Wireless TENS for Peripheral Edema (Lower Limb Swelling)

Informed Consent Form

NCT04680533

Date: 3/15/2023

Research Study Informed Consent Document

Transcutaneous electrical nerve stimulation for peripheral edema: A single arm clinical trial

Principal Investigator: Jennifer Gewandter, PhD, MPH
Co-I: Frank Akwaa, MD

This consent form describes a research study, what you may expect if you decide to take part and, important information to help you make your decision. Please read this form carefully and ask questions about anything that is not clear before you agree to participate. You may take this consent form home to think about and discuss with family or friends.

Key Information

- Being in this research study is voluntary – it is your choice.
- You are being asked to take part in this study because you have persistent lower limb swelling, which is often called edema.
- The purpose of this study is to test if a wireless transcutaneous electrical nerve stimulation (TENS) device can reduce your persistent lower limb swelling and related symptoms (such as pain, discomfort, heaviness).
- Your participation in this study will last for about 8 weeks.
- Procedures will include wearing a TENS device and Fitbit, answering questionnaires, completing daily diaries, and physical assessments.
- There are risks from participating.
    - The most serious risk is stopping use of current treatments (if you are using any), which could lead to worsening of your peripheral edema. ○ The most common risk is skin irritation from the TENS device. ○ Another risk is abnormal sensations due to the TENS device.
    - See the "Risks of Participation" section in this consent form for more information.
        - You should discuss these risks in detail with the study team.
- You might not benefit from being in this research study. The potential benefit to you might be a decrease in your persistent lower limb swelling (i.e., edema) and associated symptoms with use of the TENS device. You will receive a commercially-available TENS device at the end of the study to keep.
- If you do not want to take part in this study you may continue with the standard course of treatment or participate in another study.
- To ensure appropriate safety precautions related to COVID 19 in-person study procedures will follow the process for conducting in-person visits outlined in the Guidance for Human Subject Research.

RSRB Approval Date: 3/15/2023
Expiration Date: 3/14/2024

A flyer is available to help you understand what to expect related to keeping you and the research staff safe during COVID when an in-person study visit occurs.

Purpose of Study

The purpose of this study is to test if a wireless TENS device can reduce your persistent lower limb swelling (i.e., edema) and related symptoms.

Intervention

The TENS device is approved for marketing and use for chronic pain by the United States Food and Drug Administration (FDA). However, it is not FDA-approved for treatment of edema, and therefore is considered an experimental treatment at this time. The specific TENS devices used during this study are approved by the FDA, but the programming of the dose settings will be modified for the study. Upon completion you will get to keep a TENS Device that has the commercially-available stimulation settings.

Study Requirements

Pregnancy:

If you are currently pregnant, or you are planning to become pregnant within the next 8 weeks, you are not eligible to participate in this study.

