
- Inadequate pain relief following system implantation or increase in pain
- Persistent post-surgical pain at hardware implantation sites.
- Seroma or hematoma at surgery sites.
- Fracture of the lead(s) or failure of other system components
- Reaction to the selected antibiotics or to the Nalu device, including: rash, diarrhea, abdominal pain, nausea/vomiting, dizziness, headaches, hypersensitivity (allergic) reactions.

- Wound complications that may require medical intervention inclusive of surgical management.
- Thromboembolic events requiring medical intervention; inclusive of deep vein thrombosis and pulmonary embolism.
- Unexpected stimulation effects including but not limited to: chest wall stimulation, muscle stimulation, tremor, dyskinesia, superficial pain, cramping, and light-headedness.
- Swelling.
- Electromagnetic interference causing a change in System performance.
- Lead breakage requiring replacement of the lead.
- Hardware malfunction requiring replacement of the neurostimulator components.
- Change in stimulation that are possibly related to tissue changes around the electrodes, shifts in electrode position, loose electrical connections, and lead or extension fractures which have been described by some patients as uncomfortable stimulation (a jolting or shocking sensation).

3% or less

- Stimulation or untoward stimulation induced dysesthesias.
- Infection at implant site that may or may not require hospitalization and require treatment with antibiotic therapy or surgical intervention
- Headache.
- Bleeding.
- Pain from a non-injurious stimulus to the skin (allodynia).
- An exaggerated sense of pain (hyperesthesia).

5% or less

- Anesthetic complications - e.g. nausea, urinary retention.
- Excessive fibrotic reaction to device leading to pain and/or new pain symptoms.
- Discomfort during the treatment.
- IPG migration

5% to 15%

- Loss of therapy or unpleasant paresthesia
- Loss of therapeutic effect despite a functioning system.
- Lead migration, causing the electrodes to move from the intended location.
- Undesirable changes in stimulation sensation and/or location with or without patient movement

Unique to Nalu system (as compared to totally implanted SCS systems)

- Undesirable skin problems such as infection, irritation, blistering, tearing or allergic reactions may occur during the use of all wearable components of the Nalu Neurostimulation System.
- Skin irritation, including redness, itchiness, and bumpiness

It is not anticipated that any additional risks beyond those associated with commercial SCS will be encountered other than as described in these sections.

6.8.3 Residual Risks Associated with the Study Device, as Identified in the Risk Analysis Report.

A concerted effort is made to identify and estimate all risks for the Nalu SCS System. The Nalu risk assessment procedures ensure that all risk is thoroughly reviewed and that all individual residual risks are acceptable. The overall residual risk is also reviewed by assessing how many acceptable risks are near the unacceptable boundary and considering whether any risks needed special monitoring. A risk that receives particular attention during design and validation is direct current applied to a subject under fault conditions. The signatories believe that adequate attention is being given to multiple safeguards in the risk control measures applied to the design and to testing that shows the effectiveness of these safeguards under both normal and single fault conditions. The Nalu risk assessment procedures ensure that residual risk with these safeguards in place is in the Broadly Acceptable Range and ensures that the Nalu SCS System is considered to be adequately safe for its intended use before clinical use.

6.8.4 Risks Associated with Participation in the Clinical Investigation.

The risks associated with participation in the clinical investigation are expected to be similar to those encountered with commercial SCS therapy. Because the device is relatively new, there may be some risks associated with encountering issues that were not discovered during the pre-clinical testing and previous studies; however, this risk is being minimized to the extent possible.

Live X-ray (Fluoroscopy) is routinely used during lead placement, and often used at follow-up visits to check for lead migration. In the current protocol, the subjects are X-Rayed at the time of the trial lead placement, which is currently the standard clinical practice. This is no different than traditional stimulation. However, they will also undergo an additional X-Ray prior to enrollment to check for spinal instability (if not already available within the past 6 months), which is not standard clinical practice for all physicians. Additional optional X-Rays (at the physician's discretion) may be needed at later visits if lead or significant IPG migration is suspected, which is standard clinical practice. In additional X-Rays may be used during lead removal (dependent upon clinical site and Investigator choice, which may be as per standard clinical practice). X-Rays would also be used during implantation of the device, as per standard clinical practice. As part of everyday living, everyone is exposed to naturally occurring

background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this study for examinations above that which would be considered standard clinical practice is about 0.5 mSv. At this dose level, no harmful effects of radiation have been demonstrated as any effect is too small to measure. The risk is believed to be minimal. Ultrasonography or x-ray may be used, if needed, to estimate the depth and orientation of IPG, when troubleshooting any issues with the device.

6.8.5 Possible Interactions with Concomitant Medical Treatments.

Any medical treatments that are not compatible with the Nalu SCS System are described in the patient and surgical manuals and will be disallowed in this protocol as well.

6.8.6 Steps That Will Be Taken to Control or Mitigate the Risks.

- The investigator will receive specific training and instruction in use of the study device.
- Study subjects undergo intensive monitoring throughout the study by a multidisciplinary team.
- Study subjects will undergo extensive training at the device activation visit and subsequent follow-up visits if needed.
- Extensive pre-clinical testing was performed in order to optimize the device safety and function.

6.8.7 Risk-to-Benefit Rationale.

Spinal cord stimulation has been used for over 50 years to aid in the management of chronic pain. Despite all the many benefits outlined in section 6.8.1, some risks remain as outlined in section 6.8.2. The benefits in pain reduction and quality of life usually greatly outweigh the risks associated with SCS; which are generally minor. Additionally, the procedure itself is completely reversible as the device, including the leads, can be wholly removed. All procedures will be carried out by experienced SCS implanters. Therefore, only risks affiliated with standard SCS clinical practice are present, as no new risks have been identified for subjects who elect to participate in this study.

7 Objectives and Hypotheses of the Clinical Investigation

The primary objective of this study is to confirm the safety, efficacy, comfort, and compliance with the Nalu Neurostimulation system. Additional objectives include evaluation of responder rate and patient satisfaction with the various therapy options in subjects with chronic pain. Patient reported secondary outcomes (ODI, BDI, PGIC, EQ-5D, PROMIS sleep disturbance SF etc.) will be captured to assess patient response.

8 Design of the Clinical Investigation

8.1 General

The study is designed as a prospective, multi-center, open-label, single-arm, clinical study with each subject serving as their own control. Study subjects will be followed for up to 3-months after device activation (see Figure 2 for study schematic). The study is expected to take 2.5 years from first enrollment to last subject at last follow-up and study closure. Study bias will be reduced by including multiple centers and by prospectively collecting data. Because SCS is a known effective therapy with a long history and because the purpose of the study is to confirm device comfort and compliance, safety and patient satisfaction, a completely within-subject, single arm study design is appropriate.

Subjects will use one or more of the available therapy options or stimulation modalities during the trial phase and those receiving ≥50% relief in their back pain will continue to the permanent implant phase. Subjects who fail the trial will be considered Trial Failures and will exit the study.

The performance measures to be studied are listed in the Synopsis and described in further detail below.

