STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Exploratory study assessing the response of Restless Legs Syndrome (RLS) patients to Non-invasive Peripheral Nerve Stimulation (NPNS) during opioid medication reduction.

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CLINICAL INVESTIGATIONAL PLAN

Exploratory study assessing the response of Restless Legs Syndrome (RLS) patients to Non-invasive Peripheral Nerve Stimulation (NPNS) during opioid medication reduction.

PROTOCOL NUMBER: CT-03

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SPONSOR:

Noctrix Health, Inc.
5424 Sunol Blvd
Ste 10-451
Pleasanton, CA 94566
804-683-4279

SPONSOR REPRESENTATIVE(S):

Jonathan Charlesworth, PhD
Head of Clinical Sciences

[redacted]

[redacted]

[redacted]

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Investigator Study Acknowledgement

Read and initial below.

____ I understand this protocol contains information that is confidential and proprietary to Noctrix Health, Inc.

____ Any additional information added to this protocol is also confidential and proprietary to Noctrix Health, Inc. and must be treated in the same manner as the contents of this protocol.

____ I have read the entire protocol.

____ I understand what the protocol asks me to do as an Investigator.

____ I will conduct this study following this protocol and will make a reasonable effort to complete the study in the time noted.

____ I will provide this protocol to study staff under my direct supervision. My study staff will keep the protocol and associated documents confidential.

____ I will discuss this information with the study staff to ensure they are fully informed about the study and the test articles.

____ I will not start enrolling in this study until it is approved by a governing Institutional Review Board.

____ I understand the study may be terminated or enrollment suspended at any time by Noctrix Health, Inc., with or without cause, or by me if it becomes necessary to protect the interests of the study subjects.

_____

Name of Investigator

_____ _____

Investigator Signature Date

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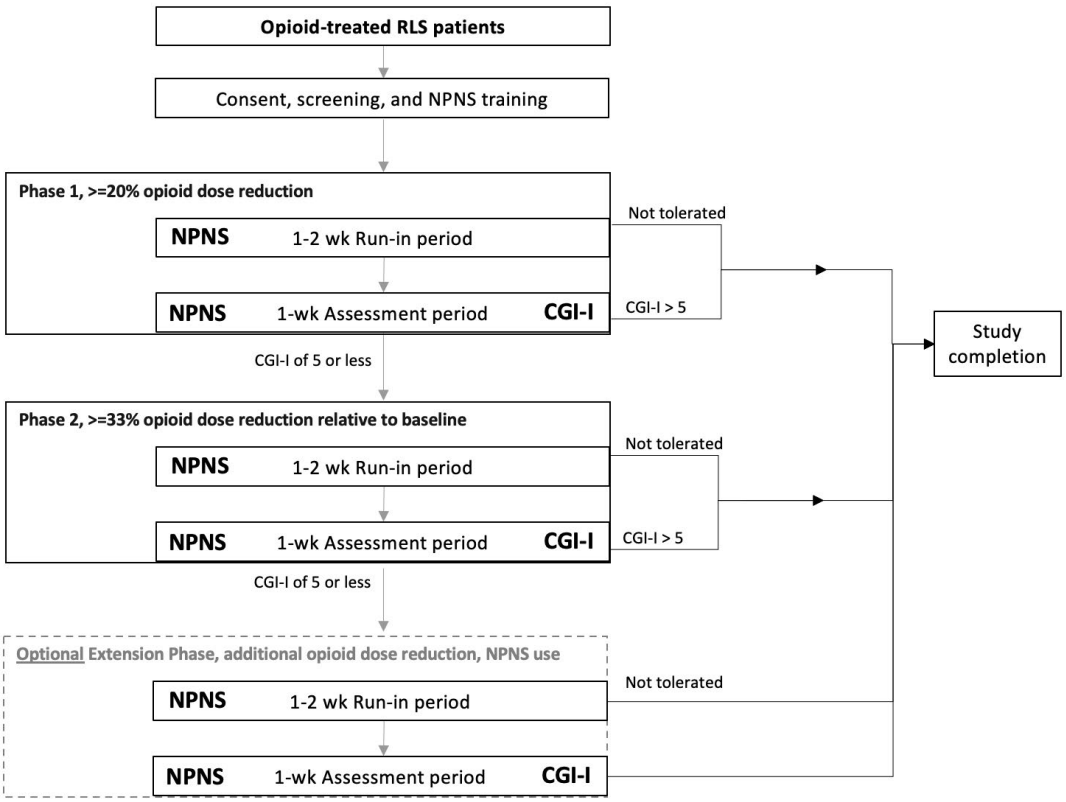
Study design overview Synopsis

Title	Exploratory study assessing the response of Restless Legs Syndrome (RLS) patients to Non-invasive Peripheral Nerve Stimulation (NPNS) during opioid medication reduction.
Study Device	NTX Neuromodulation System, an investigational NPNS device developed by Noctrix Health, Inc.
Study Objective	Assess the response of Restless Legs Syndrome (RLS) patients to Non-invasive Peripheral Nerve Stimulation (NPNS) during opioid medication reduction
Study Design	 An iterative opioid dose reduction is performed in conjunction with open-label NPNS administration. For each of the two step-downs in opioid dose (Phase 1 and Phase 2), a 1-2-wk run-in period is followed by a 1-wk assessment period. The run-in period is to ensure that any opioid withdrawal symptoms unrelated to RLS have resolved and to confirm the appropriate instructions for NPNS usage (e.g. timing and intensity). Study participation is terminated at the first phase that leads to a clinically significant

	increase in RLS severity or is otherwise not tolerated. Participants who tolerate both phases may have the option of an extension phase involving a third reduction in opioid dose.
Study Population	Adults with moderate-to-severe primary Restless Legs Syndrome (RLS) who are taking a stable dose of prescription opioids to treat RLS.
Study Participation Duration	Study participation duration in the main study period will typically be 4-6 weeks: Phase 1: 1-2 wk run-in 1-wk assessment Phase 2: 1-2 wk run-in 1-wk assessment Study duration may be somewhat shorter, such as if Phase 1 is not tolerated. Study duration may be longer, such as if run-in period is extended or depending on scheduling constraints. The optional extension phase (Phase 3) will last an additional 2-3 weeks.
Study Interventions	1. NTX Neuromodulation System (NPNS) programmed to **ACTIVE** mode 2. Dosage of prescription opioid medication will be iteratively reduced. Dosage reduction will be terminated if withdrawal symptoms become intolerable.
Maximum Study Duration	The study will be completed a maximum of 18 months after the study opens to enrollment.
Total Number of Subjects	20-40 subjects will be enrolled in the primary study Up to 10 additional subjects may be enrolled in a pilot phase Total enrollment: 20-50
Number of Sites	Up to 4 Clinical sites will participate
Study Endpoints	**Efficacy**

	Endpoint 1 (Primary Endpoint): Percentage of subjects without a clinically significant increase in RLS symptoms (i.e. CGI-I score of 5 or less relative to baseline) during the first Phase involving an opioid dose reduction of >= 20% relative to baseline. Endpoint 2: Percentage of subjects without a clinically significant increase in RLS symptoms (i.e. CGI-I score of 5 or less relative to baseline) during the first Phase involving an opioid dose reduction of >= 1/3 relative to baseline. Endpoint 3: IRLS during the first Phase with an opioid dose reduction of >= 20% relative to baseline. Endpoint 4: IRLS during the first Phase with an opioid dose reduction of >=1/3 relative to baseline. Endpoint 5: Maximal percentage reduction in opioid dose relative to baseline associated with a CGI-I score of 5 or less, averaged across subjects. **Safety** Endpoint 1: Frequency of Grade 2 of higher NPNS-related adverse events. Endpoint 2: Frequency of Grade 3 or higher NPNS-related adverse events. Endpoint 3: Percentage of subjects who are discontinued from study due to non-RLS opioid withdrawal symptoms prior to the Extension Phase. **NPNS tolerability** Percentage of subjects who withdraw from study prior to the Extension Phase citing lack of tolerability of NPNS as the primary reason for withdrawal. **Compliance** Frequency of device usage on nights with RLS symptoms during Assessment periods during Phase 1 and Phase 2.
Additional Study Assessments (as appropriate)	• Weekly assessment of opioid withdrawal symptoms (investigator may employ participant interview and/or COWS scale, as appropriate) • IRLS during run-in week • Nightly subject diary, including RLS symptoms and device usage • Automated compliance tracking – usage data collected via NTX device • Medication use assessment • Subject demographic/characterization assessment • Medication history • Follow-up questionnaire • Leg movement data collected via NTX device

Abbreviations

AE	Adverse Event
AO	Anticipated Observation
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impressions – Improvement
CRF	Case Report Form
FDA	Food and Drug Administration
DCF	Data Clarification Form
GCP	Good Clinical Practice
IRB	Institutional Review Board
IRLS	International Restless Legs Syndrome
ISO	International Organization for Standardization
MOS	Medical Outcomes Scale
NPNS	Non-invasive peripheral nerve stimulation, the intervention administered by the investigational device
NRS	Numerical Rating Scale
NSR	Non-Significant Risk
QA	Quality Assurance
RLS	Restless Legs Syndrome
SAE	Serious Adverse Event
TENS	Transcutaneous Electrical Nerve Stimulation
USADE	Unanticipated Serious Adverse Device Effect

1. Background

A clinical need has been identified of improved treatment for those suffering with primary idiopathic restless legs syndrome (RLS). Patients with RLS have a strong urge with sensations of tingling/pain, usually in their legs, and often present with a primary complaint of not being able to fall asleep regularly. This leads to significant quality of life degradation, depression, daytime sleepiness, lack of productivity and a host of downstream effects associated with lack of quality sleep.

