Wireless TENS for Peripheral Edema (Lower Limb Swelling)

Study Protocol and Statistical Analysis

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

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1. PURPOSE OF STUDY

Specific Aim 1. To test the feasibility of evaluating the efficacy of TENS for chronic edema in a single-site, single arm study.

Specific Aim 2. To estimate the potential effects of TENS on swelling (via tape measurements water volume displacement, and patient-reported swelling) pain, heaviness, weakness, discomfort, patient satisfaction with the treatment, self-reported ability to be active, quality of life, activity (measured via activity tracker), lower limb sensation, and ankle range of motion.

2. BACKGROUND AND RATIONALE

Chronic edema of the lower limbs (i.e., chronic peripheral edema) is a common condition. Peripheral edema can cause pain, heaviness, weakness, discomfort, negative body image and limit mobility and flexibility.[1] Limitations to mobility can reinforce a sedentary lifestyle, which exacerbates peripheral edema, leading to a vicious cycle of disease. Furthermore, when peripheral edema is untreated, it causes increased risk of infection and ulcers.[2] Nineteen percent of older US adults surveyed in the 2016 wave of the Health and Retirement Study[3] reported persistent lower limb swelling (manuscript in preparation). It affects many individuals, including those with obesity, older age, sedentary lifestyles, history of deep venous thrombosis, and occupations that require long periods of standing.[4, 5] Considering the high rates of obesity in the US, peripheral edema is a large and likely growing public health challenge.[4] No cure for peripheral edema exists. Some types of edema are responsive to diuretics,[4] but these medications cause frequent urination. Dietary restrictions, such as limiting salt intake, can reduce edema as well. However, lifestyle changes are challenging to implement and sustain, especially for lower income patients for which easy access to whole foods is lower. Compression stockings are generally accepted as the standard of care treatment to contain swelling associated with edema. However, many patients find compression stockings to be uncomfortable or even painful, embarrassing, hot in the summer, and itchy. Taken together, improved treatments for chronic peripheral edema are highly warranted.

Peripheral edema is caused by increased interstitial fluid volume. The interstitial fluid volume is controlled by a delicate balance between hydrostatic pressures in the plasma and interstitial space, which are controlled by the venous and lymphatic systems. Underlying health conditions affect fluid (i.e., water and dissolved solutes) flow out of the arterial end of the capillaries into the interstitial space. The majority of this fluid is reabsorbed back into the venous end of the capillaries. The remaining net increase in interstitial fluid is removed via the

lymphatic system. An increase in capillary pressure, due to insufficient venous return of blood, can cause increased bulk flow of fluid into the interstitial space. This increased bulk flow can overwhelm the lymphatic system leading to the inability to absorb, which causes peripheral edema. In addition, deficiencies in the lymphatic system can lead to peripheral edema by collection of the normal excess of fluid that flows from the capillaries into the interstitial space.[6]

Chronic venous insufficiency (CVI) is a common condition that is characterized by decreased venous return of blood that leads to venous hypertension in the lower limbs. A large population-based study found the prevalence of CVI to be 9.4% in men and 6.5% in women.[5] Decreased venous return is often caused by venous valve dysfunction, which can be caused by poor venous tone preventing the valves from closing completely to stop reflux of blood to the lower limbs. Hypertension in the capillaries of the lower limbs leads to increased hydrostatic pressure and fluid leakage and edema. Long-term hypertension negatively affects capillary tone, further exacerbating fluid leakage and edema.[2] Furthermore, venous hypertension has been linked to increased inflammation that can further exacerbate impairments in venous tone.[2] Thus, interventions that can improve venous tone could improve edema from CVI. In fact, a micro-ionized purified flavonoid fraction pharmacotherapy that can improve vascular tone has shown promise in improving CVI.[7]

Transcutaneous electrical nerve stimulation (TENS) is electrical current that is delivered through the skin. It is a safe, non-pharmacologic treatment that is commonly used to treat chronic pain. TENS has been reported to improve peripheral edema in a case series (n=3)[8] as well as in a small clinical trial that compared TENS to usual care (n=10).[9] It was also found to decrease swelling associated with complex regional pain syndrome in a small RCT.[10] In addition, our preliminary data (see Preliminary Data Section below) showed a marked improvement in peripheral edema for 3 individuals who used TENS daily for 1 to 3 weeks. TENS has been shown to stimulate the autonomic nervous system.[11] Thus, TENS could stimulate the autonomic nerves causing improvement in capillary and venous tone, which could decrease fluid leakage from capillaries as well as promote more efficient venous return leading to decreased lower limb venous hypertension. In turn, decreased lower limb venous hypertension could lead to decreased inflammation. TENS could also cause sufficient muscle contractions to sufficiently decrease the diameter of the veins to improve venous return, although high frequency TENS used in our preliminary data does not cause perceptible muscle contractions.

Because TENS can also improve pain and is a non-pharmacologic treatment, it could be an ideal therapy for peripheral edema that it is often accompanied by pain and occurs in patients with co-morbid conditions that may already have challenges with polypharmacy. The goal of this proposal is to evaluate the feasibility of studying daily TENS therapy for peripheral edema in patients with chronic venous insufficiency and evaluate its preliminary efficacy. If the results of this initial trial are promising, the data will be used to obtain funding to support a larger efficacy study that can incorporate outcomes to investigate the efficacy of the therapy and potential mechanism related to improvements in venous tone.

Preliminary data

We discovered a potentially highly novel effect of daily TENS on peripheral edema in 1 subject during a trial of TENS for chemotherapy-induced peripheral neuropathy. In addition, we have since observed a similar effect in 2 other individuals with peripheral edema. The first person had bilateral peripheral edema that was likely caused by drugs prescribed to reduce rejection of a bone marrow transplant, the second person has unilateral peripheral edema from venous insufficiency caused by a deep vein thrombosis, and the third person had peripheral edema associated with peripheral neuropathy and prolonged standing. The individuals who experienced improved edema used between 2 and 5 hours of stimulation. Table 1 provides quotations describing the effects of the TENS device on peripheral edema for the 3 individuals.

