IRB APPROVED
AS MODIFIED
Jul 23, 2021

RESEARCH SUBJECT CONSENT FORM

TITLE:	Exploratory study assessing the response of Restless Legs Syndrome (RLS) patients to Non-invasive Peripheral Nerve Stimulation (NPNS) during opioid medication reduction
PROTOCOL NO.:	CT-03 IRB Protocol #20203813
SPONSOR:	Noctrix Health, Inc.
INVESTIGATOR:	Mark Buchfuhrer, MD 11480 Brookshire Avenue, Suite 108 Downey, California 90241 United States
STUDY-RELATED PHONE NUMBER(S):	Mark Buchfuhrer, MD 562-904-1101 (24 Hours)

RESEARCH CONSENT SUMMARY

You are being asked for your consent to take part in a research study. This document provides a concise summary of this research. It describes the key information that we believe most people need to decide whether to take part in this research. Later sections of this document will provide all relevant details.

What should I know about this research?

- Someone will explain this research to you.
- Taking part in this research is voluntary. Whether you take part is up to you.
- If you don't take part, it won't be held against you.
- You can take part now and later drop out, and it won't be held against you
- If you don't understand, ask questions.
- Ask all the questions you want before you decide.

How long will I be in this research?

Study completion typically lasts 4-6 weeks, consisting of two reductions in opioid dosage (Phase 1 and Phase 2) lasting 2-3 weeks each. Depending on your current opioid dose, your study

participation could conclude after Phase 1. In some cases, the investigator may determine that you are not eligible for further participation prior to study completion. In this case, you will be compensated for the completed portion of the study.

Following completion of the study, you may have the option of participating in an additional 3 week "Extension Phase".

Why is this research being done?

The purpose of this research is to characterize the response of Restless Legs Syndrome (RLS) patients to an investigational Non-invasive Peripheral Nerve Stimulation device during a reduction in opioid medication dosage.

What happens to me if I agree to take part in this research?

If you decide to take part in this research study, the general requirements include:

- Reduce your dosage of opioid medication during the study based on the instructions of the investigator and research staff
- Use NPNS stimulation devices daily for at least 30min (you may be instructed to use stimulation each night or administer stimulation only on nights when you experience RLS symptoms)
- Complete in-home questionnaires daily
- Semi-weekly follow-ups with study staff
- Multiple clinic visits for training and assessment

Could being in this research hurt me?

The investigational device is designed to maximize comfort. However, there is a potential risk of discomfort, increase in RLS symptoms, or difficulty sleeping while wearing the device. There is also a potential risk of skin irritation from device materials. Many of these risks can be reduced by contacting the study staff for assistance using the device. There are no known long-term risks of this research. However, there may be unknown long-term risks associated with usage of the investigational device.

Additionally, reduction of opioid dosage may result in opioid withdrawal symptoms and/or an increase in the severity of RLS symptoms. You will have the right to terminate your participation and return to your original opioid dosage under the supervision of the investigator.

Will being in this research benefit me?

It is not expected that you will personally experience long-term benefits from this research. Possible benefits to yourself and others include contributing to the development of a new treatment option for RLS.

What other choices do I have besides taking part in this research?

If you choose not to participate in the study, there are many treatment options you could consider. There are multiple FDA-approved drugs indicated to treat RLS (Requip, Neupro, Mirapex, Horizant). Lifestyle changes including massages, hot baths, reduction of caffeine and alcohol intake, and moderate exercise may reduce RLS symptoms.

Your decision to participate is voluntary. Refusal to participate or discontinuation of participation will not affect your ability to receive medical treatment and there will be no penalty and you will not lose any benefits to which you would otherwise be entitled.

DETAILED RESEARCH CONSENT

You are being invited to take part in a research study. A person who takes part in a research study is called a research subject, or research participant.

Why is this research being done?

There are few medical devices that are currently available to treat RLS and the leading medications are associated with significant long-term risks – therefore, there is a significant need for additional treatment options. Peripheral nerve stimulation has been used successfully to treat other medical conditions, but its effectiveness to treat RLS is not yet known.

The purpose of this study is to characterize the tolerable, safety, and effects of non-invasive peripheral nerve stimulation (NPNS) as a new treatment option for subjects with Restless Legs Syndrome (RLS) who are currently taking opioid medication to treat their RLS symptoms. The sponsor of this study has developed an investigational device that is designed to deliver non-invasive peripheral nerve stimulation to the legs to reduce RLS symptoms. If this investigational device is safe and effective for the treatment of RLS, the sponsor aims to commercialize this device as a new treatment for RLS.

Up to 50 subjects will take part in the study.

How long will I be in this research?

