CEDARS-SINAI
SAMUEL OSCHIN COMPREHENSIVE CANCER INSTITUTE

IIT2019-08-ASHER-VOXXSOCK

Voxx Human Performance Technology Socks for Chemotherapy-Induced Peripheral Neuropathy: A Double Blind, Randomized, Controlled Crossover Trial

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

Signature: _____ **Date:** _____

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PROTOCOL REVISION HISTORY

Edits were made throughout the protocol. Substantive changes are listed below.

Protocol Version 2.0

1. Section 2.3.2.1 Change in Total Neuropathy Score modality.
2. Section 4.2.6: Clarification of exclusion criteria regarding prior participation in non-pharmacologic activities or classes such as mindfulness classes and scrambler therapies.
3. Section 6.1.1: Addition of Deep 6 Language regarding pre-screening.
4. Section 7.2.2: Addition of updated version of the Common Terminology Criteria for Adverse Events (CTCAE v.5)
5. Appendix: Addition of concomitant medications of interested (analgesics)
6. Appendix: Addition of Total Neuropathy Score Clinical Sheet

Protocol Version 3.0

1. Section 4.1, Inclusion Criteria: Removed the requirement for patients to speak English to allow for enrollment of non-English speakers.

2. Sections 6.1.2.1.1, 6.1.2.1.2 & 6.1.2.2: Removed online consent checklist, updated phone consent plan to align with current CCTO practices

3. Section 6.2.2, Procedures During Treatment & Schedule of Events Table: Added ± 2 days window for the reminder calls at Day 3, Day 7, Day 31 and Day 35

Protocol Version 4.0

1. Removal of Exclusion Criteria 4.2.2: Medical history of neuropathy from any type of nerve compression (e.g., carpal tunnel or tarsal tunnel syndrome, radiculopathy, spinal stenosis, brachial plexopathy, leptomeningeal carcinomatosis), as assessed by treating physician.

Protocol Version 5.0

1. 7.4 Safety Reporting Requirements updated to reflect most current process
2. Replacement of Docusign to RedCap for e-consenting method
3. 9.7 Adherence to Protocol updated to reflect most current process