1.1. Restless leg syndrome: Background

Restless legs syndrome (RLS) is a sensorimotor disorder that is characterized by a distressing urge to move the legs and in some cases, other parts of the body such as arms [1]. The diagnosis is made by a response to five hallmark identifying criteria instituted by the International Restless Legs Syndrome Society (IRLSS) [2], as quoted below:

> "1. An urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs.
>
> 2. The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
>
> 3. The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
>
> 4. The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day.
>
> 5. The occurrence of the above features are not solely accounted for as symptoms primary to another medical or a behavioral condition (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping)."

Diagnostically, RLS is considered either primary, often occurring within families, or secondary, developing in association with other conditions (such as iron deficiency anemia, pregnancy or end-stage renal disease).

1.2. Epidemiology

In the United States, RLS is believed to affect more than 10 million adults and an estimated 1.5 million children and adolescents [3]. About one-third of those with RLS symptoms are bothered sufficiently enough to seek medical attention. Epidemiologic studies also show that women are at least 50% more susceptible to RLS than men and RLS is more common in older adults, although it can occur in some as early as the pre-school years.

1.3. Clinical treatments available

The current standard of care involves initial prescription of dopaminergic medications – such as Requip, Mirapex, and Neupro – which initially provide symptomatic relief but often become ineffective over continued usage [4]. Tolerance to these medications is rapid and well-documented [5]; approximately 10% of patients per year become refractory to these medications, and fewer than 20% patients have sustained benefits lasting 10 years or longer [6]. It is also now understood that dopaminergic medications cause what is known as "augmentation", or paradoxical progressive worsening of RLS symptoms that is much faster than the natural progression of the condition. Due to augmentation, patients on dopaminergic medications require increasingly higher doses [7]. Maximal dosage is limited by an increasing risk of side-effects at higher doses, which include compulsive behaviors including substance abuse, hypersexuality, and gambling [8]. As a result of these downsides of dopaminergic agents, a minority of clinicians are starting to prescribe gabapentinioids (e.g. Horizant) as an alternative first-line of treatment; these medications do not typically lead to augmentation but confer risks such as respiratory depression [9], dizziness, and somnolence during the day.

For the large subpopulation of patients who become refractory to dopaminergic medications – typically due to augmentation – there are no FDA approved treatment options and no safe treatment options. As a result of tolerance, augmentation, and dosage limitations, RLS patients often continue to suffer from moderate-severe RLS symptoms while continuing to be reliant on high doses of dopaminergic medications to provide a small degree of relief. To address the massive unmet need, the leading clinicians involved with RLS advocate prescribing off-label opioids [10]. The leading options – oxycodone and methadone, have well documented risks, which include addiction,

dependence, overdose, and occasionally death. This situation is especially concerning because primary RLS typically starts in middle age or earlier and persists throughout life, thus patients may end up reliant on opioids for the final decades of their lives.

1.4. Investigational Procedure

The investigational device – the NTX Neuromodulation System – is a non-invasive nerve peripheral stimulation (NPNS) device developed by the Sponsor, Noctrix Health, Inc. and designed to stimulate the common peroneal nerve. Stimulation electrodes are positioned superficially and bilaterally on the lower legs over the head of the fibula bone, a position where the peroneal nerve is closest to the skin. This nerve target innervates regions of the lower extremities commonly associated with RLS symptoms. If successful, the trial will pave the way for a device-based therapeutic alternative that may be used to reduce opioid dosage.

1.5 Rationale

The NTX Neuromodulation System is a NPNS device designed to mimic the symptomatic relief that RLS patients experience during voluntary movement of their lower extremities. One of the fundamental diagnostic criteria for RLS is the fact that patients report short-lived symptomatic relief during voluntary movement of their legs and feet [2]. This is conceptually similar to the gate-control theory mechanism of pain relief, wherein activation of large sensory fibers suppresses pain signals. However, for RLS, it appears that muscle activation is especially effective – activating sensory fibers of the affected region of the body (e.g. via rubbing or touching) does not typically result in similar relief.

Non-invasive electrical stimulation is known to elicit muscle activation – this feature is used by two types of approved medical devices – powered muscle stimulators (21 CFR 890.5850) and external functional neuromuscular stimulators (21 CFR 882.5810). However, these devices tend to have distracting side-effects including paresthesias and phasic muscle twitches, and thus are incompatible with sleep and inappropriate for use in treating a sleep condition such as RLS. In contrast, the NPNS investigational device tested here produces waveforms that are engineered to generate muscle

activation without these paresthesias and phasic muscle twitches. Therefore, this technology may be compatible with sleep.

The NTX Neuromodulation System stimulates the peroneal nerve at its most superficial position over to the head of the fibula bone to activate muscles of the lower leg including the tibialis anterior at intensity levels that are comfortable and non-distracting. Such comfortable tonic muscle activation is designed to suppress RLS symptoms in a manner similar to voluntary movement – but unlike voluntary movement, may be compatible with sleep. Moreover, the output waveforms and intensities of the NTX Neuromodulation System are similar to Functional Electrical Neuromuscular Stimulators and Transcutaneous Electric Nerve Stimulation (TENS) Devices for treatment of pain, two classes of devices designated nonsignificant risk per 21 CFR 812.3. Therefore, there is a reasonable expectation that the NTX Neuromodulation System will lack significant risks.

This study evaluates the effects of NPNS on the symptoms of RLS during in-home participant-administered stimulation. This approach is useful for evaluating safety, usability, tolerability, and preliminary efficacy in a realistic environment - thus identifying any and all barriers to effective and tolerable use.

2. Regulatory Status

Noctrix Health has determined that the investigational device in this study – the NTX Neuromodulation System – is a non-significant risk device under 21 CFR §812.2(b); this assessment was confirmed by Western Institutional Review Board (WIRB) in a prior investigational protocol (20170487). Therefore, an approved Investigational Device Exemption (IDE) from FDA is not required to legally perform the study described herein in the US.

3. Objective

The study objective is to assess the response of Restless Legs Syndrome (RLS) patients to NPNS during opioid medication reduction. Specifically, we are investigating whether the magnitude of patient response to NPNS is sufficient to enable a clinically significant reduction in opioid medication dosage.

4. Study population overview

The study population will consist of adults with moderate-severe primary RLS. The following inclusion and exclusion criteria are designed to reduce confounding variables and reduce risk.

4.1. Inclusion criteria.

1. Subject has received a medical diagnosis of primary restless legs syndrome (RLS)
2. Subject is currently taking a stable dose of at least one prescription opioid for RLS, where the total opioid dose is less than or equal to 60mg morphine milligram equivalents (MME) per day.
3. RLS symptoms are most significant in the subject's legs and/or feet.
4. Subject possesses the necessary equipment, internet/phone accessibility, and communication ability to complete electronic questionnaires and respond to electronic communications and phone calls from the research staff throughout the in-home portion of the study.
5. Subject is 18 to 89 years of age (inclusive) when written informed consent is obtained.
6. Subject has signed a valid, IRB-approved informed consent form, can understand the requirements of the study and instructions for device usage, and can converse in English.
7. Subject has been taking a stable dose of prescription opioids for RLS for at least 30 days prior to enrollment.

4.2. Exclusion criteria

1. Subject has RLS that is known to be caused by another diagnosed condition (i.e. secondary RLS).
2. Subject was misdiagnosed with RLS, as determined by the investigator (e.g. actual diagnosis of PLMD, arthritis, leg spasms or neuropathy without comorbid RLS).
3. Subject has primary sleep disorder other than RLS that significantly interferes with sleep at the present time (e.g. unmanaged sleep apnea or general insomnia).
4. Subject has been diagnosed with one of the following conditions at any time:
   - Epilepsy or other seizure disorder
   - Severe movement disorder symptoms (Parkinson's disease, Huntington's disease, dyskinesia, dystonia)

- Deep Vein Thrombosis
- Multiple sclerosis

5. Subject has an active diagnosis of one of the following conditions:
   - Acute or chronic infection other than viral upper respiratory tract infections
   - Stage 4-5 chronic kidney disease or renal failure
   - Iron-deficient anemia
   - Severe edema affecting lower legs
6. Subject has any of the following at the location of device application.
   - Acute injury
   - Cellulitis
   - Open sores
7. Subject has a malignancy within the past 5 years (not including basal or squamous cell skin cancer)
8. Subject is on dialysis or anticipated to start dialysis while participating in the study
9. Subject has severe peripheral neuropathy affecting the lower legs and/or subject has neuropathy and is unable to clearly distinguish between symptoms of neuropathy and symptoms of RLS.
10. During NPNS calibration, subject has a sensation threshold above the upper-cutoff value (e.g. 30mA), the subject finds stimulation intensities less than 15 mA to be uncomfortable or distracting, or the device does not properly fit the subject.
11. Subject has significantly changed dose or schedule of a medication that may impact RLS symptoms within the 30 days prior to enrollment, as judged by the investigator (e.g. antidepressants, sleep medications, sedative antihistamines).
12. Subject has received an investigational drug or device within the last 30 days or is planning to receive an investigational device during the duration of the study.
13. Subject has another medical condition that may affect validity of the study as determined by the investigator.
14. Subject is unable or unwilling to comply with study requirements.
15. Moderate or severe cognitive disorder or mental illness.

