WIRELESS TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS) FOR CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY: A PHASE II CLINICAL TRIAL

URCC19085
NCT # 04367480

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- This study is open to all NCORP sites that are affiliated with URCC.

IDE: Not applicable, TENS device is currently marketed for relief of chronic pain and considered minimal risk by the FDA and thus only requires IRB approval (https://www.fda.gov/medical-devices/device-advice-investigational-device-exemption-ide/ide-approval-process#non_sig_risk)

Device(s)/supplier: TENS devices will be supplied by Neurometrix at no cost.

Distributed by: URCC NCORP Research Base

Document History	Version Date
Initial	10-18-2019
Revised	12-16-2019
Amendment 1	1-24-2020
Amendment 2	3-11-2020
Amendment 3	6-25-2021

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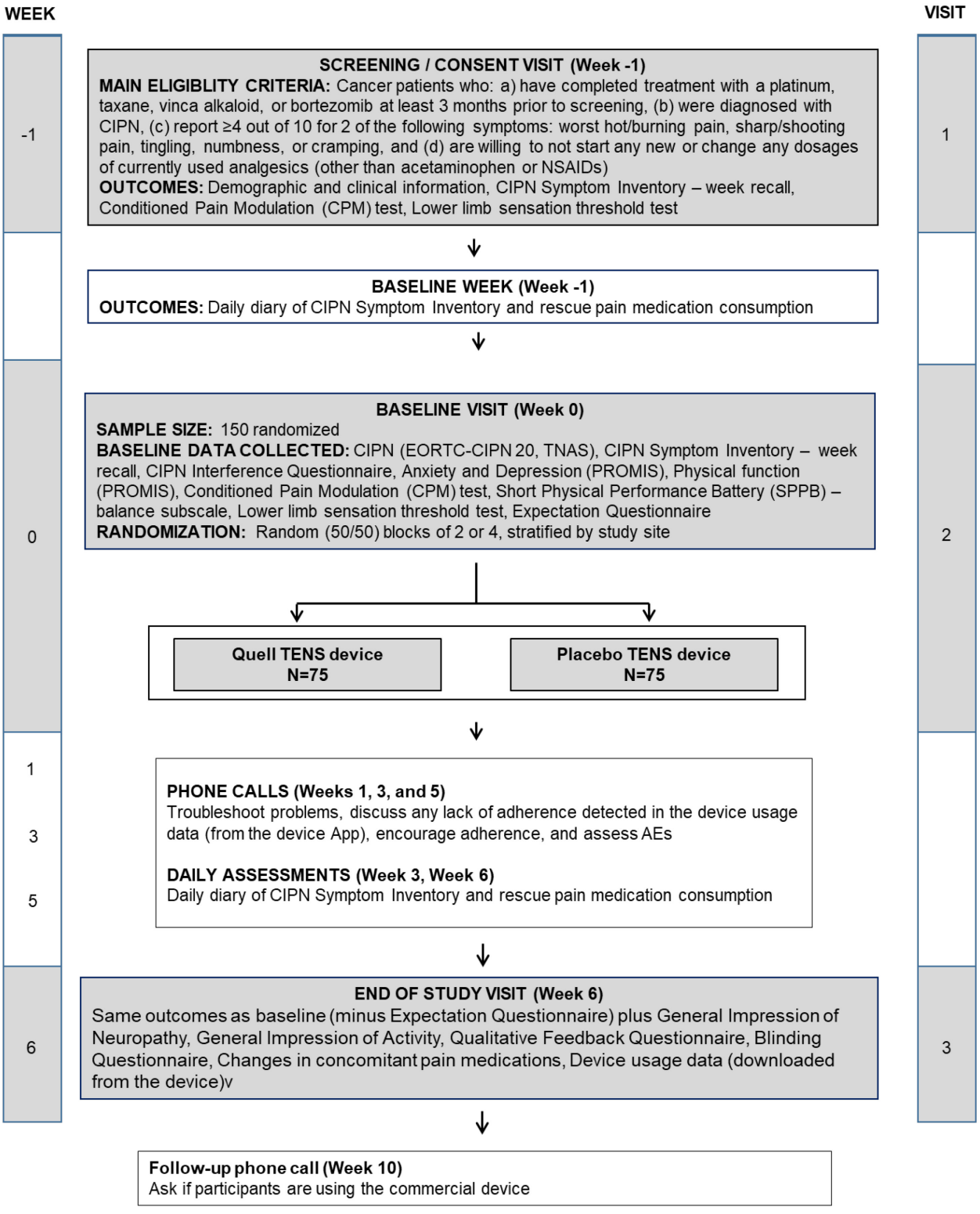
SCHEMA


WEEK
VISIT
-1
1
SCREENING / CONSENT VISIT (Week -1)
MAIN ELIGIBLITY CRITERIA: Cancer patients who: a) have completed treatment with a platinum, taxane, vinca alkaloid, or bortezomib at least 3 months prior to screening, (b) were diagnosed with CIPN, (c) report ≥4 out of 10 for 2 of the following symptoms: worst hot/burning pain, sharp/shooting pain, tingling, numbness, or cramping, and (d) are willing to not start any new or change any dosages of currently used analgesics (other than acetaminophen or NSAIDs)
OUTCOMES: Demographic and clinical information, CIPN Symptom Inventory – week recall, Conditioned Pain Modulation (CPM) test, Lower limb sensation threshold test
BASELINE WEEK (Week -1)
OUTCOMES: Daily diary of CIPN Symptom Inventory and rescue pain medication consumption
0
2
BASELINE VISIT (Week 0)
SAMPLE SIZE: 150 randomized
BASELINE DATA COLLECTED: CIPN (EORTC-CIPN 20, TNAS), CIPN Symptom Inventory – week recall, CIPN Interference Questionnaire, Anxiety and Depression (PROMIS), Physical function (PROMIS), Conditioned Pain Modulation (CPM) test, Short Physical Performance Battery (SPPB) – balance subscale, Lower limb sensation threshold test, Expectation Questionnaire
RANDOMIZATION: Random (50/50) blocks of 2 or 4, stratified by study site
Quell TENS device N=75
Placebo TENS device N=75
1
3
5
PHONE CALLS (Weeks 1, 3, and 5)
Troubleshoot problems, discuss any lack of adherence detected in the device usage data (from the device App), encourage adherence, and assess AEs
DAILY ASSESSMENTS (Week 3, Week 6)
Daily diary of CIPN Symptom Inventory and rescue pain medication consumption
6
3
END OF STUDY VISIT (Week 6)
Same outcomes as baseline (minus Expectation Questionnaire) plus General Impression of Neuropathy, General Impression of Activity, Qualitative Feedback Questionnaire, Blinding Questionnaire, Changes in concomitant pain medications, Device usage data (downloaded from the device)v
Follow-up phone call (Week 10)
Ask if participants are using the commercial device

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1. INTRODUCTION AND BACKGROUND

1.1 Rationale

CIPN occurs in approximately 60% of patients who receive neurotoxic chemotherapeutic agents (e.g., platinums, taxanes, and vinca alkaloids) and becomes chronic (i.e., lasts at least 3 months after termination of chemotherapy) in approximately 50% of those individuals.[1] Neurotoxic agents are used to treat many common cancers including breast, gastrointestinal, lung, ovarian, and myeloma, which together were estimated to make up ~40% of new U.S. cancer cases in 2018.[2] CIPN presents as a variable combination of neuropathic symptoms, commonly including burning and shooting pain, tingling, cramping, and numbness. Data from our group and that of others suggest that chronic CIPN leads to functional limitations such as impaired balance,[3, 4] increased falls,[5-8] limitations in activities of daily living (e.g., shopping),[5] and interference with walking.[9, 10] Multiple studies demonstrate that CIPN is associated with decreased quality of life in cancer survivors.[11] No gold-standard treatments are available for CIPN. While duloxetine modestly improved chronic painful CIPN in one randomized clinical trial (RCT),[12] this drug contributes to the adverse effects of polypharmacy. No treatments have been shown to mitigate the functional limitations that are associated with CIPN such as impaired balance or walking. In fact, our recent systematic review of RCTs evaluating pharmacologic treatments for CIPN found that only two trials reported performance-based function measures,[13] suggesting a gap in research methods for current CIPN RCTs. Based on its high prevalence, severity, effects on quality of life, and lack of available treatments, CIPN is among the highest priority research areas for the NCI Community Research Program (NCORP).[14, 15]

Numerous possible pathophysiological mechanisms for CIPN have been proposed. Given the expertise of our research group and the analgesic mechanisms of transcutaneous electrical stimulation (TENS) (see next section), we will focus on the potential role of the alteration of two opposing pathways that control sensation in the brain: (1) central excitatory pathways (i.e., central excitability) and (2) central descending inhibitory pathways (i.e., descending inhibition). Central excitatory pathways in the spinal cord amplify signals to the brain from the ascending sensory neurons (i.e., nociceptive neurons). In contrast, central inhibitory signals from the brainstem and spinal cord inhibit signals from nociceptive neurons.[16-18] Unlike central excitability, the function of descending inhibition can be tested in humans (via a conditioned pain modulation (CPM) test[19]) and will be investigated in the proposed study. In animal models of CIPN, dorsal horn neurons that transmit noxious sensory signals show enhanced responsiveness to noxious stimuli, suggesting enhanced central excitability.[20-23] Expression of glutamate transporters in the dorsal horns of animals with CIPN is decreased,[20, 24, 25] which would result in enhanced concentrations of the excitatory neurotransmitter glutamate. Simultaneously, endogenous opioids, which inhibit nociceptive transmission, are decreased in animal models of CIPN.[26] Finally, a study of 27 participants showed that reduced descending inhibition (measured via CPM test) was associated with more severe CIPN symptoms.[27] Together these data suggest that CIPN may be associated with enhanced central excitability and reduced descending inhibition and that our proposed intervention, TENS, reduces central excitability and increases descending inhibition (Figure 1).[28-32]