Study completion typically lasts 4-6 weeks, consisting of two reductions in opioid dosage lasting 2-3 weeks each (Phase 1 and Phase 2). Depending on your current opioid dose, your study participation could conclude after Phase 1. In some cases, the investigator may determine that you are not eligible for further participation prior to study completion. For example, this could occur due to opioid withdrawal symptoms, such as a significant increase in RLS symptoms. In this case, you will be compensated for the completed portion of the study.

Following completion of the study, you may have the option of participating in an additional 3 week "Extension Phase".

What happens to me if I agree to take part in this research?

- Initial clinic visit
- Opioid dose reduction #1 (at least 20% total reduction in dosage)
    - Reduction of daily opioid dose
    - 2-3 wks in-home nightly use of NPNS devices (you may be instructed to use stimulation each night or use stimulation only on nights when you experience RLS symptoms)
    - The study staff will contact you 3 days and 7 days after you start reduction #1, to see how you are doing and answer any questions you have about using the NPNS device. If you need extra time to adjust to the lower dose, they will contact you again at 10 days and 14 days.
    - The staff study will confirm that you have adjusted to the lower opioid dose at either the 7-day or 14-day phone call. At that point you will continue for 7 more days, before your next visit.
- Clinic visit
- Opioid dose reduction #2 (at least one-third total reduction in dosage)
    - Reduction of daily opioid dose
    - 2-3 wks in-home nightly use of NPNS devices (you may be instructed to use stimulation each night or use stimulation only on nights when you experience RLS symptoms)
    - The study staff will contact you 3 days and 7 days after you start reduction #2, to see how you are doing and answer any questions you have about using the NPNS device. If you need extra time to adjust to the lower dose, they will contact you again at 10 days and 14 days.
    - The staff study will confirm that you have adjusted to the lower opioid dose at either the 7-day or 14-day phone call. At that point you will continue for 7 more days, before your next visit.

- Clinic visit

In addition, the staff many contact you by phone periodically throughout the study to see how you are doing and ask if you have any questions regarding the use of the study device. You may also contact the study staff at any time, if you have questions or need help operating the device.

If you decide to participate in the optional Extension Phase, you will also complete the following:

- *Opioid dose reduction #3 (additional reduction in dosage)*
    - *Reduction of daily opioid dose*
    - *2-3 wks in-home nightly use of NPNS devices*
    - *The study staff will contact you 3 days and 7 days after you start reduction #3, to see how you are doing and answer any questions you have about using the NPNS device. If you need extra time to adjust to the lower dose, they will contact you again at 10 days and 14 days.*
    - *The staff study will confirm that you have adjusted to the lower opioid dose at either the 7-day or 14-day phone call. At that point you will continue for 7 more days, before your next visit.*
- *Clinic visit*

Device description

You will be given two stimulation devices to wear on each of your legs (right and left), just below your knee. Each stimulation device includes:

- NPNS electronics and controls and
- a semi-disposable patch that adheres to your skin and conducts the NPNS stimulation.

The NPNS device transmits mild electrical stimulation. You will have the opportunity to set the stimulation intensity at a comfortable level. Before you use the device in-home, you will receive training on device usage as well as a calibration session to determine the appropriate amplitude of stimulation. A representative of the study sponsor – Noctrix Health, Inc. – will conduct and/or monitor the calibration session.

You may be instructed to use stimulation each night or use stimulation only on nights when you experience RLS symptoms. To use stimulation, you will activate the NPNS device for at least 30-min. The device will shut-off automatically when stimulation is complete. After the device shuts off, you may remove it from your leg. However, if the device is comfortable, then you may continue to wear it during sleep. Training on device usage will be provided by the study staff. Devices are designed to be lightweight, wearable, and comfortable. The devices are investigational, which means they have not been cleared or approved by the FDA.

The NPNS devices are investigational and all related procedures are experimental.

Daily requirements and procedures during NPNS usage

During in-home nightly use of NPNS devices, you are expected to do the following:

- 0-5 minutes of NPNS device setup,
- At least 30 minutes of NPNS stimulation (you may be instructed to use stimulation each night or use stimulation only on nights when you experience RLS symptoms),
- Follow the specific usage instructions provided by the study staff,
- Complete and submit a 5-10min questionnaire.

Opioid dosage reduction

Opioid dosage reduction occurs through a series of step-down periods. The first step-down period (Phase 1) will involve a reduction of at least 20% of your original dose and the second step-down period (Phase 2) will be a total reduction at least one-third of your original dose. If the first step-down results in clinically significant opioid withdrawal symptoms or a significant increase in your RLS symptoms, then your participation will be concluded prior to the second step-down period.

Depending on your current opioid dose, you may be assigned to only Phase 1. If so, your total duration of participation may be 2-3 weeks instead of 4-6 weeks.

The investigator of the study, who is experienced in prescribing opioids, will supervise your dosage and progression to the second step-down period.