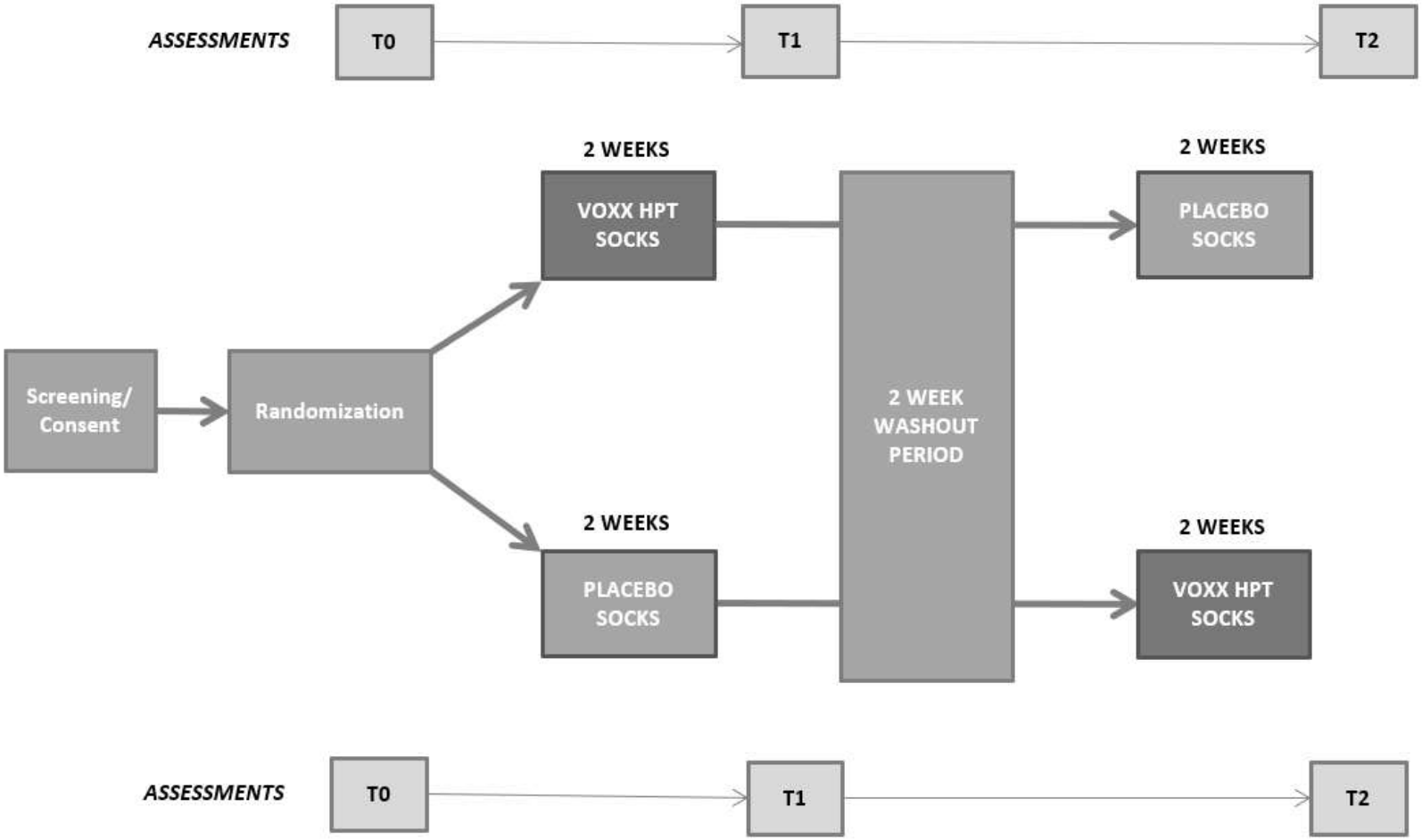
Protocol Version 6.0

1. Additional of the Torrance Site at the Hunt Cancer Center, local staff added to the protocol.

LIST OF ABBREVIATIONS

AE	Adverse Event
CIPN	Chemotherapy-Induced Peripheral Neuropathy
CTCAE	Common Terminology Criteria for Adverse Events
ESAS	Edmonton Symptom Assessment System
FACT/GOG-NTX	Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity
FDA	Food and Drug Administration
HPT	High Performance Technology
IRB	Institutional Review Board
TNSc	Total Neuropathy Score clinical
NCI	National Cancer Institute
PROMIS	Patient-Reported Outcomes Measurement Information System
SOCCI	Samuel Oschin Comprehensive Cancer Institute
TSH	Thyroid-Stimulating Hormone
TUG	Timed Up and Go
UPIRSO	Unanticipated Problem Involving Risks to Subject or Others