1.2 Literature Review

TENS is a promising therapy for CIPN. TENS is the application of electrical stimulation through the skin. It is a safe, non-pharmacologic, non-addictive, and inexpensive therapy used clinically for pain control. The waveform, frequency, and maximum current of the electrical stimulation vary among devices, but the proposed mechanisms of action are similar.[28] Evidence suggests that TENS reduces central excitability and activates descending inhibition, both of which have been implicated in CIPN in animal studies and one small human study. In animal models, TENS reduces the enhanced central excitability of nociceptive neurons induced by inflammation and nerve injury[33] and decreases the release of the excitatory neurotransmitter glutamate in the dorsal horn of the spinal cord.[32] TENS also produces analgesia in animal models by activating descending inhibition in the brainstem and spinal cord through activation of

endogenous opioid receptors.[30, 31, 34] Consistently, human studies show opioid receptor activation by TENS during pain inhibition[35] and show that TENS restores descending inhibition in individuals with fibromyalgia during a single TENS session.[29]

TENS is efficacious for chronic pain and promising for non-painful neuropathy symptoms in other conditions. The efficacy of TENS for pain is supported by its widespread clinical use as well as positive results from RCTs in various chronic pain conditions, including peripheral neuropathic pain.[29, 36-46] However, these RCTs are generally small and not blinded. RCTs including patients with diabetic peripheral neuropathy showed improvements in discomfort and in a composite neuropathy score that includes ratings of pain, numbness, and prickling sensations,[36, 37] suggesting that TENS could also reduce non-painful neuropathy symptoms. Furthermore, dysmenorrhea and writer's cramp, for which RCT data supports the efficacy of TENS [41, 43, 45] involve cramping pain, and our preliminary results suggest that CIPN-related cramping may be particularly responsive to TENS (Table 1).

Preliminary, single-arm studies of TENS treatments for CIPN from the published literature. A single-arm study showed that TENS delivered at acupuncture points by a licensed technician reduced CIPN-related numbness.[47] Another single-arm study showed that scrambler therapy, a type of TENS treatment that delivers 16 different waveforms of stimulation, reduced CIPN symptoms.[48] While these results are promising, rigorous evaluation of TENS for CIPN requires randomization and blinding. Furthermore, interventions like scrambler therapy involve expensive equipment and travel to a clinic. Our proposed research will evaluate the effects of TENS delivered with a wireless, home-based, patient-managed, economical device that has greater potential for clinical dissemination than interventions that require clinician application.

1.3 Pilot trial of wireless TENS device for CIPN from our group.

We performed a single-site, single-arm pilot study of a wireless TENS device for chronic CIPN.[49] After a baseline screening week to record daily symptoms, the participants were asked either to wear the device for one hour in the morning or one hour in the evening or to wear the device for up to 12 h/day on the continuous setting that alternates between 1h treatment and 1h rest periods. Patient Reported Outcome (PRO) measures were completed at baseline and after 6 weeks, at which time qualitative interviews were performed.

TENS effects on CIPN: Our pilot study (n=26 enrolled, 22 completed and included in Table 1 analyses) showed a significant 10% improvement in CIPN (via CIPN20[61], p=0.006). Individual lower limb symptoms (0–10 numeric rating scales (NRSs)) improved considerably (Table 1). Qualitative interviews supported these symptom improvements and the acceptability of the device (Table 2).

Table 1. TENS effects on CIPN and individual symptoms

	Baseline Mean (SD)	6-week Mean (SD)	P-value	% change
EORTC-CIPN20	40.0 (8.6)	36.0 (10.5)	0.006	-10%
Shooting pain	4.0 (3.3)	2.7 (3.0)	0.015	-33%
Hot-burning pain	3.1 (3.4)	1.5 (2.3)	0.03	-52%
Tingling	5.2 (2.4)	3.9 (2.5)	0.003	-25%
Cramping	3.2 (2.9)	1.8 (1.9)	0.002	-44%
Numbness	5.7 (1.6)	4.3 (1.8)	0.0001	-25%

Table 2. Qualitative feedback – Select quotes

- "It helps with pain, swelling… everything"
- "Cured leg cramps"
- "You can use it at home, work, or on vacation"
- "Band is easier to remember than taking pills"
- "Can take less opiates"
- "Easier to walk barefoot"
- "Nice to not feel like I am walking on sponges"
- "Couldn't feel toes in a pedicure before and now I can feel something in all toes"

Safety: Only one participant had a notable skin reaction, which is the most documented risk of TENS, and this participant wore the device for longer than 12 hours / day against our advice because of his perceived large benefit of the therapy. Three participants developed new abnormal sensations. For two of those

participants the abnormal sensations subsided after they stopped using the device. One subject preferred to continue using the device regardless of the abnormal sensations because of the perceived benefit to her CIPN symptoms.

1.4 Feasibility

A key advantage of conducting this study within the NCORP network is the demonstrated track record of the group in recruiting participants who report moderate CIPN at least 3 months after completion of chemotherapy (based on a previous successful phase III clinical trial). In that trial, 342 cancer survivors were recruited in 19 months (i.e., 18 patients/month) at the top 5 accruing NCORP sites of the URCC Research Base.[50] The proposed study was rated the #1 priority by NCORP site investigators of all the concepts that were presented at both the 2017 and 2018 University of Rochester Cancer Center (URCC) NCORP Research Base annual meetings. Eight NCORP sites have officially committed to recruiting for the study. In terms of this specific study design and intervention, data from our pilot study support feasibility. Seventy-two percent (26/36) of eligible patients received the device. This high enrollment rate, in combination with the recruitment rate in our previous NCORP RCT, suggests that recruitment of at least 13 participants per month (i.e., the recruitment goal for the proposed study) using 8 NCORP sites will be feasible. 22 of 26 (85%) participants completed the 6 weeks of treatment and the PRO assessments. Eighteen (82%) of the participants who completed the first 6 weeks of the study chose to continue wearing the device after the 6-week primary endpoint. Seventy-seven percent of the participants who completed the primary 6-week phase of the study reported that they preferred to wear the device on the continuous setting (mean ~ 8 hours/day) rather than for 2 individual 1 hour sessions. These data suggest that wearing the device on the continuous setting for 5 hours/day (i.e., 3 hours of TENS stimulation in the active group) will be acceptable to most participants. Furthermore, this should provide at least 75% of the stimulation that most participants in the pilot trial received to achieve similar treatment effects. All participants will be given and allowed to keep an active device for free upon completion of the study, further encouraging recruitment and retention.

2. AIMS/OBJECTIVES

2.1 **Primary Aim.** Obtain efficacy estimates of daily TENS on CIPN (European Organisation for Research and Treatment of Cancer-CIPN20 (EORTC-CIPN20)) to inform the design of a phase III confirmatory trial.

2.2 **Secondary Aim 1.** Obtain efficacy estimates of TENS on individual CIPN symptoms (i.e., hot/burning pain, sharp/shooting pain, tingling, numbness, cramping (measured daily via 0 – 10 Numeric Rating Scale (NRS)).

2.3 **Secondary Aim 2.** Evaluate the feasibility of conducting, within the URCC NCORP network, a multisite, modified double-blind RCT of TENS for CIPN with physiologic assessments of descending inhibition (i.e., conditioned pain modulation (CPM) test) by assessing the proportions of (a) screened patients who enroll, (b) randomized participants who adhere to the treatment and complete the primary assessment, and (c) randomized participants who complete the CPM test.

2.4 **Exploratory Aim 1** Investigate the potential effects of TENS on balance, physical function, descending inhibition, lower limb sensation, and anxiety and depression.

2.5 **Exploratory Aim 2** Establish data to support the construct validity of the Treatment-Induced Neuropathy Assessment Scale (TNAS) and CIPN symptom inventory daily diary by comparison to the EORTC-CIPN20, which is the most commonly used measure of CIPN.

