STUDY TITLE

Clinical Study Of a Micro-Implantable Pulse Generator For The Treatment of Peripheral Neuropathic Pain (COMFORT)

CLINICAL TRIALS REGISTRATION NUMBER (NCT NUMBER)

NCT05287373

PROTOCOL VERSION

Version 3.0, 20 November 2023

SAP VERSION

Version 2.0, 20 November 2023

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Clinical Study Of A Micro-Implantable Pulse Generator For the Treatment of Peripheral Neuropathic Pain (COMFORT)

Protocol Number: NAL-01-2021-US

Version: 3.0

Revision History:

Version	Date	Change Description
1.0	October 21, 2021	Initial release
1.1	January 11, 2022	Updating for consistency and typographical errors Updates to eligibility criteria
2.0	October 24, 2022	Updated inclusion criteria; added prior approved clarifications to exclusion criteria; update subject enrollment.
3.0	20 November 2023	Additional follow up added.

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 and will be maintained in the Sponsor's Trial Master File (TMF) and is available upon request.

Approval Signatures

Name	Title	Signature	Date
Patrick Martin	V.P. Clinical Affairs	DocuSigned by: Patrick Martin 6DA282CA10844F3...	Nov 20, 2023

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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 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	Clinical Study Of A Micro-Implantable Pulse Generator For the Treatment of Peripheral Neuropathic Pain (COMFORT).
Protocol Number	NAL-01-2021-US
Study Device	Nalu™ Neurostimulation System for Peripheral Nerve Stimulation (PNS)
Intended Use	The Nalu Neurostimulation System for PNS is indicated for pain management in adults who have severe intractable, chronic pain of peripheral nerve origin, as the sole mitigating agent or as an adjunct to other modes of therapy used in a multidisciplinary approach. The Nalu Neurostimulation System for PNS is not indicated to treat pain in the craniofacial region. The trial devices are solely used for trial stimulation (no longer than 30 days) to determine efficacy before recommendation for permanent (long term) device.
Study Population	Adults with chronic peripheral neuralgia who meet the inclusion/exclusion criteria of the study.
Study Objectives	Primary Objective: The primary objective of this study is to document the comparative effectiveness and safety of peripheral nerve stimulation (PNS) plus conventional medical management (CMM) versus CMM alone in the treatment of chronic, intractable peripheral neuralgia. Secondary Objectives: • To evaluate the comfort, compliance, and usability of the wearable component of the system. • Evaluate patient satisfaction and response to the system using patient reported outcomes.
Study Design	Multi-center, prospective, open-label, randomized controlled trial (RCT) comparing PNS plus CMM with CMM alone. Subjects will be randomized to receive: Arm 1: Nalu Neurostimulation System for PNS plus CMM Arm 2: CMM alone Consented subjects will receive a baseline evaluation and then be randomized 2:1 into one of two arms: 1) PNS+CMM arm or 2) CMM arm. Subjects assigned to Arm 1 will undergo a trial implant period using best clinical practices. Those subjects who pass the trial implant will receive the permanent implant. At the 3-month end point, subjects in Arm 2 will be given the option to crossover into Arm 1 beginning with a trial implant. All Arm 1 patients receiving a permanent implant will be followed for a total of36 months after permanent implantation. The study duration is expected to be 5.5 years from first enrollment to last follow up of last patient and subsequent study closure.
Population Size	Up to 150 subjects will be randomized at up to 20 centers in the United States (US). It is expected that up to 300 subjects will be consented and about 50% of these subjects will be screen failures. Sites will be allowed to enroll 1 to 2 patients as training subjects, if needed. These subjects will be randomized and implanted as detailed above. These subjects will be followed per protocol but will be analyzed only for safety.
Inclusion Criteria	Inclusion criteria for subjects: 1. Subject is between 18 to 80 years of age at the time of enrollment. 2. Subject would have been prescribed PNS therapy regardless of participation in this study; the use of the Nalu device must be on-label.

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	3. Subject has been diagnosed with one or more of the conditions listed below in the low back, shoulder, knee, or foot (including ankle): - Post-surgical/post-traumatic peripheral neuralgia including but not limited to pain due to peripheral nerve injury, post-surgical scar formation, nerve entrapment - Mononeuropathy, specified or unspecified or in diseases classified elsewhere - Other neuralgia or neuropathic pain - Osteoarthritic pain 4. Subject has chronic (defined as at least 6 months duration), intractable peripheral neuropathic pain, exclusive of the craniofacial region; any nociceptive pain must be less prominent than the neuropathic pain. Pain should have a predominant neuropathic component as per the investigator's clinical assessment. 5. Subject should have a pain score of at least 6, in the target area of pain, as recorded on the BPI-Q5 (NRS) at screening. 6. Subject is willing to cooperate with the study requirements including, compliance with the study procedures and completion of all study visits. 7. Subject reported stable pain (non-escalating) for 60 days prior to signing informed consent. 8. Subject is currently receiving CMM and has had stable pain medication use and dosage for 30 days prior to signing informed consent. 9. Subject is psychologically qualified to receive a peripheral nerve stimulator as per the clinician's standard clinical practice and judgment and does not have clinically relevant psychological condition(s) that would interfere with their ability to accurately report outcomes or complete study procedures. 10. Subject has demonstrated the ability to appropriately place the adhesive clip in the location where the IPG is most likely to be implanted. Alternatively, subject is able to appropriately use the relief belt and/or limb cuff to keep the Therapy Disc in place.
Exclusion Criteria	1. Subject currently has an active implantable medical device such as a drug pump, spinal cord stimulator, peripheral nerve stimulator, sacral nerve stimulator, deep brain stimulator, and/or cardiac pacemaker. 2. Subject has previously failed PNS or Spinal Cord Stimulation (SCS) or Dorsal Root Ganglion (DRG) therapy (trial or permanent implant). See note below. 3. Pain is completely absent at rest. 4. Patient has clinical evidence of complex regional pain syndrome (CRPS), peripheral neuralgia of metabolic origin, post-herpetic neuralgia, biochemical evidence of a metabolic or genetic neuropathy (e.g., Charcot'- Marie- Tooth Disease) or mixed motor/sensory polyneuropathy. 5. Subject has a medical condition that would prevent them from participating in the current study per investigator's or medical monitor's judgment. 6. Subject has had a successful (≥ 50% pain relief) interventional procedure within the past 3 months to treat the same pain condition(s) being examined in this study including, nerve blocks. 7. Uncontrolled depression or uncontrolled psychiatric disorders 8. Subject is currently participating in another clinical investigation with an active treatment arm.

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	9. Subject is allergic or sensitive to materials used in the device components including, skin adhesives or does not tolerate the wearable aspect of the device. 10. 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. 11. Subject has a current diagnosis of a coagulation disorder, bleeding diathesis, or progressive peripheral vascular disease that has not been medically corrected. 12. Subject has an active systemic infection. 13. Subject is unable to read and/or write in English or give informed consent. 14. Subject has a life expectancy of less than 1 year. 15. Subject has an active malignant neoplasm (metastatic or local) or evidence of paraneoplastic syndrome. 16. Subject with uncontrolled diabetes mellitus, showing signs of diabetic neuropathy, as evidenced by a neurological exam and a HbA1c test. 17. Subject has evidence of an alcohol or drug dependency within the last 6 months prior to enrollment. 18. 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). 19. Subject is nursing/breastfeeding. 20. Subject is on ≥90 mg-morphine equivalents per 24 hours. 21. Subject has undergone an ablative treatment of the target peripheral nerve, or proximal nerve trunk giving rise to the target nerve, or dorsal roots (and DRGs) that ultimately make up the target nerve. No ablative procedures directed at the spinal cord, dorsal roots, or peripheral nerve(s) being treated in the study. To note, subjects who have undergone RF ablation of the dorsal rami, cool pulsed RF of the facet innervation may be considered for enrollment. See note below. Clarifications to Exclusion Criteria # 2 and 21 Criterion #2: These procedures are allowed if the procedure was not performed on the target nerve being treated in the study and if the procedure was performed ≥ 6 months prior to consent Criterion # 21: If the patient has had an ablation ≥ 6 months prior to consent, they may be screened for the study.
Study Hypothesis	The primary effectiveness hypothesis for this study is that the responder rate, defined as percent of subjects with ≥50% reduction in Numeric Rating Scale (NRS) for the area of pain, based on the Brief Pain Inventory-Question 5 (BPI-Q5), for subjects with the PNS System is superior to the responder rate with CMM, at 3-months.
Primary Safety Endpoint	Rate of serious and non-serious adverse device events
Primary Effectiveness Endpoint	Responder rate, defined as percent of subjects with ≥50% reduction in average Numeric Rating Scale (NRS) for the area of pain from baseline, based on the Brief Pain Inventory-Question 5 (BPI-Q5), for subjects with the PNS System compared to CMM, at 3-months.

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Secondary Effectiveness Endpoints	• Percent change in pain from baseline to 3, 6, 12, 18, 24, 30 and 36-months for both arms. Comparisons between arms will be made (NRS-BPI-SF-Q5) • Percentage of responders at 6,12, 18, 24, 30 and 36-months in both arms (NRS-BPI-SF-Q5) • Percentage of responders and percent change from baseline, in the cross-over group, at 3, 6, 12, 18, 24, 30 and 36-months post-device activation (NRS-BPI-SF-Q5). • Change in patient reported outcomes (PGIC, medication use, patient satisfaction, ODI, BDI, EQ-5D, PCS) at 3, 6, 12, 18, 24, 30 and 36 months, in both arms and cross over arms. • Comfort, compliance, and usability of the external wearable components at 3, 6,12, 18, 24, 30 and 36 months, post-device activation.
Secondary Safety Measures	All device or procedure related adverse events will be recorded. The following types of events will be tabulated: • Rate of serious and non-serious adverse device events at 6, 9, 12, 18, 24, 30 and 36 months • Rate of adverse procedure effects at 3, 6, 9, 12, 18, 24, 30 and 36 months • Rate of unanticipated serious adverse device effects at 3, 6, 9, 12, 18, 24, 30 and 36 months
Secondary Outcome Measures	• Pain scores (Visual Analogue Score (VAS), BPI-Q5) • Wearable components ease of use, compliance, and comfort questionnaires • Patient Global Impression of Change (PGIC) • Patient Satisfaction • Brief Pain Inventory Short Form (BPI-SF) • EQ-5D-5L • Pain Catastrophizing Scale (PCS) • Beck Depression Inventory (BDI) • Activities of Daily Living (Oswestry Disability Index, ODI) • Pain and paresthesia maps • Pain medication use • Programming information, including stimulation parameters, impedance measurements
Statistical Considerations	The primary effectiveness hypothesis for this study is that the responder rate, defined as percent of subjects with ≥50% reduction in Numeric Rating Scale (NRS) for the area of pain, based on the Brief Pain Inventory-Question 5 (BPI-Q5), for subjects with the PNS System is superior to the responder rate with CMM, at 3-months. This study will be formally powered based on the expected efficacy of Nalu PNS therapy and CMM taken from literature. Basic statistical analyses will be completed on all endpoints including computation of averages, variances, 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 descriptive only and primarily will be used to guide further product design refinement.