Description of Study Procedures

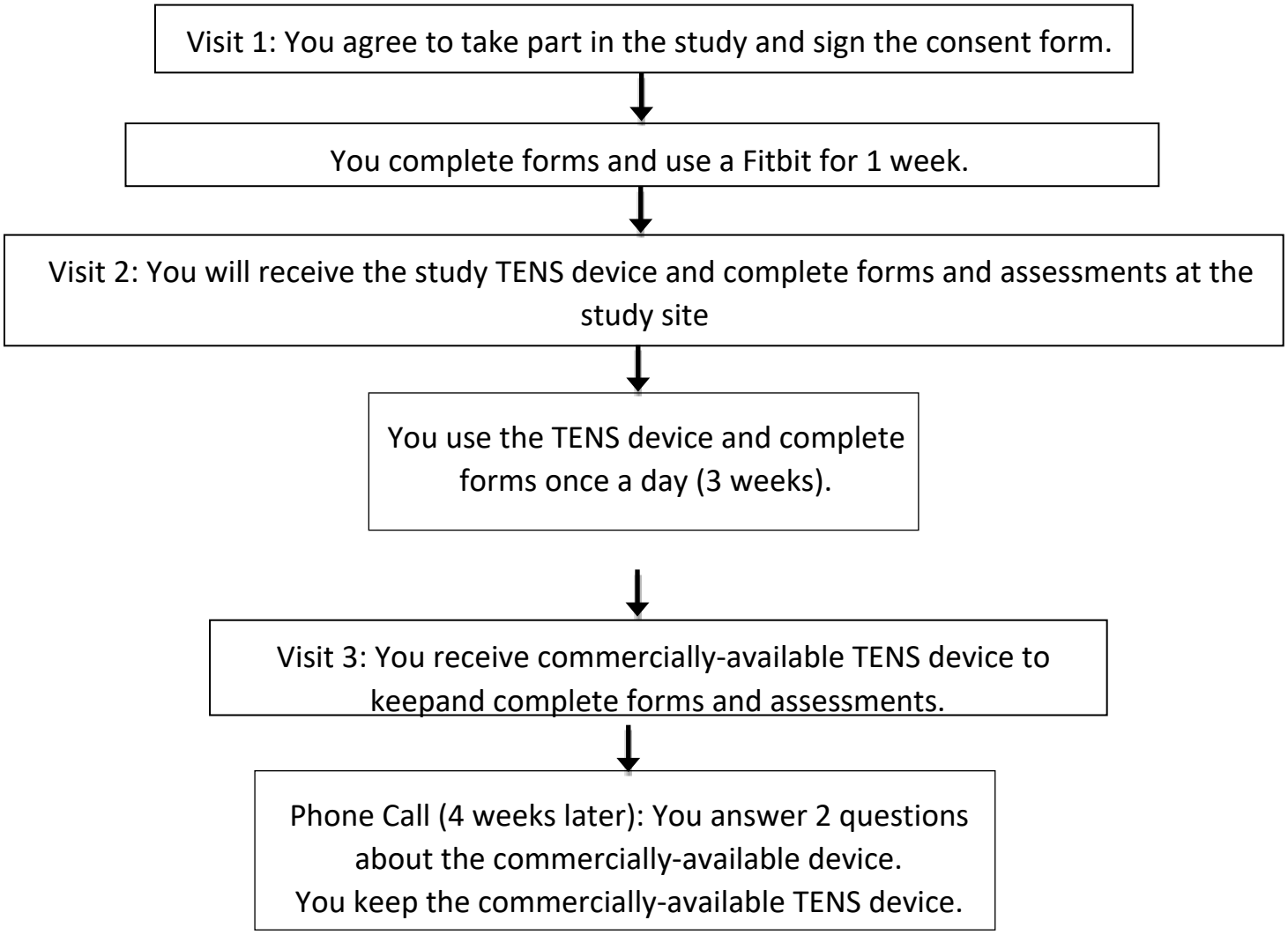
If you decide to take part in the study, you will be asked to participate for approximately 2 months. Your participation will include:

- 3 in-person visits.
- 1 phone call.
- A minimum of 4 emails or phone calls. Note, it is very important that you have an active and accessible email that you check regularly during the study. Not all study information can be delivered over the phone and accessing you email is necessary for completion of the study activities.

You will receive a Fitbit and TENS device to use as part of this study. You will get to keep the TENS device after you complete the study, the device will have the commercially-available settings. You will **NOT** get to keep the Fitbit device.

The following schedule summarizes what you will be asked to do at each point throughout the study. See the figure for an illustration of this summary.

Figure. Study schedule summary



Most in-person visits will be approximately 1 to 1.5 hours in length and 1 to 3 weeks apart.