STUDY SCHEMA



STUDY SUMMARY

Title	Voxx Human Performance Technology Socks for Chemotherapy-Induced Peripheral Neuropathy: A Double Blind, Randomized, Controlled Crossover Trial
Protocol Number	IIT2019-08-ASHER-VOXXSOCK
Phase	Pilot
Methodology	Double blind, randomized, crossover
Study Duration	1 year
Study Center(s)	Cedars-Sinai Medical Center
Objectives	Primary Objective: To gather preliminary data on the impact of Voxx HPT Socks compared to placebo socks on chemotherapy-induced peripheral neuropathy in patients with cancer. Secondary Objectives: • To assess the impact of Voxx HPT Socks compared to placebo socks on quality of life in patients with cancer experiencing chemotherapy-induced peripheral neuropathy. • To assess the impact of Voxx HPT Socks compared to placebo socks on the experience of cancer-related symptoms in patients with cancer experiencing chemotherapy-induced peripheral neuropathy. • To assess the feasibility of using Voxx HPT Socks to treat chemotherapy-induced peripheral neuropathy in patients with cancer.
Number of Subjects	We will enroll up to 30 participants in order to have 20 evaluable participants total.
Diagnosis and Main Inclusion Criteria	• Stage 1-4 cancer (all types) • Completed taxane- or platinum-based chemotherapy, vinca alkaloids, or bortezomib at least three months (90 days) ago. Current use of anti-estrogen therapy, Herceptin, or PARP inhibitors is okay. • Self-reported average neuropathic pain score of at least 4 on a 10-point scale over the past 1 month. • Clinician's diagnosis of chemotherapy-induced peripheral neuropathy • Must not have participated in a non-pharmacologic therapy specifically for the treatment of chemotherapy-induced peripheral neuropathy, including Scrambler Therapy, mindfulness meditation, or other mind-body activities within 14 days (2 weeks) prior to randomization. • Concomitant use of analgesics is permitted if the dose has been stable for at least 2 weeks prior to study enrollment • Age ≥ 18 years. • Written informed consent obtained from subject and ability for subject to comply with the requirements of the study.

1.0 BACKGROUND AND RATIONALE

1.1 Background

Chemotherapy-induced peripheral neuropathy (CIPN) symptoms are a common sequelae of neurotoxic chemotherapies (e.g., taxanes, platinums, vinca alkaloids, bortezomib) and have been reported in 20-60% of patients following treatment.[1,2] CIPN symptoms include pain, numbness, tingling, impaired sensory function, and neuropathic pain in the hands and feet.[1,2] CIPN symptoms are at times severe enough to require reductions in chemotherapy dose, which may impair treatment efficacy.[3] Although reversible if treated early, CIPN often becomes chronic, persisting for years following chemotherapy and causing significant decrements to functioning and quality of life.[4-6] To date, few effective treatments have been identified. Although ASCO recommends duloxetine, it is felt to have only a modest benefit and is associated with several unpleasant side effects. Sensory impairments predominate in chronic CIPN, and treatments for these problems have not been developed.

1.2 Rationale

Voxx human performance technology (HPT) is reported to use proprietary technology to improve energy, strength, and balance. Via a specific pattern, Voxx HPT is reported to stimulate cutaneous sensory mechanoreceptors on the bottom of the feet. In turn, a precise afferent neural response activates the brainstem regulatory function via the peripheral nervous system. The Voxx HPT proprietary pattern is woven into a sock and is drug and electrical free. Anecdotal reports have suggested benefit for a variety of conditions including chronic pain, enhanced postural stability and balance, and improved energy. No formal clinical trials have been published to date in PubMed although a recent study (unpublished) found a clinically and significant decrease among patients with painful diabetic neuropathy using HPT after 1 week of use.

The objective of this double blind, randomized, crossover pilot study is to gain preliminary data on the effects of Voxx HPT Socks versus placebo socks for the treatment of chemotherapy-induced peripheral neuropathy in patients with cancer who have completed platinum and taxane-based chemotherapies.

This research is highly relevant to cancer as CIPN is one of the most challenging side effects of cancer treatment and can substantially impair critical daily activities such as driving and exercise and impair fine motor activities involving the use of hands, thus significantly impairing quality of life. CIPN can also result in early discontinuation of treatment, thus interfering with treatment dose and efficacy.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

2.1.1 To gather preliminary data on the impact of Voxx HPT Socks compared to placebo socks on chemotherapy-induced peripheral neuropathy in patients with cancer.

2.2 Secondary Objectives

2.2.1 To assess the impact of Voxx HPT Socks compared to placebo socks on quality of life in patients with cancer experiencing chemotherapy-induced peripheral neuropathy.

2.2.2 To assess the impact of Voxx HPT Socks compared to placebo socks on the experience of cancer-related symptoms in patients with cancer experiencing chemotherapy-induced peripheral neuropathy.

2.2.3 To assess the feasibility of using Voxx HPT Socks to treat chemotherapy-induced peripheral neuropathy in patients with cancer.