3. CHARACTERISTICS OF STUDY POPULATION

3.1 Inclusion Criteria

Participants must:

1. Have completed treatment with a platinum agent, taxane, vinca alkaloid, or bortezomib at least 3 months prior to registration. See Appendix 1 for a list of drugs included in these drug classes.
2. Have a clinical diagnosis of CIPN from their physician or physician designee based on the following criteria: bilateral (i.e., present on both sides of the body), abnormal sensory symptoms in their feet or legs (e.g., hot/burning pain, sharp/shooting pain, numbness, tingling, cramping).
3. Report at least 1 non-painful symptom associated with CIPN in their lower limbs (e.g., tingling, burning that isn't reported as painful, numbness)
4. Report at least 2 of the following symptoms in their lower limbs (at their worst) as at least 4 out of 10 on a 0 – 10 NRS: hot/burning pain, sharp/shooting pain, numbness, tingling, cramping at Visit 1 (i.e., Week -1). Use the CIPN Symptom Inventory – Week Recall form (questions 1-5 ONLY) to assess these symptoms at screening.
5. Be willing and able not to start any new analgesic medications or change the dosages of any current analgesic medications (except acetaminophen (Tylenol) or NSAIDs (i.e., ibuprofen (Advil, Motrin), Naproxen (Aleve)) for the duration of the study.
6. Be able to read English (i.e., is not illiterate, can speak English, and is not blind).
7. Be at least 18 years of age.
8. Have access to a smart phone or device with an Apple or Android operating system that can be used to access the TENS device's App and ability to connect to the internet on a daily basis during the trial.

3.2 Exclusion Criteria

Participants must not:

1. Have pre-existing neuropathy of any cause documented in their medical record prior to the start of chemotherapy or respond "yes" to the question "Did you have frequent numbness, tingling, sharp/shooting pain, hot/burning pain, or cramping in your feet before you started your chemotherapy?"
2. Have unilateral CIPN symptoms (i.e., symptoms occur on predominantly only one side of the body).
3. Be currently using a TENS device for any other reason.
4. Be currently taking, or have taken in the past 3 months, medications known to cause neuropathy in a significant portion of patients (list of excluded drugs provided in Appendix 2).
5. Have an acute and symptomatic lower extremity DVT (treated DVT with resolution of symptoms is acceptable for enrollment).
6. Lower extremity edema that is 2+ or greater (i.e., slight indentation that takes less than 15 seconds to rebound).
7. Have started a new prescription pain medication or altered dosages of a prescription pain medication within the last 2 weeks.
8. Have lower extremity wounds or ulcers.
9. Have a cardiac pace maker or defibrillator.
10. Have epilepsy.
11. Have a leg that is too small or too large for the TENS device to fit securely.
12. Have missing lower limbs or amputations.
13. Have impaired decision making capacity (i.e., requires a legally authorized representative or health care proxy).
14. Be pregnant or planning to get pregnant before expected completion of the study.
15. Participate in another clinical trial for CIPN.

3.3 Source of Study Participants

a. Participants will be recruited at 8 NCORPs within the URCC Research Base network

b. Eligible participants will be aged 18 or older because the TENS device is not approved for children

Table 3. Planned Enrollment Table

Racial Categories	Not Hispanic or Latina: Female	Not Hispanic or Latino: Male	Hispanic or Latina: Female	Hispanic or Latino: Male	Total
American Indian/Alaska Native	0	0	0	0	0
Asian	6	2	0	0	8
Native Hawaiian or Other Pacific Islander	1	0	0	0	1
Black or African American	10	6	2	0	18
White	83	34	2	1	120
More Than One Race	1	1	1	0	3
Total	101	43	5	1	150

3.4 Patient Identification, Eligibility Screening, and Recruitment

Patient Identification. Potential participants will be identified in a HIPAA-compliant manner by research staff through review of scheduled outpatient appointments or chart review with clinicians (e.g., medical oncologists or nurse practitioners). Informational flyers will also be used to facilitate recruitment. In order to document reasons for ineligibility or refusal, a screening log will be completed for patients who are approached, but do not consent. This form will not collect any identifiable information or demographics unrelated to reasons for ineligibility. This information is critical to inform design of a future phase III trial.

Consent Process. Patients who meet all eligibility criteria will be provided with a copy of the CIRB-approved informed consent document to review. The investigator/investigator's designee will explain all aspects of the study in lay language and answer all questions regarding the study. Key elements of the informed consent procedure that will be explained to all participants are: 1) the fact that the study is research; 2) the prospect of potential skin irritation and new, likely reversible, abnormal sensations in their lower limbs; 3) the lack of guarantee of benefit from participation; 4) the confidentiality of the participant's responses; 5) the voluntary nature of the study; and 6) the freedom to withdraw from the study or to refuse to answer specific questions or perform specific tests at any time. If the patient decides to participate in the study, he or she will be asked to sign and date the informed consent document. All consented participants will be provided with a copy of the signed consent form.

4. REGISTRATION

4.1 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff

requiring write access to OPEN, Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes 5 person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

Table 4. RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI, consenting/treating/drug shipment receiver, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance). Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

4.2.1 IRB Approval

Because this is an NCI CIRB-approved study and all NCORPs are participating in CIRB, the NCORPs are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. IRB approval information is received from the CIRB and applied to the Regulatory Support System (RSS) in an automated process.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

4.3 Requirements for Submitting Regulatory Documents to the URCC Research Base

Submit your CIRB-approved Annual Signatory Institution Worksheet, Annual Principal Investigator Worksheet and your Informed Consent Documents to URCC_Regulatory@urmc.rochester.edu for the URCC Research Base study records.

4.4 Coordinator requirements

Up to 10 NCORPs will be allowed to participate in the study; participating NCORPs will be determined by the PI, Dr. Gewandter, based on their interest and demonstrated ability to open the study at their sites. If at all possible, each site should have 2 coordinators available to participate in the study. One will be blinded to the treatment assignment (i.e., "assessor") and will perform all of the assessments and the other will know the treatment assignment (i.e., "unblinded coordinator") and will introduce the study to the participant, teach them how to use the TENS device, and answer any phone calls regarding trouble shooting of the device. If it is not possible for the site to have 2 coordinators dedicated to the study, a single coordinator can perform all of the study activities as long as they complete both trainings. The fact that there is one coordinator should be documented so that the potential effect of the lack of blinding on the outcomes can be assessed. If only one coordinator is available at a site, all places in the remainder of the protocol that refer to the "blinded" or "unblinded" coordinator should be interpreted as the "coordinator" for that site. Sites who only have one coordinator available must obtain permission from the study PI to use a single coordinator for both roles. Permission can be requested by emailing the study mailbox at URCC_19085@urmc.rochester.edu.

4.4.1 Training for assessor

The assessor will be trained to support reliable implementation of the conditioned pain modulation (CPM) test, short physical performance battery – balance subscale, and lower limb sensation test using a combination of webinars, pre-recorded videos, in person meetings, or written materials. Each coordinator will be required to perform each evaluation on a mock participant with the Study Chair or Study Chair's designee watching (in person or via video conferencing or via previously recorded videos submitted to the Research Base) in order to ensure correct implementation. The CPM test training may also involve evaluation of the consistency at which the coordinator increases the pressure using data from the device. These processes may be repeated at the Study Chair's request depending on performance. Once the Study Chair is satisfied with the coordinator's implementation, the coordinator will be certified to act as the blinded coordinator for the study. Ideally, the same assessor will perform the baseline and endpoint assessments for an individual participant.

4.4.2 Training for the unblinded coordinator

The unblinded coordinator will be trained using a combination of webinars, pre-recorded videos, in person meetings, or written materials to use a standardized script to support consistent introduction of the TENS device to the participant and to implement calibration of the TENS device. They will also be trained on how to create a Quell health App account using a de-identified Study Email for each participant. Each coordinator will be required to perform these processes on a mock participant with the Study Chair or Study Chair's designee watching (in person or via video conferencing or via previously recorded videos submitted to the Research Base) in order to ensure correct implementation. This process may be repeated at the Study Chair's request depending on performance. Once the Study Chair is satisfied with the coordinator's implementation, the coordinator will be certified to act as the unblinded coordinator for the study.

Participating coordinators/staff will be trained to screen, consent, and enroll patients prior to beginning the study. These activities can be performed by staff members other than the assessor and unblinded coordinator.

4.5 Enrolling Participants

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a

DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

The following additional information will be requested:

a. Name of the unblinded coordinator
b. Name of assessor

An email confirmation of registration will be forwarded.

5. RESEARCH PROTOCOL/STUDY PROCEDURES

5.1 Protocol Equipment Shipping Distribution

Upon receipt of the NCORP's IRB approval for this study, and upon request from the NCORP, the Research Base will ship a study start-up package. This request should be made through the study mailbox (i.e., *URCC_19085@urmc.rochester.edu*). The start-up package will contain 1 conditioned pain modulation (CPM) test kit, 1 monofilament set, and 4 alternative size elastic bands for use with the TENS device. The CPM test kit will include a pressure algometer and test materials.

Each NCORP site will designate a research staff member to be responsible for receiving the study start-up package. The staff member will verify that the shipment contains all supplies and that the supplies are in good condition. They will verify and record the identification numbers for accuracy. The Investigational Device Accountability Record (DARF) will be used to track supplies arriving from the URCC NCORP Research Base and CPM kits and monofilament sets shipped back to the URCC NCORP Research Base at the end of the study.

5.2 Study Device

TENS is listed as nonsignificant risk in the 2006 FDA's "Significant Risk and Nonsignificant Risk Medical Devices" Guidance. [51] The device that will be used in the study has been cleared by the FDA under K152954. It is currently legally marketed in the U.S. for the relief of chronic pain. Therefore, no IDE is necessary for this study. The device is a wireless transcutaneous electric nerve stimulation (TENS) device that emits a high frequency (i.e., 60–100 Hz) stimulation (waveform is biphasic with alternating leading phase). The device is controlled by an App that is available on Apple and Android devices. The device alternates between a 1 hour treatment period and 1 hour rest period on the continuous setting. Participants will be asked to wear the device for 5 hours per day on the continuous setting every day for 6 weeks. They will be asked to alternate the leg they wear it on each day in order to minimize potential skin reactions.