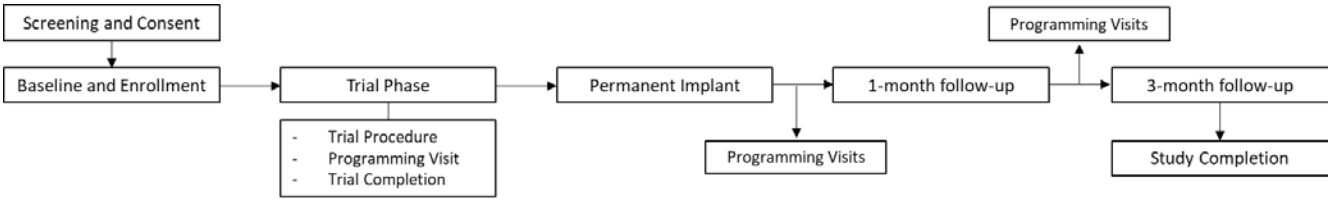


Figure 2: Study Schematic

Data to be collected is outlined in Table 1 below and detailed in sections below. The statistical analysis is described generally below.

When a lead migration, documented by x-ray, causes a clinically meaningful decrease in pain reduction (>20%) that cannot be recovered by reprogramming, a lead revision is required. In the cases when the migration and/or decrease in pain is disputed, the Medical Monitor will make the decision about when a revision is required.

Revision or replacement of leads or IPG will be offered to subject at the discretion of the clinician, if required. Any subject that requires a revision/replacement of their SCS lead or IPG prior to the 3-month time point will have their study visits restarted (Visit 5) based on the new lead/IPG placement. If the subject requires revision/replacement of their leads (trial or

permanent), during the Trial Phase of the study, their study visits will be restarted based on the revision/replacement date (restart at Visit 3), at the discretion of the clinician.

Note: Because revisions are required by the protocol to ensure therapy is maintained, they will not be considered Severe Adverse Events.

Visit Number	**1**	**2**	**3**	**NA**	**4**	**5**	**6**	**7**	**NA**	**8**	**9**	
Visit	**Informed Consent/ Screening**	**Baseline Completion & Enrollment**	**Trial Procedure/ programing**	**Programing Visits (up to 4)**	**Trial Completion**	**Perm. Implant/ programing**	**Wound Check**	**Device Activation+**	**Programing Visits (as needed)**	**30-days post-activation**	**90 days post-activation**	**Unsched.**
Window		**7-30 days from IC**	**0-15 days from Enrollment**		**3 -30 days from Trial Procedure**	**0-30 days from Trial Completion**	**1- week post-implant ± 3 days**	**2-weeks post-implant ± 5 days +**		**± 7 days**	**± 15 days**	
Informed consent	X											
Inclusion/exclusion	X	X										
Adverse event	X	X	X	X	X	X	X	X	X	X	X	X
Med. history, demographics, phys. exam, neuropsych. eval., & targeting eval.	X											
Wearable acceptance assessment	X	X										
Pregnancy test		X`				X						
VAS (in office)	X			X	X				X	X	X	
Pain diary dispensed			X	X				X	X	X		
Pain diary collected				X	X				X	X	X	
NRS (in office)	X			X	X				X	X	X	
EQ5D	X									X	X	
ODI	X									X	X	
Pain/paresthesia maps#	X*		X	X	X			X	X	X	X	
Paresthesia preference										X	X	
Pain medication use	X	X	X	X	X	X	X	X	X	X	X	X
Procedure information			X			X						
Stimulator Usability Questionnaire (2 separate questionnaires – for Scr & Fup)		X								X	X	
Wearability Daily Screening Questionnaire (& components) dispensed (visit 1) **/collected** (visit 2)	X	X										
Device performance			X	X	X	X	X	X	X	X	X	X
Physician questionnaire						X						
PGIC										X	X	
BDI	X									X	X	
PROMIS Sleep Disturbance SF	X									X	X	
X-Ray		X^	X^	X^	X^	X^	X^	X^	X^	X^	X^	X^
Photographs (optional)	X	X	X	X	X	X	X	X	X	X	X	X
Ultrasonography (optional)@			X	X	X	X	X	X	X	X	X	X

Table 1: Study Visit Data Collection. Notes: * At visits prior to the trial procedure, pain map only; all other visits have both pain and paresthesia maps.
** ± 7 days for 30 days; ± 15 days for 90 days; ` Pregnancy test may be completed at V2 or V3.
^ Optional X-Ray. Note at Baseline, a flexion extension X-Ray must be done if there is not one available within the previous 6 months. At visit 3 and 6, fluoroscopic guidance is used during procedure to place leads. An additional optional X-Ray may be done the following day to check for lead migration. # At visit 6, VAS and NRS will be completed after programming; Pain and Paresthesia maps will be completed after programming at all instances except screening. @ ultrasound may be used, if needed, when troubleshooting issues with the device.+ Timing of device activation depends on surgical technique used. See section 8.5.9

8.2 Outcome Variables

The following sections describe the data to be collected according to time points in Table 1.

8.2.1 Adverse Event Form

An adverse event (AE) form will be completed in the event of any adverse event, which documents the date that the AE occurred and categorizing the event as described below. The treatment, if any, will be recorded, and the eventual date and outcome of the AE will also be documented.

8.2.2 Medical history, demographics, physical exam, neuropsychological exam, and targeting evaluation

Subject's medical history, demographics, and physical exam information will be recorded, including height, weight, and blood pressure. A neuropsychological exam will be conducted, if needed, based on clinician's judgement of patient's psychological state, and if not already done in the previous one-year per standard of care, to ensure that the subject does not have any neuropsychological conditions that would be contraindicated for SCS therapy. During the targeting evaluation the subjects will be asked to consistently place the adhesive disc on their back. This is a dexterity test. Study candidates who cannot consistently place the adhesive disc on their back will be excluded from the study as a screen failure.

8.2.3 Wearable acceptance assessment

Subject's acceptance of the wearable accessory will be recorded including overall acceptance with the wearable concept and perceived compatibility of subject's skin with the adhesive. Study candidates who cannot envision wearing the system or who demonstrate unacceptable skin sensitivity to the adhesive will be excluded from the study as a screen failure. The belt will be tried on by each subject to ensure proper fit.

8.2.4 Pregnancy test

Subjects that are of childbearing potential will be asked to take a urine pregnancy test. If no test is administered, the reason will be documented (e.g. male, post-menopausal, surgically sterile, etc.). The results of the test will be recorded, and the test itself will be discarded according to standard medical practice. Subjects of child bearing potential must be using a reliable form of birth control, be surgically sterile or be at least 1 years post-menopausal.

8.2.5 VAS (in office)

The Visual Analogue Scale (VAS) is a subjective measure of pain. It consists of a 10-cm line with two end-points representing "no pain" and "worst pain imaginable". Subjects are asked to rate their pain by placing a mark on the line corresponding to their current level of pain. The

distance along the line from the “no pain” end to the subject’s mark is measured and recorded in millimeters. Subjects will be asked to rate their current pain, as well as pain over the preceding 24 hours and over the preceding 3 days, for their leg pain, back pain, and overall pain.

Please note that the VAS should be the first study activity completed at each visit, if applicable.

For study entry, subjects should have a back and/or leg pain score of at least 6 on the VAS.

8.2.6 Pain diary (NRS)

The Numerical Rating Scale (NRS) will be recorded by the subject for 7 days prior to most visits, or every day during the trial phase of the study. The diary also will be completed during the screening period between visits 1 and 2, for a minimum of 7 days. The diary will require the patient to rate their leg and back pain 2 times per day (using a 0 to 10 scale) – once in the morning, and once in the afternoon. They will be asked to rate their pain at similar times every day.

8.2.7 NRS (in office)

The subject is asked to make three pain ratings, corresponding to current, least and worst pain experienced over the past 24 hours for overall pain, leg and back pain. In addition, they will also be asked to rate their overall pain, leg and back pain, corresponding to least and worst pain experienced over the previous 3 days.