2.3 Endpoints

2.3.1 Primary Endpoint

2.3.1.1 Impact on chemotherapy-induced peripheral neuropathy will be *subjectively* measured by changes in scores on the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity (FACT/GOG-NTX) Neurotoxicity Subscale.

2.3.2 Secondary Endpoints

2.3.2.1 Impact on chemotherapy-induced peripheral neuropathy will be *objectively* measured by changes in scores on the Total Neuropathy Scale clinical I(TNSc) and Timed Up and Go (TUG) test.

2.3.2.2 Impact on quality of life will be measured by the changes in scores on the Patient-Reported Outcomes Measurement Information System 29 (PROMIS-29).

2.3.2.3 Impact on cancer-related symptom experience will be measured by changes in scores on the Edmonton Symptom Assessment Scale (ESAS).

2.3.2.4 Feasibility will be measured by the number of hours the socks are worn, as recorded in the patient's daily sock diary.

3.0 STUDY DESIGN

This is a double blind, randomized, crossover pilot study of Voxx HPT Socks versus placebo socks for the treatment of chemotherapy-induced peripheral neuropathy in patients with cancer. We will enroll up to 30 patients in order to have 20 evaluable patients total. Patients will be randomized 1:1 to one of the following regimens:

- Arm A: Continuous wear of Voxx HPT Socks for 2 weeks, followed by continuous wear of placebo socks for 2 weeks (separated by a 2-week washout period)
- Arm B: Continuous wear of placebo socks for 2 weeks, followed by continuous wear of Voxx HPT Socks for 2 weeks (separated by a 2-week washout period)

Patients will be evaluated at three timepoints using an objective neuropathy assessment as well as self-report questionnaires assessing chemotherapy-induced peripheral neuropathy, quality of life, and cancer-related symptoms (see Section 6.3 for assessment timepoints).

4.0 PATIENT ELIGIBILITY

4.1 Inclusion Criteria

4.1.1 Diagnosed with cancer, stage 1-4.

4.1.2 Completed taxane- or platinum-based chemotherapy, vinca alkaloids, or bortezomib at least three months (90 days) ago. Current use of anti-estrogen therapy, Herceptin, or PARP inhibitors is okay.

4.1.3 Clinical diagnosis of chemotherapy-induced peripheral neuropathy by clinician. This will be based on symptom history (paresthesias, dysesthesias, allodynia), loss of deep tendon reflexes, decreased vibratory sensation, or the presence of symmetrical stocking-glove numbness or paresthesias beginning after neurotoxic chemotherapy.

4.1.4 Self-reported average neuropathic pain score of at least 4 on a 10-point scale over the past 1 month.

4.1.5 Age ≥ 18 years

4.1.6 Concomitant use of analgesics is permitted if the dose has been stable for at least 2 weeks prior to study enrollment (no new analgesics have been added, discontinued, or changed in the 2 weeks prior to randomization).

4.1.7 Written informed consent obtained from subject and ability for subject to comply with the requirements of the study.

4.2 Exclusion Criteria

4.2.1 Syphilis, alcoholic neuropathy, diabetic neuropathy, neurological disorders, brain injury, or stroke, as assessed by the treating physician.

4.2.2 Neuropathy related to abnormal TSH or B12 levels as assessed by treating physician.

4.2.3 Current severe depression, suicidal ideation, bipolar disease, alcohol abuse, or major eating disorder, as assessed by the treating physician.

4.2.4 Currently participating in another CIPN-targeted program or trial.

4.2.5 Participated in a non-pharmacologic therapy specifically for the treatment of chemotherapy-induced peripheral neuropathy, including Scrambler Therapy, mindfulness meditation, or other mind-body activities within 14 days (2 weeks) prior to randomization.