The active device emits electrical stimulation for the entire 1 hour treatment period, resulting in 3 hours of

total stimulation in 5 hours of wear. The dosing of the active arm was increased from the minimum dosage in our pilot study to maximize the amount of TENS stimulation since longer duration of stimulation has been linked to larger effect.[52] Additionally, the company that manufactures the device encourages individuals to use the device for at least 3 sessions per day based on the usage data and pain relief results that they have collected from their App data. This prescription is likely acceptable to participants based on participant feedback from our pilot (see **Feasibility section 1.4**). The unblinded research coordinator will walk the participants through the device's calibration process, which sets the intensity at 1.8 times the participant's sensation threshold. Participants in the active group will then be instructed to increase the intensity of the stimulation to the point that it is slightly below the intensity that is uncomfortable. The device will then remember the personalized intensity setting established at this initial visit for subsequent treatment sessions. However, participants will be allowed to control the intensity of the stimulation using the App throughout the study. The strategy of asking participants in the active group to increase the intensity until the stimulation is as strong as possible without being uncomfortable is based on previous research indicating that the strongest tolerable stimulation is the most effective.[28]

The identical looking placebo device emits 2 minutes of stimulation with a 30 second ramp down of intensity followed 57.5 minutes of no stimulation in the treatment session, which results in 7.5 minutes of stimulation in 5 hours. The placebo dose is designed to minimize TENS exposure but enhance blinding. We have shown that a brief stimulation provided by a placebo device blinds participants better than a device with no stimulation.[53] Participants in the placebo group will not be prompted to increase the stimulation until it is strong but comfortable because the stimulation will not continue sufficiently long after the calibration process to do so.

5.3 Schedule of study procedures

5.3.1 Screening / Consent Visit (Day -7; -2/+3 days) (approximately 1 hour)

Eligible participants who provide informed consent will be registered and given the daily diary of CIPN symptoms and rescue pain medication consumption, and trained on how to complete it at home during the Baseline Week (i.e., between the Screening and Baseline Visits). They will complete the CPM test and lower limb sensation test. Chemotherapy treatment notes will be collected for all consented participants.

5.3.2 Reminder phone call (Day -2: -1/+1 business day)

A research staff member will call the participant to remind them of the date of their Baseline Visit and to bring the completed forms with them.

5.3.3 Baseline Visit (Day 0) (approximately 1 hour)

All participants will be randomized according to procedures in **Section 5.3.4** after they arrive for the baseline visit. They will complete the PROs, balance tests, CPM test, and lower limb sensation test. At this time the participants will be given the TENS device (see **Section 5.2** for details of the device) and sufficient electrodes for 6 weeks of the study. They will be trained on how to use the TENS device. Using a standardized script to limit variation in expectations, the unblinded coordinator will lead all participants through the calibration process to identify their ideal intensity setting. The unblinded coordinator will train the participants on how to use the device at home. The unblinded coordinator will also download the Quell Health Account App to the participant's smartphone or other device (e.g., iPad) and create a Quell Health Account using a de-identified Study Email for the participant. The Study Email will be NCORP19085xxx[xxx=*participant ID number]*@mail.com.
The coordinator will then train the participant to use the App to start the TENS therapy and to open the App at least 1x per day when their mobile device or tablet is connected to the internet so that their de-identified usage data will be uploaded to the cloud. Participants will be asked not to modify settings in the

App other than the intensity on the main screen for the 6 weeks of the study. The usage data (i.e., number of sessions per day, time the device is on the skin, and the intensity of the last session that occurred before connecting the device to the internet) will be downloaded from the Quell Health Account by the TENS device manufacturer and provided to the research team for use in promoting adherence (see **Section 5.3.7 Phone calls**). The participants will be given a daily diary to complete during Weeks 4 (i.e., day 21 – 28) and 6 (i.e., day 35 – 42) in which they will record their daily symptoms and rescue pain medication consumption.

5.3.4 Randomization/Stratification

A computer-generated randomization schedule will be used to randomize participants 1:1 to the two intervention conditions stratified by study site in random block sizes of 2 and 4. The schedule will be prepared by a URCC NCORP Research Base biostatistician. The coordinator will use the Randomization form in REDCap to obtain the randomization assignment at the Baseline Visit.

The two study arms are as follows:

a. Active TENS Device
b. Placebo TENS Device

A total enrollment of 150 participants is planned, with up to 75 participants randomized to each intervention group. Note, that participants who discontinue prior to randomization (i.e., between the screening and baseline visits) will not be replaced. It should take approximately 12 months to accrue all participants.

Table 5. Schedule of Events*

Week	Screening And Registration	Randomization	Distribution of Study Device	Self-Report Measures	Functional Exam Measures	Coordinator open participant Quell App	Adverse Event Monitoring
Screening (Visit 1)	X						
Baseline (Visit 2)		X	X	X	X		
1							X
2							
3							X
4							
5							X
6 (Visit 3)				X	X	X	X

*Daily diary completed between screening and baseline visit and during Weeks 4 (i.e., day 21 – 28) and 6 (i.e., day 35 – 42). Participants will be called 4 weeks after the end of the study (i.e., Week 10) and asked if they are using the commercial device).

5.3.5 Blinding

The active and placebo devices will look identical, light up in the same manner, and have identical packaging. We have shown that a brief stimulation provided by a placebo device blinds participants better than a device with no stimulation.[53] Participants and the research coordinators who implement the assessments (i.e., the blinded coordinator or assessor) will be blinded to the treatment assignment. An unblinded coordinator will teach the participants to use the device, following an almost identical script for both treatment groups. The script will convey that some people feel the TENS sensation more than others and sometimes the sensations fade over the duration of a treatment session. There will be 2 additions to the script for the active group. First, a section asking the participants to increase the stimulation after the initial device calibration until it first feels uncomfortable and then turn the intensity down one click (i.e., 5%

of the stimulation strength) in order to obtain the optimal "strong but comfortable" stimulation intensity. Note, that this will not be done in the placebo group because the stimulation will not continue sufficiently long after the calibration process for this to happen. Second, a sentence suggesting that the active group may increase the intensity manually during the treatment sessions if desired. The unblinded coordinator will be available to troubleshoot difficulties with the device throughout the study. This modified double-blind design will maintain a blinded outcomes assessor by having an unblinded coordinator who can respond to participants' questions that could reveal the participants' group assignments. The participants will be instructed not to discuss any aspect of the TENS device with the blinded coordinator or other participants in the study. The coordinators will be instructed not to discuss the details of the placebo device with the participants. The unblinded coordinator and the assessor will be instructed not to discuss details of study participants with each other. Blinding success will be assessed (see measures).

5.3.6 At home procedures (Days 21-28; 35-42)

Participants will complete a daily diary including the CIPN Symptom Inventory and consumed rescue analgesic medication (i.e., acetaminophen (Tylenol) or NSAIDs). They will be asked to complete it before bedtime when they are not wearing the device during weeks 4 and 6.

5.3.7 Study Phone Calls (Days 7, 21, 35; (up to + 3 working days)

At each phone call, the unblinded coordinator will assess adverse events (AEs) (see complete description of AE assessment in **Section 8**), troubleshoot adherence problems, remind participants to complete their Daily Diaries (Days 21 and 35 only), and answer participants' questions. It is important that phone calls are made only by the unblinded coordinator because participants' questions or concerns could lead to unblinding of the assessor. To facilitate targeted adherence optimization, participants' device usage data from the Device App will be monitored during the study and provided to the unblinded coordinator. Each participant's device usage data will be downloaded from their de-identified Quell health account by the staff at Neurometrix and provided to the Research Base prior to the Day 7, 21, and 35 phone calls. The Quell health account data will be identified by the unique Study Email (i.e., NCORP19085*xxx[xxx=participant ID number]*@mail.com) used to establish the account and will not identify the participants. The Research Base staff will summarize the data in a report for each participant prior to the Day 7, 21, and 35 phone calls. These reports will be provided to the unblinded NCORP site coordinator at least 1 day prior to the day of the scheduled phone call. If a participant is not using the device as prescribed, the unblinded coordinator will enquire about any problems that the participant is having with the device and help to troubleshoot those problems. They will also encourage adherence to the treatment protocol. During the Day 35 phone call, the unblinded coordinator will also remind the participant of the date and time of the 3rd study visit (i.e., Week 6 visit).

5.3.8 End of Study Visit (Day 42; +/- 5 days) (approximately 1 hour and 15 minutes)

All participants will complete the patient-reported outcome measures, balance tests, conditioned pain modulation test, and lower limb sensation test. The coordinator will also review the list of medications that the participant reported using for CIPN at the beginning of the study and ask the participant if they changed dosages of any of the medications. Any changes will be recorded in the Changes in concomitant analgesic medications form. The coordinator will ask the participant for their device and open the Quell App to ensure final data transfer to the cloud. The data will then be downloaded by the device manufacturer and sent to the Research Base. If the participant does not come to the Week 6 visit, the coordinator will call them up to 3 times to try to reschedule the visit. The rescheduled visit can occur up to 1 month after the date of the 6-week visit. If the participant refuses rescheduling, the coordinator will ask them why they are discontinuing the study. If the participant agrees to come back in, they will be encouraged to keep using the device until the rescheduled visit date.