In-person Visit 1. (approx. 1.5 hours)
You will:

- Complete the COVID pre-screening prior to your visit to the study site online.
- Come to the study site.
- Have severity of edema evaluated by the trained study staff to confirm final eligibility prior to obtaining informed consent. Review and sign this consent form.
- Be given a copy of the consent form.
- Have your leg measured by the study coordinator
- Review your contact information and preferred method of contact.
- Complete your registration or create an account for direct payments through Advarra.
- Learn how to use the Fitbit that you will use for 4 weeks of the study.
- Have your medical record reviewed for medications that may cause swelling.
- Learn how to complete the paper forms for the following week.
- Setup times and dates for the Baseline and Treatment period Endpoint visits.

The week before Visit 2.
You will:

- Complete paper forms about your symptoms daily.

- Use the Fitbit at all times other than when charging the device (including while sleeping if tolerated).
    - If your skin underneath the Fitbit becomes irritated, you will not wear it while sleeping. You may also try loosening the band on the Fitbit.
    - Fitbit is safe to wear in the shower and while swimming.

In-person Visit 2. (1 week after Visit 1; approx. 1.5 to 2 hours)
You will:

- Complete the COVID pre-screening form online before you come to the study visit.
- Bring the completed paper forms from the previous week to the study site.
- Complete electronic forms (can also be done before the visit on the computer using the provided link).
- Have your leg measured and ankle range of motion and ability to feel in your foot tested.
- Receive the TENS device you will use during the next 3 weeks of the study.
- Install the TENS device Quell application (app) on your mobile device. Learn how to use the TENS device and app.

Weeks 1 – 3 using the device at home. You
will:

- Wear the TENS device for 7 to 8 hours per day and let it run. You can wear it anytime, including while you are sleeping. However, do not wear it when you shower or bathe. You should **TURN OFF** the stimulation if you are driving a vehicle; you do not need to remove the device from your leg if you do not want to.
- Use the Fitbit at all times while awake, other than when charging the device (and sleeping if tolerated).
- Complete paper forms daily and weekly.
- Open the TENS device app while your mobile device is connected to Wi-Fi or cellular data once per day.
- Mail the paper forms that you complete at home back to the study site using prepaid postage at the end of each week or bring the paper forms with you to the study site at your next visit

In-person Visit 3. (3 weeks after In-person Visit 1; approx. 1.5 hours)
You will:

- Complete the COVID pre-screening prior to your visit to the study site online.
- Come to the study site.
- Complete electronic forms (can also be done before the visit on the computer using the provided link).
- Have your leg measured and ankle range of motion and ability to feel in your foot tested.
- Return the study TENS device and charger.
- Receive the commercially-available device to keep.
- Return the Fitbit and charger.

- Bring any of the at-home completed paper forms that you did not mail to the study site.
- Review your contact information
- Learn about the commercially-available TENS device warranty and Quell customer service troubleshooting contact information. Note, that you will have to purchase the electrodes for the device after the first 4 weeks of the study is completed.

Follow -up phone call. (1 month after Visit 3; approx. 10-15 minutes)
You will:

- Report whether you are still using the commercially-available TENS device and describe your experience with the TENS device since the last visit.
- At this time, your study participation is over, but you will keep the commercially available TENS device for your personal use.

Throughout the study you will receive phone call or email reminders to:

- Complete your paper and electronic forms at home.
- Use the TENS device and Fitbit.
- Mail back the paper forms when applicable.

Some forms will be completed on paper and others will be completed on the computer by clicking a link that will be emailed to you when it is time to complete the forms.

Study forms
If you choose to take part in this study, you will be asked to fill out paper and electronic forms with questions about:

- Your persistent lower limb swelling (i.e., edema) and related symptoms.
- How those symptoms affect your life.
- Your emotional well-being.
- Your physical function and activity.
- Changes that you experience during the study. Your opinion about the study devices.

Researchers will use this information to learn more about how well TENS works to treat lower limb swelling (i.e., edema) and the parts of your life that the lower limb swelling (i.e., edema) may interfere with.
Since these forms are being used for research, the responses you provide will not be shared with your study doctor. If you have any serious health issues or other concerns, please talk with your doctor or nurse right away.