Table 1. Preliminary data

Individual	Quotation
1	"Gets rid of a lot of the pain and swelling"
2	"I saw some significant changes in the size of my leg and foot after wearing the device for 1 week. My pitting is close to nonexistent. The device was easy to use and I look forward to using it to help alleviate future edema episodes."
3	"I have been using the TENS for about 14 days, and it's amazing. The app works great, I use it in the afternoon and at night and my pain has been reduced by at least 50%, I have almost no swelling, and I am actually sleeping soundly for the first time in months."

3. ADMINISTRATIVE ORGANIZATION

This study is a collaboration between investigators in the Anesthesiology and Perioperative Medicine and Hematology/Oncology Departments within the University of Rochester Medical Center. Subject study visits will take place within the University of Rochester Medical Center. Subject study visits will take place at the University of Rochester Medical Center, 125 Latimore Road Hematology clinic, or 2180 S. Clinton translational pain research office. Data will all be housed on secure networks or in locked filing cabinets within the Department of Anesthesiology and Perioperative Medicine.

4. STUDY DESIGN

Experimental design

This study is single center, subject will receive a wireless TENS device. The treatment period will be 3 weeks in duration. All subjects will be allowed to keep the commercially-available device for use after the study. All subjects will be called (via phone) one month after completion of the Endpoint visit and asked if they are still using their commercial device.

The study will have a single arm. The coordinator will introduce the study device, be available to answer questions about the device, and assess adverse events. Subjects will be told that we are testing whether TENS, which has shown promise in some patients but needs to be tested formally, has an effect on lower limb swelling.

Study measures

Demographic data will be collected from the medical record including age, sex, BMI, medications they are taking that could affect lower limb edema, history of diabetes, cancer, deep vein thrombosis, post thrombotic syndrome, peripheral neuropathy, and hypertension.

Feasibility (primary)

(1) Screen failure and patient refusal rates will be assessed using study records.

(2) Outcome measure completion rates will be assessed using study records.

Feasibility (secondary)

(1) Treatment adherence will be evaluated using data from the TENS device's Quell App (i.e., the number of treatment sessions/day and the time that the device was in contact with the skin). The Quell Health account within the Quell App for each subject will be setup at the Baseline visit using a de-identified, unique dummy email address created for the study to protect subjects' privacy.

Feasibility (exploratory)

(1) Potential reasons for low treatment adherence will be captured using structured qualitative interviews and used to assess potential reasons for low adherence and ways to improve a future study.

Potential Efficacy (primary) Objective assessments:

(1) Swelling The volume of water displaced by the combination of the foot and ankle, and the entire lower limb below the knee of the most affected limb at baseline will be measured using a Volumeter, which is a water displacement measurement device. The volumes will be recorded in **Volumeter Measurements** form.

Volume measurements have been used in a successful trial of compression stockings for flightinduced peripheral edema.[12]

Patient reported outcome measure (PRO):

(1) Swelling and symptoms associated with edema will be recorded in the **Edema Symptom Daily Diary** using a verbal rating scale (VRS) of swelling in the lower limbs and feet using the anchors "none", "a little bit", "quite a bit" "a lot", or "very much", [1 = none, 5 = very much]. The subject will also be asked to rate these symptoms, while thinking about the past week using the **Edema Symptom Inventory-Week Recall**, which uses the same scale as the diary and the **Edema Symptom Inventory-Week Recall 0 – 10 Scale** which uses 0 – 10 numerical rating scale (NRS) [0 = not at all, 10 = worst imaginable].

Potential Efficacy (secondary) Objective assessments:

(1) Swelling. The coordinator will use a tape measure at the arch of the foot, 1/2 and the distance between the middle of the kneecap and the ankle, and at the knee crease of both limbs regardless of which is more affected. Measurements will be recorded in the **Coordinator Lower Limb Swelling** form. Tape measurements have been used in a successful trial of compression stockings for flight-induced peripheral edema.[12]

Patient reported outcome measures (PROs):

(1) Changes in symptoms, activity, and emotions will be recorded in the **Impression of Change in Edema Symptoms** form that uses a verbal rating scale (VRS) asking subjects to report whether they have experienced changes in the symptoms. The scale uses the anchors "very much improved", "much improved", "minimally improved", "not changed", "minimally worse", "much worse", or "very much worse" [1 = very much improved, 7 = very much worse].

(2) Quality of Life will be assessed using the **Lymphoedema Quality of Life Tool (LYMQOL)** using a verbal rating scale (VRS) with anchors "not at all", "a little bit", "quite a bit", or "very much [1 = not at all, 4 = very much]. If the question is not applicable the measurable scale value is 0. Overall quality of life (Q22) is measured using a 0 – 10 numerical rating scale NRS scores [0 = poor, 10 = excellent]. The LYMQOL was developed based on interviews with patients. The initial validation study found reasonable Chronbach's alpha for items and criterion validity when compared to a general measure of quality of life.[13]

Potential Efficacy (exploratory) Objective assessments:

(1) Lower limb sensation will be measured using a monofilament threshold test (i.e., lower limb sensation test)[14] on the most affected limb at baseline. The scores will be recorded in the **Lower Limb Sensation Test Scoring Sheet**.

(2) Activity will be measured using the number of steps taken and period of time the subject is sedentary with a Fitbit activity tracker and the TENS device's Quell App.

(3) Ankle range of motion will be measured using a tape measure while the subject performs the weight-bearing lunge. The resulting measurements will be recorded in the **Ankle Range of Motion** form. This method has been shown to have good reliability when administered by a novice rater.[15]

Patient reported outcome measure (PRO):

(1) Fatigue will be assessed using the **PROMIS Fatigue –** Short Form. The PROMIS Fatigue – Short Form was created using a multisite project developed by a clinically relevant and psychometrically quality of life assessment tool for adults and children with neurologic disorders.[16] The measure uses a verbal rating scale (VRS) with anchors "never", "rarely", "sometimes" "often ", or "almost always" [1 = never, 5 = almost always].

(2) Mood, Stigma, and Sleep will be assessed using modified version of **Chronic Venous Disease Quality-of-Life Questionnaire (CIVIQ 20)**, which was developed based on a clinically relevant and psychometrically quality of life assessment tool for adults.[17] The validity was assessed using Cronbach's alpha coefficients and multi-trait/multi-item matrix analyses. The CIVIQ 20 consists of a VRS asking subjects to report whether they have experienced any of specific emotions over the past three weeks using a 1 – 5 Likerttype scale, with anchors "not at all", "a little", "moderately", "a lot", or "completely" [1 = not at all, 5 = completely].