5.3.9. Follow-up phone call (Day 70 +/-5 days)

Coordinators will call participants and ask them whether they are using the commercial device.

5.4 Study Measures

The effects of the TENS intervention on CIPN symptoms and related functioning will be measured using patient-reported outcome (PRO) measures and functional assessments (see complete list below).

Demographic and Clinical Information. Demographic information will be obtained from all participants through the use of a standardized self-report questionnaire (i.e., **On Study** form). Variables to be assessed include age, height, weight, race, ethnicity, education, current work status, and occupation. Participants will also be asked to list all medications and treatments previously or currently used to treat their CIPN. Participants will also be asked if they have diabetes, edema, and commonly overlapping pain conditions, whether they drink alcohol, and if so, how much they consume weekly. Finally, they will be asked to rank how distressing typical CIPN symptoms are for them. The following clinical variables will be assessed via medical record review for all participants and recorded on the **Clinical record information form**: "neurotoxic cancer therapy (i.e., platinum, taxane, vinca alkaloid, bortezomib) (class, agent, date of last dose), type of non-study related chemotherapies, cancer diagnosis for which participant received the neurotoxic cancer therapy, history of chemotherapy other than study related chemotherapy (Yes/No and date of last dose), history of radiotherapy (past/current/No and date of last treatment), history of hormonal therapy (past/current/No and date of last dose)", history of diabetes (Y/N), history of alcoholism (Y/N), history of common overlapping pain conditions, current edema, and current medications that could affect CIPN.

<u>Patient Reported Outcome Measures</u>

CIPN will be evaluated in 3 ways in this learning phase study. The purpose of measuring CIPN in 3 ways is to identify the best measure to use as a primary outcome measure in a confirmatory trial. The European Organisation for Research and Treatment of Cancer-CIPN20 (EORTC-CIPN20) is one of the most commonly used measures of CIPN (i.e., legacy measure), however, it includes items that are focused only on the upper extremities that may not change in response to TENS administered on the lower limb as well as items that may not be highly specific to CIPN. The Treatment-Induced Neuropathy Assessment Scale **(**TNAS) is a relatively newer measure that has less data supporting its psychometric properties, but has well established content validity and does not include questions that are focused only on the upper limbs. Finally, the CIPN symptom inventory includes similar items to the 2 validated measures, but focuses solely on the lower limbs and sensory symptoms that we hypothesize will be modified by TENS. In addition, by administering it in a daily diary and averaging the ratings over 1 week at baseline and endpoint, as is the current practice in most chronic pain trials, variability in CIPN symptoms may be minimized, therefore increasing the assay sensitivity (i.e., ability of the measure to detect a true treatment effect) of the outcome measure. By including all 3 measures we will contribute to the validation of the newer measures and hopefully identify the measure that has the best assay sensitivity for measuring CIPN in the lower limbs. See below for further description of each measure.

(1) European Organisation for Research and Treatment of Cancer-CIPN20 (EORTC-CIPN20). The primary study outcome is CIPN as measured by the EORTC-CIPN-20.[54] The EORTC-CIPN20 includes items that assess CIPN-related symptoms and functional interference in daily activities. Multiple studies support the content and construct validity of the EORTC-CIPN20 [55-57] and it was identified as the best available PRO for CIPN at the NCI CIPN planning meeting.[14] **(20-items)**

(2) CIPN Symptom Inventory. Individual CIPN symptoms will be evaluated using weekly averages of daily diary 0 –10 NRS scores [0 = no symptoms, 10= worst symptom imaginable] of sensory symptoms

including hot/burning pain, sharp/shooting pain, tingling, cramping, and numbness (**Daily Diary**). The participant will also be asked to rate these symptoms, while thinking about the past week at each visit (**CIPN Symptom Inventory – week recall**). NRS scores and their composites are frequently used to assess symptoms in cancer and pain patients (e.g., MD Anderson Symptom Inventory [58]). Furthermore, the daily diary of a single-item 0–10 NRS for pain intensity is commonly used as the basis for approval of chronic pain medications by the FDA.[59] The symptom diaries will instruct the participants to focus on the symptoms in their lower limbs and perform ratings in the evening before bed while considering the past day. Based on our preliminary data, a composite measure of these symptoms in the lower limbs may be particularly responsive to the TENS intervention. Our pilot data also indicate that the outcome that is based on the average of the weekly symptom ratings has considerably less variability than the single day ratings (i.e., standard deviation of 4.6 vs 5.7) and could significantly decrease the sample size requirement of a future trial. **(5 items)**

(3) Treatment-Induced Neuropathy Assessment Scale (TNAS). The TNAS is a PRO that assesses symptoms and functional interference from CIPN in 2 separate domains. It was developed and refined in multiple stages, including interviews with patients and clinicians to develop content valid items, and cognitive debriefing to assess the understandability of the items. It has acceptable reliability and sensitivity to change.[60, 61] **(9 items)**

CIPN interference. CIPN interference in general activity, mood, walking, normal work, relationships, sleep, and enjoyment of life will be measured using the **CIPN Interference Questionnaire,** which uses 0 – 10 NRSs [0 = does not interfere, 10 = completely interferes] adapted from the Brief Pain Inventory (BPI). [62] The BPI is a well-established measure used to assess chronic pain in clinical trials and clinically. **(7 items)**

Depression and anxiety. Depression will be measured using the PROMIS-Depression Short Form 8A (**PROMIS 1**). Anxiety will be measured using the PROMIS-Anxiety Short Form 7A (**PROMIS 2**). PROMIS is a set of person-centered measures that evaluates physical, mental, and social health in the general population and those living with chronic conditions. The measures were developed with NIH funding using state of the art psychometric techniques and include brief measures that aim to maximize precision and brevity. [63] The Depression and Anxiety Short Forms have acceptable reliability and validity in several disease contexts. [64-67] In particular, they have demonstrated internal consistency, convergent validity with legacy measures, and sensitivity to change in a sample of cancer patients.[68] **(15 items)**

Physical function. Physical function will be measured using the PROMIS-Physical Function Short Form 8b (**PROMIS 3**). In a large study of multiple clinical conditions, the PROMIS Physical Function measure was sensitive to change from interventions that would be accepted to improve physical function and was able to distinguish between groups of patients with different degrees of physical limitation. [69] In a cohort of almost 5000 cancer patients, multiple PROMIS Physical Function Short Forms showed high internal consistency and good convergent and discriminant validity.[70] **(8 items)**

Single-Item Questions

(1) **Participant expectation questionnaire.** Participant expectation regarding the likelihood of TENS helping their CIPN will be assessed using a 1 – 5 likert-type scale. The question will be phrased as follows: “How likely do you think it is that a TENS device can improve your neuropathy symptoms?” [1= Not at all Likely, 3 = Somewhat Likely, 5= Very Likely].

(2) **Overall impression of change in neuropathy.** Impression of change in neuropathy symptoms will be measured using a single question (i.e., **General Impression of Neuropathy** form) that utilizes a 1 – 7 scale adapted from the patient global impression of change (PGIC). [71] The PGIC is commonly used in chronic pain trials to assess patient’s experience of the change this beginning a treatment or clinical trial.[72]

(3) **Overall 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 patient global impression of change.[71] The PGIC is commonly used in chronic pain trials to assess patient's experience of the change this beginning a treatment or clinical trial.[72]

(4) **Blinding** will be assessed using the **Blinding Questionnaire** at the Week 6 visit by asking participants and blinded coordinators to guess which device the participant received and the basis for that guess (i.e., for participants, symptom relief vs. feel of the stimulation).

(5) **Changes in concomitant medications.** Participants will be asked if they changed any of their pain medications (other than acetaminophen or NSAIDs) throughout the study. This information will be captured on the **Changes in concomitant analgesic medications** form.

Functional Exam-Based Outcomes

Balance. Balance will be measured using the balance subscale of the Short Physical Performance Battery (SPPB). The SPPB has been used in multiple studies of cancer patients.[73-75] The SPPB balance subscale is a composite measure of timed feet together, semi-tandem, and tandem foot stands.[76] Results will be recorded in the **SPPB data collection form**

Descending inhibition. Descending inhibition will be evaluated using a Conditioned Pain Modulation (CPM) test. The CPM test is a common test used in chronic pain studies in a wide variety of patient types, including those with CIPN, [27] diabetic neuropathy, [77] osteoarthritis, [78] fibromyalgia, [79] irritable bowel syndrome, [80] carpel tunnel syndrome, [81] and low back pain. [82] The CPM tests includes 2 temporary pain stimuli, a test stimulus that is administered before and after a conditioning stimulus. The difference in the result of the test stimulus before and after the conditioning stimulus is indicative of the efficiency of the participant's descending inhibitory pathways. The CPM test has demonstrated ability to distinguish between groups as expected [83] and intra-session reliability.[84] In this case the test stimulus will be pressure and the conditioning stimulus will be brief (up to approximately 30 sec -1 minute) immersion in cold water. Specifically, the participant's pressure pain threshold (PPT) (i.e., the point at which a pressure stimulus ***first*** becomes painful) is measured on the trapezius muscle 3 times (i.e., the test stimulus). Subsequently the participant is asked to immerse their right hand in ice water (~4°C) for 15 seconds (i.e., the conditioning stimulus), at which point they will be asked to rate the pain in their hand and then 3 subsequent pressure pain threshold measures will be taken on the trapezius muscle while the hand is held in the water. Participants will be told that they may remove their hand from the cold water before the 15 seconds has elapsed if it is too painful for them. If they remove their hand prior to the 15 seconds the post conditioning stimulus PPT measurements will be taken at that time. The temperature of the water will be monitored for consistency and to ensure it does not go below 4°C. Results will be recorded in the **CPM data collection form**.