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3 Abbreviations, Acronyms, and Definitions

Term	Definition
ADE	Adverse Device Effect
AE	Adverse Event
AP	Advanced Programming
Clinic	Investigator's consulting rooms where all non-surgical research visits will be performed
Clinical Site Staff	Member of Investigators site responsible for managing the clinical trial
CMM	Conventional Medical Management
CP	Clinician Programmer
CRA	Clinical Research Associate: Nalu Medical employee or contractor responsible for execution of the monitoring plan to oversee the progress of the study at the investigational site
CRF	Case Report Form
eCRF	Electronic Case Report Form
ePRO	Electronic Patient Reported Outcomes
DCF	Data Clarification Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
EQ-5D	EuroQol-5D questionnaire
IFU	Instructions for Use
IPG	Implantable Pulse Generator
IRB	Institutional Review Board
mIPG	Micro-Implantable Pulse Generator
NRS	Numeric Rating Scale
ODI	Oswestry Disability Index questionnaire
PC	Personal Computer
PGIC	Patient Global Impression of Change
PNS	Peripheral Nerve Stimulation
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SF	Short Form
Sponsor	Nalu Medical, Inc.: 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

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4 Introduction

This is a multi-center, prospective, minimal risk, randomized controlled clinical study to document the comparative effectiveness and safety of the addition of peripheral nerve stimulation (PNS) to conventional medical management (CMM) with CMM alone in the treatment of chronic, intractable peripheral neuralgia. CMM refers to the routine medical management which patients receive to treat their pain. PNS will be provided by a FDA cleared medical device and will be used strictly in accordance with its cleared labeling. The study does not involve investigational devices (those without FDA clearance or approval) or experimental treatments or procedures.

The study will seek to enroll patients who meet the eligibility criteria for study participation and are candidates for PNS and/or CMM per standard medical practice, regardless of their participation in the study.

The research in this study involves the collection of Patient Reported Outcomes (PRO) data in the form of questionnaires and surveys (pain, comfort, compliance, quality of life, etc.), as well as patient demographics, eligibility criteria, and concomitant medications. Safety data will also be collected.

In brief, this study is collecting data regarding patients' pain, safety, and various functional outcomes, before and after PNS therapy, from patients who would have received the PNS therapy regardless of the study.

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. Neuropathic pain generally presents itself as a burning or tingling sensation as opposed to acute, sharp pain. Additionally, 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).

In particular, patients who suffer from peripheral neuropathic pain (PNP), the prevalence of which is estimated to be approximately 2.4% of the population, may require interventional treatment beyond that of typical conservative methods (O van Hecke, et. al, 2014). PNP patients typically have damaged, overstimulated, or dysfunctional nerve fibers, often because of a previous injury, which can result in debilitating, intractable pain in the limbs (Treede, 2007). Unfortunately, for many of these patients, conservative treatments that may be effective for pain of nociceptive origin may not provide lasting or meaningful relief.

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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 treatments include neurostimulation, intrathecal drug infusion, ablation, or release of surrounding scar tissue and hypertrophied ligaments. Neurostimulation may include PNS, deep brain stimulation, or spinal cord stimulation.

5.3 Peripheral Nerve Stimulation (PNS)

Device-mediated neuromodulation as a whole has experienced an impressive expansion of capabilities, which has allowed physicians to treat a wider variety of previously intractable chronic pain ailments (Slavin KV, 2011). In particular, spinal cord stimulation (SCS) has received the brunt of the literature attention and large-scale device manufacturing. However, despite the widening of chronic pain ailments targeted by SCS, there still exists a significant need for treatment of neuropathic pathologies whose treatment may simply not necessitate stimulation of the spinal cord. Furthermore, even in those patients whose peripheral neuropathies may benefit from stimulation of the nervous system upstream of the pain, there always exists the elevated risk associated with epidural access, not to mention patient reluctance to receive a spinally implanted device. Thus, PNS may be a finer instrument for the treatment of neuropathic peripheral pathologies.

PNS has been used as a treatment for chronic pain since the 1960s, and more recently has been shown in literature to be effective for carefully selected patients. In a retrospective study (Eisenberg et al. 2004), it was shown that in a wisely chosen population, PNS can alleviate pain of the extremities to a statistically and clinically significant degree. Additionally, in 2009, Calenbergh, et al. showed significant improvements in quality of life as measured by various metrics, as well as significant analgesic benefits. When compared in a randomized controlled setting, Deer. et. al demonstrated that PNS, delivered by the Bioness Stimrouter system, had a statistically and clinically significant effect on pain levels as measured between baseline and 3 months post implant when compared to placebo. However, the benchmark for patient response in this RCT was a 30% pain reduction when compared to baseline, instead of the more widely accepted 50% pain reduction benchmark.

Despite the demonstrations of PNS efficacy in treating peripheral mononeuropathies, there exists a lack of well-designed PNS studies, as well as a distinct lack of device development outside of a few major players. When both the historical and potential upsides of PNS are taken into account, the need for more analyses on PNS devices becomes clear. Although PNS involves the implantation of a medical device, it is a minimally invasive, reversible surgery. Complications are

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usually mild and resolve quickly. In particular, the Nalu system's 1.5cc volume lends itself towards minimally invasive techniques and procedures.

5.4 PNS Mechanisms of Action

Although PNS as it is known today has been used since the 1960s, it is possible to find the foundations of PNS stimulation as early as the 19th century. Julius Althaus in 1859 remarked on the reduction of nerve sensitivity through the introduction of introduced current, stating that "*…the pain which is excited by this proceeding becomes much less, after a certain time, than it was at the beginning of the operation, and a feeling of numbness is produced in the limb. …there is a morbid increase in sensibility of a nerve, as in the case of neuralgia, than if a nerve in its normal state is acted upon*." [Slavin, 2011]. However, the origins of PNS in its current state, as well as that of spinal cord stimulation, can be traced back to the gate control theory of pain, pioneered by Dr. Melzack and Dr. Wall. Following the advent of the gate control theory of pain, Wall and Sweet wrote a paper in 1967 titled "Temporary Abolition of Pain in Man." In this paper, it was revealed that indeed, supraperceptive electrical stimulation of peripheral nerves might indeed suppress painful sensations in the chosen limb (Slavin, 2011). This was the first documented clinical demonstration of a potential mechanism of action for peripheral nerve stimulation.

The neuronal basis for gate control theory relies on interneuronal inhibition. Stimulation is theorized to activate A-beta fibers, whose activation subsequently activates inhibitory neurons, influencing WDR neurons, which serve as a synaptic junction for both large and small pain fibers (Melzack R, Wall PD 1965). Thus, the theory postulates that when A-beta fibers are activated, this "gate" closes, as does the neuronal conduction of pain and the reception of neuropathic pain signals (Melzack R, Wall PD 1965).

Recently, however, the gate control mechanism of interneuronal inhibition has been called into question. Despite the transition away from the gate control theory, the interplay between large and small pain fiber recruitment remains the fundamental backbone behind PNS mechanism of action (Slavin 2011 – sources from Slavin's bibliography).

5.5 Current PNS Technology

The first PNS surgery was performed on a 26-year-old woman with clinical presentation consistent with a complex regional pain syndrome (White JC, Sweet WH. Pain and the Neurosurgeon. A Forty-Year Experience. Springfield, IL: Thomas, 1969). This implant innervated the ulnar and medial nerves, in the arm, and induced a *"pleasant tingling in the lateral three fingers and corresponding hand and stopped the pain…"* Since this first highly experimental application of PNS, the field has evolved considerably.

Modern evolutions in PNS tend to be centered on the reduction of invasiveness and mitigation of surgical trauma. When compared to spinal cord stimulators, there is significantly less room for IPGs to be implanted in the body's periphery without either causing pocket pain, erosion, or

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discomfort to the patient. In addition, due to the size of the IPGs with some SCS systems, the leads need to be tunneled extensively and across joints which could result in lead migration and could be considered traumatic to the patient. Thus, there is a notable need for smaller implantable devices.

In SCS, it is standard practice for a patient to undergo a "trial phase", where the treatment efficacy is tested using externalized leads, in order to test the device's therapy before the patient receives a permanent implant. In the current, semi-limited PNS device space, not all devices have the capability to conduct a trial period before permanent implant. This, of course, introduces uncertainty regarding the potential benefit of a given PNS implant, which is likely to suppress adoption in the clinic from both physicians and patients. Without a trial period, the best indication for successful PNS therapy is a nerve block of the indicated nerve, although a nerve block only helps to identify the pain generating nerve and is not an indication of PNS efficacy.

The Nalu PNS system allows for either four or eight contact stimulation combined with a minimally invasive mIPG (~1.5 cc in volume; micro-implantable pulse generator). The system allows for a trial implant period of up to 30 days, with a multitude of electrode configurations and therapy options.

6 **Study Device**

6.1 Summary description

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

The study sponsor manufacturers the Nalu PNS system, which has US market clearance (K183579, K191435) for the treatment of chronic pain originating from peripheral nerves. This study will be limited to patients who will receive the Nalu PNS system in order control for variables related to the specific product used for therapy, device programming, and training.

For the Nalu PNS system, neurostimulation signals are generated through internal and external components. The mIPG provides the electrical stimulation pulses that are transmitted through the leads to the desired peripheral nerve target. 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 relief belt positioned appropriately.