8.2.8 EQ5D

The EQ-5D is a standardized, validated non-disease-specific measure of health-related quality of life. The questionnaire asks about mobility, self-care, usual activities, pain/discomfort and anxiety/depression and then has the subject record a visual analogue scale of the subject’s self-rated health.

8.2.9 ODI

The Oswestry Disability Index (ODI) is a commonly used outcome-measure questionnaire designed to assess the effects of pain on activities of daily living (ADL). The questionnaire has 10 questions regarding the limitations on ADL due to pain.

8.2.10 PROMIS Sleep Disturbance Short Form Questionnaire

This is a self-administered questionnaire to assess perceptions of sleep quality, sleep depth and restoration associated with the past 7-days. The questionnaire has 8 questions, with higher scores indicating more sleep disturbances.

8.2.11 Pain/paresthesia maps

Data on the area of pain will be collected by asking subjects to highlight the areas where they are experiencing pain on a body map drawing. Paresthesia coverage will be measured by asking subjects to highlight on a body map drawing the areas where they are experiencing paresthesia, if any, during stimulation.

8.2.12 Paresthesia preference questionnaire

Subjects will be asked to answer a short questionnaire about any paresthesia they experience. This will be completed at visits 4, 8, & 9

8.2.13 Pain medication use

The subject's current pain medication regimen will be documented, including the dose of medication, the number of times per day the medication is taken, and the reason for taking the medication. Opioid usage will be documented separately on an opioid usage form.

8.2.14 Procedure information

Data on the surgical procedure will be collected, including starting and completion time of the procedure, lead placement location, and devices used during the procedure. Worksheets will be provided for study capture, and these may be completed by sponsor representatives/FCE under study staff supervision.

8.2.15 Stimulator Usability Questionnaires

At visit 2 subjects will be asked to record and rate their experience with the wearable components (Therapy Disc and adhesive clip) that they have used at home between visit 1 and visit 2. Questions will include information about the comfort, compliance and ease of use of the wearable components.

Once implanted with the IPG, at the follow-up visits subjects will be asked to record and rate their experiences with the wearable components (Therapy Disc, adhesive clip and therapy belt) used to position the Therapy Disc over the IPG. Questions will include information about the comfort and ease of use of the wearable components.

8.2.16 Wearability Daily Screening Questionnaire

Subjects will be asked to record information about the daily use of their wearables (Therapy Disc and adhesive clip). The questionnaire, in diary format will be handed out at visit 1 and taken home and completed during the baseline screening period, then returned to the clinic at visit 2. This is intended to check for any adverse reactions to the adhesive material that will be used in the study, which would prohibit subjects from continuing as they would be considered screen failures.

8.2.17 Device performance

Programming details will be recorded, including the impedances measured across the electrodes, the stimulation amplitude, rate, and pulse-width, and the programs saved to the subject's remote control. Worksheets will be provided for data capture, and these may be completed by sponsor representatives/FCE under study staff supervision.

8.2.18 Physician Implantation Procedure questionnaire

Surgeons/Physicians will be asked to rate their experience with the device, surgical tools, and other system components.

8.2.19 Patient Global Impression of Change (PGIC)

Subjects will be asked to rate their overall global impression of improvement, if any, in their activity, symptoms, emotions and overall quality of life since beginning the therapy.

8.2.20 BDI

The Beck Depression Inventory (BDI) is a questionnaire used to assess the severity of depression. It consists of 21 questions about how the subject has felt in the past week.

8.2.21 X-Ray

Subjects will have an X-Ray evaluation to ensure that they are appropriate candidates for SCS therapy (if not already available within the past 6 months) and will undergo X-Rays during trial lead placement. Additional optional X-Rays may be used the day following lead placement to check for lead migration and to assess implanted device orientation relative to the external Therapy Disc. X-Ray may be used for trial lead removal (dependent upon clinical site & Investigator decision). For subjects who had the trial phase under method 1, they will need to undergo X-Ray during implantation of permanent device. Additional optional X-Rays (at the physician's discretion) may be needed at other visits if lead or significant IPG migration is suspected, which is standard clinical practice.

8.2.22 Photographs and Video Recording

Subjects may also be asked to take photos of their lower back with or without the adhesive clip and mock disc in place and/or after clip removal or these may be taken by study personnel during any visit. The study team may look at the photos to check for proper device placement and for possible adverse skin reaction or to observe trends in either.

The surgical procedure may be recorded in the Operating Room, once written permission is obtained from the patient. Personnel recording the procedure on the video will ensure that only the surgical site is captured on video.

8.2.23 Ultrasonography

Ultrasound may be used to estimate depth and orientation of the implanted IPG and related implantable components. Ultrasound may be used at any time post-implantation and will be available as an optional diagnostic tool for troubleshooting.

All images (e.g.: X-ray, photographs, ultrasound, etc.) are to be de-identified and included in the data record of the subject in an electronic format to allow analysis at a later date.

8.3 Study Device and Comparator

Outcomes will be compared within subjects to baseline and to the published literature for SCS devices used in the treatment of chronic pain.

No other medication or medical devices will be prescribed during this study, although study subjects are allowed to continue their current medication regimen. In the event of breakthrough pain, subjects will be allowed to take their usual as-needed pain medications; these medications should be captured in the concomitant medication CRF.

Each study subject will be provided with a single Nalu SCS system up to the maximum number of subjects who will be implanted. However, devices may be replaced should the medical need arise, based upon the physician's discretion and subject's desire to continue to remain in the study.

8.4 Subjects

8.4.1 Inclusion Criteria for Subject Selection.

1. Subject is between 21 to 80 years of age at enrollment.
2. Subject has chronic (defined as at least 6 months duration), intractable neuropathic pain of back and/or leg(s); any nociceptive pain must be less prominent than the neuropathic pain.
3. Subject's pain is unresponsive to conservative treatment options within the previous 3 months.
4. Subject has a VAS score of at least 6 in the back and/or leg at screening.
5. Subject is able to distinguish between leg pain and back pain.
6. Subject is considered by the Investigator as a candidate for implantation of a spinal cord stimulator system.

7. Subject is willing to cooperate with the study requirements including compliance with the study procedures and completion of all study visits.
8. Pain symptoms should be predominantly neuropathic in nature.
9. Subject reported stable pain (non-escalating) for 30 days prior to signing informed consent.
10. Subject has had stable pain medication use and dosage for 30 days prior to signing informed consent.
11. Subject is psychologically qualified to receive a spinal cord stimulator as per the clinician's standard clinical practice and does not have clinically relevant psychological condition(s) that would interfere with ability to accurately report outcomes or complete study procedures.
12. Subject is able to independently complete the pain diary and subject questionnaires.
13. Subject has demonstrated the ability to appropriately place the adhesive disk on the low back.

8.4.2 Exclusion Criteria for Subject Selection.

1. Subject currently has an active implantable medical device such as a drug pump, spinal cord stimulator, sacral nerve stimulator, deep brain stimulator, and/or cardiac pacemaker.
2. Subject has previously failed SCS therapy (either trial system evaluation or permanent implant).
3. Subject has had an ablative procedure directed at the spinal cord including the dorsal root entry zone (DREZ) or dorsal root ganglion (DRG).
4. Subject has pain in another anatomic region besides the leg(s) and back that would interfere with their ability to accurately report pain
5. Subject has mechanical spine instability detected by > 4 mm translational movement or excessive angular movement manifested by 20 degrees greater angular movement than in an adjacent segment based on flexion/extension films of lumbar spine (imaging is required for this determination and must have been done within the past 6 months or during screening).
6. Pain is absent at rest.
7. Subject has a medical condition that would prevent them from participating in the current study per investigator's or medical monitor's judgment.
8. Subject has had a successful interventional procedure within the past 3 months to treat the same pain condition(s) being examined in this study.
9. Subject is currently participating in another clinical investigation with an active treatment arm.

