PROTOCOL TITLE: Single-Institution trial investigating the effectiveness of transcutaneous electrical nerve stimulation in taxane induced peripheral neuropathy in patients with early stage breast cancer.

WINSHIP PROTOCOL #: Winship5501-21

PRINCIPAL INVESTIGATOR:

Manali Bhave, MD
Assistant Professor
Department of Hematology and Medical Oncology
Winship Cancer Institute, Emory University
manali.ajay.bhave@emory.edu

CO-INVESTIGATORS:

Jeffrey Aldrich, MD
Hematology/Oncology Fellow
Department of Hematology and Medical Oncology
Winship Cancer Institute, Emory University
484-643-2111
jeffrey.daniel.aldrich@emory.edu

Vinita Singh, MD
Assistant Professor
Department of Anesthesiology
Emory University
vinita.singh@emory.edu

STATISTICIAN:

Jeffrey Switchenko, PhD
Research Assistant Professor
Department of Biostatistics & Bioinformatics, Rollins School of Public Health
Interim Director, Biostatistics Shared Resource, Winship Cancer Institute
718 Gatewood Road NE, Room 104, Atlanta, GA 30322
404-778-4157

jswitch@emory.edu

VERSION: (Version 1; 10/24/2021)

FUNDING SOURCE: We will be applying for a Winship Invest$ Pilot Grant January 2022. Other sources include philanthropic funds from the Glenn Family Breast Center at Emory University and PI research discretionary funds.

INVESTIGATIONAL PRODUCT (IP): TENS 7000™ by Roscoe Medical, Inc., Middleburg Heights, Ohio

☒ **Study Exempt from IDE Requirements per 21 CFR 312.2(b).**

REVISION HISTORY

Revision #	Version Date	Summary of Changes

Table of Contents

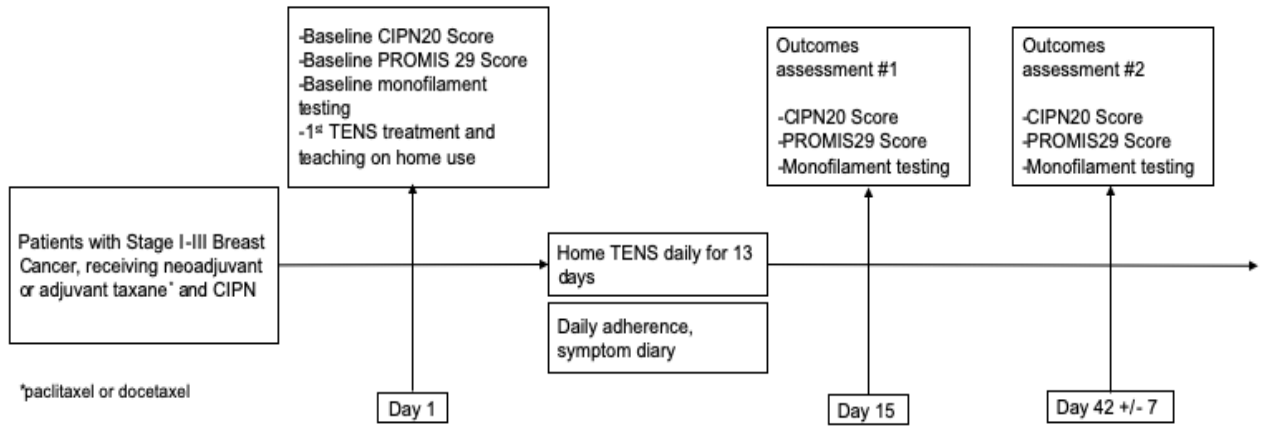
1. Study Summary

1.1 Synopsys

Title:	Single-Institution trial investigating the effectiveness of transcutaneous electrical nerve stimulation in taxane induced peripheral neuropathy in patients with early stage breast cancer.
Study Description:	This is a single-arm clinical trial, designed to evaluate the feasibility and effectiveness of transcutaneous electrical nerve stimulation (TENS) in patients with early stage breast cancer experiencing chemotherapy induced peripheral neuropathy (CIPN) while on a taxane-based regimen.
Objectives:	**Primary Objective**: • To evaluate the feasibility of daily TENS by measuring participant adherence to TENS for two weeks. **Secondary Objectives:** • To evaluate the change in patient reported outcome (PRO) measures of symptoms (e.g. pain, tingling, numbness) and functional impairment. • To evaluate the change in objective measures of neuropathy over the study period through monofilament testing. **Exploratory Objective:** • To collect data on the type and use frequency of non-TENS CIPN treatments (e.g. neuropathic agents and doses) both at baseline and over the duration of the trial (six weeks). • To measure the number of chemotherapy dose-limiting events (dose reductions, delays, discontinuations) over the duration of the trial.
Endpoints:	**Primary Endpoint:** • Feasibility: mean percent adherence of cohort to daily TENS over two weeks **Secondary Endpoints:** • Efficacy: change in a PRO, EORTC CIPN20 (CIPN20) sensory sub-score, over two weeks of daily TENS treatments • Efficacy: change in daily pain, numbness and tingling scores during two weeks of daily TENS • Efficacy: change in PROMIS29 score at two and six weeks compared to baseline • Efficacy: change in monofilament testing at two and six weeks compared to baseline • Safety: adverse events
Study Population:	27 patients ≥18 years of age with early stage (I-III) breast cancer receiving a neoadjuvant or adjuvant taxane-based regimen who have developed CIPN.
Phase:	Feasibility/Pilot

Description of Sites/Facilities Enrolling Participants:	Glenn Family Breast Center, Winship Cancer Institute of Emory University (Atlanta, GA).
Description of Study Intervention:	Patients will receive TENS daily for 14 days. On Day 1 baseline CIPN20, PROMIS29 scores and monofilament testing will be established. The first TENS treatment will be completed under supervision and the home operating procedure will be reviewed. Patients will then be given a portable TENS unit and the subsequent daily treatments (2-14) will be completed by the patient at home. Patients will record the TENS start/stop times and scores on pain, numbness and tingling each day for 14 days. Patients will return for repeat PRO scores and monofilament evaluation on day 15. A final assessment will occur on day 42.
Study Duration:	We estimate the study duration to be 1 year. We anticipate enrolling 3 patients per month for 9 months. The final 3 months would be utilized for data analysis and manuscript writing.

1.2 Schema



1.3 Schedule of Assessments

Procedures	**Screening** Day -7 to -1	**Enrollment/Baseline** Day 1	**Telephone Check-in** Day 3 + 2 days	**Study Visit 2** Day 15 + 2 days	**Study Visit 3** Day 42 +/- 7 days
Informed Consent	X				
Demographics	X	X			
Medical history	X	X			
Current medications		X		X	X
Concomitant CIPN treatments		X		X	X
Physical exam (limited)	X				
Vital signs	X				
Height	X				
Weight	X				
Performance status	X				
Pregnancy test	X				
Review TENS Operating instructions		X	X		
Administer TENS		X			
Monofilament testing		X		X	X
Baseline pain, numbness, tingling scores		X			
CIPN20 score assessment		X		X	X
PROMIS29 score assessment		X		X	X
Review adherence & symptom diary				X	X
Monitor for Adverse events		X	X	X	X

2. Objectives (and Endpoints)

OBJECTIVES	ENDPOINTS
Primary	
• To evaluate the feasibility of daily TENS by measuring participant adherence to TENS for two weeks.	• Feasibility: mean percent adherence to daily TENS over two weeks
Secondary	
• To evaluate the change in patient reported outcome (PRO) measures of symptoms (e.g. pain, tingling, numbness) and functional impairment. • To evaluate the change in objective measures of neuropathy over the study period through monofilament testing.	• Efficacy: the change in a PRO, EORTC CIPN20 sensory sub-score, over two weeks of daily TENS treatments. • Efficacy: daily pain, numbness and tingling scores during two weeks of daily TENS. • Efficacy: change in PROMIS29 scores at two and six weeks compared to baseline. • Efficacy: change in monofilament testing at two and six weeks compared to baseline.
Tertiary/Exploratory	
• To collect data on the type and use frequency of non-TENS CIPN treatments (e.g. neuropathic agents and doses) both at baseline and over the duration of the trial (six weeks). • To measure the number of chemotherapy dose-limiting events (dose reductions, delays, discontinuations) over the duration of the trial.	

3. Background

3.1 Study Rationale

There are 284,000 new cases of breast cancer projected to be diagnosed in the United States during 2021 of which approximately 90% will be early stage.[1,2] While progress has been made in better identifying early stage patients who do not require chemotherapy, it remains an essential treatment for high risk early stage breast cancer.[3] While taxanes (paclitaxel or docetaxel) remain a backbone of

neoadjuvant or adjuvant chemotherapy in early stage breast cancer, chemotherapy induced peripheral neuropathy (CIPN) is common in this group and has significant short and long-term implications.[4,5]

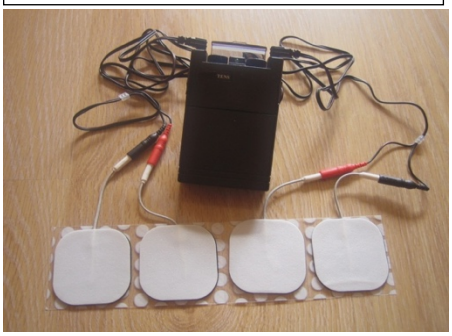
CIPN typically manifests with sensory symptoms such as numbness, tingling or pain in hands or feet and can lead to falls and worsening quality of life.[6,7] In a cohort of early stage breast cancer patients treated with weekly paclitaxel for 12 weeks, 55% experienced CIPN at 6 weeks, with frequent dose limiting events (36% required dose reduction and 14% had chemotherapy stopped early).[8] The current 2020 ASCO guidelines recommend duloxetine for painful CIPN in patients who have previously completed chemotherapy.[9] However, for those currently on chemotherapy, recommended options only include dose delay, reduction or discontinuation which may lead to inferior disease-free and overall survival in early stage breast cancer.[10-12] The guidelines recommend duloxetine as an option in chronic CIPN, however its efficacy in patients with CIPN undergoing chemotherapy is unclear. Additionally, duloxetine can take several weeks to see symptom improvement, has several potential side effects including fatigue, and contributes to polypharmacy. CIPN can cause significant long-term negative impacts on quality of life in a large population of patients with curable breast cancers, has limited treatment options, and frequently leads to chemotherapy disruption, potentially impacting long-term survival. As a result, there is a critical need for new and effective strategies to improve CIPN symptoms in patients with early stage breast cancer.