Single-Item Questions:

(1) **Expectation Questionnaire**. The subject's expectation of device efficacy will be assessed by asking the subjects: "How much do you expect the TENS device will improve your edema symptoms?" using a 1 – 5 Likert-type scale, with anchors "not at all", "a little bit", "quite a bit", "very much", or "completely" [1 = not at all, 5 = completely].

(2) **General Impression of change in Edema**. The subject's impression of change in edema symptoms will be measured using a single question (i.e., **General Impression of Edema** form) that utilizes a 1 – 7 scale adapted from the patient global impression of change (PGIC). [18] The scale uses the anchors "very much improved", "much improved", "minimally improved", "not changed", "minimally worse", "much worse", or "very much worse" [1 = very much improved, 7 = very much worse]. The PGIC is commonly used in chronic pain trials to assess subjects' experiences of the change from the beginning of a treatment or clinical trial.[19]

(3) **General Impression of change in Activity**. Impression of change in ability to be active will be measured using a single question (i.e., **General Impression of Activity** form) that utilizes a 1 – 7 scale adapted from the PGIC.[18] The measure uses the anchors "very much improved", "much improved", "minimally improved", "not changed", "minimally worse", "much worse", or "very much worse" [1 = very much improved, 7 = very much worse]. The PGIC is commonly used in chronic pain trials to assess patients' experiences of the change from the beginning of a treatment or clinical trial.[19]

Subjects will record the medications taken for edema each day on the **Edema Symptom Daily Diary**. The coordinator will ask the subject if they take certain medications known to affect swelling and if they take any medications to treat their peripheral edema. The coordinator will customize the medication diary portion of the **Edema Symptom Daily Diary** to include these medications only.

A qualitative interview will be performed to explore how subjects prefer to rate the symptoms associated with peripheral edema, what additional symptoms were not asked about, and what aspects of the subject's life are affected by their edema. The responses will be recorded on the Treatment **period Endpoint-Qualitative** forms**.**

4.1. SUBJECT POPULATION

Fifty-two subjects will be enrolled in the study. We anticipate that 150 potential subjects will be approached in order to reach this goal (i.e., 1 in 3 potential subjects will be eligible and choose to enroll). If subjects drop out after enrollment, they will not be replaced.

Vulnerable populations, including children, pregnant women, those who are unable to perform consent, and prisoners will not be eligible for this study.

4.2. STUDY INTERVENTION

TENS is listed as non-significant risk when used for chronic pain in the 2006 FDA's "Significant Risk and Non-significant Risk Medical Devices" Guidance.[20] The study device has been cleared by the FDA under K152954. It is an over-the-counter device that is approved for chronic pain. Although it will be used for a different indication in this study (i.e., peripheral edema), the TENS device will be used on the same location of the body and in the same manner as it is suggested for use in the user's manual. The device does not require a prescription and is widely available. Furthermore, TENS has been studied in patients with peripheral edema in two previous studies.[9, 10] Therefore, we believe that it poses nonsignificant risk in this study and does not require and IDE. It emits a 60–100 Hz stimulation. The device is worn on the upper calf right below the knee and secured by an elastic band. The device is controlled by an application and alternates between a 1-hour treatment period and 1-hour rest period on the automated setting. Subjects will be asked to use the device for 7 to 8 hours per day on the automated setting. They will be asked to alternate the leg they wear the device on each day in order to minimize potential skin reactions. Subjects will be allowed to use the device while sleeping (overnight use of this device is approved by the FDA for chronic pain). If they choose to do so, they will not be asked to wake early to remove the device after 8 hours and thus could receive slightly longer stimulation. How often subjects choose to use the device while sleeping will be used to inform a future study.

Device setting. The device emits electrical stimulation for the entire 1-hour treatment period, resulting in 4 hours of total stimulation in 7 to 8 hours of use.

The 7 to 8 hours of use (4 hours of stimulation) was chosen based on the experience of the 3 individuals who reported the positive effects on peripheral edema (see Preliminary data) and assuming more stimulation is better.

The devices will be stored in a locked storage room in the Translational Pain Research Program offices at 2180 S. Clinton. All study devices will be returned to the study staff after the 3-week treatment period. The devices will then be sent back to the device manufacturer (Neurometrix Inc., Woburn, MA).

5. INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria (subjects must…)

1. Have had lower extremity edema for at least 3 months.
2. Currently have edema of at least 2+ (i.e., 3-4mm depression rebounds within a few seconds, but not immediately) on the pitting scale. [21] Pitting will have been assessed by a Clinician, the clinician Co-I within 6 weeks of the screening visit or at the screening visit by the research staff.
3. Willing to not start or change the dosages of any medications that could affect edema for 2 weeks prior to enrollment, and throughout the duration of the study.
4. Not currently using diuretics to control their edema.
5. Not currently using and willing to not start using occupational therapy, physical therapy, or lymphatic massage for edema (at home or by PT) 2 weeks prior to and throughout the duration of the study.
6. Not currently using compression stockings or Velcro or bandage wraps at least 2 weeks prior to enrollment in the study or based on shared decision making of the potential subjects' clinician or the clinician co-investigator are receiving sufficiently little benefit from these therapies to warrant stopping their use for the duration of the study.
7. Have access to a smart phone or device with an Apple or Android operating system with iOS 10 or later, or Android 6 or later. iOS and Android devices must have Bluetooth Low Energy (LE, also called Bluetooth Smart) compatibility. The smart phone or device must have the ability to access the TENS device's Quell App and, the ability to connect to the cellular data or Wi-Fi on a daily basis during the trial.
8. Have an active and accessible email.
9. Be willing and able to regularly check the email provided throughout the study.
10. Be able to read English (i.e., is literate, can speak English, and is not blind) because patient-reported outcomes and consent form are only available in English.
11. Be at least 18 years of age.
12. Be able to provide informed consent.