5.0 TREATMENT PLAN

5.1. Treatment Administration

Patients will be randomized 1:1 to one of the following regimens:

- Arm A: Continuous wear of Voxx HPT Socks for 2 weeks, followed by continuous wear of placebo socks for 2 weeks (separated by a 2-week washout period)
- Arm B: Continuous wear of placebo socks for 2 weeks, followed by continuous wear of Voxx HPT Socks for 2 weeks (separated by a 2-week washout period)

Voxx HPT Socks are commercially-available, FDA-exempt compression socks that are drug and electrical free. The Voxx HPT proprietary pattern is woven into a sock that is made of 70% cotton, 25% polyester, 3% spandex, and 2% nylon. Placebo socks will be made of the same fabric and will be identical in appearance to the HPT socks.

Prior to each 2-week treatment window, patients will be provided with 6 pairs of Voxx HPT socks or placebo socks. The investigator and patient will be blinded to treatment assignment between Voxx HPT first versus placebo first.

Patients will be asked to wear the socks continuously during both waking and sleeping hours, except when showering, bathing, or swimming. The socks should only be worn by the patient and should not be shared with other members of the household.

Both the Voxx HPT Socks and the placebo socks can be washed on delicate cycle and worn repeatedly.

Patients will be asked to keep a daily record of approximately how many hours the socks were worn, and whether the socks were worn while sleeping.

5.2 Method of Assigning Subjects to Treatment Groups

Study participants will be randomized 1:1 to the two treatment arms of the study in random block sizes of 4 and 6 subjects. Randomization will occur after patients' study eligibility has been confirmed.

5.3 Blinding

As this is a double-blind study, the patient and all but two members of the study team (Team Lead and Team Manager) will be blinded to treatment arm assignment.

The following study procedures will be in place to ensure double-blind administration of study treatments:

- The Team Lead and Team Manager will remain the only unblinded members of the study team and will be responsible for participant randomization.
- Access to the randomization code will be strictly controlled.
- The Team Lead or Team Manager will be responsible for the distribution of Voxx HPT socks versus placebo socks to the study coordinator(s), who will then distribute them to the patients.
- Unblinded study staff will not administer patient assessments.
- The Voxx HPT Socks and placebo socks will be identical in design to maintain the blind.
- Packaging and labeling of Voxx HPT Socks and placebo socks will be identical to maintain the blind.

5.4 Concomitant Therapy

Concomitant medications of interest will be recorded at screening using chart abstractions and patient self-report. Concomitant use of analgesics is permitted if the dose has been stable for at least 2 weeks prior to study enrollment. Concomitant medications of interest will also be abstracted from medical record at T0, T1, and T2.

Current participation in another CIPN-targeted program or trial is not allowed.

5.5 Duration of Study Participation

The study duration per subject will be up to 10 weeks, with up to 1 month of screening and 6 weeks of treatment (including the 2-week washout period).

6.0 STUDY PROCEDURES

6.1 Screening Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent.

All screening procedures must be performed within 30 days prior to T0 (baseline) unless otherwise stated. The screening procedures include:

6.1.1 Pre-screening

Study patients will be identified by study staff, pre-screening physician clinics, and by physician referral. Additionally, the Deep 6 Cohort Builder will be used to generate lists of potentially eligible patients who have been diagnosed with cancer, stage 1-4. Eligible patients will have completed chemotherapy at least three months (90 days) prior to pre-screening and have a clinical diagnosis of chemotherapy-induced neuropathy. d. A member of the patient's treatment team will introduce the study in person, by email, or by phone, or the study team will contact the patient using the CSMC Research Interest Letter.

6.1.2 Informed Consent

6.1.2.1 In-Person Consenting

For patients who are recruited during a clinic visit, the MD-Investigator or other approved consenter will briefly introduce the study. If the patient is interested, the consent documents will be presented electronically on an iPad or on paper (based on the patient's preference). In-person electronic consenting and paper consenting procedures are outlined below.