If you complete Phases 1 and 2 without significant withdrawal symptoms, the investigator may invite you to an optional Extension Phase, which includes an additional reduction in opioid dose, as determined by the investigator.

Additional procedures and assessments

During study visits and follow-up calls, procedures include device calibration and fitting, training on proper use of devices, completion of questionnaires regarding your medical history, and completion of questionnaires regarding your experience with the devices and your experience with opioid dosage reduction. A primary goal of these sessions is to ensure that you have a positive experience.

At one or more clinic visits, instrument(s) designed for marking the human skin (body-marking pen or temporary tattoos) may be employed to mark the location of electrode placement on your legs for your reference; although these marks will be subtle and temporary, they may be noticeable to others. This is recommended but not required for continuation of participation.

What are my responsibilities if I take part in this research?

In addition to the requirements listed in the previous section, your responsibilities include the following:

- Take exactly the opioid dosage prescribed by the investigator.
- Contact the study staff at once with any questions or concerns regarding device usage or function. They are trained to troubleshoot device issues and help ensure you have the best experience with the devices.
- Contact the investigator in the case of any medical problems or concerns.

Could being in this research hurt me?

There are risks, discomforts, and inconveniences associated with any research study. These deserve careful thought. You should talk with the research team if you have any questions.

<u>You can reduce risk by contacting the research team whenever you have concerns or questions regarding the devices during the study.</u>

There are no known long-term risks of this research. However, there may be unknown risks associated with usage of the investigational device.

Potential temporary risks, discomforts, and inconveniences associated with the investigational device include:

- Temporary uncomfortable sensations during active electrical stimulation
- Difficulty sleeping while wearing the device
- Temporary increase in RLS symptoms while wearing the device
- Mild skin irritation from the device materials

Each of these potential risks and discomforts is expected to go away after device usage is terminated.

The opioid reduction procedure has the potential for additional temporary risks, discomforts, and inconveniences. Although the procedure is designed to reduce the risk of opioid withdrawal symptoms, one or more of these symptoms may occur; these symptoms may include 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. Each of these potential risks and discomforts is expected to resolve soon after you return to your original opioid dosage.

You have the right to terminate participation in the study or terminate a study procedure if and when any risks, discomforts, or inconveniences become an excessive burden. This study may involve risks that are currently unknown, so it is important you inform the research team or

Investigator of any illnesses and conditions you experience.

For women of child-bearing potential, the risks of using this device while pregnant are not known; taking part in this may hurt a pregnancy or fetus in unknown ways.

Will being in this research benefit me?

Since this is an investigational device, there are no known benefits to you while taking part in this research. It is possible that you may experience temporary relief of RLS symptoms while using the devices.

Possible long-term benefits to yourself and others include contributing to the development of a new treatment option for RLS.

What other choices do I have besides taking part in this research?

Iron supplementation may be effective for reducing RLS systems in cases of underlying iron deficiency in the brain. There is a FDA-cleared pad (Relaxis) for sleep quality in RLS patients. Lifestyle changes including massages, hot baths, reduction of caffeine and alcohol intake, and moderate exercise may reduce RLS symptoms. There are FDA-approved medications for RLS that affect dopamine levels in the brain (Requip, Neupro, Mirapex) or calcium channels (Horizant).

Your decision to participate or not participate will not affect your ability to receive medical treatment and you will not lose any benefits to which you would otherwise be entitled.

New findings

We will tell you about any new information that is likely to affect your health, welfare, or choice to stay in this research.

Remote procedures

When possible and/or necessary, in-person visits may be replaced with remote procedures to reduce risk, such as at certain times during the COVID-19 pandemic. This may reduce your requirements for travel to the clinical site but may add a requirement for you to mail and receive study-related materials.

For example, this may include:

1. For follow-up visits, a video call or telephone call may be substituted for an in-person visit.
2. For exchanging study-related items (e.g. devices and paperwork), you may be required to mail (such as with a pre-paid mailing label) and receive items instead of handing off in person.
3. Informed consent may be conducted remotely.
4. Remote training or calibration of devices, if permitted by technology.

In such cases, there may be delays associated with mailing devices, and the study duration may be increased accordingly to account for this delay.

What happens to the information collected for this research?

Your private information and your medical information may be shared with individuals and organizations that conduct or watch over this research, which may include:

- The research sponsor
- People who work with the sponsor
- Government agencies, such as the Food and Drug Administration and the Department of Health and Human Services
- The Institutional Review Board (IRB) that reviewed this research

We may publish the results of this research. However, we will keep your name and other identifying information confidential.

We protect your information from disclosure to others to the extent required by law. We cannot promise complete secrecy.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Data collected in this research might be de-identified and:

- used for future research,
- distributed to another investigator for future research without your consent,
- distributed to a business partner of the sponsor without your consent.