10. Subject is allergic to materials used in the device components including skin adhesives.
11. Subject is sensitive to skin adhesives used in the system or does not tolerate the wearable aspect of the device.
12. Subject has pending or ongoing legal issues (including unresolved worker's compensation claims or equivalent) or other conflicting secondary gain issues related to their chronic pain condition.
13. Subject has a current diagnosis of a coagulation disorder, bleeding diathesis, progressive peripheral vascular disease or uncontrolled diabetes mellitus that have not been medically corrected.
14. Subject has an active systemic infection.
15. Subject is unable to read and/or write or give informed consent.
16. Subject has a life expectancy of less than 1 year.
17. Subject has evidence of diabetic neuropathic pain on clinical exam.
18. Subject has evidence of an alcohol or drug dependency within the last 6 months of enrollment.
19. Subject is pregnant (if female and sexually active, subject must be using a reliable form of birth control, be surgically sterile or be at least 1 year post-menopausal).
20. Subject is nursing/breastfeeding.
21. Subject is on >90 mg-morphine equivalents per 24 hours.

8.4.3 Criteria and Procedures for Subject Withdrawal or Discontinuation.

Subjects may be discontinued from the study for non-treatment-related reasons only when no other option is possible. Reasons for discontinuation include, but are not necessarily limited to:

- Voluntary withdrawal from the study by the subject.
- Subject has moved from the area and is determined to be lost-to-follow-up.
- Subject is unwilling or unable to cooperate with study requirements (stimulation regimen, follow-up visits, etc.).
- Subject has an adverse event or other issue such that they can no longer continue with SCS stimulation or participate in the study.
- At physician's or medical monitor's discretion.

The reason for discontinuation will be recorded on the appropriate case report form. Discontinued subjects will not be replaced in the study.

Prior to discontinuing a subject, every effort should be made to contact the subject in an effort either to get the subject back into compliance with the protocol, or to obtain as much follow-up data as possible.

8.4.4 Point of Enrollment.

Because data must be collected on subjects to determine study eligibility, study subjects who have signed the informed consent document and who meet the inclusion/exclusion criteria will be considered to be enrolled in the study. Study subjects who sign informed consent, but do not meet the inclusion/exclusion criteria will be considered screen failures. Subjects who screen-fail for one or more reason, may be allowed to re-screen at a later time provided the reasons for previously screen-failing have been resolved (per PI and Medical Monitor). The subject will undergo all screening procedures again and will be given a new Subject ID.

8.4.5 Total Expected Duration of the Clinical Investigation.

The study is expected to last 2.5 years from first subject's enrollment.

8.4.6 Expected Duration of Each Subject's Participation.

Each study subject is expected to continue in the study until 3-months after permanent device activation. Because there is a maximum of 75 days allowed between providing Informed Consent and permanent implant and may include a revision, a subject's participation may last as long as 9 months.

8.4.7 Number of Subjects Required to be Included in the Clinical Investigation.

The study will enroll up to 250 subjects implanted with the IPG. Subjects will be enrolled and screened until the maximum number of implants are reached. The number of study subjects to be consented and screened is not expected to exceed 500.

8.4.8 Estimated Enrollment Period

It is anticipated that 1.5 years will be needed to implant the maximum number of study subjects.

8.5 Procedures

The following sections describe the activities to occur at each study visit. Study data will be collected according to Table 1. Subjects will be asked about adverse events at each study visit.

Study clinicians will oversee all study procedures. Study sponsor representatives may program the device, provide technical assistance during procedures, and assist with study data collection with the permission and oversight of the study clinicians. Source worksheets, such as procedure and programming forms, may be completed by sponsor representatives under the supervision of the study staff. Subjects will be programmed by the FCE or sponsor representatives under the supervision of the study clinicians.

Subjects may return to the clinic for unscheduled visits. The subject may require additional training on use of their device, re-programming if stimulation coverage has changed, troubleshooting of device problems, or reporting and analysis of adverse events. Some of these issues may also be resolved with a phone consultation with Clinic Staff, Field Clinical Engineer (FCE), sponsor representatives, Study Monitor or Clinical Research Staff. In addition, the Clinic Staff, along with a Sponsor FCE or other sponsor representatives, may need to call the study subjects on a regular basis to ensure proper use of the study device.

Sites may call the subjects prior to each visit to remind them to complete their study diaries and ensure that the therapy does not need to be adjusted prior to the follow-up visit.

Subjects shall be advised to keep their medications constant to the extent possible throughout the study unless a change is medically necessary.

8.5.1 Pre-Enrollment Screening

Prior to subject's signing informed consent, the study clinicians may review potential study subjects' charts to pre-screen patients based on data that is collected according to standard clinical practice.

8.5.2 Informed Consent (Visit 1)

Written Informed Consent will be obtained from each subject before commencing any study related activities, including data collection. All potential subjects will be properly informed as to the purpose of the study and the potential risks and benefits known or that can be reasonably predicted or expected. The Investigator will retain the original copy of the Informed Consent Form signed by the subject, a copy will be provided to the subject. Only the consent form approved by the Ethics Committee will be used. The Informed Consent and source documents will be checked by the monitor at monitoring visits to ensure the correct consent procedure was followed.

The following data will be collected:

- Inclusion/exclusion information
- Adverse events (following IC)
- Med. history, demographics, phys. exam, neuropsych. eval. and targeting eval.
- Wearable acceptance assessment
- VAS (in office)
- NRS (in office)
- EQ5D
- ODI
- PROMIS Sleep disturbance SF
- Pain maps
- Pain medication use

- BDI
- Photographs, as needed

Note: the VAS should be the first questionnaire completed at this visit. Subjects should have a VAS score of at least 6 in the back and/or leg for study entry.

A neuropsychological exam will be conducted, if needed, based on clinician's judgement of patient's psychological state, and if not already done in the previous one-year per standard of care, to ensure that the subject does not have any neuropsychological conditions that would be contraindicated for SCS therapy. Subjects will undergo a dexterity test to see if they are able to place the adhesive clip on their back. Subjects who cannot consistently place the adhesive clip on their back will be excluded from the study as a screen failure.

Subjects will also be given wearable aspects of the Nalu system to test at home (mock Therapy Disc and adhesive clip). Subjects may be given an adhesive releaser spray (e.g. Sensi Care®, ConvaTec, UK, or equivalent), to help with easy removal of the adhesive clip. Skin barrier films (e.g. 3M™ Cavilon™ No Sting Barrier Film, 3M, USA or equivalent) may be given to subjects to help minimize risks of skin irritation due to the adhesive clip. Subjects may be asked to take photos of their lower back with the adhesive clip and mock disc in place and/or after clip removal. The study team may look at the photos to check for proper device placement and for possible adverse skin reaction. Subjects will be given a wearability daily screening questionnaire at this time and asked to complete Wearability screening questionnaire for each day from screening to the next visit. Subjects will be instructed to hold their pain medications constant throughout the study.