Study forms at in-person visits
You will be asked to fill out these forms:

- At the time that you receive the study device.
- After you have used the study device for 3 weeks.

The electronic forms will take about 20 to 30 minutes to complete each time. You do not have to answer any question that makes you feel uncomfortable. You can choose whether to complete these electronic forms during the visit or before the visit using a computer link.

Study forms at home between visits
You will be asked to fill out these forms:

- Daily and weekly during the weeks, you are using the study TENS device.

These paper forms that you will complete daily should take no longer than 15 minutes per day. The paper forms that you will complete once per week should take no longer than 10 minutes.

Physical exams
The following additional exams, tests, and procedures are part of the research study, but would not be included in usual care. Listed below are procedures that will be done for research purposes only. They will be performed at thein-person visits.

- The ability of your foot to feel light touch will be tested with a series of small fibers.
- The range of motion of your ankle will be measured by seeing how deep of a lunge you can perform without you heel coming off the floor. This could require performing multiple slight lunges while lightly touching the wall.
- The amount of swelling in your foot and lower limb will be measured using a tape measure and a water displacement tool (you have to place your foot and lower limb in a basin of water).

These examinations should take approximately 30 to 45 minutes.

Activity data
Data indicating your activity levels during the study will be downloaded from the Fitbit device and assessed for changes throughout the study.

Medical record documentation
Study participation will be documented in your electronic health record. If you have concerns about this or to obtain more detail, you should discuss this with the study team.

Number of Subjects
Approximately 52 subjects will take part in this study. Subjects will be recruited from clinics within the University of Rochester Medical Center system.

Risks of Participation
Risks of change to current therapy used for peripheral edema or foregoing other treatment options

- If you decide together with your clinician to discontinue any therapy that you are currently using for peripheral edema (for example, compression stockings), your edema could get worse. You will have to discontinue any therapy for 2 weeks prior to starting the study and for the remainder of the study period (i.e., up to 10 weeks).
    - You will be asked to report any adverse symptoms to the study team, including worsening peripheral edema. If your peripheral edema worsens while you are on the study, you and the clinician investigator on the study will decide together whether it is best for you to discontinue the study early.
- For some people, the following treatments can be tried for peripheral edema as an alternative to the study or after study completion:

- Compression stockings, Velcro wraps, manual lymphatic drainage, short stretch bandage wrapping, pneumatic pumps, kinesiotape, acupuncture, cupping, and diuretics.

- You may consult your primary care physician about these alternative treatments before signing this consent if you would like.

TENS device risks

The list below shows the most common side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Some of the most common side effects that the study doctors know about are:

- Skin irritation.
    - The TENS device is worn for a limited amount of time each day, 7 to 8 hours, to help prevent skin irritation. If you experience skin irritation you should rotate the electrode so the gel pads touch your skin in a different spot and alert the study team.

- Abnormal sensations. In an earlier study using TENS in a different study population, 3 of the 26 subjects that received TENS felt new abnormal sensations in their feet and legs. These new abnormal sensations went away when these 3 subjects stopped using the device; however, we cannot be sure that this will always be true.
    - You will be asked at 2 times throughout the study if you have any new abnormal symptoms since starting to use the TENS device. You will also be asked to call and discuss any new symptoms that you experience at any time throughout the study by calling 585-274-0415. If you experience any abnormal sensations you will decide with the study clinician investigator if you should discontinue use of the TENS device.

Fitbit risks

- Skin irritation.
    - If you have skin irritation from wearing the Fitbit, you should stop wearing the Fitbit at night to give your skin a chance to breathe. You can also loosen the wrist band if skin irritation occurs.

- Abnormal sensations. If you feel soreness, tingling, numbness, burning or stiffness in your hands or wrists while or after wearing the Fitbit, you will be asked to stop using it.
    - You will be assessed for adverse events at least 2 times during the study while wearing the Fitbit. You will be asked if you have experienced any new symptoms or if any skin reactions have occurred. ○ You can also call the study team at any time during the study, if you have any problems wearing the Fitbit device, including discomfort.
    - If you have to discontinue use of the Fitbit due to abnormal sensation or skin irritation, you will still be able to continue with the study.