Exclusion criteria (subjects must not…)

1. Be currently using a TENS device for any reason.
2. Have an acute and symptomatic lower extremity DVT (i.e., the diagnosis of DVT is less than 3 months prior to study enrollment).
3. Have had a stroke in the past 3 months
4. Have lower extremity wounds or ulcers.
5. Have a cardiac pace maker or defibrillator.
6. Have epilepsy.
7. Have a leg that is too small or too large for the TENS device to fit securely.
8. Have cellulitis or fibrosis.
9. Have any skin condition at the site where the electrode pads adhere such that the PI/CoI think the device will not be safe for the subject.
10. Have congestive heart failure.

11. Have chronic kidney disease of stage 3 or greater.
12. Have cirrhosis of the liver.
13. Have previous surgery that removed lymphatic lower leg tissue.
14. Have a diagnosis of lower limb lymphedema.
15. Be pregnant or planning to become pregnant within the next 8 weeks.

6. RECRUITMENT METHODS

Subjects will be recruited from the URMC hematology providers, including Dr. Akwaa (CoPI) and his colleagues. In order to facilitate identification of potential subjects, the study coordinator will screen patient records of clinicians who have granted permission. The coordinator will alert the clinician to potentially eligible patients and the clinician will introduce the patient to the coordinator if they are interested in hearing about the study. Nancy Dukelow, an occupational therapist in the URMC Occupational Therapy Department has agreed to refer patients to the study. Flyers and study brochures will be used to advertise the study in waiting rooms of the hematology clinic, occupational therapy clinic, and the willing members of primary care offices that are associated with the URMC. The CTSI's Research Match program will be used to identify potentially eligible patients who are willing to be contacted directly for research.

7. CONSENT PROCESS

Prior to performing any consent-related activities the potential subjects' identification will be verified using information already known by both parties (e.g., DOB, middle name, street name). The consent process will be performed at the Pre-baseline visit by a coordinator. The potential subject will be informed that their medical care will not be changed in any way if they decide not to participate. The coordinator will review the consent form with the potential subject and allow time for questions. The potential subject will be allowed to take home the consent form and discuss it with family or friends before proceeding with consent if they so choose. After the consent form has been reviewed, the potential subject will be asked the following series of questions, by the consenter, to assess how well they understand the study: (1) If you join the study can you wear compression stockings? (2) How many in-person visits are we asking you to complete? (3) What is the longest time that you will be asked to participate in the study? If the potential subject answers any of the questions incorrectly, the information will be re-explained to them and they will be asked the question they missed a second time. The subject and the PI, Co-I, or designated study staff member will sign the consent form. A copy of the form will be given to the subject and the original will be kept in the study records in a locked cabinet and a copy will be sent to HIM to add the study to the medical record.

8. STUDY PROCEDURES

Screening Procedures
Patients of collaborating clinicians

Patient records of collaborating clinicians will be screened for initial eligibility. All eligibility criteria that can be found in the medical charts (e.g., use of diuretics for peripheral edema) will be reviewed prior to approaching potential subjects. Potentially eligible subjects will be invited by the clinician (in-person or via MyChart, phone call, or signed letter) to complete the screening process. The coordinator will ask the screening questions via phone (or in person if the subject is at the clinic for a visit with their clinician). If the potential subject has not had the severity of their edema evaluated by the clinician within 6 weeks of the Pre-baseline visit, the severity of their pitting of edema will be evaluated at the Pre-baseline visit by the trained study staff to confirm final eligibility prior to obtaining informed consent.

Individuals who call in response to flyers

Potential subjects who contact the coordinator in response to flyers or brochures placed in clinical offices will be asked all of the screening questions that they can answer on the phone. If they are potentially eligible, they will be asked if the coordinator can access their medical chart to confirm entry criteria, diagnosis of edema, medications. If the entry criteria are met, they will be invited to come in for the Pre-baseline visit, at which point the severity of their pitting of edema will be evaluated by the trained study staff to confirm final eligibility prior to obtaining informed consent.

If potential subjects are not eligible or choose not to participate, their linked health and identifying information will be destroyed. De-identified reasons for ineligibility or a choice not to participate will be documented in a screening log. De-identified data related to reasons for ineligibility or choice not to participate will be used to improve the entry criteria of a future study in order to potentially increase feasibility and generalizability.

Individuals who are identified via Facebook and Research Match

People who contact study personnel using the study Facebook ad or Research Match platform will click on a survey link, which will take them to a REDCap initial eligibility screening survey. In this eligibility screening survey, we will utilize REDCap branching logic so that as soon as a potential subject enters a response that renders them ineligible for the study, when they click 'Next', they will be prompted with the following message:

"Thank you for your time. Unfortunately, you are not eligible for this study."

The de-identified data from ineligible subjects will be kept, but they will only be asked questions in the eligibility survey up until one of the questions makes them ineligible. We are keeping this data only to find out the reasons that make people ineligible. This data will help find out, what questions are confusing to people and if there is anything that can be modified to make the protocol and workflow better.

Potential subjects who meet all of the eligibility criteria contained in the survey will be prompted with the following message on the final page:

"Thank you! You might be eligible for this study. If you are interested in learning more about our study, please provide your contact information below so that our study team can contact you."

The UR Health Research Facebook page: https://www.facebook.com/URHealthResearch, which is managed by CTSI will be hosting these recruitment materials.

Medical record documentation of study participation

After a subject provides informed consent, a copy of the signed consent form will be uploaded into eRecord. A note in eRecord will indicate that the subject has signed consent for a clinical study. The note will include the study title, that the subject will be using a TENS device for peripheral edema during the study, and the PI's contact information for questions regarding the study.

Study visit schedule

See Tables 2 and 3 for the schedule of assessments and procedures. The total duration of the study will be up to 8 weeks (1 Pre-baseline week, 1 Treatment period of 3 weeks, and one follow-up phone call 4 weeks after the Treatment period). In order to control for time-of-day factors that contribute for edema, the study visits for an individual subject should ideally all occur within a +/-2-hour time window whenever possible; although this is not required. For example, if a subject's first study visit is at 3pm, Visit 2 should occur between 1pm and 5pm.