8.5.3 Baseline Completion & Enrollment (Visit 2)

Study candidates will undergo baseline evaluations after signing informed consent and prior to the trial procedure. Baseline information will be collected by the clinical study staff to determine enrollment eligibility. The subject will be fully evaluated for the inclusion/exclusion criteria in order to determine his/her eligibility for the study. The medical monitor will also review the information available on each study candidate to ensure that the candidate is appropriate for study enrollment, based upon the inclusion and exclusion criteria. De-identified subject charts, medical records, source worksheets, x-rays and any other relevant information should be shared with the medical monitor to facilitate a thorough review.

The wearability daily screening questionnaire will be collected and reviewed with the subject. A stimulator usability questionnaire will also be completed to collect data on the wearable components. Clinic staff will assess if there have been any adverse reactions to the adhesive material which would prohibit the subjects from continuing. For subjects who tolerate the wearable component, the preferred position of the adhesive clip and disc will be documented via photos and/or markings made on the skin. A pregnancy test will be conducted for females of childbearing potential (Note: Per clinician standard medical practice, this may also be done at visit 3, prior to lead placement). Flexion extension X-Ray films may be taken (if not already

available within the past 6 months) to check for spinal instability. Subjects who do not tolerate or are unhappy with any aspect of the wearable portion of the Nalu device will be considered screen failures.

The study baseline evaluations may occur over several office visits if needed to complete all of the procedures.

The following data will be collected:

- Inclusion/exclusion information
- Adverse event
- Pregnancy test, if applicable
- Wearability daily screening questionnaire collected/Wearable acceptance assessment
- Pain medication use
- Stimulator Usability Questionnaire
- X-Ray (flexion extension films)
- Photographs, as needed

The trial procedure will be scheduled.

8.5.4 Trial Procedure & Programming (Visit 3)

The steps required to implant the SCS trial leads are described in the Nalu IFUs. Standard surgical techniques will be used, and all subjects will be implanted based on the anatomical placement of the leads at the level of T9. The implanter should attempt to place the electrode contacts from each lead such that they overlap the area of T9. Physician may choose to obtain paresthesia coverage in the OR. Please refer to the Nalu implant manual for detailed instructions. As per section 6.6, the clinical site may have a preference as to which of the two trialing methods they use i.e. percutaneous temporary leads or a buried lead.

Subjects will be trialed for 3-30 days, with multiple therapy options. Initial Programming may be done on the day of surgery or the next day.

Subjects will be given a pain diary and asked to complete it at home, for each consecutive day between visit 3 and visit 4. A remote-control App is available for subjects to use to control the device, as well as provide information about the battery life of the Therapy Disc. Use of this App is mandatory for all subjects and downloaded from a compatible device's App store. If subject does not have access to a compatible smart phone, then an iPod may be provided for the duration of the study. The FCEs or sponsor representative will provide training on how to use the App. A user guide will also be provided. The App will communicate to the Therapy Disc via Bluetooth. At the end of the study, the subjects will be allowed to keep the iPod, if they received one.

Subjects may be instructed to continue use of the adhesive releaser spray and skin barrier.

The following data will be collected

- Adverse event
- Pain/paresthesia maps completed after programming
- Procedure information
- Device performance
- NRS (diary) dispensed
- X-Ray or fluoroscopy (during procedure)
- X-Ray the day following the procedure (optional)
- Photographs, as needed
- Ultrasound, if needed

Additional tests, such as blood testing, may be conducted at the discretion of the Investigator, if this is their standard clinical practice. Details will not need to be recorded in the eCRF, unless it is linked to the reason for the subject being a screen failure or an adverse event.

8.5.5 Programming Visits (up to 4)

Subjects may have up to four (4) programming visits between Trial Lead placement (visit 3) and Trial Completion (visit 4). During these visits, subjects will be assessed and reprogrammed to optimize their therapeutic response to one or more therapy options with the Nalu Neurostimulation System. Subjects will be trialed for 3-30 days, with multiple therapy options. Subjects will complete the study questionnaires, as required and have their pain diary reviewed. A series of tests may be performed with the Nalu Trial Therapy Disc to determine additional programs that may be used during remaining portion of the study. The Nalu Trial Therapy Disc will store a maximum of 8 different programs. The subject will be given a pain diary and asked to complete it for each consecutive days prior to completion of the trial. X-rays may be taken if lead migration is suspected or to troubleshoot.

Revision and/or replacement of device components will be allowed per the clinician's judgement and after discussion with the subject. If subject requires revision/replacement of their leads (trial or permanent) during the Trial Phase of the study, their study visits will be restarted based on the revision/replacement date (starting with visit 3), at the discretion of the clinician.

The following data will be collected:

- Adverse event
- VAS (in office)
- NRS (diary) collected and dispensed
- NRS (in office)
- Pain/paresthesia maps (after reprogramming)
- Pain medication use

- Optional X-Ray or fluoroscopy
- Photographs, as needed
- Ultrasound, if needed
- Device performance

Note: the VAS should be the first questionnaire completed at this visit; all questionnaires are completed prior to programming unless specified above.

8.5.6 Trial Completion (Visit 4)

Visit 4 is a minimum of 3 days from lead insertion (visit 3), and a maximum of 30 days.

Subjects will visit the office for the completion of their trial. Subjects will complete the study questionnaires and have their pain diary reviewed. Patients will then have the trial leads or lead extensions, dependent upon which method for the trial phase (options as per section 6.6) was used, removed. This visit may occur over two separate (not necessarily adjacent) days if lead/lead extension removal cannot be scheduled for the same day as the clinic visit.

Subjects will use various therapy options during the trial phase and those who report a 50% or greater reduction in their back and/or leg pain, for one or more of the device settings used during the trial period and who meet all other screening criteria, are eligible to move on to the permanent implant portion of the study.

Subjects who fail to demonstrate a 50% or greater reduction from baseline in back and/or leg pain, will be considered trial failures and will exit the study.

The following data will be collected:

- Adverse event
- VAS (in office)
- NRS (diary collected)
- NRS (in office)
- Pain/paresthesia maps (after programming)
- Pain medication use
- Device performance
- Optional X-Ray or fluoroscopy (during lead removal, or if lead migration is suspected)
- Photographs, as needed
- Ultrasound, if needed

Note: the VAS should be the first questionnaire completed at this visit; all questionnaires are completed prior to programming unless specified above.

At the end of this visit, subjects may be given adhesive clip(s) and a mock disk to take home; subjects will be instructed to wear the adhesive clip with the disc at their preferred location when they come in for permanent implant.

8.5.7 Permanent Implant (Visit 5)

A pregnancy test will be conducted, as needed, prior to the permanent implant. Pregnant subjects will be considered screen failures as they did not meet the inclusion/exclusion criteria. Nalu leads and IPG will be implanted based upon standard clinical practice and the Nalu Implant Manual. Standard surgical techniques will be used, and all subjects will be implanted based on the anatomical placement of the leads at the level of T9. The implanter should attempt to place the electrode contacts from each lead such that they overlap the area of T9. Please refer to the Nalu implant manual for detailed instructions.

The following data will be collected

- Pregnancy test to be completed prior to implant
- X-Ray or fluoroscopy
- Adverse event
- Pain medication use
- Procedure information
- Device performance
- Physician questionnaire
- Photographs, as needed
- Ultrasound, if needed

A remote control App is available for subjects to use to control the device, as well as provide information about the battery life of the Therapy Disc. Use of this App is mandatory for all subjects; if subject does not have access to a compatible smart phone, then an iPod may be provided for the duration of the study. The FCEs or sponsor representative will provide training on how to use the App. A user guide will also be provided. The App will communicate to the Therapy Disc via Bluetooth. At the end of the study, the subjects will be allowed to keep the iPod.