The Nalu PNS System comprises:

- mIPG (Single 4 or 8 contact, Dual 4 or 8 contact)
- Implantable leads (tined and un-tined; 4 and 8 contact; 25, 40 and 60 cm configurations), lead anchor and lead extensions
- Surgical tools

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- A trial implant, which includes leads, Electrode Interface Cable, extension cable, and Trial Therapy Discs
- Externally worn rechargeable battery powered Therapy Discs to power and control the implant
- Clinician Programmer app
- Patient remote control app
- Therapy Disc Charger
- Wearable accessories (adhesive clips, limb cuffs and belts)

Nalu offers traditional tonic stimulation (sub and supra-perception) parameters as well as advanced programming (AP; sub and supra-perception) settings that operate within the established safe parameter range for electrical stimulation of the peripheral nervous system. 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-2ms
- Pulse Rate: 1 Hz to 1500 Hz
- Pulse Pattern On: 12us-1000us
- Pulse Pattern Off: 12us-1000us
- Dosage On: 1ms-1000ms
- Dosage Off: 1ms-2000ms
- 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 mIPG, Therapy Disc, and Trial Therapy Disc have unique Nalu designated model 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 Use, Indications for Use, and Population of the Study Device

6.4.1 Intended Use

Stimulation of peripheral nerves for chronic, intractable pain.

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6.4.2 Indication for Use

The Nalu Neurostimulation System for PNS is indicated for pain management in adults who have severe intractable, chronic pain of peripheral nerve origin, as the sole mitigating agent or as an adjunct to other modes of therapy used in a multidisciplinary approach. The Nalu Neurostimulation System for PNS is not indicated to treat pain in the craniofacial region.

The trial implant devices are solely used for trial stimulation (no longer than 30 days) to determine efficacy before recommendation for permanent (long term) device.

6.4.3 Study Population

For this study, the device will be studied in adults with chronic intractable peripheral neuralgia, exclusive of the craniofacial region, who meet the inclusion/exclusion criteria of the study.

6.5 Training and Experience Needed to Use the Study Device.

The Nalu PNS System will be implanted by experienced and licensed physicians who have been trained in the implant of PNS devices and on the Nalu system. Training will take place prior to the initiation of the clinical study at the site. Training will be documented for each Investigator on an appropriate training log that is to be filed in the investigators' site binder and sponsor trial files.

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

The implant procedure for the Nalu PNS system will follow the on-label implant instructions contained in the FDA cleared instructions for use (IFU). The implant of the device is not a research procedure but will be monitored to ensure on-label use.

The implant procedure for the Nalu PNS system is similar to other SCS and PNS systems that have long been used in medical practice. The Nalu PNS system is implanted in two phases: Trial Implant and Permanent Implant.

Trial Implant: The trial implant phase allows the patient and physician to determine if PNS therapy provides adequate relief prior to being implanted with a permanent device. The trial implant phase may last up to 30 days per device labeling. During the trial implant phase, the leads (one or two) are placed in a minimally invasive manner per standard of care and as described in the IFU. The leads may be placed with the aid of fluoroscopy or ultrasound, based on nerve target and physician preference. Paresthesia mapping will be performed in the OR; paresthesia mapping involves asking the subject where sensations from PNS therapy are felt and recording those on a diagram of the body. It is a part of routine care and will be captured on a CRF for documentation purposes.

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Trial leads are percutaneously externalized and connected to the Trial Therapy Disc to deliver therapy. The Trial Therapy Disc is programmed to provide optimal pain relief based on the patient's feedback. For the purpose of this study, a successful trial is defined as the patient realizing ≥50% pain relief from baseline based on the NRS score from the BPI-Q5. If the trial is successful, the trial leads will be removed, and the patient is scheduled for permanent implant. If the patient does not have a successful trial the patient may be given the option to stay in the study, in a secondary control arm, or exit the study. The secondary control arm consists of subjects who fail the trial and continue with CMM.

Permanent Implant: As with standard PNS procedures, the leads are placed in a minimally invasive manner per standard of care and as described in the IFU. The mIPG is placed in an accessible region that has been deemed comfortable and viable for the patient during the wear assessment. The leads and mIPG may be placed with the aid of fluoroscopy or ultrasound, based on nerve target and physician preference. Paresthesia mapping will be performed in the OR prior to determination of final lead location; paresthesia mapping involves asking the subject where sensations from PNS therapy are felt and recording those on a diagram of the body. It is a part of routine care and will be captured on a CRF for documentation purposes.

For additional details on the implantation procedure, refer to the Nalu PNS system manuals.

6.7 Justification for the Design of the Clinical Investigation

The research in this study involves the collection of Patient Reported Outcomes (PRO) data in the form of questionnaires and surveys (pain, comfort, compliance, quality of life, patient satisfaction, etc.), as well as patient demographics, eligibility criteria, and concomitant medications. (Figure 1)

Study participants are limited to only those patients who were prescribed use of the FDA cleared medical device (Nalu PNS system) for the treatment of peripheral nerve pain as part of their routine care; additionally, the device will be used strictly per its FDA cleared labeling. In other words, this study is simply collecting data regarding patients' pain and various quality of life measures, before and after PNS therapy, from patients who would have received the PNS therapy regardless of their study participation. The use of the PNS device and/or CMM are not research procedures.

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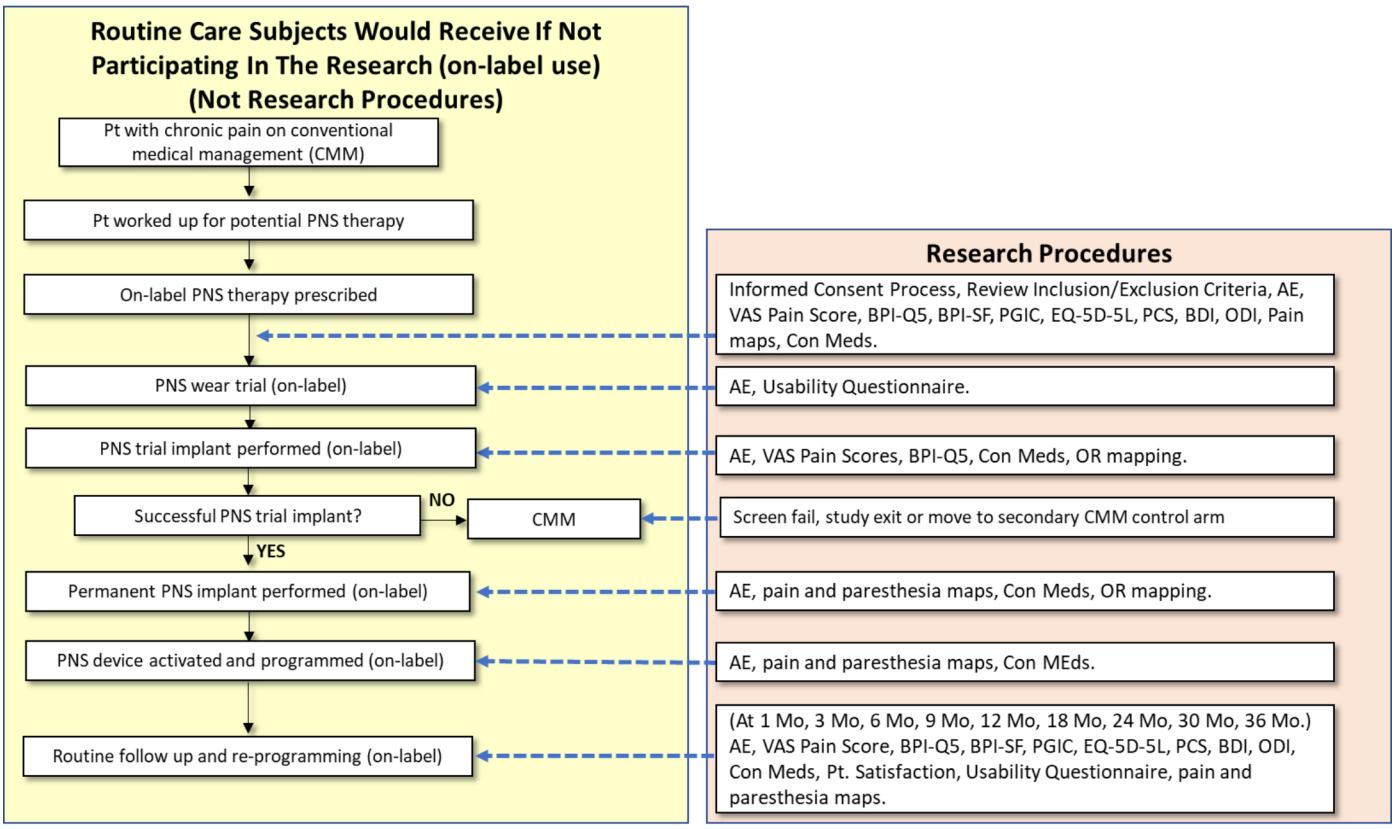


FIGURE 1: *Flow chart showing that normal and routine patient therapy is not changed (left side). Research procedures are show on the right; PRO data is collected at pre-determined points along the routine care path.*

The use of PRO data was selected because it is an established and well-accepted method to gather information on a patient's status directly from the patient[1].

The control arm, conventional medical management (CMM), was chosen because most if not all PNS therapy patients are prescribed CMM prior to PNS therapy. In this way, the study does not require that the normal and routine patient care is altered.

The active arm, PNS therapy with CMM, was chosen because it is part of the standard and routine patient care; it is commercially available in the US; it is a well-established therapy for peripheral neuropathies (specifically it is not experimental); there is no change to the normal and routine patient care. The Nalu PNS system is manufactured by the sponsor and has US market clearance.

[1] FDA Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims, released 2009.

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Randomization is used in this study to reduce the risk of bias in the study. Additionally, there is a paucity of randomized clinical studies involving PNS therapy and US insurance companies are requesting data from randomized clinical studies. Owing to the nature of the treatments in the study, specifically an implanted device compared to CMM, blinding subjects, investigators, or other study personnel, is not feasible. Similarly, it is not feasible to conduct a sham-controlled (active or passive) study at this time, given the technical limitations of the study device to truly mimic a sham.

The requirement that the Nalu PNS system will be used strictly in accordance with its FDA cleared labeling is to avoid experimental or unapproved use of the device, which could increase risk to the study participants.

Since this study involves post-market, on-label use of a medical device there is no need to conduct additional pre-clinical or clinical testing prior to this clinical investigation. The cleared medical device will be used strictly in accordance with its cleared product labeling. Device safety and efficacy was established through the regulatory process.

Because PNS is a known effective therapy with a long history (over 50 years) and the purpose of the study is to compare outcomes in real life conditions, so a post-market, on-label, open-label, randomized, controlled study is appropriate and does not introduce additional risk to the study participants or device users.

6.8 Risks and Benefits of the Study Device and Clinical Investigation

6.8.1 Anticipated Clinical Benefits.

There are no direct benefits to the subjects for participating in this clinical study, since participants would have received PNS therapy regardless of their participation in this study. Subjects will receive remuneration for their time and effort. Future patients may benefit from the advancement of science in this field.