Lower-limb sensation threshold. Lower limb sensation will be evaluated using a monofilament test threshold test. In the monofilament test, the participants are asked to close their eyes while each monofilament is applied (or not) to the dorsum of the big toe in random order 10 times (i.e., trials). With each trial, the participant is asked to state whether they think the filament touch their skin. For each set of 10 trials with a single monofilament, if the participant guesses correctly ≥ 9 times the next weaker monofilament is used. If the participant guesses correctly 7 or 8 times this filament is documented as the participant's sensation threshold. If the participant guesses correctly ≤ 6 times the next stronger filament is trialed. The participant's sensation threshold is the outcome of the test. Results will be recorded on the Scoring Sheet for the Lower Limb Sensation test and then entered in REDCap in the **Lower-limb sensation threshold data collection form**.

Feasibility Outcomes

Proportion of screened participants who enroll in the study will be extracted from study records.

Outcome measure completion rates for PROs, balance measures, CPM tests, lower limb sensation test, and Quell Health App usage will be extracted from study records. The proportion of total instances that each outcome was completed appropriately in the baseline and endpoint visits will be evaluated.

Treatment adherence will be evaluated using data downloaded from the TENS device after the Week 6 Visit (i.e., the number of treatment sessions/day and the time that the device was in contact with the skin). The following summaries regarding adherence will be explored: (1) The mean number of study days that each participant used the device for at least the amount of time prescribed based on data downloaded from the device, (2) the proportion of participants who used the device for at least 5 hours per day on at least 70% of the days based on data downloaded from the device.

Potential reasons for low treatment adherence will be captured using a **Qualitative Feedback Questionnaire**.

Reasons for ineligibility or refusal to enroll captured on the **Screening log** will be evaluated to determine if changes in the study design could greatly improve recruitment rates of a future study.

5.5 Potential Risks

There are four potential risks associated with participation in the study

(1) Physical harm associated with the intervention. There is a small risk of skin irritation at the site where the electrodes attach the TENS device to the skin. In addition, 3 of 26 participants in our pilot study reported mild worsening of neuropathy symptoms or new, abnormal sensations after starting the TENS device. Although it is unknown whether these symptoms were a physiological or psychosomatic consequence of the TENS treatment, all symptoms disappeared after stopping the TENS treatment for 2 participants. One participant felt that the new sensations were acceptable considering the perceived benefits of the TENS treatment and decided to continue using the TENS device.

(2) Physical harm associated with the assessments. The conditioned pain modulation test involves evoking pain using pressure from an algometer and temporary immersion in cold water. These pains are temporary.

(3) Emotional distress. The assessments explore participants' feelings regarding their CIPN symptoms and associated functioning. Some participants may become distressed when they think about these topics.

(4) Loss of confidentiality. Participants' data from assessments and clinical factors extracted from the medical record will need to be stored. A small chance exists that a confidentiality breech will result in participants' sensitive health information being made available to parties outside the research team. However, participants' names and contact information will be kept separately from the study data to minimize the chance of loss of confidentiality. If information from this study is published or presented at scientific meetings, participants' names and other personal information will not be used.

5.6 Emergency Study Device Disclosure

Unblinding of the study device is ONLY permitted in the case of serious and unexpected adverse events that are definitely, probably or possibly associated with the use of the study device AND if knowledge of

the study treatment arm received is necessary for interpreting the medical event and related treatment of that medical event. In such cases, the treating MD or their designee can be given the treatment group assignment from the unblinded coordinator. This event needs to be documented and the IRB notified within seven days. Documentation should be sent to the email address below and include participant ID number, site investigator, and reason for unblinding in the message:

Linda Spath
linda_spath@urmc.rochester.edu
585-275-1364

Participants that require emergency study device disclosure will discontinue use of the study device. The research team may continue to follow the study participant for assessment data with participant and treating provider approval.

5.7 Costs to the Participant

If participants do not have a data plan on their cellular phone or device, they will incur data charges associated with using the App and transferring the data to the cloud if they are not connected to a Wi-Fi source. If participants do have a data plan, it is very unlikely that they will incur extra charges for data usage because the approximate amount of data used by the App if it is opened 5 times per day is 2.5Mb, which is a fraction of the minimally available cellular data plan (i.e., 1GB) and home internet service plans (i.e., 1000GB).

5.8 Payment for Participation

Participants will not receive payment for the study. However, all participants will receive, for free, an active TENS device after completion of the study that they can keep after the end of the study.

5.9 Contraindications

With the exception of entry criteria listed in **Section 3**, there are no restrictions on who can safely use TENS. Participants should not get the TENS device wet and therefore should not, for example, wear it in the shower or when swimming. In addition, the TENS device should not be worn continuously for more than 12 hours to minimize potential skin irritation. Finally, the TENS device should not be used while driving.

5.10 Concomitant Medications

There are no limitations on concomitant medications taken at stable dosages (see eligibility criteria in **Section 3.2**).

5.11 Adherence

Treatment adherence will be monitored during the study using data downloaded from each participant's Quell Health Account. The Quell Health Account will be set up at the baseline visit using a de-identified, unique Study Email address created for the study to protect participants' privacy. These data will be used to provide real-time feedback to participants and in turn hopefully optimize adherence. Treatment adherence will be evaluated as an outcome of the study using data downloaded after the Week 6 Visit when the coordinator links the App (i.e., the number of treatment sessions/day and the time that the device was in contact with the skin).

6. STUDY DEVICE DISTRIBUTION

6.1 Availability

Active and placebo TENS devices will be supplied by the URCC NCORP Research Base.

6.2 Distribution

The active and placebo TENS devices will be supplied by the URCC Research Base. Each device includes a package of 2 electrodes. A second package of 2 electrodes will be sent with each device. Four electrodes should last approximately 8 weeks (2 weeks each). Extra electrodes can be requested from the Research Base if necessary. Devices will only be released to URCC NCORP Research Base affiliates approved to participate. Upon approval to participate, 1 active and 1 placebo device will be shipped to each site. Once a device is distributed to a participant, the site Investigator, or their authorized designee should request a replacement device be shipped to their site so that each site has 1 active and 1 placebo device in stock at all times. If more than 1 participant is enrolled on the study and both participants are completing the baseline week at the same time, the site Investigator or designee can request a second pair of devices to ensure that the correct device will be available for the participant at the Baseline visit. Devices are requested by emailing the URCC NCORP Research Base and should include complete shipping and contact information and device group (i.e., orange or blue dot sticker). All TENS devices used by participants during the study will be returned to the URCC NCORP Research Base within 3 months of completion of the 6 Week Visit.

Alexandra O'Connell
URCC_19085@URMC.Rochester.edu
585-275-1067

6.3 Device Accountability

The NCORP site, and responsible party designated at the site, must maintain a careful record of the inventory and disposition of all devices and packets of electrodes received from the URCC NCORP Research Base using the Investigational Device Accountability Record. All receipt and dispensation of study devices should be recorded, including date, participant ID# and initials, serial number from the back of the device, and blinded device label. All unused devices will be returned to URCC at the end of the study.

6.4 Packaging and Labeling

Neurometrix will provide to the Research Base the devices in identical packaging with a key that will identify the active and placebo devices via the serial numbers that Linda Spath (linda_spath@urmc.rochester.edu) will have access to. URCC Research Base staff will apply the coded labels (i.e., orange or blue dot stickers). Neither the Study Chair, Co-chairs, nor statisticians will have access to the label key so they will remain blinded until after the primary and secondary analyses are completed.

6.5 Storage

The devices will be stored at room temperature. Study devices will be stored away from heat and moisture. Study devices will be stored in a secured location that is only accessible by approved study personnel.

7. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

7.1 Primary Endpoint

The primary study endpoint is CIPN as measured by the mean European Organisation for Research and Treatment of Cancer-CIPN20 (EORTC-CIPN20) [54] score after 6 weeks of device use.

7.2 Off-Device Criteria

Participants may stop using the study device for the following reasons: (1) completed the protocol-prescribed intervention, (2) adverse event or serious adverse event, or (3) if they want to for any reason. Participants will continue to be followed, if possible, in order to collect endpoint data according to the schedule of study procedures (see **Section 5.3**).

7.3 Off-Study Criteria

The following are among the reasons that participants may leave the study: (1) the protocol intervention and any protocol-required follow-up period is completed, (2) adverse event/serious adverse event, (3) lost to follow-up, (4) withdrawal of consent, (5) death, (6) determination of ineligibility (including eligibility error), (7) pregnancy, or (8) if they want to for any reason.