6.1.2.1.1 In-Person Electronic Consenting via RedCap

The consent document (will be presented on an iPad and subjects will have the option of providing an electronic signature supported by the RedCap application. The MD-Investigator or other approved consenter will go through the regular consent process and document their discussion. Then the iPad will be transferred to the patient who will view the informed consent form. After reviewing the form, the patient will have the option to sign at the time of the clinic visit, take the consent home and return for consent or consent online from home (see Section 6.1.2.2), or decline study participation. The consenter will electronically sign ICF. Due to the low-risk nature of this study, patients will be permitted to consent on the same day. All consenting procedures are followed for online or paper consenting, including time to review consent, time to ask questions, the patient will not be rushed or coerced, the patient will be informed of the voluntary nature of research, and all other options will be discussed. All patients will be given a signed copy of the consent form and a study contact card.

6.1.2.1.2 In-Person Paper Consenting

If the patient prefers not to view the consent form electronically, a paper version of the consent form will be presented. The MD-Investigator or other approved consenter will go through the regular consent process and document their discussion by utilizing the approved discussion checklist. After reviewing the consent form, the patient will have the option to sign at the time of the clinic visit, take the consent home and return for consent or consent online from home (see Section 6.1.2.2), or decline study participation. Due to the low-risk nature of this study, patients will be

permitted to consent on the same day. All consenting procedures are followed for online or paper consenting, including: time to review consent, time to ask questions, the patient will not be rushed or coerced, the patient will be informed of the voluntary nature of research, and all other options will be discussed. All patients will be given a signed copy of the consent form.

6.1.2.2 Phone Consenting

In other cases, the MD-Investigator may introduce the study and then ask the patient if they would like to be contacted with more details. The MD-Investigator will notify study staff approved to consent to this protocol. If the patient is interested, study staff will obtain verification of the potential participant's identity by collecting at least two Electronic Health Record (EHR) identifiers, e.g., name, date of birth, social security number, address, email address, etc., and go through the regular consent process.. This discussion will be documented. The link to the secured consent will be emailed to the patient via RedCap. The patient will have the option to sign electronically via RedCap, return to the clinic to discuss and sign the consent in person with study staff, or decline study participation. Due to the low-risk nature of this study, patients will be permitted to consent on the same day. All consenting procedures are followed for in-person or phone consenting, including: time to review consent, time to ask questions, the patient will not be rushed or coerced, the patient will be informed of the voluntary nature of research, and all other options will be discussed. If the patient chooses to consent to the study, both the patient and consenter will sign the form and the patient will be given a signed copy of the consent forms.

6.1.3 Medical history

Review of complete medical, surgical, oncology and psychosocial history via chart abstraction.

6.1.4 Concomitant medications

Concomitant medications of interest will be recorded via chart abstraction and patient self-report. Concomitant use of analgesics is permitted if the dose has been stable for at least 2 weeks (no new analgesics have been added, discontinued, or changed in the last 2 weeks). Changes will not be permitted while on-study.

6.1.5 Self-reported Pain

Participants will be asked to grade their average neuropathic pain over the last month on a scale of 1-10. The participant may provide their answer verbally, electronically, or on paper.

6.1.6 Review subject eligibility criteria

6.2 Procedures On-Study

6.2.1 On-Study Procedures Prior to Treatment

T0 (Baseline) – To be completed within 2 weeks of treatment start date
Questionnaires can be emailed, mailed, or given in person.

- **Concomitant Medications**
  All current medications will be abstracted from the medical record review at T0 visit.
- **Demographics Questionnaire**

Demographic information will be collected via patient report, including gender, age, height, weight, ethnicity, race, marital status, employment status, income level, and highest level of education.