8.5.8 Wound Check (Visit 6)

One week (± 3 days) post-surgery, wound check will be performed to ensure healing, by the study doctor or designee. Nalu representatives may perform an impedance check and program the device, but patients will be sent home without a Therapy Disc and remote control.

The following data may be collected:

- Adverse Event
- Device performance (impedance and programming)

- Optional X-ray or fluoroscopy
- Photographs, as needed
- Ultrasound, if needed

8.5.9 Device Activation (Visit 7)

Note: If the implant was placed with the 2nd incision for IPG placement outside the circle, then, subjects may be activated the day of or the day after implant placement. If the 2nd incision for IPG placement is within the circle, then, device is activated at 2-weeks (± 5 days).

Two- weeks post op, the surgical site will be checked again to ensure wound healing, by the study doctor or clinician, if applicable. If the site has adequately healed, then device activation will be performed at this visit. At the discretion of the clinician, additional healing time may be needed, as necessary, to ensure complete healing of the surgical site.

Upon confirmation of healing, Nalu representatives will perform an impedance check and program the device; patients will be sent home with a Therapy Disc and remote control.

The following data will be collected:

- Adverse Event
- NRS diary dispensed
- Pain/Paresthesia maps (after programming)
- Device performance (impedance and programming)
- Patients will be given Therapy Discs and remote control to take home
- Pain medication use
- Optional X-ray or fluoroscopy
- Photographs, as needed
- Ultrasound, if needed

8.5.10 Programming Visits

Subjects may have one or more programming visits, as needed, between Device Activation (visit 7) and the 1-month follow-up visit (visit 8) as well as between 1-month follow-up (visit 8) and 3-month follow-up (visit 9). During these visits, the subjects will be assessed and reprogrammed to optimize their therapeutic response to one or more therapy options with the Nalu Neurostimulation System. Subjects will complete the study questionnaires, as required and have their pain diary reviewed. A series of tests may be performed with the Nalu Trial Therapy Disc to determine additional programs that may be used during remaining portion of the study. The Nalu Therapy Disc will store a maximum of 8 different programs. The subject will be given a pain diary and asked to complete it for at least 7-days prior to the next visit. X-rays may be taken if lead and/IPG migration is suspected or to troubleshoot.

Revision and/or replacement of device components will be allowed per the clinician's judgement and after discussion with the patient. If patient requires revision/replacement of their leads or IPG, prior to the 3-month follow-up visit, their study visits will be restarted based on the revision/replacement date (visit 5), at the discretion of the clinician.

The following data will be collected:

- Adverse event
- VAS (in office)
- NRS (diary) collected and dispensed
- NRS (in office)
- Pain/paresthesia maps (after reprogramming)
- Pain medication use
- Optional X-Ray or fluoroscopy
- Photographs, as needed
- Ultrasound, if needed
- Device performance

Note: the VAS should be the first questionnaire completed at this visit; all questionnaires are completed prior to programming unless specified above.

8.5.11 Follow-Up Visits: Visit 8- 1-month post activation; Visit 9- 3-months post activation

For the follow-up visits after permanent implant, approximately one week prior to each scheduled visit, the sites will call the subjects to remind them to complete their pain diaries and ensure that the therapy does not need to be adjusted prior to the follow-up visit. An FCE or the site may contact the subject 2-weeks prior to the follow up visit, to ensure that the subject is receiving optimal therapy.

Subjects will visit the clinic at their scheduled follow-up visit according to the schedule in Table 1. Subjects will return their pain diary and answer the scheduled questionnaires. An X-ray or fluoroscopic image of the lead and/or IPG location may be captured if lead and/or IPG migration is suspected. Subjects may be reprogrammed to improve therapy and/or to reduce unwanted stimulation effects. A series of tests may be performed with the Nalu Therapy Disc to determine additional programs that may be used during the remaining portion of the study. The Nalu Therapy Disc will store a maximum of 8 different programs.

The following data will be collected

- Adverse event
- VAS (in office)
- NRS (diary collected and dispensed)

- NRS (in office)
- EQ5D (if indicated in Table 1 for this visit)
- ODI (if indicated in Table 1 for this visit)
- PROMIS Sleep disturbance SF (if indicated in Table 1 for this visit)
- Pain/paresthesia maps (after programming)
- Paresthesia preference (if indicated in Table 1 for this visit)
- Pain medication use
- Stimulator Usability questionnaire
- Device performance
- PGIC (if indicated in Table 1 for this visit)
- BDI (if indicated in Table 1 for this visit)
- Optional X-Ray or fluoroscopy
- Photographs, as needed
- Ultrasound, if needed

Note: the VAS should be the first questionnaire completed at these visits; all questionnaires are completed prior to programming unless specified above.

Revision and/or replacement of device components will be allowed per the clinician's judgement and after discussion with the subject. If subjects requires revision/replacement of their leads or IPG, prior to the 3-month follow-up visit, their study visits will be restarted based on the revision/replacement date (visit 5), at the discretion of the clinician.

On completion of the final study visit (visit 9, 3-month follow-up), subjects will be returned to standard of care and continue device use.

8.5.12 Unscheduled Visits

Subjects may return to the clinic for additional unscheduled visits. The subject may require additional training on use of their device, programming if stimulation coverage has changed, troubleshooting of device problems, or reporting adverse events. Some of these issues may also be resolved with a phone consultation with Clinic Staff, Field Clinical Engineer (FCE), Sponsor representatives, Study Monitor or Clinical Research Staff. In addition, the Clinic Staff, or Sponsor FCE or sponsor representative may need to call the study subject on a regular basis to ensure proper use of the study device. An x-ray may be required to check for lead and/or IPG migration and if needed, ultrasound may be used; photographs may be taken as needed.

Unscheduled visits will be recorded on adverse event CRF, if appropriate, or on an unscheduled follow-up CRF. A device performance CRF will be completed if programming parameters are adjusted.

8.6 Monitoring Plan

The Investigator will permit the Study Monitor to visit the Investigational Site at regular intervals to review all of the CRFs, study related adjunctive data, and study management. These reviews are for the purpose of verifying adherence to the protocol, the completeness and accuracy of the data being entered as required by applicable regulations. The Study Monitor must be kept informed of all issues pertinent to the study. The Study Monitor will be available to discuss questions regarding AEs, removal of subjects from the study, conduct of the study or any other questions that should arise. At the final monitoring visit the Study Monitor must resolve any outstanding data deficiencies and retrieve all used and unused test articles if applicable. Data will be verified to source during the monitoring process, per the Monitoring Plan for the study. Typically, source-document verification of CRFs will be done shortly after the CRFs are completed. A Contract Research Organization (CRO) may be responsible for monitoring this clinical investigation.

The Principal Investigator should be available at some time during the monitoring visits. By agreeing to participate in this study the Investigators agree to co-operate with the study monitor to ensure that any issues are resolved.

The monitoring will occur according to a separate monitoring plan.

The various national regulatory authorities and a properly authorized employee of the Sponsor may request access to all study records, including source documents, for inspection and duplication.

A Medical Monitor will be used to review each subject's information to ensure that appropriate subjects are enrolled and to adjudicate the classification of adverse events and other medical issues that arise. A full description of the Medical Monitor's role will be provided in a separate Medical Monitor Charter.

9 Statistical Considerations

9.1 Sample Size and Primary Statistical Analysis

This study will not be formally powered, as it is a post-market data collection study. It is anticipated that up to 250 patients may be enrolled at up to 25 clinical sites. The primary statistical analyses will be completed on all safety and effectiveness measures including computation of average, variance, standard deviations, and trend analysis. Parametric and non-parametric statistics may be employed, as appropriate, to test for statistical significance or for trends in the data comparing the baseline period (absence of stimulation) and the data collected at the various study visits.