Questionnaire risks

Some of the questions in the forms may be upsetting or make you feel uncomfortable. You can skip any of the questions you do not want to answer and you can refuse any test at any time. If you refuse any question or test at any time you may continue to participate in the study.

Advarra Risk

Advarra will be used as the direct payment system for your study payments During registration or creation of your account on the site, Advarra may collect any or all of the following information, (i) your name, (ii) home or business address, (iii) professional information, including specialty or nature of concern, (iv) organization with whom you are affiliated and its address, and (v) your email address. When you visit the site using your personal smart device, they may automatically record information that your browser sends like, the name of the domain and host from which you access the Internet; the Internet Protocol (IP) address of the computer or smart device you are using; the date and time you access the site or make uploads or post to the site; and the Internet address of the website from which you linked directly to the site. This Information does not include any Personally Identifiable Information and we refer to this information as non-identifiable Information.

There is still a risk that a third party could gain access to any Information provided to or collected through this Site. To mitigate these risks, any data breaches and, potential identification of subjects, Advarra has security measures in place to protect electronically transmitted information. They are frequently reviewing and consistently trying to improve the security of the site. They do not collect and you will not be asked to submit any "protected health information" as defined in HIPAA**.**

Invasion of Privacy/Breach in Confidentiality

Because this study involves collecting personal, identifiable information about you, there is a potential for invasion of privacy or breach in confidentiality. To minimize this risk, we will assign you a study number instead of labeling the information we collect from you with your name or medical record number. All of the information we collect will be stored in a secure manner and only study team members will have access to it.

There are organizations that may look at or have copies of some of the de-identified information in your study records. However, your name and contact information will not be put in the database. They must keep your information private, unless required by law to give it to another group.

These organizations are:

- Neurometrix, the company that is providing the TENS devices and owns the Quell App that will allow us to access your usage data.
- Fitbit, the company that owns the Fitbit secure cloud database that will allow us to access your activity data. Fitbit Inc. will have access to your Fitbit de-identified data for up to 90 days after the Fitbit is deactivated and deregistered at Visit 3.
- Advarra, the company that is providing the payment system that will deliver the study payments and reimbursements will receive access to some of your information required by federal treasury law to issue payments to you.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, NCT # 04680533 as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

The study team may be notified if you receive other health care services at URMC or its Affiliates (e.g., visit to the emergency room). In addition, the following individuals may know you participated in research and may see results of testing conducted for this study:

- Staff at the University of Rochester Medical Center and its Affiliates (e.g., Strong Memorial Hospital, Highland Hospital, URMC primary care, specialist physician offices) who have a reason to access your electronic health record.
- Health care providers who are involved in your care at a facility that is not part of the University of Rochester Medical Center and its Affiliates and who have reason to access your electronic health record.
- Individuals who request a copy of information from your health record for activities such as treatment or payment (e.g., medical insurance companies, worker's compensation).

Benefits of Participation

The potential benefit to you from being in this study is that your lower limb swelling (i.e., edema) and associated symptoms (e.g., pain, discomfort, heaviness) may decrease with use of the TENS device and that you can keep the commercially-available device (list price $299) at the end of the study. However, you will have to purchase electrodes for use of the device (list price $29.95/~4 weeks of use) after the 3 study visits are completed.

Alternatives to Participation

The alternative to participation is to not participate and continue to receive usual care from your clinician.

Costs

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the standard care, just as you would if you were getting the usual care for your edema. Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

You and/or your insurance provider will NOT have to pay for the TENS device if you take part in this study.

You and/or your insurance provider will NOT have to pay for the costs of study related of tests, exams, procedures and devices, while you take part in this study.

Taking part in this study may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your edema. You may have more travel costs, need to take more time off work, or have other additional personal costs.