- **Total Neuropathy Score clinical (TNSc)** – *Physician or Nurse Assessed*
  The TNSc is a 6-item tool that combines patient report of subjective sensory and motor symptoms, deep tendon reflexes, manual muscle testing of distal muscles, pin sensibility, and quantitative vibration thresholds using a Biothesiometer®. Total score ranges from 0-24 points, with higher scores indicating worse neuropathy. **Timed Up and Go Test (TUG)**
  The TUG is a standard test used to assess balance and fall risk.[7] The test measures the time taken by an individual to stand up from a standard arm chair, walk a 10 feet, turn around, walk back to the chair, and sit down.
- **Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity (FACT/GOG-NTX), Version 4; *Neurotoxicity Subscale Only***
  The FACT/GOG-NTX Neurotoxicity Subscale is a validated 11-item self-report questionnaire that evaluates symptoms and concerns associated specifically with chemotherapy-induced neuropathy.[8]
- **Patient-Reported Outcomes Measurement Information System 29 (PROMIS 29)**
  PROMIS-29 is a collection of short form instruments which encompass 7 PROMIS domains (depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, and ability to participate in social and activities) in addition to a single item assessing pain intensity. The PROMIS 29 contains 4 items per domain plus one pain intensity item, totaling 29 items. Each domain is scored separately.
- **Edmonton Symptom Assessment System (ESAS)**
  The ESAS is a validated, self-administered tool used to screen and measure common symptoms among patients with cancer.[9] It consists of 10-items rated on a numerical scale (0=best, 10=worst) assessing pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, sleep, appetite, and wellbeing. If a patient rates their score in between two numbers, the researchers will round up to the nearest higher number. ESAS scores can be obtained via chart abstraction if completed within visit window.
- **Sock Dispensing**
  Patients on Arm A will be given 6 pairs of Voxx HPT socks along with a start date on when the patient should begin wearing the socks (start date = Day 1). Patients will be asked to wear the socks continuously during both waking and sleeping hours for two weeks from that start date, except when showering, bathing, or swimming.

  Patients on Arm B will be given 6 pairs of placebo socks along with a start date on when the patient should begin wearing the socks (start date = Day 1). Patients will be asked to wear the socks continuously during both waking and sleeping hours for two weeks from that start date, except when showering, bathing, or swimming.

  Patients will be told that the socks can be washed on delicate cycle and worn repeatedly. Patients will be asked not to let others wear the socks during the course of the trial.

  The investigator and patient will be blinded to treatment assignment.

- **Daily Sock Diary Instruction**

Patients will be given the Daily Sock Diary form and asked to keep a daily record of approximately how many hours the socks were worn, and whether the socks were worn while sleeping.

Day 0 – One Day before Treatment Start Date *(-2 days)*

- A phone call will be made to the patient to remind them to start wearing their socks the following day (Day 1), and to keep daily records of approximately how many hours the socks were worn.

6.2.2 Procedures During Treatment

WEEK 1

- **Continuous Sock Wearing** (Arm A: Voxx HPT Socks; Arm B: Placebo)
- **Daily Sock Diary Entries**
  Patients will be asked to keep a daily record of approximately how many hours the socks were worn, and whether the socks were worn while sleeping.
- **Reminder Calls**
  Phone calls will be made to the patients on Day 3 (+/- 2 Days) and Day 7 (+/- 2 days) to remind the patients to wear their socks and to monitor for any adverse events. Thereafter, patients will be able to call a study coordinator with any questions or concerns.

WEEK 2

- **Continuous Sock Wearing**
- **Daily Sock Diary Entries**

WEEK 3 *(WASHOUT)*

- **T1 – Day 15 (+3 days)**
  All procedures below are completed for research only.
  - **Concomitant Medications of Interest**

  Current medications of interest will be abstracted through medical record review at T1 visit.
  - **TNSc** – *Physician or Nurse Assessed*
  - **TUG**
  - **Questionnaires** (can be emailed, mailed, or given in person)
    - **FACT/GOG-NTX v4, Neurotoxicity Subscale**
    - **PROMIS-29**
    - **ESAS**
  - **Sock Diary Submission** – Patients will be asked to submit their daily sock diaries to the coordinator.
  - **Sock Return** – Patients will be asked to return all study socks to the study coordinator.
  - **Sock Dispensing –** Patients will be given 6 new pairs of socks, according to assigned arm:
    - Patients on Arm A will be given 6 pairs of placebo socks along with a start date on when the patient should begin wearing the socks (start date = Day 29). Patients will be asked to wear the socks continuously during both waking and sleeping hours for two weeks from that start date, except when showering, bathing, or swimming.
    - Patients on Arm B will be given 6 pairs of Voxx HPT socks along with a start date on when the patient should begin wearing the socks (start date = Day 29). Patients will be asked to wear the socks continuously during both waking and sleeping hours for