3.2 Clinical Experience

Transcutaneous Electrical Nerve Stimulation and rationale for its use in CIPN

TENS consists of a portable unit (Figure 1) that delivers electrical impulses through electrodes attached to the skin. Adjustable parameters include wave amplitude, duration and frequency. Current evidence suggests that TENS may be beneficial for a variety of non-cancer pain syndromes including fibromyalgia and diabetic peripheral neurpathy.[13,14] As shown in animal and human studies, hyper-excitability within ascending spinal cord pathways, as well as a decrease in descending inhibitory tracts, contributes to CIPN symptoms.[15,16] TENS has been shown to counteract this disordered signaling by reducing afferent excitability and increasing central inhibition through activation of opioid receptors.[17,18] Based on this understanding, early phase clinical trials have explored the effectiveness of TENS at improving CIPN symptoms.

Figure 1. Portable TENS unit



Gewandter et al completed a study of 29 patients with chronic CIPN who were treated with a portable home-based TENS unit for up to six weeks.[19] Patients reported a 13% improvement (p=0.004) in the European Organization for Research and Treatment of Cancer CIPN20 (CIPN20) score, a 20-item patient reported outcome (PRO) questionnaire validated in CIPN.[20-22] Sixty-three percent of tested patients had improvement (p <0.0001) in monofilament testing. No serious adverse events attributed to TENS occurred and qualitative interviewing demonstrated positive feedback on its ease of use. While this study demonstrated that TENS is a safe, potentially efficacious treatment for chronic CIPN, adherence to patient-operated TENS therapy conducted at home was not reported. Another trial in chronic CIPN utilized TENS as the control arm and showed improvement in CINP20 sensory scores after two weeks with benefit remaining during weeks four through ten in patients who completed TENS therapy.[23] We identified one study evaluating TENS for CIPN in patients on chemotherapy with 5-Fluorouracil or

paclitaxel.[24] While this study did not show differences in patient reported outcomes (PROs) between those receiving TENS versus a sham-TENS, the trial was not powered to detect a difference between groups. Additionally, only patients who developed grade one or two neuropathy after one cycle of chemotherapy were enrolled in the study. As a result, it remains unclear whether patients with more severe neuropathy or those who develop CIPN after multiple cycles of chemotherapy would benefit from TENS.

Trial design

We are proposing a single-institution, single-arm trial in patients with early stage breast cancer on a taxane-based regimen experiencing CIPN. We plan to enroll 27 patients over a nine-month period who will receive daily TENS therapy for 14 days with follow up on day 15 and a final assessment on day 42 +/- 7 days. Evaluation after two and six weeks was chosen as prior studies have shown improvement in chronic CIPN symptoms after two weeks of TENS treatment with some benefit remaining at six week follow up.[23] Additionally, since adherence has not been previously demonstrated, a two-week intervention was deemed reasonable and feasible within the one-year time frame of the trial. While individuals with other cancer types can also experience CIPN we are limiting enrollment to early stage breast cancer in this pilot study as most of these patients are treated with taxane-based regimens and therefore have high rates of CIPN. If this study demonstrates feasibility and signs of efficacy in this group, we plan to conduct a larger study, possibly in the cooperative groups, to confirm efficacy of TENS over current clinical practice (chemotherapy dose adjustments and neuropathic agents).

Rationale for primary endpoint, feasibility

Our primary endpoint for the trial is the feasibility of a patient-operated, home-based daily TENS therapy for CIPN. We plan to measure adherence to the 1-hour TENS treatments by utilizing a patient-entered daily compliance diary. Adherence for each patient will be determined by summing the number of fully completed TENS treatments and then dividing by 14 (the number of prescribed sessions over two weeks). While there are not published data on TENS compliance, adherence for other supportive treatments during chemotherapy, like scheduled anti-emetics, have been estimated to be 65% in patients with early stage breast cancer.[25] Given the short time period of the intervention in our trial (two weeks) and the significant motivation of patients experiencing CIPN to find an effective treatment *we hypothesize a mean adherence of 75% to TENS in our cohort.*

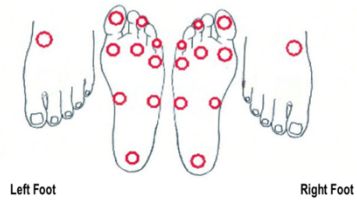
Rationale for secondary endpoints, patient reported outcome scores

The CIPN20 score, a PRO, was selected as it has previously been validated in CIPN. It consists of a 20-item questionnaire that includes questions regarding symptoms and functional abilities in the following domains: sensory (9 questions), motor (8 questions), and autonomic (3 questions). Each question is on a 1-4 point scale (1= “not at all”, 2= “a little”, 3 = “quite a bit”, 4 = “very much”). Scores in each domain are added to obtain a “sum score” which is then linearly converted to a 0-100 scale. Other studies in CIPN have demonstrated CIPN20 sensory sub scores are more severe than the other domains[26] and in keeping with previously established definitions, we anticipate a baseline mean CIPN20 sensory score of 15.[21,27] *We hypothesize that TENS will improve the mean CIPN20 sensory score by 20%, an absolute improvement in score of 3.* An improvement of 3 was chosen as the minimum improvement in CIPN20 sensory score for

patients to experience clinical benefit has been reported to be at least 2.5.[28] To measure day-to-day symptom changes an additional PRO, daily scores of pain, numbness and tingling on a 0-10 numerical rating scale, will also be recorded. In order to capture changes in participants' physical, mental, and social health over their time on the trial, the Patient-Reported Outcomes Measurement Information System (PROMIS) 29 questionnaire will be used. There are four questions in each domain (physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, pain interference) with responses graded on a 1 ("not at all) to 5 ("very much"). PROMIS29 is not disease-specific but has previously been utilized in patients with breast cancer.[29]

Secondary endpoints, monofilament testing

Figure 2. Touch points for Neuropen



In conjunction with the CIPN20 assessment, monofilament testing will be completed at baseline, on day 15 and day 42. At each assessment two neuropathy scores will be calculated using Neuropen, a two-sided monofilament (40 g and 10 g). The 40 g end evaluates sensation to sharpness and pain (small nerve fibers), while the 10 g end measures protective touch and pressure sensation (large nerve fibers). During each of the three assessments 10 sites on the patient's dominant foot will be evaluated with each end of the Neuropen. At each touch point (Figure 2) the patient will be asked if they feel pressure (10 g end) or a sharp pain (40 g end). For each category a negative response (i.e. patient does not feel the monofilament touch) will result in one-point. Patients will have two scores ranging from 0-10 with higher scores correlating to more severe neuropathy.

Exploratory endpoints

As evidence suggests that chemotherapy dose delays, reductions, and early discontinuations (dose-limiting events) may lead to inferior survival in this patient population, we plan to track the number of dose-limiting chemotherapy events of participants over the duration of the trial. Given that this patient population is receiving treatment with curative intent and knowing the implications of early chemotherapy discontinuation, patients will not be prohibited from using alternate pharmacologic and non-pharmacologic therapies to manage CIPN symptoms while on the study. To determine if there is potential confounding by these other therapies, we will collect the type, dose and frequency of alternate CIPN treatments, such as neuropathic agents, at baseline and over the course of the trial.

Rationale for Participation

Our single institution trial examining TENS as a treatment for early CIPN while on chemotherapy aims to provide a solution to a critical unmet need. As CIPN is a frequent occurrence in patients with a common cancer, improving this condition has the potential to positively impact the lives of thousands of patients every year. Adding to the urgency, there are few effective treatments for the condition, and the current practice of chemotherapy dose modification may hinder patients' long-term survival. Our study is innovative as no previous publications have demonstrated the feasibility or efficacy of TENS for CIPN symptoms developing while on chemotherapy. We believe Emory is uniquely positioned to conduct this trial given our breast cancer population is approximately 40% African American (AA). AAs are disproportionally affected by taxane-induced CIPN and more frequently require dose reductions

compared to Non-Hispanic White patients.[30] Therefore, we predict that there will be great interest for this trial and we plan to publicize it both at our weekly breast working group meeting and through the Winship social media platforms.

Hypothesis

We believe that utilizing TENS for CIPN while on chemotherapy will be both feasible and demonstrate efficacy. Specifically, we hypothesize that the mean adherence of the cohort to daily TENS over two weeks will be 75%. Additionally, we anticipate a mean cohort baseline CIPN 20 sensory score of 15 with a 20% improvement at the end of two weeks.