16. Subject has prior experience with Noctrix Health NPNS devices.
17. Subject has active implantable medical devices anywhere in the body (including pacemakers), or metal implant at the site of study device electrode application.
18. Subject has known allergy to electrode gel, polyurethane foam, or lycra.
19. Subject is pregnant or trying to become pregnant.
20. Subject has undergone a major surgery (excluding dental work) in the previous 30 days.
21. Subject has another medical condition that may put the subject at risk as determined by the investigator.

5. Investigational Device

5.1. Description

The NTX Neuromodulation System is positioned and worn bilaterally on the legs with stimulation electrodes over the head of the fibula bone, thus targeting the common peroneal nerve – this nerve target innervates regions of the lower extremities commonly associated with RLS symptoms.

The NTX Neuromodulation System for each leg will consist of (1) one stimulation unit, (2) two or more electrodes, and (3) a mechanism for secondary attachment to leg, described below.

- The (1) stimulation unit will:
    - be battery-powered and contain a rechargeable battery and connector for recharging,
    - contain a circuit board that generates the stimulation waveform,
    - contain controls that the subject can use to activate stimulation,
    - contain controls that the subject can use to adjust the intensity of stimulation within a range programmed by the researcher,
    - contain an electronic connection mechanism to deliver a stimulation waveform to the electrodes,
    - contain an interface that the researcher can use to program the range of stimulation intensities, program the mode of stimulation (active or sham), and download data on compliance and functionality.

- The (2) electrodes will:
    - be hydrogel-coated electrodes similar to those used for transcutaneous electrical nerve stimulation (TENS) applications,
    - be disposable, allowing for at least 1 nights of use by the same subject,
    - be attached to the stimulation device by using shielded, insulated wires, snaps, magnetic connectors, conductive adhesives, or similarly secure connectors,
    - each have a surface area between 5cm2 and 50cm2.
- The (3) secondary attachment mechanism will:
    - secure the electrode to the body via straps and/or biocompatible adhesives.

Description of stimulation parameters:

- Pulse amplitude range:
    a. Device capability: 1mA-40mA (over 2kOhm load, limited by maximum of 60V)
    b. Protocol range: 10mA-40mA
- Pulse width:
    a. Device capability: 80-250 microseconds (depending on frequency)
    b. Protocol range: 80-250 microseconds (depending on frequency)
- Pulse shape:
    a. Device capability: Charge-balanced
    b. Protocol specification: Same as device capability
- Frequency:
    a. Device capability: 2 kHz – 6 kHz
    b. Protocol range: 2kHz – 6 kHz
- Duty cycle:
    a. Device capability: 25-100%
    b. Protocol range: 25-100%
- Duration:

a. Device capability: dependent on waveform parameters (see above), nominally 30min-120min
b. Protocol range: up to 60 minutes per session, up to 120 minutes per day

5.2. Instructions for Use and Administration

5.2.1. Route of administration

The NTX Neuromodulation System is designed to stimulate the common peroneal nerve; stimulation electrodes within the device are positioned superficially and bilaterally on the lower legs over the head of the fibula bone, a position where the peroneal nerve is closest to the skin. This nerve target innervates regions of the lower extremities commonly associated with RLS symptoms.

5.2.2. Dosage and dosage regimen

The dosage depends on the intensity and duration of stimulation:

1. Setpoint stimulation intensity. The setpoint stimulation intensity will be the lesser of (a) the maximal intensity that the subject reports is non-distracting and comfortable, as determined in the calibration session described in the instructions for device use and (b) the maximal intensity for each set of stimulation parameters, as determined based on device output capabilities.

2. Participants will be allowed to adjust stimulation intensity from the setpoint, but only within a limited pre-programmed range. For example, participant may increase intensity if symptoms are severe or reduce intensity if symptoms are mild.

3. Participants may be instructed to administer stimulation each night or only administer stimulation when RLS symptoms are present.

4. Stimulation may be activated for up to 120 minutes per day, depending on the timing, duration, and severity of RLS symptoms for the specific subject.

5.3. Contraindications

The following are contraindications to device usage:

- Diagnosis of epilepsy or other seizure disorder,
- Active medical device implant anywhere in the body, including but not limited to pacemakers, spinal cord stimulators, deep brain stimulators

- Metal implant at the site of study device electrode application
- Known allergy to device materials (or severe previous reaction to medical adhesives or bandages)
- Cellulitis, open sores, or acute injury at or near the location of device electrode application

6. Risks

6.1. Investigational device risks

NPNS devices such as NTX Neuromodulation System result in a known potential for the following anticipated observations, which are typically mild to moderate, transient in nature, and resolve over time.

- Mild skin irritation from use of adhesive electrodes and/or secondary attachment mechanism.
- Discomfort, paresthesia, or otherwise irritating or uncomfortable sensations during active electrical stimulation.
  - *This risk is reduced by calibrating the stimulation intensity.*
- Temporary interference with sleep while wearing the device:
  - For some individuals, device may be uncomfortable, thus interfering with sleep while wearing the device.
  - For some individuals, this device may interfere with preferred sleep positions, thus interfering with sleep during usage.
- Temporary increase in RLS symptoms while wearing the device:
  - For some individuals, this device may interfere with voluntary leg movements used to relieve RLS symptoms, thus leading to a temporary increase in RLS symptoms.
  - In some cases, this device may otherwise lead to a temporary increase in RLS symptoms during active stimulation for other reasons.
    - *This risk may be reduced by calibrating the stimulation intensity and/or adjusting the schedule of stimulation.*

6.2. Risks associated with study procedures

6.2.1. Opioid withdrawal procedure

Opioid withdrawal symptoms can occur during dosage reduction, specifically for rapid dosage reduction of short-acting, high-dose opioids. In contrast, the protocol here involves gradual dosage reduction (approximately 25% per week) of primarily long-acting (e.g. methadone, oxycodone), and exclusively low-dose (below 60 MME) opioids. Therefore, we expect a low risk of opioid withdrawal symptoms. However, it is possible that one or more symptoms that are associated with opioid withdrawal [11] may occur, such as the following: agitation, restlessness, and anxiety, depression, insomnia, yawning, increased tearing or watery eyes, runny nose, sweating, shivering, trembling, or goosebumps, muscle aches or joint pain, nausea or vomiting, abdominal cramps, diarrhea. Subjects will undergo a weekly investigator assessment and subjects with clinically significant withdrawal symptoms will be excluded from further participation. Moreover, subjects with intolerable withdrawal symptoms will have the option to discontinue participation at any time and revert to their original opioid dosage.

7. Adverse Events

Anticipated observations (e.g. common treatment effects) and adverse events occurring during the study will be recorded. Descriptions of anticipated observations and AEs will include the date of onset, the date it ended, the severity, the relationship to study device, and the outcome. All reported AEs will be summarized by the number of subjects reporting AEs, system organ class (where applicable), severity, seriousness, and relationship to study device.

The study Investigator and Coordinator will evaluate, characterize and record in the Case Report Form (CRF) all adverse events (AEs) occurring in all subjects from the time of enrollment to study exit (or premature withdrawal). Adverse events unresolved at study exit will be followed by the Investigator until resolution occurs or at least 60 days after the subject's participation in the study is complete. AEs may be reported spontaneously by the subject or detected by the Investigator or Coordinator. AEs should be evaluated for diagnoses not just symptoms (i.e., "angina", not "chest pain").

In addition to verbatim terms, the Sponsor may categorize all AEs using MedDRA preferred terms (PT) and system organ classes (SOC). Analysis may report both verbatim and MedDRA terms.

7.1. Adverse Event Definitions

An **adverse event** (AE) is any untoward medical occurrence, independent of its association with the investigational device. AEs also include any adverse laboratory signs or physical exam findings.

A **serious adverse event** (SAE[1]) is any AE that:

- led to a death,
- led to a serious deterioration in the health of the subject that:
- resulted in a life-threatening illness or injury,
- resulted in a permanent impairment of a body structure or a body function,
- required in-patient hospitalization or prolongation of existing hospitalization,
- resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function
- or led to fetal distress, fetal death or a congenital abnormality or birth defect.

A **device-related SAE** is an event meeting the SAE definition above that is also rated as probably or definitely related the investigational device. No device-related SAEs have been reported in prior studies.

Note that an elective or pre-planned hospitalization for a condition that did not worsen during the study is not an AE.

An **unanticipated serious adverse device effect** (USADE) is any SAE that is 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).

7.2. AE Severity and Relatedness

[1] Definition from ISO14155:2011

Each AE occurring in the study will be characterized by the study Investigator as to severity (Table 1) and relatedness (Table 2).

Table 1. AE Severity Grading System.

Grade	Brief description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental ADL[a]
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to adverse event

[a]'Instrumental ADL' refers to activities of daily living such as preparing meals, shopping for groceries or clothes, using the telephone, and managing money. [b]'Self-care ADL' refers to bathing, dressing and undressing, feeding oneself, using the toilet, taking medications, and not being bedridden. From the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 NCI, NIH, DHHS. May 29, 2009 NIH publication #- 09-7473.

Table 2. AE Relatedness Grading System.*

Grade	Relationship of AE to study device	Description
5	Definite	An event that follows a reasonable temporal sequence from administration of the study device; that follows a known or expected response pattern to the study device; and that is confirmed by improvement on stopping.

4	Probable	An event that follows a reasonable temporal sequence from administration of the study device; that follows a known or expected response pattern to the study device; and that is unlikely to have been caused by concurrent/underlying illness or other drugs, procedures, or other causes.
3	Possible	An event that follows a reasonable temporal sequence from administration of the study device; that follows a known or expected response pattern to the study device; but may have been caused by concurrent/underlying illness, drugs, procedure, or other causes.
2	Unlikely	An event that does not follow a reasonable temporal sequence from administration of the study device; that does not follow a known or expected response pattern to the study device, or most likely was caused by concurrent/underlying illness, drugs, procedure, or other causes, because of their known effects.
1	Not related	An event almost certainly caused by concurrent/underlying illness, drugs, procedure, or other causes.