9.2 Secondary Analyses

Each of the study performance measures along with pain relief and stimulation side effects will be evaluated with the Nalu system and compared to baseline. These data will be analyzed by an analysis of variance that includes the effects of subjects and study period.

9.3 Analyses of Safety

AEs associated with the Nalu device and procedure will be tabulated.

10 Data Management

10.1 Reporting and Recording of Data

All study data will be recorded in the Case Report Forms (CRF) in an Electronic Data Capture (EDC) System. The CRF is expected to be completed within five to seven business days from the subjects visit. Where possible, all CRF data should originate from a verifiable medical record (this may include source worksheets as well as programming worksheets completed by representative of the sponsor). CRFs can only be completed by designated study staff or the study subject as appropriate and as recorded on the delegation of authority log. The electronic audit trail within the system will be used to track all changes in the data subsequent to verification of the entered data.

Source documents are required for each subject enrolled. These may include source worksheets as well as programming worksheets, which may have been completed by representatives of the sponsor. Any corrections to source notes should be made by scoring through the original value with a single line and writing the new value next to the original entry with the designated study staff initialing and dating the new entry. Correction fluids should never be used on any document.

All eCRFs and source documents should be made available to the Study Monitors. They will verify that all data entered in the eCRFs are accurate against the source. Visual and computer error checks will be carried out as appropriate, and the investigational site will be queried on errors concerning completeness and consistency of the data on the eCRFs.

Confidentiality of data shall be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access.

10.2 Record Storage and Retention

Applicable laws and Good Clinical Practice (GCP) require that a copy of all study records (e.g., Informed Consent documents, source documents, study records, etc.) which support CRFs of this study, must be retained in the files of the responsible Investigator for 2 years after the research has been completed or longer if required by the Sponsor.

If the Principal Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept responsibility. Nalu Medical must be notified in writing of the name and address of the new custodian.

11 Amendments to the Protocol

Any amendments to this protocol must be prepared by the Study Monitor and/or Sponsor and approved by Nalu Medical, the Investigator, and the local authority (IRB/EC) before implementation.

12 Deviations from the Protocol

This study will be conducted as described in this protocol and in accordance with ISO14155:2011, and local regulations.

All protocol deviations must be documented in detail on the appropriate CRF and reported to Nalu Medical. Protocol deviations will be classified as major and minor deviations. Deviations that are considered major should be reported to Nalu Medical within 5 working days of becoming aware of such deviation.

Examples of major protocol deviations include:

- Enrolling a subject who does not meet all of the inclusion/exclusion criteria.
- Enrolling a subject without properly obtaining informed consent.

Other protocol deviations may also be considered major if they affect the well-being of a subject or seriously compromise the integrity of the data.

Protocol deviations shall be reported to the Ethics Committee as per local requirements.

If a study site continues to deviate from the protocol, a corrective and preventive action plan will be created to be followed by the site. If the site does not comply with the plan, it may be disqualified from further participation.

13 Device Accountability

Devices will be carried by the FCE or sponsor representative to the site at the time of surgery. No devices will be stored at the clinical site except for adhesive clips and sprays. In case devices are shipped to or kept at the site, the Investigator must keep an accurate accounting of any study equipment stored at the site. The serial and/or lot number of each device used by the subject will be recorded on source documents and the CRF. All study product packaging will comply with local regulations.

Any unused product will be returned as instructed and documented on the accountability form.

14 Statements of Compliance

The clinical investigation will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki.

The clinical investigation will comply with ISO 14155:2011(E) and any regional and/or national regulations as appropriate.

The clinical investigation will not begin until the required approval/favorable opinion from the IRB or regulatory authority has been obtained, if appropriate.

Any additional requirements imposed by the IRB or regulatory authority shall be followed, if appropriate. Clinical trial insurance will be retained as required by the IRB and regulatory authorities.

15 Informed Consent Process

Written Informed Consent must be obtained from all subjects before recruitment into the study. All potential subjects must be properly informed as to the purpose of the study and the potential risks and benefits known or that can be reasonably predicted or expected. The Investigator will retain the original copy of the Informed Consent Form signed by the subject and a duplicate will be provided to the subject. Only the consent form approved by the IRB/EC must be used.

In the event of a protocol change that is not consistent with the subject's signed informed consent, a new consent form will be presented, discussed, and signed prior to the subject's continuation in the study. The new consent form will be approved by the appropriate IRB. As information on the device's safety or effectiveness or other information that would influence the subject's consent to study participation, such information will be provided to the sites and study subjects as needed.

16 Adverse Events, Adverse Device Effects, and Device Deficiencies

16.1 Definitions

Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigation medical device. Notes: 1) Because the protocol requires surgical procedures, mild pain, swelling, etc. should not be considered untoward and not considered an AE; however, any event that is more severe or lasts longer than typical should be considered an AE. 2) The protocol requires that the use of medical adhesive to hold the Therapy Disc over the implanted IPG. These adhesives may cause mild redness, irritation or

	itching, similar to that seen with a medical bandage. These events should not be considered untoward and are not AEs unless they are more severe or last longer than typical. 3) Subjects in the study, by definition, have chronic pain in the leg(s) and back. Unless the pain is worsened (more frequent or more severe), then chronic pain in these areas should not be considered untoward and should not be considered an AE. 4) Subjects may experience unpleasant sensations, such as twinges, mild feelings of electrical shock, paresthesias, and/or pain, during the course of the programming procedures. If the condition resolves immediately with re-programming, then these events should not be considered as untoward and are not AEs.
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. Note: this definition includes adverse events resulting from insufficient or inadequate Instructions for Use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Event (SAE)	Any adverse event that: • Led to death • Led to serious deterioration in the health of the subject that either resulted in: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient or prolonged hospitalization, or o 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 Note: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan (CIP), without serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE)	An adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. Per 21 CFR, Part 812.3(s), Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death 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.

Device Deficiencies	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Note: Device deficiencies include malfunctions, use errors, and inadequate labelling.

16.2 AE and Device Deficiency Documentation

All AEs will be monitored for all participants, from the time of signing consent through to the final study visit. All AEs, including SAEs, must be detailed in the source documents and reported in a timely manner to the Sponsor by completing an AE page in the CRF. Each unique event must be documented separately.

AEs can be based upon subject report, questionnaires, medical reports or other medical examinations. AEs should be documented in terms of a medical diagnosis. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the Investigator or reported by the subject at each study visit. For each medical diagnosis or sign and/or symptoms the Investigator will provide information on dates (onset/resolution), severity, relationship to the medical device, action(s) taken and outcome.

Any AEs should be followed until the event is resolved (with or without sequelae). If an event is ongoing at the time of study completion or termination, the participant will be followed until resolution or Investigator determination that the subject's condition is stable. Documentation of stabilisation must be recorded in the participant's source documents. If the Investigator learns of any SAE at any time after a participant has been discharged from the study, and he/she considers the event reasonably related to the study device and/or study procedure, the Investigator will record the occurrence in the subject's source documents and promptly notify the Sponsor.

If adverse events occur, the first concern will be the safety of the subject. Appropriate medical intervention will be made as soon as possible. Treatment of any AEs is at the sole discretion of the Investigator and according to current good medical practice. Any medication administered for the treatment of an AE should be recorded in the eCRF.