4. Study Intervention/Investigational Agent

4.1 Description

For this clinical trial we will be using the TENS 7000™ manufactured for Roscoe Medical, Inc., Middleburg Heights, Ohio. This TENS unit has two channels with two electrodes associated with each channel. It has adjustable pulse width, amplitude and frequency. In brief, patients will place two TENS electrodes on each upper or lower extremity, depending on whether symptoms are hand-or foot-dominant. The TENS unit pulse width will be set to 100 µs, and amplitude will be self-adjusted until stimulation is strong, but comfortable without muscle contractions. For the first 30 minutes the pulse frequency will be set to a low setting (target: 2 Hz, range: 2-10 Hz) and increased to high frequency (target: 120 Hz, range: 100-150 Hz) for the subsequent 30 minutes. Patients will return on day 15 for assessment. A final evaluation will take place on day 42 +/- 7 days to determine if TENS demonstrates a durable response.

TENS 7000.
This device is designed to be used for temporary relief of pain associated with sore and aching muscles in the shoulder, waist, back, upper extremities (arm) and lower extremities (leg) due to strain from exercise or normal activities. The TENS 7000™ is FDA approved as an over-the-counter device for pain relief (registration establishment number 3005170249, regulation number 882.5890). We are proposing utilizing this device for symptoms associated with CIPN such as pain, numbness and tingling. We believe this study utilizes the TENS unit within accordance of its FDA approval and is therefore exempt from IDE requirements.

4.2 Drug/Device Handling

The TENS 7000™ is FDA approved as an over-the-counter device for pain relief (registration establishment number 3005170249, regulation number 882.5890). We are proposing utilizing this device for symptoms associated with CIPN such as pain, numbness and tingling. We believe this study utilizes the TENS unit within accordance of its FDA approval and is therefore exempt from IDE requirements.

The TENS devices will be securely stored by clinical research staff during the clinical trial. Patients who have signed the informed consent, completed baseline testing and received training on TENS use will be provided a new unit to take home. They will be instructed to be the sole user of the device and to not

allow others to utilize the device during the clinical trial. At the conclusion of the trial the participants will be able to keep the TENS device if they choose.

4.3 Accountability

The TENS device provided for this study will be used only as directed in the study protocol. Participants on trial who receive the study-provided TENS unit will be instructed to be the sole users of the device per the provided instructions. Adherence is a central aim of the clinical trial and will therefore be closely measured. Patients will utilize a treatment diary daily during the two weeks of TENS treatment to measure adherence.

5. Procedures Involved

5.1 Study Design

This clinical trial is a pilot study in order to determine the feasibility and efficacy of TENS for CIPN developing while on a taxane-based regimen for patients with early stage breast cancer. Twenty-seven patients with early stage breast cancer receiving neoadjuvant or adjuvant taxane-based chemotherapy who develop at least grade 1 CIPN (NCI CTCAE v5.0 grading system) as determined by their treating medical oncologist will be eligible for this study. The study will consistent of a seven-day screening period, two-week treatment period, and a four-week follow up period. During the screening period patients will provide written informed consent to participate in the study before completing any protocol-specified procedures or evaluations not considered to be part of the patient's standard care. Procedures that were performed for standard of care prior to signing informed consent may be used for screening purposes (e.g., physical exam) as long as the procedures were completed within the seven-day screening period.

The two-week treatment period will begin with the enrollment/baseline visit (day 1), which will take place at the new patient appointment with the anesthesia pain physician. At that visit the patient's signed informed consent will be verified and baseline data (e.g. medical history, physical exam, height/weight etc.) will be obtained if not already completed during the seven-day screening period. Patients will complete baseline PRO assessments (CIPN20 score; pain, numbness, tingling symptoms on 0-10 score, PROMIS29 questionnaire) and monofilament testing. Patients will be evaluated by the anesthesia-pain physician and the first TENS treatment will be completed during the baseline (day 1) visit per the operating instructions (separate document) and reviewed with the patient. Participants will then be given their TENS unit, operating instructions and diary form (Appendix B) to take home. On Day 3 each participant will receive a call from the clinical research coordinator (CRC) to ensure they understand how to operate the TENS unit and to answer any questions. On Day 15 patients will return, and post-TENS CIPN20 and PROMIS29 scores, as well as monofilament testing will be collected. The daily diary will be reviewed and any adverse events will be recorded. During the subsequent four weeks patients will have the option to continue using TENS if they feel it is benefiting them. During this period participants will continue using TENS for one-hour per day under the same settings outlined in the operating instructions from the 14 day intervention period. During weeks 3-6 the diary entries will be once weekly. Regardless of whether patients continue TENS past the 14 day intervention period, the last visit will take place on day 42 +/- 7 days when the third CIPN20 and PROMIS29 scores will be collected in addition to the final monofilament testing.

5.2 Dosing and Administration

TENS

TENS therapy will be administered for a total of 14 daily treatments. The first treatment will take place at the enrollment/baseline visit on Day 1. The TENS electrode pad placement and first treatment will be supervised by the anesthesia-pain physician. The TENS operating procedure will be reviewed with the patient and any questions on TENS use will be answered. The patient will then complete the subsequent 13 daily one-hour treatments at home. Refer to the TENS operating procedure for detailed instructions on TENS use. Patients will utilize TENS for CIPN symptoms in the fingers or toes, depending on whether the pain/numbness/tingling is hand or foot dominant. The following adjustable TENS settings will be specified in the operating instructions: pulse width, amplitude, and frequency. The pulse width will be set to 100 µs, and amplitude will be self-adjusted until stimulation is strong, but comfortable without muscle contractions. For the first 30 minutes the pulse frequency will be low (target: 2 Hz, range: 2-10 Hz) and then raised to a high frequency (target: 100 Hz, range: 100-150 Hz) for the subsequent 30 minutes. The specific settings will be determined by the anesthesia-pain physician at the first treatment visit.

5.3 Definition of Treatment-Limiting Toxicity

Severe adverse events attributed to TENS have not been reported in previous clinical trials utilizing TENS for chronic CIPN.[19,23] However, in these studies mild contact dermatitis or ecchymosis on the skin at the site of electrode placement have been reported. Other mild reported adverse events in a minority of participants included “burning” or “restlessness”, as well as new paresthesia, pain or cramping in the extremities.

A treatment-limiting toxicity is defined as an adverse event or abnormal laboratory value assessed as definitely treatment related that occurs while utilizing TENS treatment and meets any of the criteria listed in the table in section 5.4 below. National Cancer Institute Common Terminology Criteria for Adverse events version 5.0 (NCI CTCAE v. 5.0) will be used for all grading.

Criteria for defining treatment-limiting toxicities

Management and treatment modifications associated with adverse events are outlined in Section 5.4.

5.4 Treatment Modification

The PI and our TENS knowledge expert (Co-investigator Dr Singh) will review all newly reported symptoms during the trial to ensure that they are appropriately attributed to CIPN, TENS or other causes. The investigator(s) will determine whether dose modification or discontinuation is required per the guidance below.

Table: Dose Modification for Adverse Events Associated with TENS

Adverse Event	Treatment Modification

Rash attributed to TENS	• Grade 1: continue TENS • Grade 2: move electrodes to new site off the affected skin • Persistent grade 2 or ≥ grade 3: permanently discontinue
Pain in extremities attributed to TENS	• Grade 1: continue TENS • Grade 2: decrease TENS intensity by one level on the intensity dial. If pain remains unchanged further reduce intensity, again by one level. • Persistent grade 2 or ≥ grade 3: patient will contact PI and will permanently discontinue TENS
Muscle cramping attributed to TENS	• Grade 1: continue TENS • Grade 2: decrease TENS intensity by one level on the intensity dial. If cramping remains unchanged further reduce intensity, again by one level. • Persistent grade 2 or ≥ grade 3: permanently discontinue
Paresthesia attributed to TENS	• Grade 1: continue TENS • Grade 2: decrease TENS intensity by one level on the intensity dial. If paresthesia remains unchanged further reduce intensity, again by one level. • Persistent grade 2 or ≥ grade 3: permanently discontinue

5.5 Concomitant medications

Concomitant medications or other treatments for CIPN will be permitted while participants are on trial. However, from the time the informed consent is signed until the conclusion of the two-week intervention period adding new CIPN treatments or escalating current CIPN therapies will be discouraged given the possibility of confounding the effect of TENS. To further mitigate possible confounding, participants will have to remain on a stable dose of a neuropathic agent without dose increase for the 7 days prior to the first TENS treatment (day 1). Given that it is unclear if TENS will work for all participants and worsening CIPN could hinder a patient's ability to complete curative intent chemotherapy, patients will be encouraged to contact our PI if their CIPN symptoms worsen while on TENS. The PI will work with our anesthesia pain co-investigator and the participant's primary medical oncologist to determine if a new CIPN treatment or escalation of a current therapy should be instituted while on TENS. Examples of other CIPN medications and therapies that patients may be on:

- duloxetine
- gabapentin
- pregabalin
- amitriptyline/nortriptyline

Prohibited Concomitant Medications or Treatments for CIPN:

No CIPN treatments will be prohibited, however escalation of current CIPN treatment or addition of new CIPN treatments is strongly discouraged while undergoing TENS as detailed above.

5.6 Study Procedures

Before study entry, throughout the study, and following TENS discontinuation, various clinical and diagnostic evaluations are outlined. The purpose of obtaining these detailed measurements is to measure feasibility, efficacy and safety. The Schedules of Assessments during the screening and treatment period is provided following the Protocol Synopsis.

Screening Phase

The Screening Phase is the time between the date a patient provides written informed consent and the patient begins TENS therapy. Data collection and procedures during this time period include patient demographics, eligibility requirements, medical history, limited physical examination/vital signs, ECOG performance status assessment, adverse events, serious adverse events, and, pregnancy testing (if applicable). Screening procedures will be performed up to 7 days prior to initiation of TENS treatment. All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the screening window or 7 days. Only AEs deemed to be serious and related to protocol mandated and not routinely performed procedures have to be reported during this phase.