** AEs occurring before treatment with the study device will be categorized as unrelated to the study device.*

7.3. Adverse Event Reporting

Investigators must report all SAEs to the study Sponsor and governing IRB within 3 business days or according to local IRB guidelines. Investigators should call the study sponsor immediately upon becoming aware of the occurrence of an SAE. The sponsor will contact the independent medical reviewer, to assist in assessing any safety concerns, if needed. The Investigator should be able and willing to provide further information on the specific event when requested by the study Sponsor. If the Investigator learns of an SAE that occurs within 1 month after the subject completes the study, he/she should notify the Sponsor. Investigators must also report all AEs to the governing IRB as determined by that IRB.

Prompt AE evaluation:

- protects the safety of study subjects;
- aids in understanding the overall safety profile of the device;

- prompts, if necessary, modification to the study protocol
- allows improvements in study design or procedures; and
- adheres with standard good clinical practices.

8. Device Tracking

The Sponsor will send the Investigator investigational devices. The Investigator must house study devices in a secure location.

The Investigator must carefully and completely track receipt, use and disposition of all investigational devices. The Sponsor will track sending and receiving of devices. The Sponsor will monitor site device accountability periodically.

If a Sponsor representative or designee is present at the time of use, he/she may directly take possession of used device(s). All devices will be returned to the Sponsor after the study is complete.

9. Device Deficiencies and Malfunctions

Throughout the study, the Investigator and study staff will report and document all device deficiencies and malfunctions related to the identity, quality, durability, reliability, safety or performance of the device. This includes reporting of device deficiencies/malfunctions that did not lead to an AE but could have if: 1) suitable action had not been taken, 2) intervention had not been made, or 3) circumstances had been less fortunate. If possible, the Investigator should return devices suspected of deficiency or malfunction to the Sponsor for analysis.

10. Ethical and Regulatory Considerations

10.1. Compliance with Good Clinical Research Practice

This study will be conducted in compliance with the principles of the Belmont Report, the Declaration of Helsinki, with the current Good Clinical Practice (GCP) guidelines and with other applicable regulations. The Investigator and all study staff will conduct the study in compliance with this protocol. Voluntary informed consent will be given by every subject prior to the initiation of any study-related procedures. The rights, safety and well-being of the study subjects are the

most important considerations and prevail over the interests of science and society. All personnel involved in the conduct of this study must be qualified by education, training and experience to perform their assigned responsibilities.

10.2. Confidentiality of Data

All information and data sent to the Sponsor, Contract Research Organizations, or the Independent Medical Reviewer concerning subjects or their participation in this study will be considered confidential. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the subject. The principal investigator consents to visits by the staff of the Sponsor and its authorized representatives and the U.S. Food and Drug Administration or any other governmental body to review the study subjects' medical records including any test or laboratory data.

10.3. Institutional Review Board (IRB) and Informed Consent

Before study initiation, the Investigator must have written and dated approval from the IRB for the protocol, consent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects. The Investigator should also provide the IRB with a copy of the product labeling, information to be provided to subjects and any updates. The Investigator will submit documentation of the IRB approval to the Sponsor. Copies of all correspondence with the IRB regarding this study must be sent to the Sponsor.

The IRB-approved consent form must include all elements required by FDA, state, and local regulations, and may include appropriate additional elements.

The Investigator/designee will explain the study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved informed consent form. The Investigator must provide the subject with a copy of the consent form in a language the subject understands. The Investigator will maintain documentation that informed consent was obtained prior to the initiation of any study-specific procedures.

Withdrawal of IRB approval of the Investigator's part in the investigation must be reported to the Sponsor within 5 working days.

10.4. Protocol Compliance

The Investigator will comply to the extent possible with the IRB-approved protocol. All deviations from the protocol must be documented. The Investigator will notify the Sponsor immediately if a deviation from the protocol was required to protect subject safety.

10.5. Protocol Revisions

Revisions to the study protocol can be made only by the study Sponsor. A revised protocol can be put into place only after governing IRB approval. All administrative letters must be submitted to the IRB for their information.

New or altered consent forms required by the IRB due to a protocol change must be signed by all subjects currently enrolled in the study and must be used for any subsequent subject enrollment.

10.6. Study Monitoring

Representatives of the Sponsor will visit all study to perform monitoring and data management functions, and provide participating sites with relevant contact information, as necessary. Study monitors may change periodically over the course of this study. All monitors will be qualified to perform their assigned responsibilities, and participating investigators/site personnel will be notified of any changes as they occur.

On-site and/or remote monitoring of all participating sites will be frequent enough to assure continued acceptability of the data by assessing site compliance with the study protocol, adherence to data collection procedures, and maintenance of study records. Scheduled site visits will include, but are not limited to, the following:

- Site initiation visit: prior to enrolling subjects, an on-site or remote initiation visit will be conducted by clinical study personnel to review this study protocol and discuss CRF completion

and transmittal procedures. Alternatively, a meeting may be conducted for several sites at a common location.

- Interim monitoring site visit: on-site and/or remote monitoring visits will be conducted at all sites to assess the progress of the study and identify any concerns that result from review of the study records, study management documents, or subject informed consent documents. To assure the integrity of the data, a representative number of individual subject records and other supporting documents will be compared to CRFs completed at the site to determine that:

  - The study protocol is being followed, and only eligible subjects are being enrolled; variances, if they occur, are recorded and reported as appropriate.
  - Informed consent is properly documented.
  - Adverse events are being reported appropriately.
  - Information recorded on CRFs is complete, accurate and legible.
  - Subjects failing to complete the clinical study and the reason for failure are properly recorded.
- Final monitoring/Close-out site visit: a final visit to participating sites may be made by the study monitor, if necessary. Any ongoing responsibilities will be discussed with the investigator and/or site personnel as appropriate.

At the close of the study at an investigational site, appropriately trained personnel appointed by the Sponsor will perform a close-out process via the telephone or on-site. The purpose of this visit is to collect all outstanding study data documents, ensure that the investigator's files are accurate and complete, review record retention requirements, ensure final accounting of all investigational devices shipped to the investigator, provide for appropriate disposition of any remaining supplies, and ensure that all applicable requirements are met for the study. The observations and actions made during the intervention will be documented and communicated to the investigator.

Representatives of government regulatory authorities may also evaluate the study records, source documents, Investigator, study staff and facilities.

The Investigator should immediately notify the Sponsor of any audits of this study by any regulatory agency, and must promptly provide copies of any audit reports.

10.7. Safety Reporting

The Sponsor is responsible for ongoing safety evaluation in this study protocol. Sponsor activities regarding safety include:

- classification of all AEs
- review of all AEs reported in the study
- confirm site's classification of AEs in terms of severity and relatedness to the study device
- review of severity and relatedness with the study Investigator, especially when there is disagreement between the Investigator and the sponsor
- review of device deficiencies and malfunctions, including determination and documentation of whether deficiencies/malfunctions could have led to an SAE
- ensuring the reporting of all SAEs and device deficiencies/malfunctions that could have led to an SAE to the IRB and, if required, regulatory authorities in a timely fashion
- informing all site Investigators in writing of all SAEs at all sites in a timely fashion
- updating the risk analysis and assessment of corrective or preventive actions potentially required as a result of new information obtained in the investigation

The Sponsor will evaluate all serious adverse events against US reporting requirements (Medical Device Reporting, 21 CFR 812) and Medical Device Directive (vigilance incident reporting) as per its standard operating procedures. The Sponsor will investigate each SAE to determine whether the event represents an unanticipated serious adverse device effect (USADE, see Section 7). The Sponsor will report any event to regulatory authorities, Investigators and reviewing IRBs/ECs as necessary. If an investigation shows that a USADE presents an unreasonable risk to subjects, the Sponsor will terminate all investigations or parts of investigations presenting that risk as soon as possible. The Sponsor will only resume a terminated investigation after corrective actions have

taken place, site Investigators are informed and IRBs/ECs have been notified and given approval to resume the study.

10.8. Case Report Forms

Study data will be collected using standardized paper Case Report Forms. CRFs will be printed on 2-part NCR paper (or equivalent) so that both the site and Sponsor will have copies of the CRFs. Each CRF will be designed to accommodate the specific features of the trial design. Modification of a CRF will only be made if deemed necessary by the study sponsor. ACRF is required and should be completed for each included subject. The Investigator has ultimate responsibility for the collection and reporting of all data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The eCRFs must be signed by the investigator to attest that the data contained therein are true.

The site will be provided with general CRF Completion Guidelines that can be located in the Study Operations Manual, which will assist in data entry and data issues/questions. All persons allowed to enter or change CRF data must appear on the Delegation of Responsibilities Log.

The Sponsor will monitor CRFs to identify possible data errors. Data queries that arise on CRFs that have been retrieved from the site, will be resolved using a Data Clarification Form (DCF). All data discrepancies will be resolved prior to database lock.

10.9. Quality Assurance Audits

Sponsor representatives or designees may conduct site quality assurance (QA) audits during the study. The Investigator must agree to provide the auditor with direct access to all relevant documents and discuss any findings with the auditor.

In the event of an inspection by the FDA or other regulatory authorities, the Investigator must give the inspector direct access to relevant documents and to discuss any findings with the inspector. The Investigator must notify Noctrix, Inc. in the event of a FDA site audit.