6.8.2 Anticipated Adverse Device Effects.

Participation in this study does not increase the risk of adverse device effects. Despite all such benefits, some risks remain, which are anticipated in line with those reported with other commercially available systems, as detailed in the device IFU. The implantation of a PNS device is a surgical procedure, and thus involves risks commonly associated with surgery such as: infection, hematoma, seroma, pain, and neurological deficit. In addition to the known surgical complications, reoperation or revision surgeries may be required due to complications with the device itself.

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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 PNS 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 PNS 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 include the risk of disclosure of a subject's study data, and inconvenience related to compliance with completing the study forms.

For participants randomized to the control arm there is a risk of delay of administration of the prescribed PNS therapy. However, the 3-month time period for control subjects to crossover to the active arm is consistent with the company's commercial experience for the time required for insurance approval of the PNS therapy. In fact, in cases where coverage of PNS therapy is denied by a patient's insurer, such patients will not receive the prescribed PNS therapy; in such cases a 3-month delay would be a preferred option.

6.8.5 Possible Interactions with Concomitant Medical Treatments.

Any medical treatments that are contraindicated in the Nalu PNS system product labeling are disallowed in this protocol.

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

- Data will be stored in secure manner, including password protected electronic data capture (EDC) systems.
- Data collected will be de-identified to maintain privacy in case of a data breech.
- The investigators are selected for their expertise in PNS procedures and therapy.
- Investigators will receive extensive training on the use of the PNS system.
- 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.

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6.8.7 Risk-to-Benefit Rationale.

This is a minimal risk study evaluating patients' perception of the on-label use of an FDA cleared medical device and conventional medical management. There are no unapproved or experimental devices or procedures used in this study. Data collected during this study will be de-identified. Peripheral Nerve Stimulation has been used for over 50 years to aid in the management of chronic pain. The risks and benefits are outlined in this section. The benefits in pain reduction and quality of life usually greatly outweigh the risks associated with the PNS procedure or the device itself. 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 PNS physicians and implanters. Therefore, only risks affiliated with standard PNS clinical practice are present, as no new risks have been identified for subjects who elect to participate in this study.

7 Hypotheses, Objectives and Endpoints of the Clinical Investigation

7.1 Primary Effectiveness Hypothesis

The primary effectiveness hypothesis for this study is that the responder rate, defined as percent of subjects with ≥50% reduction in Numeric Rating Scale (NRS) for the area of pain, based on the Brief Pain Inventory-Question 5 (BPI-Q5), for subjects with the PNS System is superior to the responder rate with CMM, at 3-months.

7.2 Primary Objective

The primary objective of this post-market, open-label, minimal risk, randomized clinical study is to document the comparative effectiveness and safety of the addition of peripheral nerve stimulation (PNS) to conventional medical management (CMM) versus CMM alone in the treatment of chronic, intractable peripheral neuralgia.

7.3 Secondary Objectives

- To evaluate the comfort, compliance, and usability of the wearable component of the system.
- Evaluate patient satisfaction and response to the system using patient reported outcomes

7.4 Primary Endpoint

The primary effectiveness endpoint is the percentage of responders at 3-months, in both arms; comparisons will be made between arms. Responders are defined as "percent of subjects with ≥ 50% reduction in average Numeric Rating Scale (NRS), for the area of pain from baseline", based on the Brief Pain Inventory- Q5 (BPI-SF-Q5) where, 0= no pain and 10= worst pain imaginable.

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The primary safety endpoint is the rate of serious and non-serious adverse device events, at 3-months.

7.5 Secondary Endpoints

- Percent change in pain from baseline to 3, 6, 12, 18, 24, 30 and 36-months, for both arms. Comparisons between arms will be made (NRS-BPI-SF-Q5)
- Percentage of responders at 6, 12, 18, 24, 30 and 36-months in both arms (NRS-BPI-SF-Q5)
- Percentage of responders and percent change from baseline, in the cross-over group, at 3, 6 , 12, 18, 24, 30 and 36-months post-device activation (NRS-BPI-SF-Q5).
- Change in patient reported outcomes (PGIC, medication use, patient satisfaction, ODI, BDI, EQ-5D, PCS) at 3, 6, 12, 18, 24 and 30 and 36- months, in both arms and cross over arms.
- Comfort, compliance, and usability of the external wearable components at 3, 6,12, 18, 24, 30 and 36- months, post-device activation, in both arms and cross-over arm (Stimulator Usability Questionnaire).
- Rate of serious and non-serious adverse device events at 6, 9, 12, 18, 24, 30 and 36-months.
- Rate of adverse procedure effects and unanticipated serious adverse device effects at 3, 6, 9, 12, 18, 24, 30 and 36 months.

8 **Design of the Clinical Investigation**

8.1 General

The objective of this minimal risk clinical study is to document the comparative effectiveness and safety of the addition of peripheral nerve stimulation (PNS) to conventional medical management (CMM) with CMM alone in the treatment of chronic, intractable peripheral neuralgia.

CMM refers to the routine medical management patients receive to treat their pain; all medication and procedures that are part of the CMM will only be part of the routine clinical care and any drugs or devices must be FDA approved or cleared. PNS will be provided by an FDA cleared medical device and will be used strictly in accordance with its cleared labeling. The study does not involve investigational devices (those without FDA clearance or approval) or experimental treatments or procedures. The study is a multi-center, open label, randomized, controlled study to establish superiority of PNS with CMM over CMM alone.

Only patients who are to receive PNS therapy and are already receiving CMM as part of their routine clinical care are allowed to enroll in this study (there are other eligibility criteria that must be met). Since the use of the PNS system and CMM are part of the individual's routine care, they are not study procedures or the subject of this study.

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The research in this study involves the collection of Patient Reported Outcomes (PRO) data in the form of questionnaires and surveys (pain, comfort, compliance, quality of life, etc.), as well as patient demographics, eligibility criteria, and concomitant medications. Safety data will also be collected.

Subjects who meet all eligibility criteria will be randomized 2:1 into the active and control arm, respectively. Subjects who do not meet eligibility criteria are "screen failures" and will exit the study.

The 2-arms of the study are:

1) Arm 1: PNS+CMM- Active Arm
2) Arm 2: CMM alone- Control Arm

Subjects who are randomized into the active arm will receive PNS plus CMM and will be followed, at pre-determined, protocol specified intervals, for 36-months post-activation. In addition to therapy with the PNS system, subjects in this arm will maintain their current CMM regimen. Once patients receive a permanent implant per standard of care, the device will be activated and programmed within the cleared labeling to ensure optimal pain relief. The device may be re-programmed, as needed, to ensure optimal pain relief. Patients will exit the study after their 36 month follow up visit.

Subjects who are randomized into the control arm, will maintain a CMM regimen and will be followed, at pre-determined, protocol specified intervals, for 36-months post-randomization. This arm will serve as the control for comparisons to the active arm. At the end of 3-months, subjects in the control arm may be allowed to cross-over and receive a PNS system. This determination will be based on criteria outlined in Section 8.4.4; these criteria are the same used in routine care to ensure patient safety. Subjects who opt to cross-over will have the PNS system implanted per standard of care, beginning with a trial, similar to the active arm. Once the patients receive the permanent implant, the device will be activated and programmed within the cleared labeling to ensure optimal pain relief per usual and routine care as done with the active arm. The device may be re-programmed as needed per standard of care. Control arm patients who opt to cross over will exit the study after their 36 month follow up visit (marked from the time of device activation). Control arm subjects who choose not to cross-over will continue in the Control arm out to 36 months from the point of randomization.

All subjects will continue with their CMM, defined as the best standard of care for each individual patient, as determined by the investigator. Below listed are some common treatments that may be offered to subjects by the investigators:

- Oral medication, including analgesics, NSAIDs, neuromodulating agents, antidepressants
- Topical applications (example, CBD Oils, Lidocaine patches, pain patches, compound creams)
- Physical therapy and rehabilitation
- Psychological management
- Acupressure and acupuncture

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- Cognitive behavior therapy
- Nerve Blocks: Nerve blocks may be administered during the study, within the first 6-weeks of enrollment. From this point to 3-mos FU, no nerve blocks will be allowed. If patient needs a nerve block in this time frame, the 3-month FU visit should be pushed out to at least 6-weeks after block. After 3-month FU visit, if subject needs a nerve block, they may receive it, but the ensuing FU visit should be pushed out to at least 6-weeks after block.
- Epidural Steroid Injections (ESI): Epidurals may be administered during the study, within the first 6-weeks of enrollment. From this point to 3-mos FU, no ESI will be allowed. If patient needs an epidural in this time frame, the 3-month FU visit should be pushed out to at least 6-weeks after ESI. After 3-month FU visit, if subject needs an epidural injection, they may receive it, but the ensuing FU visit should be pushed out to at least 6-weeks after ESI.
- Transcutaneous electric nerve stimulation

Subjects in both arms will be followed at protocol specified time-points from enrollment to study completion.

The study duration is expected to be 5.5 years from first enrollment to last follow up of last patient and subsequent study closure. Study bias will be reduced by randomizing subjects to the different arms, use of CMM in both arms, use of multiple centers, limiting device use to only that is consistent with its cleared labeling to minimize variability in patient care and programming, and by prospectively collecting data.