The following procedures will be performed during the **Screening Visit**:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Limited physical exam
- ECOG Performance Status
- Vitals signs, weight and height
- Clinical laboratory tests for:
    - Serum or urine pregnancy test (for women of childbearing potential)

Treatment Phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments (Section 1.3). Screening procedures performed within 7 days of the first treatment day do not need to be repeated on the first treatment day.

- Review of current medications and indications
- Review of concomitant CIPN treatments
- Patient Reported Outcome Measures
- Monofilament testing
- Administer TENS
- Review adherence and symptom diary

5.7 Description of Study Procedures

Medical history

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

Physical examination (limited)

Physical examinations should be conducted according to the Schedule of Events. Limited physical examinations should be conducted at screening/baseline (evaluate all major organ systems, including the following categories: general, heart, lungs, abdomen, extremities, integumentary, neurologic, and psychiatric). Other examinations may be focused, at the discretion of the Investigator, to identify changes from baseline or evaluate changes based on the patient's clinical symptoms. Weight/height/vital signs at screening/baseline visit only.

Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules. Body weight is also recorded along with vital signs.

Clinical laboratory tests

The following clinical laboratory tests will be performed (see the Schedule of Assessments)

- Pregnancy test (female subjects of childbearing potential only)

Review of current medications

At the first day of treatment each participants' active medications will be reviewed including their indication. This is important as certain psychoactive medications (e.g. SNRI class of anti-depressants) can be utilized for psychiatric or neuropathic syndromes, such as CIPN.

Review concomitant CIPN treatments

At baseline and during the six-week trial other non-TENS pharmacologic CIPN treatments (including dose and frequency) will be tracked at each visit.

Patient Reported Outcome Measures

European Organization for Research and Treatment of Cancer CIPN20 (CIPN20) score is a frequently used PRO measure and has been validated for assessing CIPN.[20-22] It is a 20-item questionnaire that measures sensory (9 questions), motor (8 questions) and autonomic (3 questions) symptoms and function on a 1-4 point scale (1= "not at all", 2= "a little", 3 = "quite a bit", 4 = "very much"). The sub-scores are added to obtain a "sum score" which is then linearly converted to a 0-100 scale. This will be assessed at baseline and each follow up visit.

Daily pain, numbness, tingling scores. To monitor day-to-day symptom changes, patients will record scores of pain, numbness, and tingling on a 0-10 numerical rating scale in their daily treatment diary for each day of TENS therapy for the two-week intervention period. Scores will also be measured at baseline. During weeks 3-6 patients will have the option to continue TENS use if they choose and will record symptoms at the end of weeks 3, 4, 5 and 6.

Patient-Reported Outcomes Measurement Information System 29 (PROMIS29). This is an additional PRO score that will be used to monitor changes in a patient's physical, mental, and social health over the trial. It consists of four questions in each of the following groups: physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities, and pain interference. Each response is on a five-point scale (5 = "never", 4 = "rarely", 3 = "sometimes", 2 = "usually", 1 = "always"). The final question relates to pain intensity and is graded on a 0-10 scale (0 = "no pain", 10 = "worst imaginable pain"). This will be assessed at baseline and each follow up visit.

Review daily adherence and symptom diary

At the Day 15 treatment assessment each participant's 14-day adherence/symptom diary will be reviewed for completeness. The diary will include space for the daily pain, numbness, and tingling scores to be recorded. Each diary will also include space to record possible side effects from TENS, issues with operating the unit or other feedback. The diary will have free text space for patients to write their overall impression of TENS as a treatment for CIPN at the end of two-weeks. The diary responses will be reviewed at the Day 15 visit. If patients have significant side effects, worsening CIPN, or issues with operating the TENS unit they will be encouraged to contact the clinical trial team as soon as possible, rather than waiting until the Day 15 assessment. For patients that continue on TENS after Day 15, patients will continue weekly diary entries that will be reviewed at day 42 visit.

Monofilament testing

For an objective assessment of neuropathy monofilament testing will be completed utilizing Neuropen, a two-sided monofilament (40 g and 10 g). Ten touch points will be utilized on the patient's dominant foot with each end of Neuropen. At each touch point the patient will be asked if they feel pressure (10 g end) or a sharp pain (40 g end). For each category a negative response (i.e. patient does not feel the monofilament touch) will result in one-point. Patients will have two scores ranging from 0-10 with higher scores corresponding to increasing neuropathy severity.

6. Data

Samples and data collected under this protocol may be used to study **breast cancer**. Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

7. Sharing of Results with Participants

In general, study staff will not provide any individual results to subjects (ex. outcome trial results or results from a subject's individual testing). If something of urgent medical importance to the participating subjects is found, the PI (or co-Is) will inform the subject, although we expect that this will be a very rare occurrence. Data will only be used for research.

8. Study Timelines

Milestone	Site	Year 1 (2022)				Year 2 (2023)			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Participant Accrual*	Emory Glenn Family Breast Center, Winship Cancer Institute	3	9	9	6				
Final assessments completed, trial concludes	All study sites					X			
Data analysis	All study Sites						X		
Abstract and manuscript submission	Offices of Manali Bhave, Jeffrey Aldrich, Jeffrey Switchenko						X		

***Numbers reflect total number of patients accrued to the protocol by the end of the indicated quarter. Each patient will be enrolled on the trial for a total of six weeks +/- 7 days.**

At the conclusion of the study, during Year 2, an abstract of our findings will be submitted to the annual San Antonio Breast Cancer Symposium. The publication plan is to submit a manuscript of our finding to *Clinical Breast Cancer* also during Year 2.

Enrollment period: 9 months starting March 1, 2022. See above study timelines.

8.1 Duration of therapy

Patients will be treated with TENS for two weeks or less if any of the following occur prior to the conclusion of the treatment period:

- Death
- Unacceptable toxicity
- Investigator's decision to discontinue treatment
- Patient decision to discontinue treatment
- Patient withdraws consent
- Lost to follow up

In the event of a patient's withdrawal, the Investigator will make every effort to complete the End of Treatment procedures specified in the Schedule of Events. As specified in Section 5.1 if patients are having benefit from TENS during the 14 day intervention period and would like to continue TENS during weeks 3-6, they may do so for one-hour each day under the same operating parameters. If they continue using TENS weeks 3-6 they will complete weekly entries in the adherence and symptom diary.

8.2 Duration of follow-up

Patients will be followed for approximately four weeks (Safety Follow-up) after the two-week TENS treatment. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. Patients will have a final follow up visit on Day 42 regardless of whether they continued TENS during weeks 3-6.

Patient records may be reviewed until death to assess their CIPN outcomes. Survival information may be collected by clinic visit, email, or telephone after ending protocol treatment and until the study is terminated, the patient dies, or the patient is lost to follow-up.

A participant will be considered lost to follow-up if he fails to return for the two scheduled follow up visits and is unable to be contacted by the study site staff after three attempts at contact by phone.
The following actions must be taken if a participant fails to return to the clinic for a required study visit:
The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

9. Inclusion and Exclusion Criteria

In general, this proposed clinical trial is seeking patients who have been identified by their treating medical oncologist to have at least CTCAE grade 1 or higher peripheral sensory or motor neuropathy in hands or feet while on taxane chemotherapy.

For questions concerning eligibility, please contact Dr. Jeffrey Aldrich or the study PI, Dr. Manali Bhave.

a) Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.
b) Women of child bearing potential (FCBP) must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation.

Inclusion Criteria

1. Biopsy proven stage I-III breast cancer actively undergoing neoadjuvant or adjuvant chemotherapy regimen that contains paclitaxel or docetaxel.
2. At least CTCAE grade 1 CIPN in hands or feet attributed to taxane chemotherapy.
3. Actively undergoing paclitaxel or docetaxel with plans to continue during the two-week TENS treatment.
4. Age ≥18 years.
5. For females of child-bearing potential, negative serum or urine pregnancy test within 14 days prior to starting TENS
6. Given the potential concern that TENS could induce uterine contractions or interfere with fetal cardiac conduction, female of child-bearing potential (FCBP) must have a negative serum or urine pregnancy test prior to starting therapy.
7. FCBP must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of TENS treatment. Should a woman become pregnant or suspect she is pregnant during the two weeks of TENS, she should inform her treating physician immediately. A female of childbearing potential (FCBP) is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

8. Willingness and ability of the subject to comply with scheduled visits, TENS administration plan, other study procedures, and study restrictions.
9. Evidence of a personally signed informed consent indicating that the subject has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential risks and discomforts, potential benefits, and other pertinent aspects of study participation.

Exclusion criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Skin wounds, skin breakdown or edema at the site of TENS electrode pad placement
2. History of epilepsy
3. Implanted electronic device including a cardiac pacemaker, defibrillator, pain pump etc.
4. Pre-existing neuropathy
5. Prior exposure to neurotoxic chemotherapy
6. Previous use of TENS for CIPN
7. Prisoners or an adult who is unable to consent
8. Pregnancy

10. Vulnerable Populations

We encourage participation from members of any sex and ethnic group in this trial. No recruitment restrictions will be performed based on sex or minority status. No person shall, on the grounds of race, color, or national origin, be excluded from participation in, or be denied the benefits of, enrollment in this protocol.

11.Local Number of Participants

We will be recruiting 27 participants at Winship. We are expecting to have to enroll (consent) 30 participants to reach our recruitment goal of 27 at Winship (10% loss to screen failure or to withdrawal between time of informed consent and starting TENS). Patients will be registered after signing of the informed consent document and meeting all entry requirements.