10.10. Records Retention

The Investigator must maintain all study records (including device disposition, informed consents, source documents, correspondence, regulatory documents, contracts etc.) for at least 2 years after study completion. At the Investigator's discretion, all records may be sent to the Sponsor for permanent storage.

The Investigator must contact the Sponsor or designee prior to destroying any records associated with this study. If the Investigator withdraws from the study, all study-associated records must be transferred to a mutually agreed upon designee. Written notification of such a transfer must be given to the Sponsor or designee.

10.11. Publication and Reporting of Study Results

The study will be registered with clinicaltrials.gov before the first subject is enrolled. Study results will be documented in a study report that will be signed by Noctrix representatives and by the Principal Investigator of the entire Study. Individual site Principal Investigators will not be required to sign this report.

If the results of this Noctrix sponsored study will be published, all standard editorial and ethical practices, will be followed. Results from multi-center studies must be published or presented at congresses only in their entirety with data pooled from all centers. Individual Investigators may not publish data from individual centers, unless granted specific written permission by Noctrix to do so.

The list of authors of any formal publication or presentation of study results may include, as appropriate, representatives of Noctrix.

11. Personnel Responsibilities

11.1. Principal investigator responsibilities:

Investigators are responsible for ensuring the investigation is conducted according to all signed agreements, the study protocol, and applicable regulatory agency regulations (21 CFR 812), which include:

a) Permit monitor inspection of facilities and records.

b) Permit FDA and other government health authorities' inspection of facilities and records.

c) Submit protocol and informed consent to IRB and await approval.

d) Submit proposed amendments to protocol and informed consent to IRB and await approval, unless the change reduces the risk to subjects.

e) Obtain informed consent of subjects.

f) Implement study in accordance with protocol.

g) Complete case report forms.

h) Record and explain deviations from protocol and report to monitor.

i) Submit annual progress reports, final reports, and adverse effect reports to IRB and sponsor.

j) Record the receipt, disposition, and return of study devices.

k) Refrain from promoting study or study articles in such a way that the potential participant will be biased in his/her responses.

l) Maintain medical histories of subjects.

m) Retain records for two years following FDA approval of marketing application.

n) Titrate opioid dosage in accordance with protocol.

11.2. Sponsor Responsibilities

Listed below are the Sponsor's responsibilities for this study.

a) Assure IRB approval of protocol and informed consent is obtained.

b) Select and train monitors.

c) Select investigators.

d) Train investigators in device use.

e) Obtain Agreement Letter and curriculum vitae and proof of appropriate licensure of investigator and other study staff.

f) Control shipment of investigational devices.

g) Conduct day-to-day administration of study.

h) Investigate unanticipated, device related adverse effects.

i) Document protocol deviations and violations.

j) Obtain statement of financial disclosure.

k) Administer, assist, and/or oversee calibration for each subject.

12. Duration

The study will be completed a maximum of 18 months after the study opens to enrollment.

13. Study design

The study design consists of iterative opioid dose reduction relative to baseline opioid dose (the week prior to study entry). Each Phase of the study includes NPNS usage and an opioid dosage reduction as shown in Table 3 below. As discussed in Section 13.1, the baseline opioid dose will partly determine whether a subject is eligible to continue to Phases 2 and 3.

- Phase 1 involves a total reduction in opioid dose of >=20% relative to the starting dose.
- Phase 2 involves a total reduction in opioid dose of >=1/3 relative to the starting dose.
- Optional phase 3 involves a further reduction in opioid dose.

Table 3. Study design phases

Phase	Duration	Description	Opioid dosage Reduction relative to baseline	NPNS usage	Efficacy endpoint evaluation
1	1-2 wks	Run-in	Smallest reduction of ≥20% relative to baseline	Yes	No
	1-wk	Assessment		Yes	Yes
2	1-2 wks	Run-in	Smallest total reduction of ≥1/3 relative to baseline that is also a reduction relative to Phase 1	Yes	No
	1-wk	Assessment		Yes	Yes
3 (optional)	*1-2 wks*	*Run-in*	*Additional reduction relative to Phase 2*	*Yes*	*No*
	1-wk	*Assessment*			

13.1 Accounting for between-subjects variation in starting opioid dose

The study has been designed to account for between-subjects variation in the starting dose and quantal dose of opioid medication, while also allowing calculation of standardized efficacy endpoints. The opioid dose reduction process is complicated by that fact that that there are quantal doses of opioid medication. For example, for methadone, which is commonly prescribed for RLS, the minimum pill size is 5mg and the quantal size is 2.5mg because pills can be broken in half.

All subjects initially participate in Phase 1, which involves the smallest reduction in opioid dose of greater than or equal to 20% of the starting dose. Subjects who tolerate Phase 1 without a clinically significant increase in RLS symptoms will advance to Phase 2, which involves the smallest additional reduction in opioid dose that also represents a total reduction of greater than or equal to 1/3 of the starting dose. Subjects who tolerate Phase 2 without a clinically significant increase in RLS symptoms will have the option to complete Phase 3, which involves an additional reduction in opioid dose. Once the subject completes a Phase where no further reduction is possible (e.g. a subject reaches 0mg in Phase 1 or 2), they will complete the study at the end of that Phase.

For example, in the case of methadone, the minimal quantal dose reduction is 2.5mg. Therefore, for methadone (**Table 4**):

- a subject on a 10mg starting dose would reduce to 7.5mg (25% reduction) in Phase 1 and 5.0mg (50% total reduction) in Phase 2. The endpoints related to >=20% reduction would be evaluated in Phase 1 and the endpoints related to >=1/3 reduction would be evaluated in Phase 2.
- a subject on a 7.5mg starting dose would reduce to 5.0mg (1/3 reduction) in Phase 1 and 2.5mg (2/3 total reduction) in Phase 2. The endpoints related to both >=20% reduction and >=1/3 reduction would be evaluated in Phase 1.
- a subject on a 5.0mg starting dose would reduce to 2.5mg (50% reduction) in Phase 1 and 0mg (100% total reduction) in Phase 2. The endpoints related to both >=20% reduction and >=1/3 reduction would be evaluated in Phase 1.
- a subject on a 2.5mg starting dose would reduce to 0mg (100% reduction) in Phase 1 and complete the study at the end of Phase 1. The endpoints related to both >=20% reduction and >=1/3 reduction would be evaluated in Phase 1.

Subjects who tolerate Phases 1 and 2 without a clinically significant increase in RLS symptoms and are at a non-zero dose of opioids will have the option to complete Phase 3, which involves an additional reduction in opioid dose.

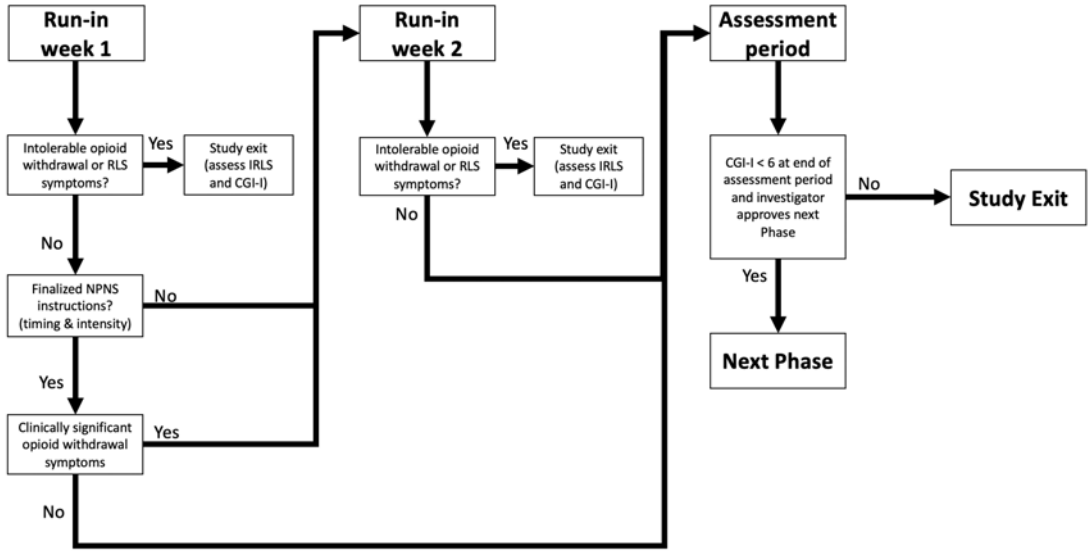
Table 4. Example of reductions during Phases 1 and 2 for methadone

	Example table of percent reductions for methadone *(minimum quantal size for methadone is 2.5mg, one-half of a 5mg pill)*									
Starting dose	**20**	100	87.5	75.0	62.5	50.0	37.5	25.0	12.5	
	17.5	100	85.7	71.4	57.1	42.9	28.6	14.3	0.0	
	15	100	83.3	66.7	50.0	33.3	16.7	0.0		
	12.5	100	80.0	60.0	40.0	20.0	0.0			Phase 1
	10	100	75.0	50.0	25.0	0.0				Phase 2
	7.5	100	66.7	33.3	0.0					
	5	100	50	0.0						
	2.5	100	0.0							
		0	**2.5**	**5**	**7.5**	**10**	**12.5**	**15**	**17.5**	
		Dose in Phase 1 or Phase 2								

13.2 Run-in and Assessment periods

Each Phase involves a 1-2 week run-in period followed by a 1-week assessment period. Assessment periods are primarily designed for endpoint evaluation. Run-in periods are designed for two reasons: (i) to provide a run-in phase to optimize instructions for NPNS device self-administration (e.g. timing and intensity) and (ii) so that any opioid withdrawal symptoms unrelated to the RLS condition resolve prior to the assessment period. Each run-in period will last a minimum of 1-week and a maximum of 2-weeks. The investigator is permitted to adjust the instructed schedule of opioid medication and/or NPNS usage during a Step-Down based on clinical evaluation of response to opioid treatment and NPNS.