A basic study flow chart is as follows:

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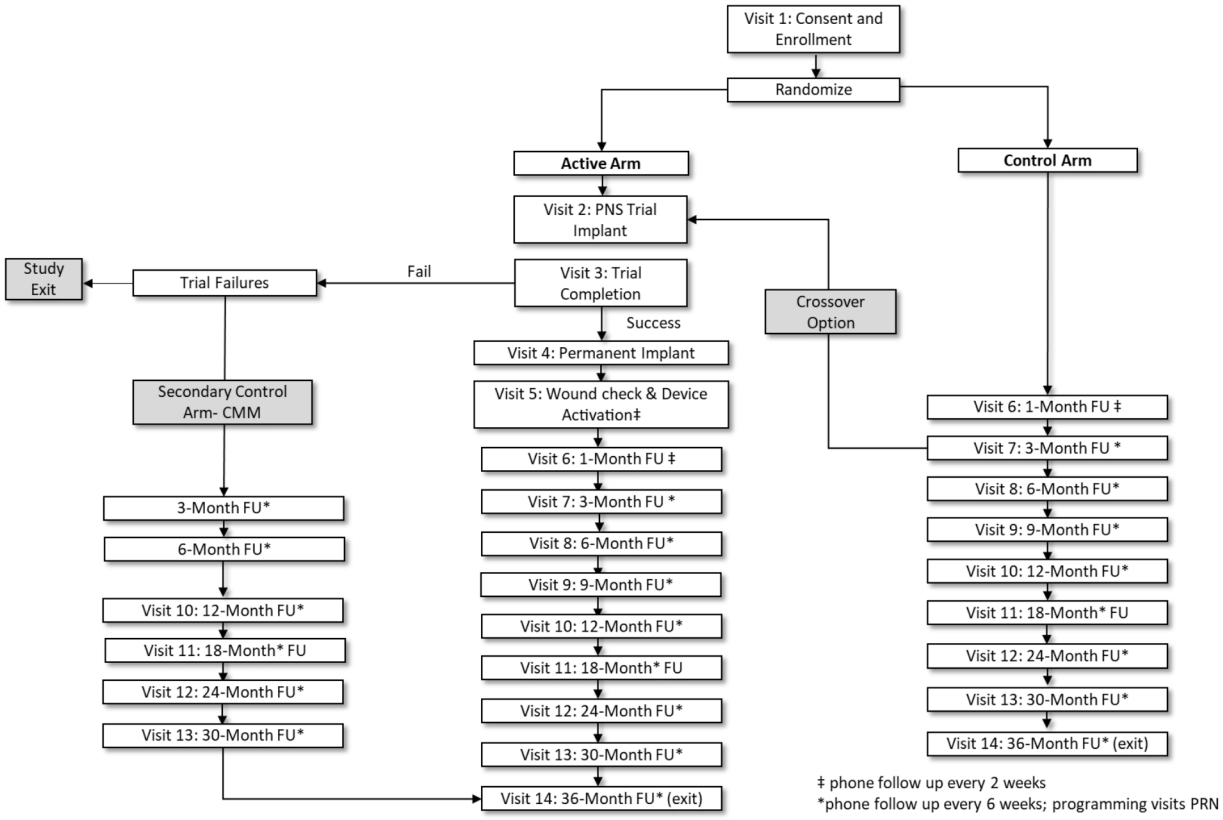


Figure 2: *Study Flow Chart*

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

Data to be collected is outlined in Table 1 below and detailed in sections below. The statistical analysis is described generally below but will be detailed in a Statistical Analysis Plan (SAP).

No replacement is planned for subjects that are lost-to-follow-up or are withdrawn. Sites will be allowed to enroll 1 to 2 patients as training subjects, if needed. These subjects will be randomized and implanted as detailed above. These subjects will continue to be followed per protocol but will be analyzed only for safety.

Revision or replacement of leads and/or IPG will be offered to subject at the discretion of the clinician, if required. Any subject that requires a revision/replacement of their PNS lead or IPG prior to the 3-month time point will have their study visits restarted (Visit 4) based on the new lead/IPG placement. If the subject requires revision/replacement of their trial leads, during the Trial Implant Phase of the study, their study visits will be restarted based on the revision/replacement date (restart at Visit 2), at the discretion of the clinician.

Note: Revisions and/or replacement of leads and/IPG will be considered as an extension to the treatment and should be considered part of routine patient management; they will not be

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recorded as Serious Adverse Events. The migration should be captured as an ADE and the intervention should be recorded as a revision and/or replacement.

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Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	NA
Visit	Informed Consent/ Enrollment	Trial Implant Procedure/ programing	Trial Implant Completion	Permanent Implant	Wound check and activation	1-month FU visit	3-months FU visit	6-month FU visit	9-month FU visit	12-month FU visit	18-month FU visit	24-month FU visit	30-month FU visit	36-month FU visit	Re-programming Visits (Optional)
Window**		0 -30 days from randomizat-ion	3-30 days from Trial implant	0-30 days from Trial implant Completion	7 ± 5 days from V4	30 ± 5 days from V5	90 ± 7 days from V5	185 ± 15 days from V5	270 ± 15 days from V5	365 ± 30 days from V5	550 ± 60 days from V5	730 ± 60 days from V5	912 ± 60 days from V5	1095± 90 days from V5	NA
Informed consent	X														
Inclusion/exclusion	X														
Adverse event	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Med. History, demographics, physical exam, psychological evaluation	X														
Wear Assessment*	X														
Pregnancy test*	X	X		X											
VAS	X		X			X	X	X	X	X	X	X	X	X	X
BPI-Q5	X		X			X	X	X	X	X	X	X	X	X	X
BPI	X						X	X		X	X	X	X	X	
EQ5D	X						X	X		X	X	X	X	X	
ODI	X						X	X		X	X	X	X	X	
Pain/paresthesia maps#	X	X	X		X	X	X	X	X	X	X	X	X	X	X
PCS	X						X	X		X	X	X	X	X	
Pain medication use	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization	X														
Stimulator Usability Questionnaire	X						X	X		X	X	X	X	X	
Programming Information		X		X	X	X	X	X	X	X	X	X	X	X	X
Patient Satisfaction							X	X		X	X	X	X	X	
PGIC							X	X		X	X	X	X	X	
BDI	X						X	X		X	X	X	X	X	

* Standard of care, not research procedure; #paresthesia maps not collected at visit 1.

Note: Control arm windows are from randomization not activation

** For control arm, windows are calculated from randomization.

See Section 8.5.12 for details on phone calls between visits.

Table 1: Research Data Collection Schedule

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8.2 Outcome Variables

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

8.2.1 Adverse Events

Once consent is signed, adverse events related to the study device or procedure (ADE, APE) should be collected and documented on the AE form in a timely manner. Serious Adverse Device Effects (SADE) should be solicited from subjects at each visit; appropriate documenting and reporting procedures should be followed. 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 applicable. 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, psychological evaluation

Subject's medical history, demographics, and physical exam information will be recorded, including height, weight. A psychological 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 psychological conditions that would be contraindicated for PNS therapy.

8.2.3 Pregnancy test

Pregnancy is a contraindication for use of the Nalu PNS system. In order to ensure on-label use of the Nalu PNS system during this study, the lack of pregnancy will be confirmed by a urine pregnancy test. Subjects that are of childbearing potential will be required to take a urine pregnancy test prior to trial implant and permanent implant. 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 childbearing potential must be using a reliable form of birth control, be surgically sterile, or be at least 1 years post-menopausal.

8.2.4 Pain Outcomes- VAS and BPI-Q5

The Visual Analogue Scale (VAS) is a subjective measure of pain. It consists of a 10-cm line with two endpoints 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 peripheral nerve pain in the indicated region.

The BPI-Q5, is a NRS based pain rating question, from the Brief Pain Inventory Questionnaire. The question asks subjects to rate their average pain on a scale of 0 to 10, where *0= No Pain and 10= Pain as bad as you can imagine.*

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8.2.5 EuroQol Quality of Life Questionnaire

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.

8.2.6 Oswestry Disability Index

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.

8.2.7 Brief Pain Inventory

The Brief Pain Inventory (BPI) asks questions about pain relief, pain quality, and the patient's perception of the cause of pain. It uses 0 to 10 numeric rating scales (NRS) for item rating. The BPI asks patients to rate their pain at the time of responding to the questionnaire (pain now), and also at its worst, least, and average over the last 24 hours. The BPI asks for ratings of the degree to which pain interferes with mood, ambulation and other physical activity, work, social activity, relations with others, and sleep. The mean of these scores may be used as a pain interference score.

8.2.8 Patient Satisfaction

Subjects will be asked to rate their overall satisfaction with the Nalu PNS system using a 5-point Likert scale, at post-activation FU visits.

8.2.9 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.

8.2.10 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.

8.2.11 Stimulator Usability Questionnaires

On completion of device wear assessment, subjects will be asked to record and rate their experience with the wearable components (Therapy Disc, adhesive clip and/or relief belt, and/or

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limb cuff). 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/or relief belt and/or limb cuff) used to hold the Therapy Disc over the IPG. Questions will include information about the comfort and ease of use of the wearable components.

8.2.12 Programming Information

Device programming and reprogramming are part of the normal on-label use of the Nalu PNS system and as such is not a research procedure. In order to ensure that the device is used on-label and is optimized for each patient programming details will be recorded. Programming details will be captured in the clinical programmer, including but not limited to 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 under study staff supervision.

8.2.13 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.

8.2.14 Beck's Depression Inventory (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.

8.2.15 Pain Catastrophizing Score (PCS)

PCS is a questionnaire that characterizes the tendency to magnify the value of the pain. It consists of 13-items and asks subjects to reflect on past painful experiences, and to indicate the degree to which they experience each of the 13 thoughts when experiencing pain.

8.2.16 Photographs

During the wear study, subjects may be asked to take photos, of the applicable area, 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. This helps to document the best identified location for post-implant clip placement and also guide IPG placement.

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8.3 Study Device and Comparator

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

All medications, procedures, and medical devices used by the subjects are part of their normal routine care and not considered research related. No other medication or medical devices will be prescribed during this study, although study subjects are allowed to continue CMM, as needed. 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.

8.4 Study Subjects

8.4.1 Inclusion Criteria for Subject Selection.

Inclusion criteria for subjects:

1. Subject is between 18 to 80 years of age at the time of enrollment.
2. Subject would have been prescribed PNS therapy regardless of participation in this study; the use of the Nalu device must be on-label.
3. Subject has been diagnosed with one or more of the conditions listed below in the low back, shoulder, knee, or foot (including ankle):
    - Post-surgical/post-traumatic peripheral neuralgia including but not limited to pain due to peripheral nerve injury, post-surgical scar formation, nerve entrapment
    - Mononeuropathy, specified or unspecified or in diseases classified elsewhere
    - Other neuralgia or neuropathic pain
    - Osteoarthritic pain
    -
4. Subject has chronic (defined as at least 6 months duration), intractable peripheral neuropathic pain, exclusive of the craniofacial region; any nociceptive pain must be less prominent than the neuropathic pain. Pain should have a predominant neuropathic component as per the investigator's clinical assessment.
5. Subject should have a pain score of at least 6, in the target area of pain, as recorded on the BPI-Q5 (NRS) at screening.
6. Subject is willing to cooperate with the study requirements including compliance with the study procedures and completion of all study visits.
7. Subject reported stable pain (non-escalating) for 60 days prior to signing informed consent.
8. Subject is currently receiving CMM and has had stable pain medication use and dosage for 30 days prior to signing informed consent.