12.Recruitment Methods

Investigators, nurses, and/or data managers review lists of cancer patients who have cancer and will determine if there are patients who might be eligible for a clinical trial. The nurse/data manager reviews accessible medical records to screen further for eligibility. The nurse reviews the eligibility with the physician.
Subjects will be identified by their treating physicians. Clinical care team at Winship will inform potential subjects about the known benefits and potential risks of the clinical trial. Some of the subjects recruited for this protocol will be patients being treated at Emory and under the care of one or more of the study investigators. Some potential subjects will be identified by their treating physician and referred to Emory for possible participation in the protocol.

We will actively advertise the trial at the weekly Emory Glenn Family Breast Center working group meeting, which is attended by Emory breast medical oncologists. We believe that raising awareness of this clinical trial among providers will assist in boosting enrollment on the trial. To further increase awareness of the trial among potential participants receiving cancer care outside of Emory we will coordinate a social media campaign to advertise the study.

No incentives are provided to patients for trial participation.

Study personnel will notify Winship Central Subject Registration (WCSR) by email at winshipcsr@emory.edu, once subject has been consented for a trial.
Email notification must be done within 24 hours after consent has been obtained and it will include scanned copies of:

- Signed patient consent form
- HIPAA authorization form
- Emory Research Management System (ERMS; *https://erms.emory.edu*) Enrollment Fax Cover

The WCSR will enter the subject into the OnCore Research Management System, which is the system of record for Winship Cancer Institute Clinical Trials.

Enrolling a subject requires careful screening and determination of eligibility.

Eligible patients will be enrolled on study centrally at Winship Cancer Institute by the Study Coordinator. When all required test results are available, complete the eligibility checklist and provide the checklist and the supporting documentation to the IRB approved investigator for review and sign-off. Once the investigator (sub-investigator, Co-Investigator) has signed the eligibility checklist, enrollment may proceed. Oncore and ERMS must be updated to reflect eligibility and on treatment status.

Following enrollment, patients should begin protocol treatment within___7_____ business days. Issues that would cause treatment delays should be discussed with the Principal Investigator.

13.Withdrawal of Participants

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant unable to receive TENS.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form who do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and receive the study

intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

14.Risks to Participants

CIPN is a frequent side effect of taxane-based chemotherapy and lacks effective treatments. Therefore, this trial is highly relevant, as it seeks to establish TENS as a possible new CIPN therapy. TENS has been employed as a treatment modality for a variety of pain syndromes for decades, is available over-the-counter, and overall has minimal risks. Serious adverse events due to TENS were not reported in two previous clinical trials investigating the role of TENS in chronic CIPN. Minor adverse events that were reported to be possibly related to TENS included contact dermatitis or ecchymosis on the skin at the site of electrode placement and pain, paresthesia, or cramping in the extremities. One study reported minor adverse events in 4 of 46 patients (9%)[23] and the other reported minor adverse events in 6 of 22 (27%)[19] participants. All mild adverse events resolved after discontinuation of TENS. For these possible adverse events see Section 5.3 and 5.4 for definitions and management of treatment-limiting toxicities, should they occur. Patients will be able to record adverse events in their Daily TENS diary, which will be reviewed at the Day 15 assessment. If a severe adverse event occurs during the 14-day TENS treatments, patients will be instructed to contact the research staff immediately rather than waiting until Day 15 assessment.

- **Skin injury:** The electrode pads also have the potential to cause skin irritation, which patients will be instructed to monitor for and if it occurs pads may have to be moved to a different location on the skin. While not reported in two previous clinical trials, since TENS utilizes electricity there is a theoretical potential for burns. Patients will be instructed to utilize TENS only within the parameters as outlined in the operating procedure and will monitor the skin for any injury.
- **Pain extremities:** Mild pain, cramping and paresthesia in the extremities have been reported during TENS use. Patients will be instructed to monitor for this and will be recording daily symptom scores as part of the TENS diary.
- **Electrocution:** As TENS involves the flow of electrical current, electrocution is a risk. To mitigate this risk patients will be instructed on the risks and instructed to use TENS only per the provided operating directions and to not share the unit with others. TENS should not be used near water, while sleeping, driving or operating machinery given the potential risk for electrocution or involuntary muscle contractions. TENS electrode pads should not be placed on the throat/neck, head, eyes, chest, or genitals given the risk for electrocution, muscle spasm, or disruption of normal electrical processes (e.g. arrhythmia)
- **Pregnancy:** While TENS is at times employed during pregnancy in the lower back, there are theoretical risks such as induction of uterine contractions or interference with fetal heart conduction. Therefore, pregnancy will be an exclusion criteria for this trial.
- **Data security:** Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subjects' PHI. All records will be kept in a locked file cabinet or maintained in a locked room at the participating sites. Electronic files will be password protected behind an academic institutional firewall. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to the PHI that is collected. Any publications from this study will not use information that will identify subjects. Organizations that may inspect and/or copy research records maintained at the participating sites for quality assurance

and data analysis include groups such as the National Cancer Institute (NCI) and Food and Drug Administration (FDA).

15. Potential Benefits to Participants

There is no guarantee of benefit to subjects who enroll in this protocol. However, pre-clinical studies and previous clinical trials in chronic CIPN suggest that TENS may have efficacy in CIPN. Therefore, this clinical trial is necessary to determine if there are signs of benefit for individuals experiencing CIPN while on chemotherapy.

16. Data Management and Confidentiality

16.1 Biostatistical Plan

We are proposing a single-arm clinical trial in which all enrolled patients will receive TENS therapy over two weeks. The optimal length of TENS treatment for patients experiencing CIPN while on chemotherapy is unknown, but two weeks was selected based on evidence from TENS usage in chronic CIPN.[23] We aim to enroll three patients per month over a nine-month period. Baseline demographic and clinicopathologic characteristics will be summarized with descriptive statistics.

16.1.1 Primary endpoint

Feasibility: To evaluate the feasibility of daily TENS by measuring mean percent adherence of the cohort to daily TENS over two weeks. Adherence for each trial participant will be calculated by summing the number of one-hour TENS sessions completed and dividing by 14 total treatments. Adherence for the cohort will be summarized descriptively using mean, median, standard deviation, and range. We hypothesize a mean adherence of 75% for the cohort after two consecutive weeks of daily TENS therapy.

16.1.2 Secondary Endpoints

Change in CIPN20 sensory sub-score: Change in CIPN20 sensory sub-score over two weeks of daily TENS will be calculated. CIPN20 sensory scores will be compared between baseline and after two weeks of TENS therapy using a paired t-test or Wilcoxon signed rank test, where appropriate.

Pain Score: When logging their TENS use each day patients will also record scores of pain, numbness, and tingling on a 0-10 numerical rating scale so that day-today symptom changes can be monitored. Descriptive statistics such as mean, median, standard deviation, and range will be reported, with comparisons between time points conducted using paired t-tests or Wilcoxon signed rank tests, where appropriate.

Change in PROMIS29 score: Change in PROMIS29 score at two and six weeks compared to baseline. Descriptive statistics such as mean, median, standard deviation, and range will be reported.

Change in monofilament testing: Change in monofilament testing at two and six weeks compared to baseline. Descriptive statistics such as mean, median, standard deviation, and range will be reported.

Safety: Adverse events will be monitored throughout the trial and summarized descriptively using frequencies and percentages. CTCAE v.5 criteria will be used to grade all toxicities.

16.1.3 Sample size considerations

We hypothesize that TENS will improve the mean baseline CIPN20 sensory score from 15 to 12 points (20% improvement). We anticipate enrolling 27 patients for a one-arm paired design in order to detect a change in CIPN20 score of 3 with 80% power and a type 1 error of 0.05. This assumes a change in standard deviation (SD) of 5 with a study attrition rate of 11%. There is not an accepted threshold value in the aggregate CIPN20 score that defines CIPN and a variety of baseline CIPN20 sensory scores have been reported in the literature. Lavoie Smith et al compared baseline CIPN20 sensory scores in patients who received neurotoxic chemotherapy (20.17, SD 5.38) to those that did not (9.77, SD 1.71).[21] In an intervention trial for chronic CIPN by Smith et al patients in the placebo and treatment arms had baseline CIPN20 sensory scores of 15.83 (SD 4.49) and 13.47 (SD 5.73), respectively.[31] Based on reported values, it was concluded that a mean baseline CIPN20 sensory score of 15 was reasonable. A mean change in CIPN from 15 to 12 was chosen in order to balance the constraints of sample size while ensuring that a detected improvement with TENS is clinically meaningful. The minimal clinically important difference in CIPN20 sensory score has been reported to be between 2.5 to 5.9.[28] No change in CIPN20 sensory score SD after TENS was identified in the literature. Therefore a change in SD was projected to be 5, based on estimates that the CIPN20 SD at baseline and at two weeks would be 5 with a correlation coefficient of 0.5.

16.1.4 Analysis populations

All subjects enrolled in the study who receive TENS therapy will be included in the analysis for all endpoints (feasibility, efficacy, safety).

16.1.5 Safety monitoring

Adverse events will be collected as a secondary endpoint. Attributions for adverse events will be completed by study investigators and reviewed by the PI. Safety oversite will be provided by the DSMC, as outlined in section 17.

Stopping Rules: After 10 patients are enrolled, we will stop the study if any of the following rates of toxicities are exceeded: 1) >50% of patients develop grade 3 or higher rash attributed to TENS; 2) >50% of patients develop grade 3 or higher pain attributed to TENS; 3) >50% of patients develop grade 3 or higher muscle cramping attributed to TENS; 4) >50% of patients develop grade 3 or higher paresthesia attributed to TENS. **16.2 Data**

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Data and/or data forms will be submitted in the clinical management system - Online Collaborative Research Environment (ONCORE)- per Winship SOP 4.2 Data Completion Metrics.
All information in original records and certified copies of original records or clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial is considered source data. Source data are contained in source documents, which can be original records or certified copies of hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. Case Report Forms (CRFs) - Source data may be collected in the source documents or entered directly onto the case report forms.