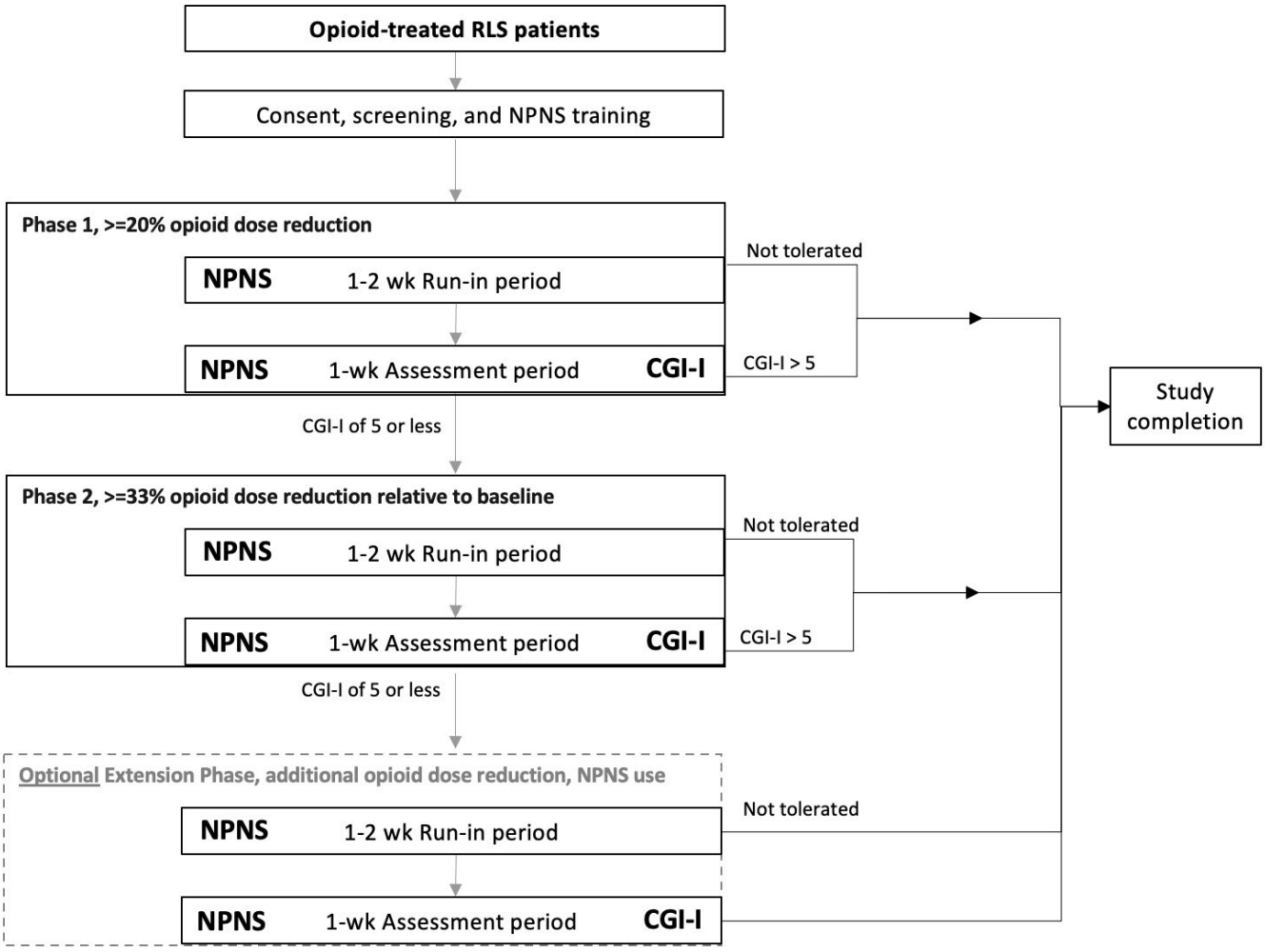
Figure 1. Flowchart of Run-in and Assessment periods for Phases 1 & 2



Additionally:

- If clinically significant opioid withdrawal symptoms *unrelated to* RLS become intolerable during the run-in period for a given Phase, participation will be discontinued and data from the subject will not count towards the efficacy endpoints for that Phase.
- If opioid withdrawal symptoms *related to* RLS become intolerable at any point during a run-in period, participation will be discontinued and the subject will count towards the efficacy endpoints for that Phase.
- The investigator may decide that participation should be discontinued at any time if there are excessive opioid withdrawal symptoms, even if those symptoms are tolerable.
- If opioid withdrawal symptoms become intolerable mid-week during a run-in period, participation will be discontinued.
- In all cases, efficacy outcome measures CGI-I and IRLS will be assessed at study exit but will not be included in analysis of the efficacy endpoints unless opioid withdrawal symptoms *related to* RLS was the primary reason for discontinuation.
- The Extension Phase is optional and requires approval by both the investigator and the participant. The structure of this phase is similar phases 1 and 2.

Figure 2. Flowchart of study design



14. Blinding

Subjects will be informed that they are receiving the active investigational treatment.

15. Investigator Qualifications

Investigators must have experience in the administration of opioids, as documented on their Curriculum Vitae and/or in a statement of the investigator's relevant experience, including dates, location, extent, and type of experience. Each Investigator must undergo training conducted by Noctrix Health, on the study device prior to study initiation.

16. Study Procedures

16.1. Recruitment

Recruitment will initially focus on patients whose opioid medications are managed by a Study Investigator at the time of study entry. Recruitment may be expanded if additional subjects are needed to meet the enrollment target. Subject eligibility will be determined based on the inclusion and exclusion criteria detailed above. Eligible applicants who chose to participate and sign the informed consent form will be enrolled in the study. A pre-screening call may be completed prior to the first in-person visit (and thus prior to consent) to exclude ineligible applicants prior to the in-person visit. Patients not referred by the investigator may be contacted by the investigator to establish whether they meet criteria for clinical RLS; applicants who do not meet clinical criteria for a diagnosis will be excluded from remaining parts of the study. Eligibility is contingent on scheduling constraints, such as research facility and research staff availability.

16.2. Informed consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure, with the exception of pre-screening. The participant must receive a paper or electronic copy of the signed and dated consent document. The signed copy of the consent document must be retained in the study binder in paper or electronic format. The schedule of visits and procedures is provided in Table 2.

16.3. Screening

Potential participants will be screened for eligibility based on the criteria in Section 4 above. A subject who is eligible and signs the study consent will be considered a study subject, and will be assigned a

study ID number, will be considered enrolled and will count towards the study's sample size. A subject who withdraws or is removed from the study prior to receiving any study treatment will not count towards the study's sample size.

16.4. Pilot phase

Up to 10 subjects may be enrolled in a pilot phase. For each site, subjects enrolled in the pilot phase will precede subjects enrolled in the primary study. Subjects enrolled in the pilot phase will be specified at the time of enrollment such that their data will not be included in the analysis.

16.5. Baseline Assessments

The participant completes an IRLS questionnaire describing their symptoms and experiences over the past week and a demographic/characterization assessment including questions about their history of RLS symptoms and medication(s).

16.6. Device calibration and training

During the baseline (Eval #1) visit, the devices are calibrated for the subject and the thresholds are programmed into the devices. The calibration process is designed to identify the maximally effective settings that are comfortable for each subject. The calibration process is also used to evaluate Exclusion Criterion #10. Therefore, subjects may be excluded immediately following calibration and prior to training and study enrollment. The sponsor may administer the calibration and/or assist in administering the calibration.

Following calibration, subjects are trained on proper usage of the device, including positioning of the electrodes on their legs. Instrument(s) designed for marking the human skin (body-marking pen or temporary tattoo) may be employed to mark the locations of electrode placement.

16.7. Study Treatment Description

Study subjects are instructed to self-administer treatment for at least 30 minutes on each night that they experience RLS symptoms. Study subjects may self-administer up to four 30-min sessions per day, as needed based on RLS symptoms. The instructions for timing of these "as needed" doses will be determined at the discretion of the investigator and research staff, based on the RLS symptoms experienced by the subject.

16.8. Leg movement data collection

The NTX Neuromodulation System may have the capability to collect data on leg movements, such as by using accelerometers and/or gyroscope sensors, while the participant is wearing the devices. These data may be collected during this study and used for subsequent algorithm development.

16.9. Evaluation and study assessment schedule

The following evaluation calls and/or visits are scheduled, as outlined in Table 5 below:

Phase 1

- Evaluation 1: Enrollment, including consent, screening, device calibration, and training on device usage.
- Evaluation 2: (3-days after Eval. #1) Phone follow-up to assess NPNS use, medication use and opioid withdrawal tolerability.
- Evaluation 3: (7-days after Eval. #1) Phone follow-up to assess RLS severity, NPNS usage, and opioid withdrawal tolerability.
- Evaluation 4: (10-days after Eval #1) *Optional Evaluation, if additional time for adjusting to opioid reduction is needed.* Phone follow-up to assess NPNS usage, medication use, and opioid withdrawal tolerability,
- Evaluation 5: (14-days after Eval #1) *Optional Evaluation, if additional time for adjusting to opioid reduction is needed.* Phone follow-up to assess RLS severity, NPNS usage, and opioid withdrawal tolerability.
- Evaluation 6 (**Assessment period**): (7-days after last Eval. (3, 4 or 5)). Phone or Office follow-up to assess RLS severity (including CGI-I), NPNS usage, and opioid withdrawal tolerability. Second opioid reduction occurs, and Phase 2 of the study begins. If subject was unable to tolerate opioid withdrawal symptoms complete study exit assessments and close-out participation for the subject.