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9. Subject is psychologically qualified to receive a peripheral nerve stimulator as per the clinician's standard clinical practice and judgment and does not have clinically relevant psychological condition(s) that would interfere with their ability to accurately report outcomes or complete study procedures.
10. Subject has demonstrated the ability to appropriately place the adhesive clip in the location where the IPG is most likely to be implanted. Alternatively, subject is able to appropriately use the relief belt and/or limb cuff to keep the Therapy Disc in place.

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, peripheral nerve stimulator, sacral nerve stimulator, deep brain stimulator, and/or cardiac pacemaker.
2. Subject has previously failed PNS, Spinal Cord Stimulation (SCS), or Dorsal Root Ganglion (DRG) therapy (trial or permanent implant). See note below.
3. Pain is completely absent at rest.
4. Patient has clinical evidence of complex regional pain syndrome (CRPS), peripheral neuralgia of metabolic origin, post-herpetic origin, biochemical evidence of a metabolic or genetic neuropathy (e.g., Charcot'- Marie- Tooth Disease) or mixed motor/sensory polyneuropathy.
5. Subject has a medical condition that would prevent them from participating in the current study per investigator's or medical monitor's judgment.
6. Subject has had a successful (≥50% pain relief) interventional procedure within the past 3 months to treat the same pain condition(s) being examined in this study including nerve blocks.
7. Uncontrolled depression or uncontrolled psychiatric disorders
8. Subject is currently participating in another clinical investigation with an active treatment arm.
9. Subject is allergic or sensitive to materials used in the device components including skin adhesives or does not tolerate the wearable aspect of the device.
10. 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.
11. Subject has a current diagnosis of a coagulation disorder, bleeding diathesis, or progressive peripheral vascular disease that has not been medically corrected.
12. Subject has an active systemic infection.
13. Subject is unable to read and/or write in English or give informed consent.
14. Subject has a life expectancy of less than 1 year.
15. Subject has an active malignant neoplasm (metastatic or local) or evidence of paraneoplastic syndrome.

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16. Subject with uncontrolled diabetes mellitus, showing signs of diabetic neuropathy, as evidenced by a neurological exam and a HbA1c test.
17. Subject has evidence of an alcohol or drug dependency within the last 6 months prior to enrollment.
18. 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).
19. Subject is nursing/breastfeeding.
20. Subject is on ≥90 mg-morphine equivalents per 24 hours.
21. Subject has undergone an ablative treatment of the target peripheral nerve, or proximal nerve trunk giving rise to the target nerve, or dorsal roots (and DRGs) that ultimately make up the target nerve. No ablative procedures directed at the spinal cord, dorsal roots, or peripheral nerve(s) being treated in the study. To note, subjects who have undergone RF ablation of the dorsal rami, cool pulsed RF of the facet innervation may be considered for enrollment. See note below.

Clarifications to Exclusion Criteria # 2 and 21

Criterion #2: These procedures are allowed if the procedure was not performed on the target nerve being treated in the study and if the procedure was performed ≥ 6 months prior to consent

Criterion # 21: If the patient has had an ablation ≥ 6 months prior to consent, they may be screened for the study.

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.).
- Non-compliance with protocol requirements or device usage
- Subject has an adverse event or other issue such that they can no longer continue with PNS 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.

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8.4.4 Criteria and Procedures for Cross-Over from Control to Active Arm

Subjects will be given the option to cross-over from the control arm to the active arm if they meet all of the below criteria:

- Meet all inclusion/exclusion criteria
- Less than 50% pain reduction with current treatment
- Investigator agreement to allow cross-over

Subjects who do not meet the above criteria will remain in the CMM arm to study completion.

8.4.5 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/or Medical Monitor). The subject will undergo all screening procedures again and will be given a new Subject ID.

Sites will be allowed to enroll 1 to 2 patients as training subjects, if needed. These subjects will be randomized and implanted as detailed above. These subjects will continue to be followed per protocol but will be analyzed only for safety.

8.4.6 Total Expected Duration of the Clinical Investigation.

The study is expected to last 3.5 years from first subject’s enrollment.

8.4.7 Expected Duration of Each Subject's Participation.

A subject’s participation from consent to exit may range from 38 months for those randomized to the active arm and up to 42 months total for those randomized to the control arm with cross-over.

8.4.8 Number of Subjects required to be Included in the Clinical Investigation.

The study will enroll up to 150 randomized, evaluable subjects. 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 300.

8.4.9 Estimated Enrollment Period

It is anticipated that up to 2 years will be needed to randomize the maximum number of study subjects.

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8.5 Procedures

The following sections describe the research related activities to occur at each study visit. Study data will be collected according to Table 1. Subjects will be asked to provide PRO data regarding adverse events and change in medications, including pain medication, at each study visit.

Study clinicians will oversee all study procedures and directly perform the implant procedure. 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 sponsor representatives under the supervision of the study clinicians.

Subjects may return to the clinic for unscheduled visits per routine clinical practice. The subject may require additional training on use of their device, troubleshooting of device problems, or reporting of adverse events. Some of these issues may also be resolved with a phone consultation with Clinic Staff, sponsor representatives, Study Monitor or Clinical Research Staff. In addition, the Clinic Staff, along with sponsor representatives, may call the study subjects on a regular basis to ensure proper use of the PNS system.

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

Rescue medications may be available in case of breakthrough pain or new pain conditions.

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 Visit 1: Informed Consent and Enrollment

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 study will utilize e-consents, to the extent possible; a copy of the electronically signed consent forms will be provided to the subject. In case paper consents are used, the Investigator will retain the original copy of the Informed Consent Form signed by the subject and 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. Each subject who signs consent will assigned with a unique subject ID which is used to identify their study records throughout the study. A urine pregnancy test will be administered to applicable subjects

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prior to trial lead placement as per standard of care. Pregnant subjects will be considered as screen-failures and exited from the study.

The following research data will be collected:

- Inclusion/exclusion
- Adverse events (following IC) and pain medication use
- Med. history, demographics, physical exam, psychological evaluation
- Stimulator Usability Questionnaire
- BPI- SF
- BPI-Q5
- ODI
- VAS
- EQ5D
- PCS
- BDI
- Pain maps
- Photographs, as needed

Inclusion/Exclusion Criteria: Subject's eligibility for study participation will be assessed using the Inclusion and Exclusion criteria listed in sections 8.4.1 and 8.4.2. Each subject should meet all the inclusion criteria and none of the exclusion criteria to be eligible for study participation. All eligibility criteria should be assessed and confirmed prior to randomization. If subject does not meet one or more criteria, they are excluded from the study as "screen-failures".

Note- Area of pain: the four areas of pain being examined in this study are low back, knee, foot (including ankle) or shoulder. Subjects should have pain in one of the listed areas to be eligible for the study. This is based on an identified peripheral nerve which is responsible for the pain. Patients with bilateral knee and foot are excluded from the study, i.e. multiple IPGs are not allowed.

Physical Exam, Medical History, and Medication History: A detailed physical exam is conducted by the clinician at this visit with emphasis on area of pain. In addition, patient's medical history is collected at this visit and should be updated as needed throughout the study. Subject's current list of medications is recorded, including but not limited to pain medications (both opiate and non-opiate) and should be updated throughout the study.

Psychological Evaluation: A psychological evaluation should be conducted, if not already done in the previous one-year per standard of care, to ensure that the subject does not have any psychological conditions that would be contraindicated for PNS therapy. This should be completed prior to randomization. This is standard of care and not considered research data.

Dexterity Test: Per cleared device label, subjects will undergo a dexterity test to see if they are able to place the adhesive clip, relief belt, or limb cuff in the region where their IPG will most

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likely be implanted. If the patient is unable to place the adhesive clip, relief belt, or limb cuff appropriately, their caregiver will be trained to help with this process.

Device Wear Assessment: Subjects will also be given wearable aspects of the Nalu system to test at home (mock or non-functional Therapy Disc, adhesive clip, relief belt, and/or limb cuff). 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 the adhesive clip location 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. Subject will be assessed for external wearable acceptance and tolerability. If subject does not tolerate the external wearable components, they will be considered a screen failure and exited from the study. This is considered standard of care for the study device and is included in the Nalu PNS system labeling.

Phone Call for Wear Assessment: Wear assessment should be done for a minimum of 7-days. At the end of wear assessment, the clinical staff and/or sponsor representative will call the subject via phone to discuss subject's experience with the external components of the device and if subject had any adverse reactions to the adhesive material. A stimulator usability questionnaire will be completed to collect data on the wearable components. For subjects who tolerate the wearable component, the preferred position of the adhesive clip and disc will be documented.

Baseline Questionnaires/ Patient Reported Outcomes: Subjects will complete the VAS, BPI-Q5, BPI, BDI, ODI, PCS, EQ-5D and Pain Maps during this visit. This will be considered the baseline for future comparisons. These assessments will be collected electronically, using the ePRO system, and maybe done in-clinic or remotely. If needed, paper forms will also be available for subjects to use, though this is not preferred.

Adverse Events: Once consent is signed, adverse events related to the study device or procedure (ADE, APE) should be collected and documented on the AE form in a timely manner. Serious Adverse Device Effects (SADE) should be solicited from subjects at each visit; appropriate documenting and reporting procedures should be followed.

Randomization: On confirmation of eligibility, subjects will be randomized into one of the 2 arms, i.e., active arm or control arm. This is considered an extension of visit 1 and a separate clinic visit is not needed. Randomization will be done in a 2:1 ratio (active to control), via permuted block randomization, and stratified by site.

Subjects who are randomized to the control arm will skip visit 2 through 5. They will complete these visits after the 3-month endpoint if they are eligible to cross-over.

Note: for study entry, subject should have a score of at least 6 or greater on the BPI-Q5 (*average pain on a 0-10 scale; 0= no pain; 10= pain as bad as you can imagine)*.

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8.5.3 Visit 2: Trial implant Procedure (0-30 days from randomization)

Trial Implant Procedure is part of the routine patient care and is included in the Nalu PNS system labeling. It will be scheduled 0-30 days randomization. Trial leads will be placed at this visit. A urine pregnancy test will be administered to applicable subjects prior to trial lead placement as per standard of care. Pregnant subjects will be considered as screen-failures and exited from the study.

Surgical Procedure: The surgical procedure is part of the routine care associated with the Nalu PNS system and is not a study procedure. The steps required to implant the PNS trial leads are described in the Nalu Surgical Manual and all trial leads must be placed per the process described in the manual, i.e., on-label. Standard surgical techniques will be used. Subjects will be trialed using the temporary trial implant method where leads are externalized and connected to a Trial Therapy Disc via the Electrode Interface Cable. Intra-operative paresthesia mapping will be used to guide electrode positioning for all subjects during the procedure, irrespective of nerve target. Impedance measurements will be taken to ensure robust communication and proper device functioning. Data on procedure will be collected.