To ensure appropriate safety precautions related to COVID-19 when conducting in-person study procedures, the process for conducting in-person visits outlined in the Guidance for Human Subjects Research will be followed. (https://www.urmc.rochester.edu/coronavirus/coronavirus-research/guidanceforresearchers/human-subjects-research.aspx). A RSRB approved flyer is available to help subjects understand what they can expect when a study visit occurs.

Table 2: Schedule of events

Events	**Pre-Baseline visit (Visit 1)**	**Baseline period (1 week)**	**Baseline visit (Visit 2)**	**Treatment period (3 weeks)**	**Treatment endpoint (Visit 3)**
Final eligibility check*	X				
Consent	X				
Instruct subjects how to use Fitbit device	X				

Instruct subjects how to complete at-home paper PROs	X				
Use Fitbit daily		X		X	
Complete daily or weekly at-home paper PROs	X	X		X	
Distribute of study TENS device and teach subject how to use it			X		
Complete visit electronic PROs			X		X
Functional exam measures			X		X
Leg measurements	X		X		X
COVID Screening form	X		X		X
Open subject's Quell App and Fitbit while connected to Wi-Fi			X[1]		X
Adverse event monitoring[2]				X	X
Qualitative interview					X
*If edema has not been assessed by a clinician within 6 weeks of Pre-baseline visit. [1] Pair only the Fitbit device [2] Additional phone call after 1 week of TENS use					

SCREENING / CONSENT

Reminder 1: (phone call) (1-2 days prior to Visit 1). Remind the potential subject (and record in the **Telephone Contact Form)**:

- To complete the COVID-19 pre-screen questionnaire prior to the visit.
- Of the date, time of their Visit 1.

Visit 1: Pre-baseline (In-person / Day -7)

If the potential subject has not had the severity of their edema evaluated by the clinician within 6 weeks of the Pre-baseline visit, the severity of their pitting of edema will be evaluated at the Pre-baseline visit by the trained study staff to confirm final eligibility prior to obtaining informed consent.

The coordinator will perform the informed consent process as per description above. The coordinator will confirm whether the subject has received a copy of the URMC and Affiliates

Notice of Privacy Practices; if not, the subject will receive a copy of the URMC and Affiliates Notice of Privacy Practices.

The coordinator will confirm the following with the subject: whether the subject has active email for preferred method of contact, active Phone # for preferred method of contact, whether or not it is acceptable to leave messages about the study at the provided phone number

The coordinator will perform leg measurements and document them. The coordinator will help the subject setup the Fitbit device, review the user guide and discuss how to use the Fitbit. They will ask the subjects to use the Fitbit at all times (unless they cannot tolerate it while sleeping) until Visit 2.

The coordinator will help the subject register or create an account for direct payments through Advarra Participant Payments, if they do not already have one. The coordinator will provide the subject with the Information Sheet for Advarra Participant Payments. The coordinator will review the two visits that study payments will be initiated through the direct payment system.

The subject will report any medications that could affect their edema. In addition, a coordinator will check the medical record for medications that may cause swelling. The subject will be asked to write in these medications on the medication diary in which the subjects will be asked to document use of medications that could affect edema.

The coordinator will explain how to complete the at-home (paper) PROs.

PRE-BASELINE ASSESSMENT PERIOD

Week -1: (subject will complete at home)

- Subject will use the Fitbit device at all times while awake.
- Subject will setup their Advarra account and choose payment type payments
- Subject will complete the **Edema Symptom Pre-Baseline Daily Diary**.
- The coordinator will setup times and dates for the **Baseline visit**, **Treatment period Endpoint** visit and follow-up phone call.
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Reminder 2: (phone call or email) (1 day prior to Visit 1)
Remind the subject (and record in the **Telephone Contact** form):

- Of the date, time, and location of their next in-person study visit.
- To complete the COVID-19 pre-screen questionnaire prior to the visit.
- To complete the visit PROs online via REDCap prior to the visit.
- To bring their completed at-home (paper) PROs from Week -1.
- To bring their Fitbit and mobile device.
- To wear pants with a loose leg.

TREATMENT PERIOD

Visit 2- Baseline visit: (In-person / Day 0 up to + 5_days)
The coordinator will download the Quell App to the subject's mobile device, setup a Quell Health account for the subject (using valid de-identified study email address and password) and help them pair the TENS device to their mobile device and calibrate it. They will introduce the concept of TENS and describe how it is likely to feel to the subjects using a standardized script. They will give the subject 2 electrode strips along with the TENS device, which should be sufficient for the 3-week duration of the treatment period of the study. They will provide the subject with the subject guide to help them with at-home use and ask them to use the device between 7 to 8 hours per day. They will also ask them to open the Quell App once a day while the device is connected to cellular data or Wi-Fi to transfer the data to the Quell Health account. If the subject plans to use cellular data, the coordinator will setup the Quell App to allow the use of cellular data in the settings.

The coordinator will review the **Edema Symptom Daily Diary, Edema Symptom Inventory Week Recall, and Edema Symptom Inventory-Week Recall 0-10 Scale** forms and teach the subject how to complete them.

The coordinator will perform the ankle range of motion and lower limb sensation tests and measure the subject's lower limbs using the volumeter and tape measure.

The subject will complete the visit related patient-reported outcome measures (PROs) at the study visit if they were not completed previously using the REDCap link.

Weeks 1-3: (subject will do at home)

- Subject will use the Fitbit Device at all times.
- Subject will use the TENS device for 7 to 8 hours / day either day, night, or asleep.
- Subject will complete the **Edema Symptom Daily Diary, Edema Symptom Inventory Week Recall, and Edema Symptom Inventory-Week Recall 0-10 Scale.**

Phone Call 1: (Day 7, up to +2 days)

- AE assessment: The coordinator will ask the subject using an open-ended question whether any new symptoms have occurred since starting the study. If so, the coordinator will record the AE in the **AE form** in REDCap.
- Adherence discussion: The coordinator will discuss any adherence problems observed in the data from the Quell App.
- Reminder 3: remind the subject (and record in the **Telephone Contact Form**):
- To complete at-home (paper) PROs for Week 2 (Days 7-14).
- To mail completed at-home (paper) PROs from Week 1 back using the prepaid postage provided or bring it with them on their next visit
- To use the Fitbit consistently.