All documentation of adverse events, records of TENS unit dispensation, and all IRB correspondence will be maintained for at least 2 years after the investigation is completed.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

Data collected under this protocol may be used to study breast cancer. Data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to data.

17. Provisions to Monitor the Data to Ensure the Safety of Participants

Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Classification of an Adverse Event

Severity of Event

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be

pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Adverse Event and Serious Adverse Event Reporting

Expectedness

Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Adverse Event Reporting

From the time of treatment allocation through 28 days following the end of the two-week intervention, all adverse events, that begin or worsen after informed consent, **must be recorded** by the investigator or designee at each examination on the Adverse Event case report forms/worksheets.
The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.
Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF/worksheet.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 1 to 5 will be used to characterize the severity of the Adverse Event.
If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form (or EOT/SEC/Survival Information in NOVDD). The occurrence of adverse events should be sought by non-directive questioning of the patient (patient) during the screening process after signing informed consent

and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (patient) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes) or Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 9.2 and which seriousness criteria have been met (include for NCDS trials).
7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4. All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.
Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Serious Adverse Event Reporting

For the time period beginning at treatment allocation through **28** days after the two-week TENS intervention, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to TENS, must be **submitted on an SAE form** and assessed by PI in order to determine reporting criteria to regulatory authorities, IRB, DSMC, FDA or Sponsor.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable.
All subjects with serious adverse events must be followed up for outcome.
Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode **within 24 hours** of the investigator receiving the follow-up information.
An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.
Any SAEs experienced after the reporting period described above should only be reported to FDA/IRB if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the **Serious Adverse Event Report Form**; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form, and submit the completed form.
Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets. All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Definition of unanticipated problems (UP) and reporting requirements

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or an outcome that meets **all** the following criteria: Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. This study will use the OHRP definition of unanticipated problems. Incidents or events that meet the OHRP criteria for UPs require the creation and completion of a UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information: Protocol identifying information: protocol title and number, PI's name, and the IRB project number; A detailed description of the event, incident, experience, or outcome; An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP; A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP. The IND sponsor will make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

The Data and Safety Monitoring Committee (DSMC)

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of

the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

I. Include and explain these additional points in all protocol data safety monitoring plans as they pertain to your study:

This study has been deemed Moderate Risk by PRMC which typically requires review by DSMC within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. However, since the enrollment period of this trial is 9 months, we plan for the DSMC to review 2 of the first 5 subjects within 6 months from the date that the first subject is accrued. We anticipate that subsequent monitoring will take place after the first 6 months of enrollment. The population continuing to receive intervention will be monitored on a study-by-study basis. At minimum, 10% of subjects accrued since previous monitoring will be reviewed. An additional subject (or subjects) may be selected based on previously noted monitoring deficiencies or at DSMC discretion. Continued monitoring will occur in six month intervals for the population continuing to receive intervention until the completion of the trial.

Monitoring Table

DSMP Requirement	How this Requirement is Met	Frequency	Responsible Party(ies)
Real-time review of participant data during initial data collection.	This requirement will be met per Winship's NCI approved DSMP	This happens every time information is obtained.	DSMC
Site Monitoring at pre-determined intervals: The Principal Investigator has a responsibility to ensure that the study is following all aspects of the protocol.	This requirement will be met per Winship's NCI approved DSMP	biannually	DSMC

100% review of regulatory files	DSMC monitors will review the protocol, amendments, informed consent documents, IRB submissions and meet with the principal investigator for clarification of study objectives	*Reviewed at a minimum of first and close-out visits*	DSMC
100% review of consent forms	Monthly QA check of 5-10 randomly selected consents to validate Central Subject Registration (CSR) and PRMS to conduct QA consent checks in real time as subjects are registered in OnCore vis CSR process	biannually	PRMS, QM
Review of credentials, training records, the delegation of responsibility logs (if applicable)	The Winship Associate Director for Clinical Research will establish the scope and allocate staff support to include procedures for obtaining charts, facilitating access to the electronic medical record, etc	biannually	DSMC
Comparison of case report forms (CRF) to source documentation for accuracy and completion	The PI is responsible for ensuring that instances of egregious data insufficiencies that may impact the scientific integrity of the trial	biannually	DSMC
Review of documentation of all adverse events	During the monitoring process, the DSMB reviews trial safety data for stopping rules, deviations, study amendments, accrual rates and monitoring reports for therapeutic investigator-initiated clinical trials and any other trial as deemed necessary	biannually	DSMC
Monitoring of critical data points (eligibility, study endpoints, etc.)	Once a trial is selected for monitoring, the assigned monitor will randomly select subject(s) for review based on parameters in Table 1 or 2 as noted above. Although the principal investigator and applicable study team members will receive notification of trial monitoring in advance, the subject selection will not be revealed in advance of the monitoring visit.	biannually	DSMC
Laboratory review of processing and storage of specimens	the assigned monitor will randomly select subject(s) for review based on parameters in Table 1 or 2 as noted above	Reviewed at first and close-out visits and at least biannually	DSMC

Assessment of laboratory specimens stored locally	If accrual at time of initial monitoring is> IO but :S 20, I 0% of subjects will be monitored at minimum. Thereafter, monitoring will not occur unless accrual reaches 30	Reviewed at first and close-out visits and at least biannually	DSMC
Test article accountability review	In addition to a comprehensive review of available toxicity data, the DSMC reviews all internal monitoring reports of trials under its purview	Reviewed at first and close-out visits and at least biannually	DSMC
Accountability logs, dispensing records, and other participant records	If accrual at time of initial monitoring is> IO but :S 20, I 0% of subjects will be monitored at minimum. Thereafter, monitoring will not occur unless accrual reaches 30	biannually	DSMC
For FDA regulated studies, the following requirements apply:	monitoring activities meet the FDA's requirements as delineated in 21 CFR 50, 21 CFR 56, 21 CFR 812 for studies conducted under an IDE and 21 CFR 312 for studies conducted under an IND.	Timing, frequency, and intensity of monitoring	DSMC
Monitoring methods (may include centralized, on-site, and self-assessment)	The internal monitoring team is independent from any study protocol and does not perform any trial-related specific duties in order to uphold an unbiased approach to study monitoring. Oversight of the monitoring process and identification/assignment of studies for monitoring is provided by the Manager of the Internal Monitors.	biannually	DSMC

a. How often will the data be analyzed?

Both clinical trial endpoints and safety data will be reviewed at regular intervals (weekly) by PI and study team, in addition to the periodic review by DSMC. See further specifics under Data Security in section “14. Risks to Participants”

b. Plan for recording, grading and reporting adverse events.

As described in the section above regarding serious event reporting, the time period beginning at treatment allocation through 28 days after the two-week TENS intervention, any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to TENS, must be submitted on an SAE form and assessed by PI in order to determine reporting criteria to regulatory authorities including IRB and DSMC. Grading is outlined in the above section on Classification of an Adverse Event.

c. How will oversight of the study team be carried out?

Oversight of the progress and safety of the trial will be provided by the PI and DSMB. Serious adverse events are not anticipated, but any occurring will be documented and reported according to Emory IRB policies and procedures. Cumulative adverse events and study progress summary will be communicated to the IRB at the time of continuing review.

d. How will study team be trained on study procedures?

Our TENS expert, Dr. Vinita Singh, will be selecting the TENS pad placement and providing instruction to all trial participants on the use of TENS. All participants will receive the same TENS operating instructions. Each provider performing monofilament testing with Neuropen will undergo standardized training.

18. Provisions to Protect the Privacy Interests of Participants

Participants will be assured of their voluntary participation in the study, their choice to answer or not answer any question, and the protocol for maintaining confidentiality.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification

number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

19. Economic Burden to Participants

The study sponsor (Emory) will pay for certain items and services the subject may receive in this study. Subjects will have to pay for the items or services for which the study sponsor does not pay. The sponsor will not pay for regular medical care. If subjects have insurance, Emory will submit claims to the insurance for items and services that the sponsor does not cover. The cost of the TENS unit will be covered by the study sponsor. The study visits will take place at regularly scheduled anesthesia-pain and medical oncology clinical visits and therefore will billed as regular medical care. Emory will send in only those claims for items and services that it reasonably believes the insurance will pay and that the sponsor has not paid. The actual amount that participants have to pay depends on whether or not they have health insurance and whether or not that insurance will pay for any research study costs. Generally, insurance companies will not pay for items and services that are required just for a research study. Some insurance companies will not pay for regular medical treatment or treatment for complications if in a study. If subject does not have insurance, Emory will review that particular case as part of its program for low-income patient care. The standard policies of that program will apply. The program will figure out if subjects have to pay any costs for taking part in the study and what those costs will be.

20. Consent Process

The initial informed consent discussion will occur in Winship Cancer Institute or the Emory Clinic. The informed consent will be obtained by the prospective participant's breast medical oncologist.

At Winship Cancer Institute, the informed consent is an ongoing, interactive process rather than a one-time information session. The consent form document is designed to begin the informed consent process, which provides the patient with ongoing explanations that will help them make educational decisions about whether to begin or continue participating in the trial. The research team knows that a written document alone may not ensure that the patient fully understands what participation means. Therefore, the research team will discuss with the patient the trial's purpose, procedures, risks and potential benefits, and their rights as a participant. The team will continue to update the patient on any new information that may affect their situation.

Consent will be obtained prior to any research-driven procedures. The investigator will assess the patient's capacity during his/her encounters with him or her. The investigator will give the person providing consent adequate opportunity to read the consent document before it is signed and dated.

It will be explained to prospective participants that the study involves research, the purpose of the research, the expected duration of participation, as well as the approximate number of participants to be enrolled. The study procedures, and identification of research procedures v. non-research will also be thoroughly discussed. It will be explained to participants that participation is voluntary and that the subject may discontinue at any time.