Trial Implant Duration and Programming: Trial implant and programming are part of the routine care associated with the Naul PNS system and is not a study procedure. Subjects will be trialed for 3-30 days per approved labeling, though clinician preference for trial duration should be considered. Initial Programming may be done on the day of surgery or the next day. Subjects will be programmed per cleared device labeling; the goal of the trial implant is to optimize stimulation parameters to ensure the subject passes the trial implant and is eligible for a permanent implant. Data on stimulation parameters will be collected at this visit.
During the implant trial phase, sponsor representatives, and study staff will be in contact with subjects to guide them through the various programs, troubleshoot, if necessary, and to assess how the subject is responding to their stimulation programs. The subject may be brought in for additional programming visits during the trial implant period, to reprogram for efficacy, as is done in routine clinical use of the Nalu PNS device. Any contact with the subject will be recorded on a phone contact log.

Questionnaires: Pain and Paresthesia maps will be completed by the subject after programming.

Subject Training and Remote Control: Subjects will be trained on device use including the remote-control app and the Therapy Disc. 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. This may be 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 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 will be instructed on use of the adhesive remover spray and skin barrier.

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Adverse Events and Concomitant Medication: Adverse events related to the study device or procedure (ADE, APE) should be collected and documented on the AE form in a timely manner. Serious Adverse Device Effects (SADE) should be solicited from subjects at each visit; appropriate documenting and reporting procedures should be followed. Medication use will be updated, as applicable.

The following research data will be collected

- Adverse event, concomitant medication
- Pain/paresthesia maps completed after programming
- Programming parameters
- Photographs, as needed

Additional tests, such as blood testing, may be conducted at the discretion of the Investigator, if this is their standard clinical practice and are not study procedures. 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.

8.5.4 Re-Programming Visits, if needed

Re-programming for Efficacy: Per routine clinical care, subjects may have re-programming visits during the Trial Implant Phase; re-programming is not a research procedure. To ensure compliance with the protocol and GCP, these visits will be documented. Such visits would occur between Trial Lead implant (visit 2) and Trial implant Completion (visit 3). During these visits, subjects will be assessed and reprogrammed to optimize their therapeutic response to one or more therapy options with the Nalu PNS system. 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. Programming parameters given to the patient will be recorded.

If a reprogramming visit occurs the following information may be obtained, as needed:

Adverse Events and Concomitant Medication: Adverse events related to the study device or procedure (ADE, APE) should be collected and documented on the AE form in a timely manner. Serious Adverse Device Effects (SADE) should be solicited from subjects at each visit; appropriate documenting and reporting procedures should be followed. Medication use will be updated, as applicable.

Questionnaires/ Patient Reported Outcomes: Subjects will complete the VAS, BPI-Q5, Pain and Paresthesia maps (after programming) during this visit. These assessments will be collected electronically, using the ePRO system, and maybe done in-clinic or remotely. If needed, paper forms will also be available for subjects to use, though this is not preferred.

Revision and/or replacement: Per routine clinical care, revision and/or replacement of device components will be allowed per the clinician's judgement and after discussion with the subject. Revision and/or replacement is not a research procedure. If subject requires

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revision/replacement of their leads during the Trial implant Phase of the study, their study visits will be restarted based on the revision/replacement date (starting with visit 2), at the discretion of the clinician.

The following research data will be collected:

- Adverse event and medication
- VAS
- BPI-Q5
- Pain/paresthesia maps (after reprogramming)
- Programming parameters

8.5.5 Trial implant Completion (Visit 3; 3-30 days from trial implant)

Per routine clinical care, visit 3 is a minimum of 3 days from lead insertion (visit 2), and a maximum of 30 days (30 days is the maximum allowed time per cleared product labeling). As specified above, trial implant phase duration should be determined by the clinician based on their preference, standard of care and subject needs.

Success Criteria during Trial Implant: Subjects will use various therapy options during the trial implant phase. Those who report a 50% or greater reduction in their pain, for one or more of the device settings used in the trial phase and who meet all other screening criteria, are eligible to move on to the permanent phase of the study. While not specified in the device labeling, this threshold is typically used by clinicians and cited in the literature as a marker for a successful trial implant.

Subjects who fail to demonstrate a 50% or greater reduction from baseline in their area of pain, will be considered trial failures. Trial failures may exit the study or may be given the option to continue in study participation in the secondary control arm, i.e. using CMM only. These patients will continue to be followed for 36-months with FU visits at 3, 6, 12, 18, 24, 30 and 36-months from entering this arm.

Lead Removal: Patients will then have the trial leads removed. This is part of the routine care associated with the Nalu PNS system and is not a study procedure. 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.

Questionnaires/ Patient Reported Outcomes: Subjects will complete the VAS, BPI-Q5, Pain and Paresthesia maps (prior to trial lead removal) during this visit. These assessments will be collected electronically, using the ePRO system, and maybe done in-clinic or remotely. If needed, paper forms will also be available for subjects to use, though this is not preferred.

Adverse Events and Concomitant Medication: Adverse events related to the study device or procedure (ADE, APE) should be collected and documented on the AE form in a timely manner. Serious Adverse Device Effects (SADE) should be solicited from subjects at each visit; appropriate

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documenting and reporting procedures should be followed. Medication use will be updated, as applicable.

The following research data will be collected:

- Adverse event and concomitant medication
- VAS
- BPI-Q5
- Pain/paresthesia maps (prior to lead removal)
- Photographs, as needed

At the end of this visit, subjects will be given adhesive clip(s) and a mock disc 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.

8.5.6 Permanent Implant (Visit 4) - 0-30 days from Trial implant Completion

The Permanent Implant visit should be completed within a maximum of 30 days from trial implant completion, for subjects randomized to the active arm. Subjects randomized to the control arm will receive a permanent implant, if eligible for cross-over, after the 3-month endpoint visit. Subjects will be given a urine pregnancy test as per standard of care, prior to surgical procedure. Pregnant subjects will be considered as screen-failures and exited from the study.

Programming: Per usual clinical care and per cleared device labeling, initial programming may be carried out, post-operatively, to ensure proper device function and communication between the IPG and Therapy Disc. Programming is a part of the routine care associated with the Nalu PNS system and is not research procedure. Subjects will not be activated at this visit i.e. subjects will be instructed to not use the device until the next visit (visit 5) to ensure complete healing of the surgical site. In order to ensure on-label use of the Nalu PNS system these activities will be documented.

Subject Training and Remote Control: Subjects will be trained on device use, including the remote control app and the Therapy Disc. 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. The app may be 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 training on the Nalu PNS system and providing an iPod as remote control is part of the routine care associated with the Nalu PNS system and are not research procedures. The 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. Instructions on use of the adhesive remover spray and skin barrier may be reiterated. Though they may be sent home with the device (clips and TD), subjects should be instructed not to start active therapy until visit 5 is complete.

Adverse Event and Concomitant Medication: Adverse events related to the study device or procedure (ADE, APE) should be collected and documented on the AE form in a timely manner.

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Serious Adverse Device Effects (SADE) should be solicited from subjects at each visit; appropriate documenting and reporting procedures should be followed. Medication use will be updated, as applicable. Medications prescribed for post-operative pain relief should be recorded on the concomitant medication form.

The following research data will be collected

- Adverse event and medication use
- Programming information, if applicable
- Photographs, as needed

8.5.7 Wound Check and Device Activation (Visit 5; 7± 5 days from V4)

Per standard clinical practice, one week ± 5 days post-surgery, wound check will be performed to ensure healing, by qualified study staff or clinic staff. If the site(s) has adequately healed, then device activation will be performed at this visit. Again, per standard clinical practice, at the discretion of the clinician, additional healing time may be needed, as necessary, to ensure complete healing of the surgical site.

Programming and Activation: Upon confirmation of healing, a sponsor representative will perform routine device checks and program the device to optimize pain relief. Programming and activation are part of the routine care associated with the Nalu PNS system and are not research procedures. Subjects will be programmed per the device's cleared labeling. Patients will be sent home with therapy discs, clips and relief belt and a remote control. Subjects will be instructed to use paresthesia-independent programs prior to paresthesia-based programs. Data on stimulation parameters will be collected at this visit.

Patient Reported Outcomes/Questionnaires: Pain and paresthesia maps will be administered to the subjects after programming.

Revision and/or replacement: Per routine clinical care and the cleared device labeling, 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 and/or IPG during the Permanent Implant Phase of the study, their study visits will be restarted based on the revision/replacement date (starting with visit 4), at the discretion of the clinician. Revision and/or replacement are part of the routine care associated with the Nalu PNS system and are not research procedures.

Adverse Event and Concomitant Medication: Adverse events related to the study device or procedure (ADE, APE) should be collected and documented on the AE form in a timely manner. Serious Adverse Device Effects (SADE) should be solicited from subjects at each visit; appropriate documenting and reporting procedures should be followed. Medication use will be updated, as applicable.

The following research data will be collected:

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- Adverse Event and medication use
- Pain/Paresthesia maps (after programming)
- Programming Information
- Photographs, as needed

8.5.8 Additional Permanent Phase Reprogramming Visits (if needed)

Per routine use of the Nalu PNS system, additional programming of the device may be needed to further optimize the therapeutic response. Reprogramming is part of the routine care associated with the Nalu PNS system and is not a research procedure. Programming of the Nalu PNS system requires an in-person clinic visit. Such visits occurring after the actual Visit 5 but before Visit 6 will be considered an extension of Visit 5 and should be recorded on the programming visit CRF. If such visits are required the following data may be captured at each visit, as needed:

Adverse Events and Concomitant Medication: Adverse events related to the study should be collected and documented on the AE form in a timely manner. Serious Adverse Events (SAE) should be solicited from subjects at each visit; appropriate documenting and reporting procedures should be followed. Medication use will be updated, as applicable.

Questionnaires/ Patient Reported Outcomes: Subjects will complete the VAS, BPI-Q5, Pain and Paresthesia maps (after programming) during this visit. These assessments may be collected electronically, using the ePRO system, and maybe done in-clinic or remotely. If needed, paper forms will also be available for subjects to use, though this is not preferred.

The following research data will be collected:

- Adverse event and medication
- VAS
- BPI-Q5
- Pain/paresthesia maps (after reprogramming)
- Programming parameters

Note: the BPI-Q5 should be the first questionnaire completed at this visit followed by the VAS; all questionnaires are completed prior to programming unless specified above.