Reminder 4 (email) (Day 14, up to +2 days)

Remind the subject (and record in the **Telephone Contact Form**):

- To complete at-home (paper) PROs for Week 3 (Days 51-21).
- To mail completed at-home (paper) PROs from Week 2 back using the prepaid postage provided or bring it with them on their next visit
- To use the Fitbit consistently.

Reminder 5: (phone call or email) (1-2 days prior to Visit 3) Remind the subject (and record in the **Telephone Contact Form**):

- Of the date, time, and location of their study visit.
- To complete the COVID-19 pre-screen questionnaire prior to the visit.
- To complete the visit PROs online via REDCap prior to the visit.
- To bring their completed at-home (paper) PROs from Week 3, TENS device with the box and the charger, Fitbit with the box and the charger, and mobile device.
- To wear loose fitting pants.
-

Visit 3- Treatment period Endpoint (Primary): (In-person; Day 21 up to +5 days)

The coordinator will:

- Collect the completed at-home (paper) PROs from Week 3, the study TENS device and Fitbit.
- Complete the physical assessments (i.e., ankle range of motion and lower limb sensation tests and measure the subject's lower limbs using the volumeter and tape measure).
- Ask the participant about AEs.
- Open the Quell App on the subject's mobile device while it is paired with Wi-Fi to ensure data transfer the Quell Health Account.
- Pair the TENS device with the subject's mobile device to ensure data transfer for adherence data.
- Pair the subject's Fitbit with the Study iPad to transfer the activity data.
- Deactivate and deregister the Fitbit through account settings.
- Subject will receive the company's commercially-available device to keep.
- Initiate the $75 study payment through the direct payment system Advarra.
- Either the coordinator or the study PI will perform the Treatment period Endpoint Qualitative Interview.

The subject will complete the visit PROs at the study visit, if they were not completed previously using the REDCap link.

Follow-up phone call (Phone call) (1-month up to + 7 days)

The coordinator will:

- Ask the subject if they are still using the TENS device. Discuss their overall experience with the use of TENS device. Responses will be recorded on the **1-month follow-up form**.

Table 3: Edema schedule of data collection.

FORMS	Screening	Prebaseline period	Treatment period	Treatment period Endpoint
Subject Forms (REDCap or paper)				
On Study		X		
Edema Symptom Daily Diary			X	X
Edema Symptom Daily Diary-Pre-baseline[1]		X		
Impression of Change in Edema Symptoms				X
Expectation Questionnaire[3]			X	
CIVIQ 20[3]			X	X
LYMQOL[3]			X	X
PROMIS Fatigue[3]			X	X
Edema Interference Questionnaire[3]			X	X
General Impression of Edema[3]				X
General Impression of Activity[3]				X
Edema Symptom Inventory-Week Recall		X	X	X
Edema Symptom Inventory-Week Recall 0-10 Scale		X	X	X
Treatment period Endpoint-Qualitative Feedback				X
Coordinator Forms (REDCap or paper)				
Eligibility checklist (Medical record, Clinicianreported, and Patient-reported items)[1]	X			

Consent form		X		
Clinical Record Information		X		
TENS Device Settings			X	
Coordinator Lower Limb Swelling		X	X	X
Volumeter Measurements			X	X
Lower Limb Sensation Threshold			X	X
Ankle Range of Motion			X	X
COVID pre-screen form		X	X	X
Telephone Contact		X	X	X
Adverse Event (AE) form[2]				X

[1] Forms are completed during the weeks 1, 2, and 3 and being returned by mail to the research team.
[2] Adverse events will also be assessed after Week 1 via phone
[3] Form can be completed via REDCap by subject prior to or at Visit 1, Visit 2, and Visit 3

General policies regarding contacting subjects: If subjects have chosen to be contacted by email but do not respond to email reminders, they will be called up to 2 times for that specific reminder. If a subject does not attend a phone Call or in-person visit, they will be called up to 3 times to try and reengage the subject in the study. If any phone calls are interrupted or stopped short for any reason, including technological difficulties, a subsequent phone call will be setup to complete the necessary research tasks. Rescheduling of visits can occur up to 1 week after the original visit was scheduled, which will be scheduled within the time-frame indicated in the protocol section for each visit.

The only difference between the commercially-available TENS device's programming and the study TENS device is the size of the intensity increase with a button tap. The maximum allowable intensity is the same as the commercially-available TENS device. Thus, there is no major safety concern if a subject fails to return to the study and continues to use one the study devices, therefore no further attempts other than those outlined above will be made to contact subjects to retrieve the study TENS devices to minimize intrusion in subjects' lives.

9. **RISKS TO SUBJECTS**

Potential risks from stopping use of compression stockings or wraps: If subjects choose to forgo use of compression stockings or wraps to start the trial, there is a risk that their edema could worsen during the study. We have minimized this risk by only enrolling subjects who are not experiencing a significant of benefit from these therapies (i.e., entry criteria: "based on shared decision making of the potential subjects' clinician or the clinician co-investigator [the potential subject is] receiving sufficiently little benefit from these therapies to warrant stopping their use for the duration of the study"). Subjects will be asked to call the study staff if they feel as though their swelling or symptoms are worsening and they will decide together with the clinician Co-I if they should stop using the TENS device and resume using compression stockings or wraps.

Potential risk of not trying currently available treatment options: For some people, the following treatments can be tried for peripheral edema, (1) compression stockings, (2) Velcro wraps, (3) manual lymphatic drainage, (4) short stretch bandage wrapping, (5) pneumatic pumps, (6) kinesiotape, (7) acupuncture, and (8) cupping. For potential subjects who have not been offered these treatments in the past, choosing to join the study and forgoing these treatments could lead to a worse outcome than if they tried one of these alternative treatments. The potential subjects will be informed of these alternative treatment options and given the opportunity to consult their primary care physician or the clinician Co-I regarding whether they should consider the alternative treatments prior to starting the study.