Phase 2

- Evaluation 7: (3-days after Eval. #6) Phone follow-up to assess NPNS use, medication use and opioid withdrawal tolerability.
- Evaluation 8: (7-days after Eval. #6) Phone follow-up to assess RLS severity, NPNS usage, and opioid withdrawal tolerability.
- Evaluation 9: (10-days after Eval #6) *Optional Evaluation, if additional time for adjusting to opioid reduction is needed.* Phone follow-up to assess NPNS usage, medication use, and opioid withdrawal tolerability,
- Evaluation 10: (14-days after Eval #6) *Optional Evaluation, if additional time for adjusting to opioid reduction is needed.* Phone follow-up to assess RLS severity, NPNS usage, and opioid withdrawal tolerability.
- Evaluation 11 (**Assessment period**): (7-days after last Eval. (8, 9 or 10)). Office follow-up to assess RLS severity (including CGI-I), NPNS usage, and opioid withdrawal tolerability. Third opioid reduction occurs, and extension Phase 3 of the study begins if subject chooses to participate. If subject chooses not to continue with the extension Phase 3, complete study exit assessments and close-out participation for the subject.

Optional Extension

- Evaluation 12: (3-days after Eval. #11) Phone follow-up to assess NPNS use, medication use and opioid withdrawal tolerability.
- Evaluation 13: (7-days after Eval. #11) Phone follow-up to assess RLS severity, NPNS usage, and opioid withdrawal tolerability.
- Evaluation 14: (10-days after Eval #11) *Optional Evaluation, if additional time for adjusting to opioid reduction is needed.* Phone follow-up to assess NPNS usage, medication use, and opioid withdrawal tolerability,
- Evaluation 15: (14-days after Eval #11) *Optional Evaluation, if additional time for adjusting to opioid reduction is needed.* Phone follow-up to assess RLS severity, NPNS usage, and opioid withdrawal tolerability.

- Evaluation 16 (**Assessment period**): (7-days after last Eval. (13, 14 or 15)). Office follow-up to assess RLS severity (including CGI-I), NPNS usage, and opioid withdrawal tolerability. Complete study exit assessments and close-out participation for the subject.

Evaluations 1, 6, 11 and 16 are intended to be in-person and all other Evaluations are designed to be remote interactions (calls or video calls). Evaluations 1, 6, 11 and 16 may be replaced by remote interactions to the extent needed to reduce risk to participants and to the extent that technology allows for remote interactions. The proposed follow-up timelines are estimates, and they can be flexible as needed, within a +/- window of two days for each evaluation.

The schedule of each subjective study-related assessment, including endpoints, are shown in Table 5A below. Participants in the Extension Phase will complete an additional schedule of assessments as illustrated in Table 5B, which follow a similar structure to the assessments in Phase 2.

In addition to these assessments, the devices automatically log quantitative compliance, usage data, and leg movement data throughout the duration of the study.

The following are completed by subject: IRLS, Daily questionnaire, Medication use assessment, Step-down assessment questionnaire.

The following are administered and completed by the investigator or designee: Screen for inclusion/exclusion, Informed consent, Study entry questionnaire, CGI-I, Opioid-related symptom assessment, AE assessment.

Table 5A. Schedule of Assessments

	Baseline		Opioid Reduction Phase 1				Opioid Reduction Phase 2					Exit or Extension
			Acclimate to Opioid Reduction (7-14 days)				7 days from last Eval (3, 4, or 5)	Acclimate to Opioid Reduction (7-14 days)				7 days from last Eval (8, 9, or 10)
	Pre-screening	Eval. #1 (clinic visit)	Eval. #2 (call) 3-days	Eval #3 (call) 7-days	Eval. #4 (call)* 10-days	Eval #5 (call)* 14-days	Eval. #6 (call or visit) End of Phase 1/ Start of Phase 2	Eval. #7 (call) 3-days	Eval #8 (call) 7-days	Eval. #9 (call)* 10-days	Eval #10 (call)* 14-days	Eval. #11 (clinic visit) End of Phase 2/ Start of Phase 3
Pre-screen inclusion/exclusion	X											
Screen inclusion/exclusion		X										
Informed consent		X										
Study entry questionnaire		X										
NPNS calibration & IFU training		X										
Dispense NPNS Device		X										
Calculate baseline opioid dose		X										
Incremental Opioid Dose Reduction		X					X					O
Review Daily Questionnaire			X	X	O	O	X	X	X	O	O	X
CGI-I							X					X
IRLS		X		X		O	X		X		O	X
Medication use assessment			X	X	O	O	X	X	X	O	O	X
Opioid withdrawal assessment			X	X	O	O	X	X	X	O	O	X
AE assessment				X		O	X		X		O	X
Step-down assessment questionnaire							X					X

*(O) = Optional, if additional time for adjusting to opioid reduction is needed.

Table 5B. Extension Phase Schedule of Assessments

	Opioid Reduction Phase 3 (Optional)				Study Exit
	Acclimate to Opioid Reduction (7-14 days)				7 days from last Eval (13, 14 or 15)
	Eval. #12 (call) 3-days	Eval #13 (call) 7-days	Eval. #14 (call)* 10-days	Eval #15 (call)* 14-days	Eval. #16 (clinic visit) End of Phase 2/ Start of Phase 3
Review Daily Questionnaire	X	X	O	O	
CGI-I					X
IRLS		X		O	X
Medication use assessment	X	X	O	O	X
Opioid withdrawal assessment	X	X	O	O	X
AE assessment		X		O	X
Step-down assessment questionnaire					X

*(O) = Optional, if additional time for adjusting to opioid reduction is needed.

16.10. Study Exit

Study exit will typically occur either at the end of either Phase 1 (Eval #6), Phase 2 (Eval #11), or Phase 3 (Eval #16), based on the guidelines provided in Section 13. Study exit may occur earlier if the opioid reduction in a phase is not tolerable; if so, a final clinic visit will be scheduled to conduct the final assessments.

When the final follow-up visit is complete, the Investigator/coordinator will complete the study exit CRF. Adverse events unresolved at study exit will be followed by the Investigator until resolution occurs or at least 60 days after the subject's participation in the study is complete.

Both IRLS and CGI-I will be administered at study exit.

16.11. Extension Phase

Subjects who tolerate Phases 1 and 2 without a clinically significant increase in RLS symptoms and are at a non-zero dose of opioids will have the option to complete an extension phase consisting of an additional reduction in opioid dose.

16.12. Subject Discontinuation

A subject may be removed from the study prior to completion for any of the following reasons:

- Voluntary withdrawal of consent
- Adverse event preventing further study participation
- Investigator believes risk of further subject participation outweighs benefit
- Persistent non-compliance or lost to follow-up
- Pregnancy
- Subject no longer meets inclusion criteria
- Reduced opioid dosage is not tolerable, as evaluated by the subject or the investigator
- Subject fails to comply with reduced opioid dosage
- Subject changes dosage of non-opioid medications known to interfere with sleep or RLS symptoms, including sleep medications, antidepressants, sedative antihistamines.

The Investigator or research staff will complete a study exit form in the CRF for any subject who prematurely discontinues from the study. If discontinuation was the result of an AE, the AE will also be recorded in the CRF.

Upon discontinuation, subjects will receive partial compensation commensurate with their completed Phases.

16.13. Study Termination

The Sponsor may terminate the study as a whole or at individual study sites under the following circumstances:

- Suspicion of risk to subjects, including occurrence of high rate of known AEs or unexpectedly high rate of unexpected AEs

- Poor site compliance with the study protocol
- Inadequate site enrollment
- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary
- Persistent non-compliance with IRB or regulatory requirements
- Persistent failure to comply with obligations arising from the clinical trial agreement
- Other business reasons (e.g., insolvencies or business entity liquidation)

The sponsor will document reasons for study suspension and notify relevant site Investigators and governing IRBs. If suspension occurred because of a safety issue, all Investigators will be notified. When terminating the study, the sponsor and Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

17. Study Endpoints

17.1. Efficacy

In the absence of an adjunctive treatment, a reduction in opioid dose will cause an increase in RLS symptoms. The efficacy of NPNS will be assessed by its capacity to prevent this increase in RLS symptoms. Subjects who discontinue due to nonspecific opioid withdrawal symptoms will not be included in the efficacy analysis but will be considered in the safety analysis. Efficacy endpoints will be calculated during the Assessment period except in cases of dropout during the run-in period(s); Section 13.2 describes how efficacy endpoints will be calculated in cases of dropout during the run-in period(s).

17.1.1. Efficacy Endpoints

Endpoint 1 (Primary Endpoint): Percentage of subjects without a clinically significant increase in RLS symptoms (i.e. CGI-I score of 5 or less relative to baseline) during the first Phase involving an opioid dose reduction of >= 20% relative to baseline.

Endpoint 2: Percentage of subjects without a clinically significant increase in RLS symptoms (i.e. CGI-I score of 5 or less relative to baseline) during the first Phase involving an opioid dose reduction of >= 1/3 relative to baseline.

Endpoint 3: IRLS during the first Phase with an opioid dose reduction of >= 20% relative to baseline.