8.5.9 Scheduled Follow-Up Visits

Active Arm: Visit 6- 1-month post activation (± 5 days); Visit 7- 3-months post activation (± 7 days); Visit 8- 6-months post activation (± 15 days); Visit 9- 9-months post activation (± 15 days); Visit 10- 12-months post activation (± 30 days); Visit 11- 18 months post activation (± 60 days); Visit 12- 24 months post activation (± 60 days); Visit 13- 30 months post activation (± 60 days); Visit 14- 36 months post activation (± 90 days). These visits may be conducted remotely if appropriate.

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Control Arm: Visit 6- 1-month post randomization (± 5 days); Visit 7- 3-months post randomization (± 7 days); Visit 8- 6-months post randomization (± 15 days); Visit 9- 9-months post randomization (± 15 days); Visit 10- 12-months post randomization (± 30 days); Visit 11- 18 months post randomization (± 60 days); Visit 12- 24 months post randomization (± 60 days); Visit 13- 30 months post activation (± 60 days); Visit 14- 36 months post activation (± 90 days). These visits may be conducted remotely if appropriate.

For the follow-up visits after permanent implant, approximately two-weeks prior to each scheduled visit, the subjects may be contacted to remind them of their upcoming visit and ensure that the therapy does not need to be adjusted prior to the follow-up visit. A sponsor representative or the site staff may contact the subject prior to the follow up visit, to ensure that the subject is receiving optimal therapy. If subject does not require to be reprogrammed at any of the follow-up visits, the visit may be completed remotely, at the discretion of the investigator or delegated study team. Study questionnaires will be sent via remote ePRO to the subject's email for completion.

Questionnaires/ Patient Reported Outcomes: Subjects, irrespective of treatment or control arm, will complete the VAS, BPI, BPI-Q5, Pain and Paresthesia maps (after programming, if applicable), BDI, ODI, PCS, EQ-5D, PGIC and the Stimulator Usability Questionnaire during this visit, as applicable. These assessments will be collected electronically, using the ePRO system, and maybe done in-clinic or remotely. If needed, paper forms will also be available for subjects to use, though this is not preferred.

Programming/Re-programming for Efficacy: Subjects may be reprogrammed at a follow-up visit, if needed. Reprogramming is part of the routine care associated with the Nalu PNS system and is not a research procedure. Subjects will be assessed and reprogrammed to reduce unwanted stimulation effects and/or optimize their therapeutic response to one or more therapy options with the Nalu Neurostimulation System. Programming parameters given to the patient will be recorded.

Adverse Events and Concomitant Medication: Adverse events related to the study device or procedure (ADE, APE) should be collected and documented on the AE form in a timely manner. Serious Adverse Device Effects (SADE) should be solicited from subjects at each visit; appropriate documenting and reporting procedures should be followed. Medication use will be updated, as applicable. This data will be collected for all subjects in the study, both treatment and control arm.

Revision and/or replacement: 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 and/or IPG during the Permanent Implant Phase of the study, their study visits will be restarted based on the revision/replacement date (starting with visit 4), at the discretion of the clinician. Revision and/or replacement are part of the routine care associated with the Nalu PNS system and are not research procedures.

The following research data will be collected

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- Adverse event and medication use
- VAS
- BPI-Q5
- BPI (if indicated in Table 1 for this visit)
- EQ5D (if indicated in Table 1 for this visit)
- ODI (if indicated in Table 1 for this visit)
- Pain/paresthesia maps (after programming)
- Stimulator Usability questionnaire (if indicated in Table 1 for this visit)
- Programming Information
- PGIC (if indicated in Table 1 for this visit)
- BDI (if indicated in Table 1 for this visit)
- PCS (if indicated in Table 1 for this visit)
- Patient Satisfaction (if indication in Table 1 for this visit)

Note: the BPI-Q5 and VAS should be the first questionnaires completed at these visits; all questionnaires are completed prior to programming unless specified above.

On completion of the final study visit (visit 14, 36-month follow-up), subjects will be returned to standard of care and continue device use.

8.5.10 Additional Reprogramming Visits (if needed)

Per routine use of the Nalu PNS system, additional programming of the device may be needed to further optimize the therapeutic response. Programming and reprogramming are part of the routine care associated with the Nalu PNS system and are not research procedures. Programming of the Nalu PNS system requires an in-person clinic visit. If such visits are required the following data should be captured at each visit:

Adverse Events and Concomitant Medication: Adverse events related to the study should be collected and documented on the AE form in a timely manner. Serious Adverse Events (SAE) should be solicited from subjects at each visit; appropriate documenting and reporting procedures should be followed. Medication use will be updated, as applicable.

Questionnaires/ Patient Reported Outcomes: Subjects will complete the VAS, BPI-Q5, Pain and Paresthesia maps (after programming) during this visit. These assessments may be collected electronically, using the ePRO system, and maybe done in-clinic or remotely. If needed, paper forms will also be available for subjects to use, though this is not preferred.

The following research data will be collected:

- Adverse event and medication
- VAS
- BPI-Q5
- Pain/paresthesia maps (after reprogramming)

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- Programming parameters

8.5.11 Unscheduled Visits (both arms)

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, Sponsor representatives, Study Monitor or Clinical Research Staff. In addition, the Clinic Staff, 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 the appropriate CRFs.

8.5.12 Sponsor Follow-up Checks (both arms)

The sponsor representative will call the patient at a pre-scheduled time and review their current condition in terms of pain relief, adverse events, device issues etc. If needed, as a follow-up, the patient may be scheduled for an unscheduled visit or programming visit. This visit will be documented on a log. The sponsor follow-up checks may be conducted by phone or a video call, depending on patient preference. The Sponsor follow up checks will occur as follows:

- Active Arm: 2-weeks post-activation, between device activation (visit 5) and 1-month FU (visit 6).
- Control Arm: 2 weeks post-randomization, between randomization and 1-month follow up visit (Visit 6)
- Every 6 weeks between Visit 7 and Visit 14.

8.5.13 Cross-over of Control Arm

Subjects in the control arm will be followed at 1, 3, 6, 9, 12, 18, 24, 30 and 36-months post randomization. On randomization, subjects in the control arm, will continue to maintain their current conventional medical management regimen for 3-months.

Subjects will continue with their CMM, defined as the best standard of care for each individual patient, as determined by the investigator. Below listed are some common treatments that may be offered to subjects by the investigators:

- Oral medication, including analgesics, NSAIDs, neuromodulating agents, antidepressants
- Topical applications (example, CBD Oils, Lidocaine patches, pain patches, compound creams)
- Physical therapy and rehabilitation
- Psychological management
- Acupressure and acupuncture
- Cognitive behavior therapy

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- Nerve Blocks: Nerve blocks may be administered during the study, within the first 6-weeks of enrollment. From this point to 3-mos FU, no nerve blocks will be allowed. If patient needs a nerve block in this time-frame, the 3-month FU visit should be pushed out to at least 6-weeks after block. After 3-month FU visit, if subject needs a nerve block, they may receive it, but the ensuing FU visit should be pushed out to at least 6-weeks after block.
- Epidural Steroid Injections: Epidurals may be administered during the study, within the first 6-weeks of enrollment. From this point to 3-mos FU, no ESI will be allowed. If patient needs an epidural in this time-frame, the 3-month FU visit should be pushed out to at least 6-weeks after ESI. After 3-month FU visit, if subject needs an epidural, they may receive it, but the ensuing FU visit should be pushed out to at least 6-weeks after ESI.
- Transcutaneous electric nerve stimulation

At the end of 3-months, subjects in the control arm may be allowed to cross-over and receive a PNS system. This determination will be based on criteria outlined in section 8.4.4. If subjects in the CMM arm choose not to cross-over, they may continue in the CMM arm out to 36 months from the point of randomization. The decision to cross-over or stay in the CMM arm should be made within 30-days of completion of the 3-month endpoint. If subjects cross-over, they will undergo a Trial implant to ensure they can get relief from the PNS system, as detailed in Section 8.5.3. If they have a successful trial implant phase, they may receive a permanent PNS system, as outlined in Section 8.5.6. If subjects receive a PNS system, they will follow the above visit schedule from Visit 4 on and will be followed at 1 month post activation and 3-, 6-, 9-, 12, 18, 24, 30 and 36-months post activation. Cross over subjects who do not have a successful trial, may opt to exit study or continue in the study in a secondary control arm.

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.

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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 may be used to review 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 Effectiveness Analysis

Details are contained in the Statistical Analysis Plan, which is in a separate document.

9.2 Secondary Analyses

Details are contained in the Statistical Analysis Plan, which is in a separate document.

9.3 Safety Analyses

Details are contained in the Statistical Analysis Plan, which is in a separate document.

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.

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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 will be prepared by the Sponsor and approved by Nalu Medical and the local authority (IRB) before implementation.

12 **Deviations from the Protocol**

This study will be conducted as described in this protocol and in accordance with ISO14155:2020, 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 IRB as per local requirements.

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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 may be carried by a sponsor representative to the site. 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 14155:2020 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.

The clinical investigation at each site will not begin until the required agreement(s) (Clinical Trial Agreement, Financial Agreements) have been signed.

The clinical study will be financially sponsored by Nalu Medical, Inc.

15 Informed Consent Process

Written informed consent or electronic consent (eConsent) must be obtained from all subjects before any study related procedures are undertaken. 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. The current consent form approved by the IRB 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

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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 peripheral pain. 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:
	  ○ a life-threatening illness or injury, or
	  ○ a permanent impairment of a body structure or a body function, or
	  ○ in-patient or prolonged hospitalization, or
	  ○ medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
	• Led to fetal distress, fetal death or a congenital abnormality or birth defect

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	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 device and study procedure related AEs will be collected and monitored for all subjects, from the time of signing consent through to the final study visit. All device and procedure related 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 and/or study procedure, the Investigator will record the occurrence in the subject's source documents and promptly notify the Sponsor.

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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 CRF or 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 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 or via email to the sponsor representative.

The Investigator is required to notify the IRB 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, from date of first awareness, by the investigator or designee.

As additional information becomes available, the event should be updated in the CRF/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 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 Sponsor 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 medical monitor and/or 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.

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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 this Study or any of the investigations at one or more sites for administrative or business reasons at any time.

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

19 Publication Policy

Nalu Medical intends to submit the results of this investigation for publication. 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 IRBs 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)

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.

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/eCRFs 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

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may inspect the records with or without permission from the Sponsor. Monitors, auditors, and other authorized representatives of Nalu Medical, the IRB(s) 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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