Potential risks of the TENS device: The known potential risks include skin irritation at the electrode sites; however, precautions can be taken to minimize the occurrence of skin irritation (i.e., not wearing the device 24 hours/day for multiple days without taking a break). We have also observed new abnormal sensations in the feet with use of the TENS device in a previous pilot study. In all cases we observed these abnormal sensations were reversible upon stopping use of the device. Subjects will be instructed to contact the study team if they experience new, abnormal sensations in their lower limbs. They will discuss these symptoms with the clinician Co-I and decide together whether it is in their best interest to discontinue use of the device. The principal investigator in consultation with the co-investigator have the ability to remove any subject from the study, who in the clinician Co-I's opinion is being exposed to undue risk from adverse events.

Subjects will be instructed that the TENS device should not be used when getting wet (e.g., in the shower or while swimming) or while driving. Having to remove the device (when getting wet) / turn off the stimulation or remove the device (when driving) may cause inconvenience; this potential inconvenience is unavoidable.

Potential risks associated with the Fitbit: Use of the Fitbit requires registering the Fitbit. We will register the Fitbit with a valid de-identified study email address and password. Fitbit Inc. will have access to the subject's Fitbit de-identified data via the secure cloud database up to 90 days after the Fitbit is deactivated and deregistered. This fact is unavoidable and will be clear in the informed consent form.

Risk associated with breach of confidentiality: Although we will do everything in our power to secure the data from the study, there is a risk that someone outside the study staff will gain access to the data. The risk of breach of confidentiality will be minimized by locking paper forms in a secure filling cabinet and storing electronically entered data on a password protected network drive. Data will be entered electronically via the University of Rochester's secure REDCap system or directly into Excel on a University of Rochester computer. Each subject will receive a unique ID number. All data forms will have only the ID number. A master key that links the study ID numbers with the subjects will be kept in a separate file, also on a University of Rochester secured network drive. Only the study staff will have access to the data. The exception is de-identified data that are collected via the Apps, to which the companies (i.e., Neurometrix and Fitbit) will also have access (see subsequent paragraphs).

We will use the Quell App with the TENS device to retrieve the subjects' adherence data while on the study. The Quell App stores the data received from the TENS device. The TENS device transmits data (data received from TENS device) to a secure online cloud database. To protect against data breaches during data transmission from the TENS device to the Quell App the data is encrypted based on an encryption key that is specific to each wearable device. The data from the secure online cloud database will be sent from Neurometrix via encrypted email to the study team. Data from the emails will be downloaded only to URMC encrypted laptops or desktops and stored on password protected URMC network drives.

We will use the Fitbit software with the Fitbit device to retrieve activity data during the study. Data recorded on the subjects' Fitbit device is transferred from the device to cloud servers to URMC laptop secure server. During the transfer of data from the device to the cloud the data is encrypted to protect from data breaches.

The alternative to participation is not participating and continuing usual care with the subject's clinician.

The risks of e-mail use can include but are not limited to the possible introduction of viruses into the subjects' computer systems, the interception, alteration, forwarding, or used without authorization or detection, circulated, forwarded, stored electronically and on paper, the broadcasting of e-mails to unintended recipients due to the nature of e-mail address to be easily misaddressed. To mitigate these risks the following steps and procedures will be taken during the study. Communications between the study team and the subject will be filed stored on a password protected UR drive and discarded once the study is complete. E-mails containing sensitive medical information will be encrypted. Subjects' email contact information will be verified at minimum 3 times during the study.

Advarra will be used as the direct payment system for study payments. During registration or account creation on the site, Advarra may collect any or all of the following subject information, (i) name, (ii) home or business address, (iii) professional information, including specialty or nature of concern, (iv) organization with whom they are affiliated and its address, and (v) email address. When they visit the site using their personal smart device, the site may automatically record information that their browser sends like, the name of the domain and

host from which they access the Internet; the Internet Protocol (IP) address of the computer or smart device they are using; the date and time they access the site or make uploads or post to the site; and the Internet address of the website from which they 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 the 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 subjects will not be asked to submit any "protected health information" as defined in HIPAA**.**

10. POTENTIAL BENEFITS TO SUBJECTS

Subjects' lower limb swelling (edema) and associated symptoms (e.g., pain, discomfort, heaviness) may decrease with use of the TENS device. All subjects will receive the TENS device with the commercially-available stimulation settings (list price $299) to keep at the end of the study. However, they will have to purchase electrodes for continued use of the device (list price $29.95/~4 weeks of use).

11. COSTS FOR PARTICIPATION

If the subject does not have a monthly data plan, they may incur some minimal data usage costs when connecting to the Quell App.

Other than the above-described costs the subjects and insurance companies will not be responsible for any study-related costs. However, if a subject requires medical attention as a result of being in the study (e.g., requires a cream for skin irritation), the subject will be responsible for the costs of those interventions.

12. PAYMENT FOR PARTICIPATION

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

Payment received for participation in research is considered taxable income. If subjects 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. They will be sent a copy of this form and a copy will be sent

to the IRS. Depending on the amount they are paid, they may be asked to submit a W-9 form, which includes their Social Security Number.

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13. SUBJECT WITHDRAWALS

Subjects will be withdrawn if they become pregnant during the study because pregnancy can cause edema and change the study outcome. The PI can withdraw any subject who is at risk or is unable to participate further due to new identification of conditions that are contraindicated with use of TENS (e.g., epilepsy). Data that have already been collected will be included in the analyses.

The subject may be withdrawn from the study if they do not keep appointments for study visits, specifically in the beginning of the study.

If the subject misses the baseline period visit and does not attend rescheduled visits with in the 7-day grace period they will be withdrawn from the study prior to registration or distribution of the treatment device.

The subject may be withdrawn from the study if they cannot complete study activities.

If the subject's baseline daily diary entries have more than 4 days or greater missing they will be withdrawn from the study before registration or distribution of the treatment device.

If subjects withdraw from the study, reasons for withdrawal will be documented and data collected up until the point of withdrawal will be included in the analyses unless the subject indicates that they do not want their previously collected data used. Subjects will be allowed to refuse any study activity and can still remain in the study if they are willing. Subjects who withdraw from the study will not be replaced.

14. PRIVACY AND CONFIDENTIALITY OF SUBJECTS AND RESEARCH DATA

Research staff members will only approach subjects after introduction by a clinician either inperson or via MyChart, phone call, or signed letter. While on the study, subjects will not be contacted via phone, email or, video call more frequently or for reasons other than those stated in the protocol.