All device deficiencies, including serious incidents (a device deficiency that might have led to a SADE if a) suitable action had not been taken, b) intervention had not been made, c) if circumstances had been less fortunate), shall be documented throughout the study in the source documents and appropriately reported on a device deficiency page of the eCRF.

16.3 Reporting of events

Any SAE, SADE, USADE must be reported to the Sponsor or designee by the Investigator within 24 hours of first learning of the event. Notification should be made by completion of the SAE form in the eCRF.

The Investigator is required to notify their institution and/or ethics committee in accordance with their local requirements.

Any device deficiency that might have led to SADE should be reported to the sponsor or designee within 3 days.

As additional information becomes available, the event should be updated in the eCRF and provided to the sponsor or designee.

Non-serious AEs should be reported at the next routine contact.

16.4 AE Classification

The Investigator will classify each AE according to the Adverse Event Form. If the AE is serious or the Investigator feels that the device contributed in any way to the AE, the Investigator must report the event to the Sponsor and the EC/IRB as per above. It is the Investigators responsibility to assess the intensity of (mild, moderate, severe), as well as determine the causality and potential relationship of the event to the study device or procedure (unrelated, unlikely, possible, probable, definite). The Sponsor may ask for further clarification and information to support the AE classification. If sufficient questions arise, the Sponsor may ask the Medical Monitor to adjudicate the classification.

16.5 Safety Monitoring

The Medical Monitor will be responsible for initial review of all events reported as serious. Further information may be sought from the investigational site. If required, additional review of the events will be sought from sponsor's clinical advisory board. Events will be reviewed to check relatedness and seriousness to enable appropriate reporting to the ethics and regulatory bodies, as well as take any appropriate action with regards to study continuation.

17 Vulnerable Population

No vulnerable populations will be included in this investigation.

18 Suspension or Premature Termination of the Clinical Investigation

Nalu Medical reserves the right to discontinue any Study or any of the investigations at one or more sites for administrative reasons at any time, such as but not limited to, a decision to discontinue further clinical investigations with the test article, improper conduct of the Study by the Investigator, or inability to obtain the number of subjects required by the protocol, etc.

Should this occur, any enrolled implanted subjects at the site will be offered the option of device explant or device inactivation.

19 Publication Policy

Nalu intends to submit the results of this investigation for publication upon completion of the study. The study will also be posted on clinicaltrials.gov prior to the first subject being enrolled.

A final study report will be prepared in accordance to regulations and will be provided to the ECs and/or other agencies as required. After the initial study data have been published, additional data may be published by the study investigators. All publications of the data in any format are subject to review and approval by the study sponsor.

20 Administrative Requirements and Quality Assurance

20.1 Institutional Review Board (IRB)/ Ethics Committee (EC)

Before study enrollment commencement, the Investigator must provide the Sponsor with a copy of the approval notice for the protocol and informed consent forms, signed by the IRB/EC.

20.2 Investigator Agreements

Before study enrollment, all investigators must sign the protocol and provide a copy of their curriculum vitae. Any new investigators will sign the protocol before being added to the study. Investigators may be required to sign a financial disclosure agreement.

20.3 Participant Confidentiality

Confidentiality of participant data will be maintained at all times by each individual involved in the study. All source data and CRFs will be secured against unauthorized access. Each participant involved in this study will be assigned a unique identifier. The Investigator will maintain a confidential study participant list identifying all participants. This list will contain the assigned study participant's unique identifier and name. The Investigator is responsible for keeping this list confidential. Participant anonymity will be maintained in all study reports and in any publication. All information generated in this study should be considered as highly confidential and should not be disclosed to any person not directly concerned with the study without prior written permission from the Sponsor. However, competent regulatory authorities may inspect the records with or without permission from the Sponsor. Monitors, auditors and other authorized representatives of Nalu Medical, the EC approving this study, and other regulatory agencies, as appropriate, will be granted direct access to the study participants' original medical and study records for verification of the data and/or clinical trial procedures.

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22 Addendum 1: Considerations during COVID-19 restrictions

This addendum provides clarification and guidance to the sites on how best to conduct visits and consent procedures remotely due to the current global COVID-19 pandemic. It is our hope that the study is run as smoothly as possible, with minimal disruption to participants, their safety being our priority, and in accordance with ISO-14155 guidelines. Below are the proposed changes.

Given the current circumstances surrounding the COVID-19 pandemic, some participants may not be able to come to the clinical site for their protocol required visits. Some of our clinical sites are working on skeleton staff and other restrictions, depending on the measures taken to curb the spread of the virus. Participants may prefer not to come to the sites as they may be in self-isolation and/or do not want to travel due to the current situation. These are in-line with and dependent on the local governmental policies surrounding self-isolation and social distancing norms; the sponsor encourages sites and study participants to comply with the local governments' policies and procedures surrounding COVID-19. This will ensure that the study staff, participants and the sponsor's FCE remain safe and healthy. We encourage clinical sites to take the necessary precautions to ensure a safe environment to the participants or sponsor representatives are visiting the clinic.

Informed Consent:

If potential subjects are able to come to the site for their visits then they will be consented on-site. If they are unable to visit the site and need to be consented remotely, then the following should be followed to consent study participants.

- Send the updated consent to the patient via email, physical mail or other preferred methods of communication and give them time to read and review the document. Each patient should be sent two copies of the updated consent. They will sign both, keep one and return the other to the site for signature, once oral consent is obtained. A fully signed consent (i.e. signed by both subject and site staff) will be given to the subject when they come in to the clinic next.
- Set up a telephone call or video-call with the patient to review the details of the consent, study procedures and answer any questions or concerns they may have and orally consent them. This should then be supplemented by written documentation (e.g. email, letter etc.), confirming the oral/verbal consent for participation.
- The process should be documented in the source documents to maintain an audit trail.

Subject Visits:

Site visits may be replaced, as needed, by remote visits by phone or video-conferencing; the following are some of the measures being taken to allow for patients to complete the visit required procedures remotely.

1. Study staff and/or sponsor FCE may conduct visit remotely, if programming is not required, via telephone or video-conferencing. If programming or reprogramming is required, the subject will need to come in for an on-site visit.
2. Subjects may complete questionnaires electronically and electronic signatures of subjects and study staff, if required, will be acceptable. Dates should be entered next to signatures.
3. Questionnaires may also be sent to subjects by physical mail with addressed return envelopes, for them to complete and return to site.
4. Questionnaires may be sent by email; subjects will be asked to print the questionnaires, complete them and send by physical mail to the site or scan them and send electronically. Addressed return envelopes will be provided.
5. If participants do not have the equipment or knowledge to complete forms electronically or conduct videos, and staff cannot readily post the questionnaires, staff can read the questions to the participants over the phone and complete the questionnaires on behalf of the participants and record that this is how the form was completed. If possible, the participant can sign or initial the (printed) questionnaires at their next visit to the site.
6. Physical examinations will be conducted when necessary, at the discretion of the clinician.
7. Subject visits may be postponed or delayed as deemed necessary and may result in visits being out of window.

Study Supplies:

If participants need study supplies (adhesive clips, barrier sprays, adhesive removers), these will be sent to the subject at the site staff's earliest opportunity by physical mail.

If earliest opportunity is later than when the participant needs these supplies, the participant will be instructed to use the therapy belt while they wait for delivery to ensure they can receive therapy in the interim.

It is expected that some protocol deviations will arise due to this crisis, including but not limited to

- Missed visits, if sites are forced to close or subject is in self-isolation
- Visits out of window
- All visit required procedures may not be conducted