The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

You will be required to use an application to control the TENS device. The TENS Quell App is free to download. You will need to transfer information from the application in order for the research staff to monitor how often you are using the TENS device. The amount of data used by the application is minor compared to the smallest available cellular data plans so it is highly unlikely that you will incur extra costs for use of the application if you have a data plan. If you do not have a cellular data plan you will have to pay for the data costs associated with application unless you connect to the Internet using Wi-Fi only

Payments

You will be paid $75 total for taking part in this study. The payment of $75 will be initiated at inperson Visit 3. For this study we will use a subject payment system called Advarra Participant Payments. The system allows three ways to provide payment. You can choose: a reloadable debit card; direct deposit; or mailed paper checks. The study team will help you create a "subject profile" in the system. In order to provide payment, you will need to enter your name and date of birth into your subject profile. Depending on which payment method you choose, you may also need to enter your email address and banking information. If you already have an Advarra account (because you are in another study that uses this system), your existing profile will be used to provide payment. See the 'Information Sheet for Advarra Participant Payments' for additional information.

Payment received for participation in research is considered taxable income. If you receive $600.00 or more in any one calendar year from UR or its affiliates, the University is required to report this information to the Internal Revenue Service (IRS) in a 1099 (Miscellaneous Income) form. You will be sent a copy of this form and a copy will be sent to the IRS. Depending on the amount you are paid, you may be asked to submit a W-9 form, which includes your Social Security Number.

You will get to keep the device with the commercially-available settings (list price: $299). However, you will have to purchase the electrodes for use after the study period is over ($29.95/~4 weeks of use).

Confidentiality of Records and Authorization to Use and Disclose Information for Research Purposes

The University of Rochester makes every effort to keep the information collected from you private. In order to do so, your personal identifying information will be kept separate from your data. All data forms will include only a subject ID and will be kept either in locked cabinets or on password protected University of Rochester Medical Center (URMC) network drives. Sometimes, however, researchers need to share information that may identify you with people that work for the University, regulators or the study sponsor.

If you have never received a copy of the URMC and Affiliates Notice of Privacy Practices, please ask the investigator for one.

What information may be used and given to others?

The study doctor will get your personal and medical information. For example:

- Research records
- Records about phone calls made as part of this research
- Records about your study visits
- Past and present medical records related to the study, including records of external providers that are available via your electronic health record at URMC & Affiliates
  Results of medical tests

Who may use and give out information about you?

- The study investigators and the study staff
- URMC and Affiliates

Your de-identified information may be given to:

- The Department of Health and Human Services
- The University of Rochester
- Data Monitoring Committee
- Neurometrix (the manufacturer of the TENS device and owner of the Quell App)
- Fitbit (the manufacturer of the Fitbit device)
- The U.S. Food and Drug Administration (FDA) may also need to inspect study records at some point during the study or even after it has been completed. In the event that this should occur, every effort will be made to keep identifying information about you private.
- Advarra (the site providing the participant payment system)

Why will this information be used and/or given to others?

- To do the research
- To study the results
- To see if the research was done correctly

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

May I review or copy my information?

Yes, but only after the research is over.

How long will this permission be valid?

This permission will last indefinitely.

May I cancel my permission to use and disclose information?

Yes. You may cancel your permission to use and disclose your health information at any time. You do this by sending written notice to the study investigator. Upon receiving the written notice, the study team will no longer use or disclose your health information and you will not be able to stay in this study. Information that has already been gathered may need to be used and given to others for the validity of the study.

May I withdraw from the study?

Yes. If you withdraw your permission to be in the study, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?

No. There is a risk that your information will be given to others without your permission.

<u>Circumstances for Withdrawal</u>

If your edema worsens, the clinician investigator may decide that it is in your best interest to discontinue the study and you may be withdrawn.

You will be withdrawn if you report that you have become pregnant during the study. Subjects who become pregnant before the end of the study will not be given the commercially-available TENS device.