Refusal to participate or withdraw will not involve a penalty or loss of benefits to which the participant is otherwise entitled. Refusal will in no way affect the participant's future are. The participant will also be told of the possible consequences of the decision to withdraw from the research, and procedures for orderly termination of participation.

Any significant new findings developed during the course of the research that may affect the participant's willingness to continue to participate will be provided. Also explained will be anticipated circumstances

under which the subject's participation may be terminated by the investigator without the participant's consent.
Prospective participants will be provided with a description of any reasonably foreseeable risks or discomforts as well as a description of any benefits to the participant or to others that might be reasons expected from the research. Alternative procedures or courses of treatment will also be thoroughly discussed.
Prospective participants will also be given detailed information describing the extent to which confidentiality of records identifying the participant will be maintained and what records may be examined by the research staff, IRBs, sponsor, their representatives, and possibly the FDA or OHRP.
Also communicated to the participant will be an explanation that emergency medical care will be arranged for a study-related illness or injury, and an explanation of whether funds are set aside to pay for this care and/or compensation, and if so by whom (e.g., sponsor, subject, insurer). The participant is told the source of the study's funding.
All participants will be told of any additional costs that may result from participation in the research.
Consent will be done in person or remotely through secured email, phone or by electronic consenting using one of the methods that is Emory LITS approved (e.g. DocuSign) when available. We will follow Emory's guidance on use of electronic informed consent.

Non-English-Speaking Participants

A certified translator/interpreter will be present during the consenting process and all questions and concerns will be answered by the treating physician.

A Short Form in that specific language will be used. A certified translator/interpreter will be present during the consenting process and this will be documented. We will use what's available on Emory IRB website. For the languages that are not available, we will have the short form translated to that language and submit the IRB for review and approval prior to use. Process to Document Consent in Writing: Winship SOP 2.1:"Obtaining Informed consent for Interventional clinical trial" will be followed.

Participants who are not yet adults (infants, children, teenagers): N/A

Cognitively Impaired Adults: N/A

Adults Unable to Consent: N/A

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception): N/A

21. Setting

The research will be conducted at the Winship Cancer Institute of Emory University. Specifically, screening and Day 15 visits will take place at the patient's medical oncology appointments. The baseline/Day 1 and Day 42 assessments will take place at the anesthesia-pain provider clinic visits.

Potential participants will be identified in medical oncology clinics, multidisciplinary cancer clinic, surgical oncology clinics, multidisciplinary tumor board at Emory University.

22. Resources Available

Emory University was founded in 1836 and is a national center for teaching, research, and service. Emory University has been named as one of the nation's top 25 universities for more than a decade by the U.S. News and World Report. Emory University research partners include the Georgia Institute of Technology, the University of Georgia, Morehouse School of Medicine, the US Centers for Disease Control and Prevention, Children's Healthcare of Atlanta, and the Georgia Clinical and Translational Science Alliance (GACTSA). Emory University researchers received $734 million from external funding agencies in fiscal year 2018, including approximately $441 million in funding from federal agencies, $359 million of this from the National Institutes of Health (NIH).

Winship Cancer Institute (Winship) is Georgia's first and only National Cancer Institute (NCI)-designated Comprehensive Cancer Center (P30CA138292) and is dedicated to the integration of innovative clinical and basic science research with outstanding patient care for the prevention, treatment and control of cancer. First designated in 2009, Winship's NCI designation was renewed in 2012 and 2016, achieving an "outstanding" rating. Winship earned the prestigious Comprehensive Cancer Center designation from the NCI in 2016, after demonstrating that its outstanding programs are reducing the cancer burden on the state of Georgia through research conducted in its laboratories, its clinical trial program, and its population-based science. The institutional support for Winship was rated as 'exceptional' by the review panel.

The **Winship Clinic Building C** houses the primary offices and clinical space for cancer services including the medical oncology, hematology, and surgical oncology clinics, the radiation oncology program, and the Winship Ambulatory Infusion Center. In summer 2017, Emory Healthcare completed the expansion of **Emory University Hospital Tower** on Clifton Road. This nine-floor facility adds 144 inpatient beds to the hospital, of which more than 80% are dedicated to cancer care. The hospital expansion also accommodates cancer patient-specific intensive care units, an expanded BMT Unit with peri-transplant clinics to facilitate continuity of care, and a 24-hour cancer urgent care center, which serves as both a triage facility and short stay treatment center for patients with cancer-related medical concerns.
The **Winship Phase I Unit**, on the fourth floor of the Emory University Hospital Tower, is the largest unit in Georgia dedicated to the earliest and most critical phase of new cancer therapy evaluation. There is space for 15 private treatment bays, four clinic rooms, its own lab for doing patient blood work, a dedicated secure medication room, computer workspace for research and other support staff, and a "fast track" bay with three chairs for rapid use in patients who, for example, might need only a research lab test done.

As determined by the statistical power calculation we anticipate enrolling 27 patients for this clinical trial (approximately three patients per month over a nine-month accrual period). We believe this is feasible based on institutional data showing that approximately 15-20 patients per month with early stage breast cancer are started on taxane-based chemotherapy at Emory.

We anticipate that the screening and signing of the informed consent will take place with the patient's treating medical oncologist. Patients will be referred to anesthesia-pain for clinical assessment and treatment of CIPN. The Day 1/baseline visit will take place at the initial anesthesia-pain referral appointment. At that appointment, the CRC will review the participants' medications (including those for CIPN), and obtain baseline CIPN20/PROMIS29 scores, as well as initial pain, numbness and tingling scores. The anesthesia-pain physician will discuss TENS, obtain baseline monofilament testing, review TENS operating instructions, as well as identify the proper electrode pad placement and TENS settings for each participant. The participant will then complete the first 1-hour TENS treatment during the appointment.

On Day 3, the CRC will call each participant to ensure they understand the TENS operating procedures and to answer any other questions. The Day 15 assessment will take place at each participant's regularly scheduled medical oncology appointment. At that time the CRC will review the patient's diary from the first two-weeks (and enter information into Redcap), review medication changes, discuss any possible TENS adverse events, and repeat CIPN20/PROMIS29 assessments. The medical oncology physician or advanced practice provider will complete the monofilament assessment. The Day 42 assessment will take place at the anesthesia-pain follow up appointment where the CRC will review the diary, review medication changes, discuss any possible TENS adverse events, and repeat the final CIPN20/PROMIS29 assessments. The anesthesia-pain provider will complete the final monofilament assessment. All providers administering the monofilament testing with Neuropen will undergo the same training in order to limit inter-provider variability in testing.

23. Multi-Site Research when Emory is the Lead Site

N/A

24. References

1. Cancer Facts & Figures 2021. American Cancer Society. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2021/cancer-facts-and-figures-2021.pdf. Published 2021. Accessed2021.
2. Breast Cancer Facts & Figures 2019-2020. American Cancer Society. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2019-2020.pdf. Published 2019. Accessed2021.
3. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer. *New England Journal of Medicine.* 2018;379(2):111-121.
4. Jones S, Holmes FA, O'Shaughnessy J, et al. Docetaxel With Cyclophosphamide Is Associated With an Overall Survival Benefit Compared With Doxorubicin and Cyclophosphamide: 7-Year Follow-Up of US Oncology Research Trial 9735. *J Clin Oncol.* 2009;27(8):1177-1183.
5. De Laurentiis M, Cancello G, D'Agostino D, et al. Taxane-based combinations as adjuvant chemotherapy of early breast cancer: a meta-analysis of randomized trials. *J Clin Oncol.* 2008;26(1):44-53.
6. Kolb NA, Smith AG, Singleton JR, et al. The Association of Chemotherapy-Induced Peripheral Neuropathy Symptoms and the Risk of Falling. *JAMA Neurol.* 2016;73(7):860-866.
7. Salehifar E, Janbabaei G, Alipour A, Tabrizi N, Avan R. Taxane-induced peripheral neuropathy and quality of life in breast cancer patients. *J Oncol Pharm Pract.* 2020;26(6):1421-1428.
8. Timmins HC, Li T, Trinh T, et al. Weekly Paclitaxel-Induced Neurotoxicity in Breast Cancer: Outcomes and Dose Response. *Oncologist.* 2021;26(5):366-374.
9. Loprinzi CL, Lacchetti C, Bleeker J, et al. Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of Adult Cancers: ASCO Guideline Update. *Journal of Clinical Oncology.* 2020;38(28):3325-3348.
10. Joensuu H, Fraser J, Wildiers H, et al. Effect of Adjuvant Trastuzumab for a Duration of 9 Weeks vs 1 Year With Concomitant Chemotherapy for Early Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: The SOLD Randomized Clinical Trial. *JAMA Oncol.* 2018;4(9):1199-1206.
11. Qi W, Wang X, Gan L, Li Y, Li H, Cheng Q. The effect of reduced RDI of chemotherapy on the outcome of breast cancer patients. *Sci Rep.* 2020;10(1):13241.
12. Zhang L, Yu Q, Wu XC, et al. Impact of chemotherapy relative dose intensity on cause-specific and overall survival for stage I-III breast cancer: ER+/PR+, HER2- vs. triple-negative. *Breast Cancer Res Treat.* 2018;169(1):175-187.
13. Dailey DL, Rakel BA, Vance CGT, et al. Transcutaneous electrical nerve stimulation reduces pain, fatigue and hyperalgesia while restoring central inhibition in primary fibromyalgia. *Pain.* 2013;154(11):2554-2562.
14. Kumar D, Marshall HJ. Diabetic peripheral neuropathy: amelioration of pain with transcutaneous electrostimulation. *Diabetes Care.* 1997;20(11):1702-1705.
15. Cata JP, Weng HR, Chen JH, Dougherty PM. Altered discharges of spinal wide dynamic range neurons and down-regulation of glutamate transporter expression in rats with paclitaxel-induced hyperalgesia. *Neuroscience.* 2006;138(1):329-338.
16. Nahman-Averbuch H, Yarnitsky D, Granovsky Y, et al. Pronociceptive pain modulation in patients with painful chemotherapy-induced polyneuropathy. *J Pain Symptom Manage.* 2011;42(2):229-238.