8.0 REPORTING ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by federal regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's common terminology criteria for adverse events (CTCAE), version 5.0. The CTCAE is available at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50.

The relationship to the study intervention and the severity of each adverse event as judged by the investigator must be recorded. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms, using the codes provided.

8.1 Definitions

Adverse event (AE) is any untoward medical occurrence associated with the use of a medical product, which does not necessarily have a causal relationship with its use. An adverse event can be any unfavorable and unintended sign (including abnormal laboratory test results), symptom, or disease temporally associated with the use of the study product or not considered related to the study product. The relationship of each adverse event to the study interventions must be recorded as one of the choices on the scale described below.

Table 6. 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

8.2 Serious Adverse Event (SAE).

A serious adverse event is defined as any adverse medical event (experience) that results in at least one of the outcomes listed below:

1. Death
2. Life-threatening
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
4. Results in persistent or significant disability/incapacity with substantial disruption of the ability to conduct normal life functions.
5. Congenital anomaly/birth defect.
6. A medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon medical judgment, it may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Hospitalization (or prolongation of hospitalization). For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.

8.3 Reporting

Adverse events will be assessed by phone in weeks 1, 3, and 5 and at the Week 6 visit. At each participant visit and phone call, the site study staff will assess adverse events by asking participants if they have experienced any new symptoms since starting the experimental treatment. They will ask specifically if any skin reactions have occurred.

All adverse events, whether observed by study staff or investigator, elicited from or volunteered by the participant, should be documented. Each adverse event will include the date of onset, date of resolution, severity, and the relationship to the study device or study procedures, and any action taken with respect to the study device or intervention.

Recording of the adverse events will occur once the participant signs the consent form until the participant goes off study.

Adverse events will be reported to the URCC NCORP Research Base using REDCap, which can be accessed from the URCC NCORP website.

Table 7. Reportable adverse events

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

Serious adverse events requiring expedited reporting via CTEP-AERS are described below in **Section 8.4**. Serious adverse events not requiring expedited reporting through CTEP-AERS should be entered into REDCap and URCC notified within 10 calendar days of learning of the event.

All recorded adverse events reported to the URCC Research Base will be reported to the Data Safety Monitoring Committee.

All adverse events that in the opinion of the investigator are clinically significant will be documented and followed according to good medical practices.

8.4 Responsibilities for Expedited Reporting

URCC NCORP Research Base affiliates are required to notify the URCC Research Base if a participant has an adverse event requiring expedited reporting. All SAEs that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the Adverse Event Expedited Reporting System, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task.

Commercial reporting requirements are provided in the table below. The commercial device used in this study is the Quell TENS Device.

Table 8. Expedited reporting requirements for adverse events experienced by participants who have received study device/intervention within 30 days of the last administration of commercial study device/intervention.

Attribution	Grade 4		Grade 5(a)	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			CTEP-AERS	CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS	CTEP-AERS

CTEP-AERS. Indicates an expedited report is to be submitted via CTEP-AERS within 10 calendar days of learning of the event (b).

1. This includes all deaths within 30 days of the last use of the commercial study device, regardless of attribution. Any death that occurs more than 30 days after the last use of commercial study device and is attributed (possibly, probably or definitely) to the device/intervention and is not due to cancer recurrence must be reported according to the instructions above.
2. Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Research Base in order to complete the evaluation of the event.

For more information see:
https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

Table 9. Contact Information for NCI Safety Reporting:

Website for submitting expedited reports	http://eapps-ctep.nci.nih.gov/ctepaers
AEMD Help Desk (for CTEP)*	301-897-7497 Monday through Friday, 7:00 AM to 7:00 PM (US Eastern Time)
Fax for expedited report supporting Medical Documentation for CTEP Trials	301-230-0159 (Back-up FAX: 301-897-7404)
AEMD Help Email:	aemd@tech-res.com
Technical (e.g., IT or computer issues ONLY) Help Phone *	1-888-283-7457 or 301-840-8202
CTEP-AERS Technical Help Email	ncictephelp@ctep.nci.nih.gov
CTCAE v 5 Help/Questions Email	ncicctcaehelp@mail.nih.gov
CTEP-AERS FAQs link	https://eapps-ctep.nci.nih.gov.ctepaers/help/webhelp/CTEP-AERS%20FAQ.htm
CTEP-AERS Computer based training link	https://ctep.cancer.gov/protocolDevelopment/ electronic_applications/adverse_events.htm

Office phone and fax are accessible 24 hours per day 7 days a week (The AEMD phone line is staffed from Monday through Friday, 7:00 AM to 7:00 PM ET. Any phone call after these hours will go to voicemail. Please leave contact information and the phone call will be returned the following business day.

Follow-up of SAE. Site staff will send follow-up reports as requested when additional information is available. SAEs will be followed until resolved, especially for those related to the commercial study device.

9. STUDY MONITORING

9.1 Data Management Summary

This project will collect data in multiple formats: paper documents and electronic questionnaires (REDCap).

When written, hard-copy (paper) data are received at the URCC NCORP Research Base, they are processed as follows:

1. Data are visually checked line by line for missing, duplicate, ambiguous or unreasonable responses and if found, the originating site is queried for such data.
2. In response to a query, the form is amended per good clinical practice (GCP) the change is documented and the form is re-submitted to the research base.
3. All paper forms are scanned via Teleforms software into tables in an Access database. Again, any missing, duplicate or ambiguous data found at this step generates a query to the originating site.
4. The electronic database tables are visually checked, line by line, against the corresponding forms for accuracy.
5. Queries are also generated if data are not received within 14 days of the assessment.
6. When all data have been received on any given case, a chart audit is performed to ensure receipt and accuracy of all required data.
7. All paper documents are stored in locked file cabinets or in locked, limited access file rooms. The electronic Access databases of those scanned documents are on password protected drives located behind University of Rochester firewalls, with limited access.

Data entered into REDCap are reviewed for accuracy and stored in the University of Rochester secure REDCap database. Queries are generated for any questionable or late data.
On-site audits are conducted at least every three years in accordance with NIH/NCI Clinical Trials Monitoring Branch (CTMB) guidelines. The primary objective of an on-site audit is to document compliance of the NCORP site with protocol and regulatory requirements, verify accuracy of data by comparing submitted data to source documents at the NCORP site, and to provide information on good clinical practices in study conduct and data management. The equivalent of 10% of cases accrued at the site will be audited. All auditing is done as per NIH/NCI CTMB Guidelines.

9.2 Schedule of Data Collection

Table 10. Forms to Be Kept

FORMS	Screening	Baseline	Week 6
Participant Forms (paper)			
On-Study		X	
Expectation Questionnaire		X	
EORTC CIPN20		X	X
Daily Diary (CIPN symptoms / rescue medication usage)*		X	X
CIPN Symptom Inventory – week recall	X	X	X
TNAS		X	X
PROMIS 1		X	X
PROMIS 2		X	X

PROMIS 3		X	X
CIPN Interference Questionnaire		X	X
General Impression of Neuropathy			X
General Impression of Activity			X
Blinding Questionnaire			X
Qualitative Feedback Questionnaire			X
Coordinator Forms (REDCap[1], paper[2])			
Eligibility checklist (Medical Record, Clinician-reported, and Patient-reported items)[1]	X		
Consent form[2]	X		
Clinical record information form[1]	X		
TENS Device Settings form[1]		X	
CPM data collection form[1]	X	X	X
SPPB Balance form[1]		X	X
Lower-limb sensation threshold data collection form[1]	X	X	X
Coordinator blinding question[1]			X
Changes in concomitant analgesic medications form[1]			X
Adverse Event (AE) Form[1]**			X
	Screening log completed for patients who are approached, but not consented Submit chemotherapy treatment notes from participant's medical record at Screening Telephone Contact Sheet to be completed with each phone call		

* Daily diary will be completed during the week between the Screening and Baseline visits (collected at the Baseline Visit) and during Weeks 4 (i.e., day 21 – 28) and 6 (i.e., day 35 – 42) (collected at 6 Week visit).
** Adverse Events are also assessed during Week 1, 3, 5 phone calls

9.3 Data and Safety Monitoring Plan

Data Safety Monitoring Committee. The Director of the URCC delegates responsibility for continued review and monitoring of all clinical trials conducted by the URCC to the James P Wilmot Cancer Center (JPWCC) DSMC. This committee provides oversight of study progress and safety by review of accrual and adverse events at annual (or biannual) meetings. Any adverse event requiring expedited review per protocol will be submitted to the JPWCC DSMC for determination as to whether further action is required. Interim meetings are scheduled, as needed, to address specific issues that require immediate attention to assure participant safety. The DSMC:

1. Reviews assigned clinical trials conducted at the URCC for progress and safety
2. Reviews all adverse events requiring expedited reporting as defined in the protocol
3. Reviews reports generated by the URCC data quality control review process
4. Submits recommendations for corrective actions to the Protocol Review Committee and the Principal Investigator

The DSMC will review study progress and cumulative reports of adverse events either bi-annually or annually (determined by the DSMC). Once the final protocol is submitted to NCI, the protocol will be submitted to the Peer Review Committee for review and frequency of review determined. An overall

assessment of accrual and adverse events will enable the committee members to assess whether significant benefits or risks are occurring that would warrant study closure. Interim meetings are scheduled, as needed, to address specific issues that require immediate attention to assure participant safety

The URCC will notify the NCORP sites immediately of any serious safety concerns identified by the DSMC. DSMC reports will be available for download on the research base website.