Information about a Certificate of Confidentiality for this research

Dr. Mark Buchfuhrer has received a Certificate of Confidentiality from the government which will help protect the privacy of research subjects. The certificate protects against the involuntary release of information about subjects collected during the course of this research. The researchers involved in this study cannot be forced to disclose any information collected in this study in any legal proceedings.

However, the subject may choose to voluntarily disclose the protected information and this certificate does not prohibit such voluntary disclosure. Furthermore, the parties listed in the Confidentiality section of this consent form may review our records under limited circumstances and this certificate does not prohibit such disclosure.

Who can answer my questions about this research?

If you have questions, concerns, or complaints, or think this research has hurt you or made you sick, talk to the research team at the phone number listed above on the first page.

This research is being overseen by an Institutional Review Board ("IRB"). An IRB is a group of people who perform independent review of research studies. You may talk to them at 855-818-2289, researchquestions@wcgirb.com if:

- You have questions, concerns, or complaints that are not being answered by the research team.
- You are not getting answers from the research team.
- You cannot reach the research team.
- You want to talk to someone else about the research.
- You have questions about your rights as a research subject.

What if I am injured because of taking part in this research?

Contact the research team and/or Investigator immediately in the event that you experience a research related injury.

All forms of medical diagnosis and treatment – whether routine or experimental – involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Investigator and the research team will assist you in obtaining appropriate medical treatment.

In the event that you have an injury or illness that is directly caused by your proper use of the device during this study, then the study sponsor will be responsible for costs that are not

covered by your insurer, managed care plan, or other benefits program. The study sponsor will not be responsible for costs associated with any injury or illness caused by improper use of the device or use of the device by individuals not enrolled in the study.

You do not waive any liability rights for personal injury by signing this form.

Can I be removed from this research without my approval?

The person in charge of this research can remove you from this research without your approval.

Possible reasons for removal include but are not limited to:

- You no longer meet criteria required for inclusion in the study.
- Failure to follow the instructions of the Investigator and/or research staff including:
    - Not following instructions for using the investigational devices
    - Not using the investigational devices
    - Not following the suggested opioid dosage
    - Not keeping your scheduled appointments and/or follow-up calls
- Safety concerns
    - You have a side effect that requires stopping the research
    - It is in your best interest based on the judgment of the investigator
- The research is canceled by the FDA or sponsor or your research site is terminated
- You become pregnant

We will tell you about any new information that may affect your health, welfare, or choice to stay in this research.

What happens if I agree to be in this research, but I change my mind later?

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time. Your decision will not affect your ability to receive medical treatment and you will not lose any benefits to which you would otherwise be entitled.

If you decide to withdraw your consent to participate in this study, you should notify the research team immediately so that they can coordinate:

- Returning your devices
- Documenting your withdrawal
- Following up on any side-effects that you have experienced

Will I be paid for taking part in this research?

Compensation will be provided at the time you leave the study. You will be compensated $50 for completing Visit 1, even if you do not pass screening. You will be paid an additional $200 for following instructions during Phase 1 and attending the second clinic visit, even if you are removed due to side-effects of reduced opioid dosage. You will be paid an additional $200 for following instructions during Phase 2 and attending the final clinic visit, even if you are removed due to side-effects of reduced opioid dosage. Participants who complete the Extension Phase will receive an additional $150. Subjects who travel over 75 miles for Clinic Visits will be reimbursed an additional $0.56 a mile, for the miles they traveled over 150 miles round trip, based on the distance for the top result on google maps. For example, if you live 100 miles away, your round trip total will be 200 miles, therefore you will be reimbursed an additional $28.00 per visit for the 50 miles the exceed 150 miles. Any travel reimbursement under 150 miles round trip is already calculated into the visit compensation listed below. Reimbursement will be limited to a maximum of 400 miles round-trip.

	Compensation
Clinic Visit 1	$50
Phase 1	$200
Phase 2	$200
Total	**$450**
(optional) Extension phase	*additional $150*

In cases of voluntary or involuntary withdrawal, you will be compensated for the portion of the study that you completed prior to withdrawal.

This payment is intended to compensate you for your time and for costs of travel to each of the clinic visits; you are responsible for these travel costs and will not be provided additional compensation beyond the amounts indicated above.

Will it cost me money to take part in this research?

There are no expected additional costs to you from your participation in this research.

Statement of Consent:

Your signature documents your consent to take part in this research, including:

- Acknowledgement of all the information provided herein,
- Agreement to participate in and comply with the clinical investigation,
- Agreement to use my personal data for the purpose of the clinical investigation,
- Agreement to inform my personal physician of my participation.

Signature of Adult Participant	Date
Print Name of Adult Participant	
Signature of Person Obtaining Informed Consent	Date
Print Name of Person Obtaining Informed Consent	