17. Ma YT, Sluka KA. Reduction in inflammation-induced sensitization of dorsal horn neurons by transcutaneous electrical nerve stimulation in anesthetized rats. *Exp Brain Res.* 2001;137(1):94-102.
18. Leonard G, Goffaux P, Marchand S. Deciphering the role of endogenous opioids in high-frequency TENS using low and high doses of naloxone. *Pain.* 2010;151(1):215-219.
19. Gewandter JS, Chaudari J, Ibegbu C, et al. Wireless transcutaneous electrical nerve stimulation device for chemotherapy-induced peripheral neuropathy: an open-label feasibility study. *Support Care Cancer.* 2019;27(5):1765-1774.
20. Postma TJ, Aaronson NK, Heimans JJ, et al. The development of an EORTC quality of life questionnaire to assess chemotherapy-induced peripheral neuropathy: the QLQ-CIPN20. *Eur J Cancer.* 2005;41(8):1135-1139.
21. Lavoie Smith EM, Barton DL, Qin R, Steen PD, Aaronson NK, Loprinzi CL. Assessing patient-reported peripheral neuropathy: the reliability and validity of the European Organization for Research and Treatment of Cancer QLQ-CIPN20 Questionnaire. *Quality of Life Research.* 2013;22(10):2787-2799.
22. Kieffer JM, Postma TJ, van de Poll-Franse L, et al. Evaluation of the psychometric properties of the EORTC chemotherapy-induced peripheral neuropathy questionnaire (QLQ-CIPN20). *Qual Life Res.* 2017;26(11):2999-3010.
23. Loprinzi C, Le-Rademacher JG, Majithia N, et al. Scrambler therapy for chemotherapy neuropathy: a randomized phase II pilot trial. *Support Care Cancer.* 2020;28(3):1183-1197.
24. Tonezzer T, Caffaro LAM, Menon KRS, et al. Effects of transcutaneous electrical nerve stimulation on chemotherapy-induced peripheral neuropathy symptoms (CIPN): a preliminary case-control study. *J Phys Ther Sci.* 2017;29(4):685-692.
25. Shih V, Wan HS, Chan A. Clinical predictors of chemotherapy-induced nausea and vomiting in breast cancer patients receiving adjuvant doxorubicin and cyclophosphamide. *Ann Pharmacother.* 2009;43(3):444-452.
26. Cavaletti G, Cornblath DR, Merkies ISJ, et al. The chemotherapy-induced peripheral neuropathy outcome measures standardization study: from consensus to the first validity and reliability findings. *Ann Oncol.* 2013;24(2):454-462.
27. Mols F, Beijers T, Vreugdenhil G, van de Poll-Franse L. Chemotherapy-induced peripheral neuropathy and its association with quality of life: a systematic review. *Supportive Care in Cancer.* 2014;22(8):2261-2269.
28. Yeo F, Ng CC, Loh KWJ, et al. Minimal clinically important difference of the EORTC QLQ-CIPN20 for worsening peripheral neuropathy in patients receiving neurotoxic chemotherapy. *Support Care Cancer.* 2019;27(12):4753-4762.
29. Matthys MB, Dempsey AM, Melisko ME, et al. Incorporation of Patient-Reported Outcomes Measurement Information System to assess quality of life among patients with breast cancer initiating care at an academic center. *Cancer.* 2021;127(13):2342-2349.
30. Schneider BP, Shen F, Jiang G, et al. Impact of Genetic Ancestry on Outcomes in ECOG-ACRIN-E5103. *JCO Precis Oncol.* 2017;2017.
31. Smith TJ, Razzak AR, Blackford AL, et al. A Pilot Randomized Sham-Controlled Trial of MC5-A Scrambler Therapy in the Treatment of Chronic Chemotherapy-Induced Peripheral Neuropathy (CIPN). *J Palliat Care.* 2020;35(1):53-58.

Appendix A: Patient Reported Outcome Questionnaires

ENGLISH

EORTC QLQ – CIPN20

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31	Did you have tingling fingers or hands?	1	2	3	4
32	Did you have tingling toes or feet?	1	2	3	4
33	Did you have numbness in your fingers or hands?	1	2	3	4
34	Did you have numbness in your toes or feet?	1	2	3	4
35	Did you have shooting or burning pain in your fingers or hands?	1	2	3	4
36	Did you have shooting or burning pain in your toes or feet?	1	2	3	4
37	Did you have cramps in your hands?	1	2	3	4
38	Did you have cramps in your feet?	1	2	3	4
39	Did you have problems standing or walking because of difficulty feeling the ground under your feet?	1	2	3	4
40	Did you have difficulty distinguishing between hot and cold water?	1	2	3	4
41	Did you have a problem holding a pen, which made writing difficult?	1	2	3	4
42	Did you have difficulty manipulating small objects with your fingers (for example, fastening small buttons)?	1	2	3	4
43	Did you have difficulty opening a jar or bottle because of weakness in your hands?	1	2	3	4
44	Did you have difficulty walking because your feet dropped downwards?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week :	Not at All	A Little	Quite a Bit	Very Much
45 Did you have difficulty climbing stairs or getting up out of a chair because of weakness in your legs?	1	2	3	4
46 Were you dizzy when standing up from a sitting or lying position?	1	2	3	4
47 Did you have blurred vision?	1	2	3	4
48 Did you have difficulty hearing?	1	2	3	4
Please answer the following question only if you drive a car				
49 Did you have difficulty using the pedals?	1	2	3	4
Please answer the following question only if you are a man				
50 Did you have difficulty getting or maintaining an erection?	1	2	3	4

PROMIS–29 Profile v2.0

Please respond to each question or statement by marking one box per row.

	Physical Function	**Without any difficulty**	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDANX01	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
HI7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

26 June 2016

 Page 1 of 3

PROMIS–29 Profile v2.0

	Fatigue **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
FATEXP41	How run-down did you feel on average? ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Sleep Disturbance **In the past 7 days…**	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
Sleep109	My sleep quality was.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep116	My sleep was refreshing.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Ability to Participate in Social Roles and Activities	**Never**	**Rarely**	**Sometimes**	**Usually**	**Always**
SRPPER11_CaPS	I have trouble doing all of my regular leisure activities with others.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER18_CaPS	I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER23_CaPS	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER46_CaPS	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Pain Interference **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PAININ9	How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31	How much did pain interfere with your ability to participate in social activities? .	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ34	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

26 June 2016

PROMIS–29 Profile v2.0

Pain Intensity

In the past 7 days…

Global07	How would you rate your pain on average?.....	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst imaginable pain**

APPENDIX B: TENS Diary

Day of Treatment	TENS Start Time (AM/PM)	TENS End Time (AM/PM)	Total TENS Time (min)	Pain Today (0-10)[A]	Tingling Today (0-10)[A]	Numbness Today (0-10)[A]	Issues/Adverse Events[B]
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							

[A]Rate the symptom from 0-10 with 0 being the least to 10 being the most severe PRIOR to using TENS today
[B]Please explain any issues or side effects you have with using TENS

End of two-week treatment period question:

1) What is your overall impression of TENS therapy after using it for two weeks? Would you like to continue using it for the next 4 weeks?

Weeks 3-6 TENS Use:

End of Week	How many days out of 7 did you use TENS?	How long was each TENS session? (Goal 60 minutes)	Pain Today (0-10)[A]	Tingling Today (0-10)[A]	Numbness Today (0-10)[A]	Issues/Adverse Events[B]
3						
What is your overall impression of TENS during week 3?						
4						
What is your overall impression of TENS during week 4?						

End of Week	How many days out of 7 did you use TENS?	How long was each TENS session? (Goal 60 minutes)	Pain Today (0-10)[A]	Tingling Today (0-10)[A]	Numbness Today (0-10)[A]	Issues/Adverse Events[B]
5						
What is your overall impression of TENS during week 5?						
6						
What is your overall impression of TENS during week 6?						

APPENDIX C Abbreviations and definition of terms

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	Aspartate aminotransferase
BoR	Best objective response
BP	Blood pressure
C	Cycle
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CR	Complete response
CSA	Clinical study agreement
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
$C_{trough,ss}$	Trough concentration at steady state
CXCL	Chemokine (C-X-C motif) ligand
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation or special term	Explanation
eCRF	Electronic case report form
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
ILS	Interstitial lung disease
IM	Intramuscular
IMT	Immunomodulatory therapy
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System

Abbreviation or special term	Explanation
IWRS	Interactive Web Response System
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Minister of Health, Labor, and Welfare
miRNA	Micro-ribonucleic acid
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non–small-cell lung cancer
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PDx	Pharmacodynamic(s)
PFS	Progression-free survival
PFS2	Time to second progression
PGx	Pharmacogenetic research
PK	Pharmacokinetic(s)
PR	Partial response
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid
RR	Response rate
RT-QPCR	Reverse transcription quantitative polymerase chain reaction

Abbreviation or special term	Explanation
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SCLC	Small cell lung cancer
SD	Stable disease
SNP	Single nucleotide polymorphism
SoC	Standard of Care
T_3	Triiodothyronine
T_4	Thyroxine
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBDC	Web-Based Data Capture
WHO	World Health Organization