You may be withdrawn from the study if you do not keep appointments for study visits.

You may be withdrawn from the study if you do not keep appointments for study visits, specifically in the beginning of the study.

If you miss the Baseline visit and do not attend rescheduled visits with in the 7-day grace period you will be withdrawn.

You may be withdrawn from the study if you cannot complete study activities.

If the baseline daily diary entries have more than 4 days missing you will be withdrawn from the study before you receive the study device.
The PI or Co-I can withdraw any subject who is at risk or is unable to participate further due to new medical conditions. Data that have already been collected will be included in the analyses. Subjects who are withdrawn due to safety issues will not receive the commercially-available device.

New Study Information

If we discover any new information that might make you change your mind about continuing in the study, we will let you know.

Sponsor Support

The University of Rochester is receiving the TENS devices for free from Neurometrix. Neurometrix is also providing funds to support the effort of study coordinators working on this project.

Financial Disclosure Statement

The Investigator, Dr. Jennifer Gewandter, receives payment as a consultant from (Neurometrix), the manufacturer providing the device in this study. Please feel free to ask Dr. Gewandter or other study staff any questions you may have about her consulting with this study.

Commercial Profit

We will use your information and/or samples for research only. However, the results of this research might someday lead to the development of products (such as a commercial cell line, a medical or genetic test, a drug, or other commercial product) that could be sold by a company. You will not receive money from the sale of any such product.

Return of Research Results

In general, we will not give you any individual results from your participation in the study. If we find something of urgent medical importance to you, we will inform you, although we expect that this will be a very rare occurrence.

Contact Persons

For more information concerning this research or if you feel that your participation has resulted in any research related injury, emotional or physical discomfort, please contact**:** Frank Akwaa, MD at 585-275-5863.

Please contact the University of Rochester Research Subjects Review Board at 265 Crittenden Blvd., CU 420628, Rochester, NY 14642, Telephone (585) 276-0005 or (877) 449-4441 for the following reasons:

- You wish to talk to someone other than the research staff about your rights as a research subject;
- To voice concerns about the research;
- To provide input concerning the research process; In the event the study staff could not be reached.

Voluntary Participation

Taking part in this study is voluntary. You are free not to take part or to withdraw at any time, for whatever reason. No matter what decision you make, there will be no penalty or loss of benefit to which you are entitled. In the event that you do withdraw from this study, the information you have already provided will be kept in a confidential manner.

Use of E-mail for Communication in Research

You will receive communications about this study via email, Email communications between you and the study team may be filed in your research record.

Emails will be used for appointment reminders, mailing reminders, and sending you links to surveys that need to be filled out at home or can be filled out ahead of study visits to limit the time spent at in-person visits.

Email communications may be sent or received in an unencrypted (unprotected) manner. Therefore, there is a risk that the content of the communication, including your personal information, could be shared beyond you and the study team. Your consent below indicates that you understand this risk. The University of Rochester is not responsible for any interception of messages sent through email.

SIGNATURES/DATES

After reading and discussing the information in this consent form you should understand:

- Why this study is being done;
- What will happen during the study;
- Any possible risks and benefits to you;
- Other options you may have instead of being in the study;
- How your personal information will be protected;
- What to do if you have problems or questions about this study.

Subject Consent

I have read (or have had read to me) the contents of this consent form and have been encouraged to ask questions. I have received answers to my questions. I agree to participate in this study. I have received (or will receive) a signed copy of this form for my records and future reference.

_____

Subject Name (Printed by Subject)

_____ _____

Signature of Subject Date

Person Obtaining Consent

I have read this form to the subject and/or the subject has read this form. I will provide the subject with a signed copy of this consent form. An explanation of the research was given and questions from the subject were solicited and answered to the subject's satisfaction. In my judgment, the subject has demonstrated comprehension of the information. I have given the subject adequate opportunity to read the consent before signing.

_____

Name and Title (Print)

_____ _____

Signature of Person Obtaining Consent Date