Endpoint 4: IRLS during the first Phase with an opioid dose reduction of >=1/3 relative to baseline.

Endpoint 5: Maximal percentage reduction in opioid dose relative to baseline associated with a CGI-I score of 5 or less, averaged across subjects.

Of the 5 efficacy endpoints, only Endpoint 5 considers data during the Extension phase.

17.1.2. Definition of Opioid Dose

Baseline opioid dose will be defined as the total weekly opioid dose that the subject reports taking during the week prior to study entry (7 days ending in EVAL 1). This value will be used to calculate the opioid doses for each Phase. If a subject reports taking a different opioid dose than instructed during an Assessment Period, the actual subject-reported opioid dose will be used to calculate the efficacy endpoints. In cases where a subject is taking multiple opioids concurrently, the morphine milligram equivalent (MME) will be used to standardize the baseline opioid dose, to calculate the opioid dose for each Phase, and to calculate opioid dose for the efficacy endpoints.

17.1.3. Efficacy Analysis

Endpoints 1 and 2 are calculated with the following formula, respectively for Phases 1 and 2:

100%*((X-Y)/(N-M)), where

- N = Number of subjects who entered the Run-in period for the Phase.
- M = Number of subjects excluded during Run-in period due to non-RLS opioid withdrawal symptoms.
- Y = Number of subjects excluded during Run-in period primarily due to intolerable RLS symptoms.
- X = Number of subjects who complete Assessment period with no clinically significant worsening in Clinical Global Impression-Improvement scale (CGI-I) relative to Baseline, where a clinically significant worsening is defined by a score of 6 (Much worse) or 7 (Very much worse).

17.1.4. Planned subgroup analysis

Subgroup analysis will be planned based on the location of RLS symptoms in the body, for the following subgroups:

- subjects who experience RLS symptoms that are most significant below the knees (lower legs and/or feet)
- subjects who experience RLS symptoms that are most significant above the knees (upper legs) or equally significant above and below the knees

17.1.5. Criterion for Success

If Endpoint 1 is greater than 50 percent, then the study will pass the Primary Efficacy endpoint.

17.2. Safety

Safety will be assessed primarily based on response to NPNS. However, the proportion of subjects excluded due to non-RLS opioid withdrawal symptoms will also be considered in the safety analysis.

17.2.1. Safety Endpoints

Endpoint 1: Frequency of Grade 2 of higher NPNS-related adverse events, as indicated by a relatedness assessment of Probable or Definite.

Endpoint 2: Frequency of Grade 3 or higher NPNS-related adverse events.

Endpoint 3: Percentage of subjects who withdraw from study during Phase 1 or Phase 2 citing lack of tolerability of NPNS as the primary reason for withdrawal.

Endpoint 4: Percentage of subjects who are discontinued from study due to non-RLS opioid withdrawal symptoms during Phases 1 or 2.

Endpoint 5: Percentage of subjects who withdraw from study citing lack of tolerability of NPNS as the primary reason for withdrawal during Phase 1

Endpoint 6: Percentage of subjects who withdraw from study citing lack of tolerability of NPNS as the primary reason for withdrawal during Phase 2.

Endpoint 7: Percentage of subjects who are discontinued from study due to non-RLS opioid withdrawal symptoms during Phase 1.

Endpoint 8: Percentage of subjects who are discontinued from study due to non-RLS opioid withdrawal symptoms during Phase 2.

Additional exploratory endpoints:

Endpoint 9: Reduction in severity of side-effects related to opioid use (not withdrawal) that were present at baseline during Phase 1 and Phase 2 assessment periods.

** Note that data from the Extension Phase is included in analysis of Endpoints 1 and 2 but not analysis of Endpoints 3-9.*

17.2.2. Safety Analysis

AEs occurring at any time during the study will be described and the investigator or designee will grade its severity, its relationship to device usage, and its relationship to opioid withdrawal.

The frequency of the following categories of AEs will be determined: device-related AEs, AEs related to opioid withdrawal, AEs unrelated to opioid withdrawal, SAEs. Additionally, side-effects related to baseline opioid usage, which were present at study entry, will be tracked weekly to detect potential improvement during opioid reduction and thus evaluate Endpoint 5.

Device-related will be defined as a relatedness grade of 3, 4, or 5.

17.2.3. Criterion for Success

No Grade 3 or higher device-related adverse events and fewer than 20% of subjects with Grade 2 device-related adverse events.

17.3. NPNS Tolerability

NPNS tolerability will be quantified based on the percentage of participants who voluntarily withdraw from the study prior to the Extension Phase citing lack of tolerability of NPNS treatment as the primary reason for withdrawal, as quantified by selection of response #3 on a questionnaire similar to the one below.

Primary reason for withdrawal:

- I want to return to my original opioid dosage because:
  - (1) my RLS symptoms have gone up after I reduced my opioid dosage
  - (2) I experienced other opioid withdrawal symptoms after I reduced my opioid dosage
- (3) Use of the NPNS devices was uncomfortable or otherwise intolerable
- (4) Other

The criterion for success will be fewer than 20% of subjects who begin NPNS treatment withdrawing for this reason.

17.4. Compliance

Compliance will be measured based on digital tracking of the timing and duration of each NPNS device usage during the Assessment weeks of Phase 1 and Phase 2. A "*night of compliant use*" will be defined as a minimum of 25 minutes of active NPNS stimulation between 5pm and 8am during an Assessment week. "*Total assessment nights*" will be defined as the total nights spent by all subjects in Assessment weeks. "*Total assessment nights with RLS symptoms*" will be defined as the total nights spent by all subjects in Assessment weeks when the subject reports RLS symptoms on the Daily questionnaire. If a subject is removed from the study before the end of an Assessment week, such as due to an adverse event or for personal reasons, data from that Assessment week will not be included in the compliance analysis. In cases where digital tracking logs are incomplete or unavailable, the data will not be included in the compliance analysis.

- For participants who are instructed to administer stimulation each night, percentage compliance will be calculated using the following formula:
    - 100%*(nights of compliant use)/(total assessment nights)
- For participants who are instructed to administer stimulation only on nights with RLS symptoms, percentage compliance will be calculated using the following formula:
    - 100%*(nights of compliant use)/(total assessment nights with RLS symptoms)

The global criterion for success will be percentage compliance of ≥ 70%, based on the weighted average of individual compliances (i.e. weighting nights equally instead of weighting participants equally).

17.5. Exploratory Analysis

Additional statistical analysis that is exploratory in nature may be performed, which may include but is not limited to analysis of data from the Extension Phase.

18. Remote procedures

During and after the COVID-19 pandemic, replacing some in-person visits with remote interactions may be necessary, for example to reduce risk to subjects and/or to comply with local, state, or federal regulations. In such cases, the study records will indicate which in-person visits were replaced with remote interactions. The allowable study duration may be expanded as needed to allow delay intervals for mailing and receiving programmed devices.

In such cases, one of more of the following approaches may be taken:

1. Remote calibration and training. Remote calibration and training, where possible, will be coordinated by mailing a calibration/training device to the subject, conducting calibration and training via a video call using the calibration/training device, and then mailing programmed devices to the subject using the settings determined during the calibration. Alternatively, the same devices used in the study may be used for calibration/training.
2. Remote follow-up visits. Remote follow-up visits, where possible, will be completed via call or video call, during which the required study assessments will be administered.
3. Devices may be returned using a pre-paid mailing label, as needed.
4. Remote consent. Remote consent procedures will follow the recommendations set forth in the "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" [12]. For example, or more of the following procedures listed in the guidance will be used to confirm consent:
    a. eConsent via a compliant digital platform;
    b. confirmation of consent by an impartial witness via three-way call or video conference;
    c. remote explanation of consent followed by in-person signature of informed consent document (to minimize duration of in-person interaction).

19. References

1. Allen, R.P. et al. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med. (2003). doi: 10.1016/s1389-9457(03)00010-8
2. 2012 Revised IRLSSG Diagnostic Criteria for RLS. Available at: http://irlssg.org/diagnostic-criteria

3. Allen, R. P. *et al.* Restless legs syndrome prevalence and impact: REST general population study. *Arch. Intern. Med.* (2005). doi:10.1001/archinte.165.11.1286

4. Silber, M.H. Treatment of restless legs syndrome and periodic limb movement disorder in adults. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2020

5. García-Borreguero, D. & Williams, A. M. Dopaminergic augmentation of restless legs syndrome. *Sleep Medicine Reviews* (2010). doi:10.1016/j.smrv.2009.11.006

6. Lipford, M.C. and Silber, M.H. Long-term use of pramipexole in the management of restless legs syndrome. Sleep Med. 2012; 13: 1280–1285

7. Hening, W.A. et al. An update on the dopaminergic treatment of restless legs syndrome and periodic limb movement disorder. Sleep (2004). doi: 10.1093/sleep/27.3.560

8. Cornelius, J.R, Tippmann-Peikert, M., Slocumb, N.L., Frerichs, C.F., Silber, M.H. Impulse control disorders with the use of dopaminergic agents in restless legs syndrome: a case-control study. Sleep. 2010 Jan;33(1):81-7.

9. FDA Drug Safety Communication 12-19-2019. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin.

10. Silber, M. H. *et al.* The Appropriate Use of Opioids in the Treatment of Refractory Restless Legs Syndrome. *Mayo Clin. Proc.* (2018). doi:10.1016/j.mayocp.2017.11.007

11. Wesson, D. R., & Ling, W. (2003). The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs, 35(2), 253–9.

12. FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency. Available at: https://www.fda.gov/media/136238/download