Only study personnel, including the principal investigators, co-investigators, and research staff will have access to the study data. The Quell (i.e., TENS device) App will be setup using a deidentified study email so that the data collected via the application will not be identifiable by anyone outside of the study team. Paper data forms will be locked in a secure office and electronic data will be stored on a password protected, encrypted network drive. Each subject will receive a unique ID number. Data will be entered electronically via the
University of Rochester's secure REDCap system or directly into excel on a University of Rochester computer. A master key that links the study ID numbers with the subjects will be kept in a separate file, also on a University of Rochester secured network drive.

The Fitbit (i.e., Fitbit device) account registration will be setup using a de-identified study email and password combination for each subject, so that the data collected via the Fitbit device and secure cloud database will not be identifiable by anyone outside of the study team. The account will use a de-identified placeholder for the first and last name. Demographic details such as weight, height and DOB are collected to ensure accurate data capture. The subject's device account settings will be set to the highest privacy-protection options available for the device interface. At Visit 3 the coordinator will deactivate and deregister the Fitbit, which will delete the de-identified data from the device immediately and from the Fitbit secure cloud database within 90 days.

The fact that the subject is enrolled in the research study will be indicated in their electronic medical record. The eRecord note will indicate that the subject will be using a TENS device for their peripheral edema for 3 weeks during the study and that providers can contact the PI for questions regarding the subject's participation in the study.

15. DATA AND SAFETY MONITORING PLAN

Adverse Event (AE) Definition

An adverse event (AE) is any symptom, sign, illness, or experience, which develops or worsens during the course of the study, whether or not the event is considered related to study intervention (Table 4).

Table 4. Attribution. Categories to define the relationship between the adverse event and study device/intervention.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is clearly NOT related to the study device /intervention
Unlikely	The AE is doubtfully related to study device /intervention
Possible	The AE may be related to study device/intervention
Probable	The AE is likely related to study device/intervention
Definite	The AE is clearly related to study device/intervention

Serious Adverse Event

A serious AE is defined as any adverse medical experience that results in any of the following outcomes:

- death;
- is life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- requires medical or surgical intervention to prevent permanent impairment or damage.

Recording Adverse Events

AEs will be assessed by phone after 1 week of the intervention is started, at the 3rd in-person study visit. The study staff will assess adverse events by asking subjects if they have experienced any new symptoms since starting the experimental treatment. They will ask specifically if any skin reactions have occurred.

AEs will be recorded in the **AE form**, including the date of onset, date of resolution, description of the AE, severity, whether or not the AE is considered serious, any action taken to treat the AE, likelihood that the AE is related to the experimental device, any change to the experimental device usage in response to the AE, and whether the RSRB was notified regarding the AE. Any AEs will be followed up as clinically appropriate by the Co-I /medical monitor (MM). Table 5 indicates the types of AEs (i.e., by severity level / attribution category) that will be recorded and reported to the RSRB during annual reviews.

Table 5. Reportable adverse events

Adverse Event					
Attribution	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Unrelated			recorded	recorded	recorded
Unlikely			recorded	recorded	recorded
Possible	recorded	recorded	recorded	recorded	recorded
Probable	recorded	recorded	recorded	recorded	recorded
Definite	recorded	recorded	recorded	recorded	recorded

Responsibilities for Reporting Serious Adverse Events

All serious AEs will be recorded in the AE form. Serious AEs will be reported to the RSRB if they are considered unanticipated and related to use of the TENS device or involves increased risk to subjects or others than was previously known or expected. If an AE is reportable, it will be reported to the RSRB using the "Reportable Event" form in the online IRB click system within 10 calendar days of the investigator or research staff member's learning of the event.

Data Monitoring

The study team will review the data and patient safety after the first five subjects are enrolled and then every 6 months. Subject enrollment will not be paused during these reviews. The PI will submit annual progress reports of these data to the Safety Monitor (Nimish Mohile, MD). Dr. Mohile is a neurologist who is familiar with the TENS device from a previous study of the device used by subjects with chemotherapy-induced peripheral neuropathy. The reports will include: the number of patients enrolled, and for each treatment: withdrawals, AEs possibly, probably, or definitely associated with the therapy, all serious AEs both expected and unexpected, dose adjustments, and responses observed. The PI will maintain a database of all

AEs with toxicity grade and information regarding treatment-required complications, or sequelae.

16. DATA ANALYSIS PLAN

Missing Data

All efforts will be made to prevent missing data. Due to the exploratory nature of the study, missing data will not be accommodated statistically.

Sample Size Estimation

We plan to recruit 52 people for this study because it is what we think is feasible given our resources and should provide sufficient information to determine whether there is a reasonable potential efficacy signal to move forward to a randomized clinical trial.

Aim1. Feasibility Analyses

(1) Descriptive statistics will be used to summarize all feasibility outcomes. (2) Common themes in subject-reported reasons for low adherence will be summarized in the qualitative data.

Aim 2. Preliminary Efficacy

(1) Primary preliminary efficacy: Preliminary efficacy for the water volume displacement outcome and the Edema Symptom Daily Diary will be assessed using Wilcoxon sign-ranked test comparing the outcomes from Baseline and Treatment Endpoint.

(2) Secondary preliminary efficacy: Similar analyses to those in the primary preliminary efficacy aim will be used for the secondary efficacy outcomes.

Due to the exploratory nature of the study, no adjustments will be made for multiplicity.

Exploratory Analyses

1) Similar analyses to those in the primary preliminary efficacy aim will be used to assess changes between Baseline and Treatment Period Endpoint for the continuous exploratory efficacy outcomes.

2) The percentage of subjects whose monofilament threshold improves between Baseline and Double-blind Endpoint will be compared using a Fisher's exact test.

3) Trajectories of changes in activity (measured via the Fitbit) and changes in swelling (measured via NRS swelling and symptoms ratings) will be visually inspected and compared to investigate whether increased activity precedes and therefore may contribute to decreased swelling.

4) Qualitative analysis techniques will be used to analyze the cognitive interview data to improve self-report measurements for peripheral edema.

5) We will explore the data for patterns to see if people with different causes of edema seem to benefit from the treatment more frequently than others. These qualitative analyses will be used to inform future entry criteria.

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