In general, outcome data are not made available to individuals outside of the JPWCC DSMC until accrual has been completed and all participants have completed their treatment. At this time, the JPWCC DSMC may approve the release of outcome data on a confidential basis to the trial Principal Investigator for planning the preparation of manuscripts and/or to a small number of other investigators for purposes of planning future trials. Any release of outcome data prior to the JPWCC DSMC's recommendation for general dissemination of results must be reviewed and approved by the JPWCC DSMC.

Safety Coordinator. All adverse events reported to URCC are entered into a REDCap database and can be monitored through automated reports. The Safety Coordinator monitors adverse event rates utilizing this database. If the study has had two or more of the same SAEs reported in a month or more than six of the same SAEs in six months, the DSMC will review the summary of SAEs, discuss events with the Study Chair, and conduct a more detailed review with the Study Chair. The Data Safety Monitoring Chair will determine if further action is required. The Safety Coordinator:

1. Forwards all adverse events requiring expedited reporting to the URCC Data Safety Monitoring Committee Chair who determines if immediate action is required
2. Maintains a database of all adverse events requiring expedited reporting
3. Ensures all reports are available for all meetings of the DSMC
4. Monitors adverse event rates utilizing the study database.

9.4 Record Retention

Clinical records for all participants, including REDCap forms, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with Health Insurance Portability and Accountability Act (HIPAA), Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) regulations and guidelines, and NCI/DCP requirements, unless the standard at the site is more stringent. Records will be retained for at least five years after the date of completion of the research. The records should be accessible for inspection and copying by authorized persons of the Food and Drug Administration.

10. STATISTICAL CONSIDERATIONS

10.1 Quality Control. Established standardized data quality procedures are used for all URCC NCORP Research Base studies. Data will be entered on scannable (Teleforms) or electronic forms in REDCap and electronically transferred to Microsoft Office databases. Data will be inspected visually. Data distributions will be evaluated to identify any outliers that will be inspected for possible mistakes. If no mistake is found for an outlier, it will remain in the data. Statistical analyses will be performed using SAS, JMP, or R as appropriate.

10.2 Analysis set and Missing Data. All participants who are randomized will be included in the analyses. All efforts will be made to prevent missing data. We will use multiple imputation methods that assume missing at random for the primary and secondary analyses. A sensitivity analysis using pattern mixture methodology that assumes missing not at random will be used to evaluate the impact of missingness on the results.[85]

10.3 Sample Size Estimation. Since this is a phase II preliminary efficacy trial, the primary analysis will be performed at the two-tailed 20% significance level (i.e., alpha=0.2).[86] A sample size of 126 evaluable participants will provide 80% power to detect a 0.4 effect size (standardized mean difference) in the primary analysis. Assuming 15% withdrawal, we will randomize 150 participants.

10.4 Primary Analysis. The effects of TENS on CIPN will be estimated using analysis of covariance (ANCOVA). The model will include CIPN20 at Week 6 as the outcome, treatment group as the factor, and study site and the baseline CIPN20 score as covariates. Additionally, to explore potential large impacts of cancer type, chemotherapy class (i.e., platinum, taxane, other), and analgesic consumption (≥30% vs. <30% decrease in number of days acetaminophen and/or NSAIDs were taken), we will add these factors to the above model for sensitivity analyses. We will also perform subgroup analyses separately based on these factors to identify possible differential intervention effects to inform the design of a future study. Distributional assumptions (e.g. normality of residuals) will be evaluated and, if necessary, appropriate transformations or nonparametric methods will be used.

10.5 Secondary Analyses. ANCOVA analyses as in the primary analysis will be used for individual symptoms (i.e., hot/burning and sharp/shooting pain, numbness, tingling, and cramping (0 – 10 NRS)). For each of the symptoms, baseline and Week 6 scores will be calculated as the mean of weekly daily diary scores during the week between Screening and Baseline and Week 6, respectively.

10.6 Exploratory Analyses.
(1) ANCOVA analysis as in the primary will be used to investigate the effects of TENS on exploratory outcomes (i.e., balance (SPPB balance subscale), descending inhibition (CPM test), physical function (PROMIS short form), CIPN-interference in daily life, CIPN measured by TNAS and CIPN symptom inventory composite measure, depression and anxiety (PROMIS short forms)) at baseline and at Week 6 visits.

(2) Analysis of variance (ANOVA) or an appropriate non-parametric method (e.g., Wilcoxon test) if the normality assumption is not satisfied will be used to evaluate the between arm differences in participant-perceived changes in CIPN symptoms and participant-perceived change in ability to be active.

(3) Descriptive statistics will be used to characterize the distribution of descending inhibition as measured by CPM at baseline. Additionally, the correlation of descending inhibition with CIPN severity (via CIPN20, TNAS, and symptom NRS scores) will be evaluated using a Spearman's correlations.

(4) To explore the predictive effects of baseline descending inhibition on response to TENS, ANCOVA analysis will be used to investigate whether baseline descending inhibition predicts the effect of TENS on CIPN. The model will include CIPN20 at Week 6 as the outcome, baseline CPM test result, treatment group, and baseline CPM test result x treatment group interaction as factors, and study site and the baseline CIPN20 score as covariates.

(5) To explore mechanistic associations between changes in descending inhibition and CIPN symptoms, we will use mediation analysis technique (the method initially formalized by Baron and Kenny,[87] extended to clinical trial settings by Kraemer,[88] and methodologically updated by MacKinnon et al.[89, 90]). Specifically, we will use path modeling to estimate indirect (mediation) effects of changes in the CPM test on CIPN symptoms, and bootstrapping to estimate the 95% confidence intervals. The MPlus software will be utilized.

(6) The proportion of participants who decreased "as-needed" usage of acetaminophen and NSAIDs (defined as taking acetaminophen or NSAIDs, on average, at least 30% fewer days per week in the last week of the trial compared to the baseline week) will be compared by groups using a Chi-Square test.

(7) The proportion of participants who report, for the impression of change in CIPN symptoms question "very much improved", "much improved", "minimally improved", "no change", "minimally worse", "much worse", and "very much worse") will be compared between treatment groups using a Cochran Armitage Trend Test.

(8) The proportion of participants whose sensation threshold from the monofilament test improved will be reported together with the 95% confidence interval (CI) and tested against the null hypothesis of no improvement.

(9) Descriptive statistics and 95% CIs will be used to assess the percentage of participants and outcome assessors that correctly identify the group to which the participant was assigned as well as the basis for the guesses.

(10)Test, re-test reliability for the CPM test will be evaluated using Intraclass correlation coefficients (ICCs). Test, re-test reliability for the lower limb sensation threshold test will be measured using Kappa statistics.

10.7 Sensitivity analyses.

(1) Primary and secondary analyses will be repeated in the subset of participants who adhere to the treatment (i.e., adhere to the treatment on $\geq$ 70% of the study days).

10.8 Feasibility analyses.

(1) Descriptive statistics will be used to summarize the following quantitative feasibility outcomes:
- (a) The proportion and 95% CI of screened (i.e., approached) patients who enroll in the study.
- (b) The proportion and 95% CI of randomized participants who adhere to the treatment and complete the primary assessment.
- (c) The proportion and 95% CI of randomized participants who complete the CPM test.
- (d) The proportion and 95% CI of randomized participants who use the device for at least 5 hours / day on at least 70% of the study days.

(2) The participant-reported reasons for low adherence will be summarized by identifying common themes in the qualitative feedback questionnaire.

10.9 Evaluation of Toxicity/Adverse Events

Descriptive statistics will be used to summarize AEs in active and placebo device groups. SAEs will be summarized separately as will AEs concluded to be likely related to the treatment.

10.10 Interim Analysis

No interim analyses are planned due to the fact that TENS is considered nonsignificant risk by the FDA per the 2006 FDA's "Significant Risk and Nonsignificant Risk Medical Devices" Guidance. [51]

10.11 Ancillary Studies

Not applicable

11. ETHICAL AND REGULATORY CONSIDERATIONS

11.1 Form FDA 1572

Not applicable.

11.2 Other Required Documents (IND studies only)

Not applicable.

11.3 Institutional Review Board Approval

Prior to initiating the study and receiving study devices, the Investigators at the NCORP will obtain written approval to conduct the study from the NCI Central IRB. Should changes to the study become necessary, protocol amendments will be submitted to the Division of Cancer Prevention (DCP) PIO according to DCP Amendment Guidelines. The DCP-approved amended protocol must be approved by the CIRB prior to implementation of any changes.

11.4 Regulatory Approval Process of the Informed Consent Document

Prior to study initiation, the informed consent document will be reviewed and approved by National Cancer Institute (NCI) Division of Cancer Prevention (DCP), and the Central IRB (CIRB). Any subsequent changes to the informed consent must be approved by NCI DCP and CIRB prior to initiation.

11.5 Submission of Regulatory Documents

All regulatory documents should be forwarded to the URCC as follows:

URCC_Regulatory@urmc.rochester.edu

11.6 Other

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

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