two weeks from that start date, except when showering, bathing, or swimming.
    - Patients will be reminded that the socks can be washed on delicate cycle and worn repeatedly. Patients will be reminded not to let others wear the socks during the course of the trial.
    - The investigator and patient will be blinded to treatment assignment.
  - **Daily Sock Diary Instruction –** Patients will be reminded to keep a daily record of approximately how many hours the socks were worn and to note whether the socks were worn while sleeping.

WEEK 4 *(WASHOUT)*

- **Day 28 – One Day before Crossover Treatment Start Date** *(-2 days)*
  A phone call will be made to the patient to remind them to start wearing their socks the following day (Day 29), and to keep daily records of approximately how many hours the socks were worn.

WEEK 5

- **Continuous Sock Wearing**
- **Daily Sock Diary Entries**
- **Reminder Calls**
  Phone calls will be made to the patients on Day 31(+/- 2 Days) and Day 35(+/-2 Days) to remind the patients to wear their socks and to monitor for any adverse events. Thereafter, patients will be able to call a study coordinator with any questions or concerns.

WEEK 6

- **Continuous Sock Wearing**
- **Daily Sock Diary Entries**

Any patient who stops study treatment early will be encouraged to return to the study center for all study visits. The reason(s) for any study or assessment discontinuation will be documented.

6.2.3 T2 (End of Treatment Visit) – Week 7, Day 43 (+3 days)

All procedures below are completed for research only.

- Concomitant Medications of Interest
  Current medications of interest will be abstracted through medical record review at T2 visit.
- **TNSc** – *Physician or Nurse Assessed*
- **TUG**
- **Questionnaires** (can be emailed, mailed, or given in person)
  - **FACT/GOG-NTX v4, Neurotoxicity Subscale**
  - **PROMIS-29**
  - **ESAS**
- **Sock Return –** Patients will be asked to return all study socks to the study coordinator.
- **Sock Diary Submission** – Patients will be asked to submit their daily sock diaries to the coordinator.

Time and Events Table

	Screening	**T0 (Baseline)** within 2 weeks of treatment start date		*Treatment*				**T1***		*Crossover Treatment*				**T2*** (End of Treatment Visit)
Day			**0**	**1**	**3**	**7**	**8-14**	**15**	**28**	**29**	**31**	**35**	**36-42**	**43**
Week				**1**	**1**	**1**	**2**	**3**	**4**	**5**	**5**	**5**	**6**	**7**
Informed Consent	X													
Medical History	X													
Concomitant Medications of Interest	X	X						X						X
Pain Assessment (Self-Report)	X													
Assessment of Eligibility	X													
Demographics Questionnaire		X												
TNSc (Physician or Nurse Assessed)		X						X						X
TUG		X						X						X
FACT/GOG-NTX – Neurotoxicity Subscale		X						X						X
PROMIS-29		X						X						X
ESAS		X						X						X
Socks Dispensed to Patients		X						X						
Socks Returned by Patients								X						X
Treatment Implementation				Continuous Sock Wearing; See Section 6				*WASHOUT PERIOD*		Continuous Sock Wearing; See Section 6				
Sock Diary Entries				*Daily Entries*						*Daily Entries*				
Sock Diary Submission								X						X
Patient Reminder Phone Calls			X^		X^1	X^1			X^		X^1	X^1		
Adverse Event Monitoring					X	X					X	X		

*Time point has a +3 day window
^Day 0 and Day 28 reminder calls have a -2 day window
X^1 Day 3, Day 7, Day 31 and Day 35 reminder calls have a ±2 day window

6.4 Removal of Subjects from Study

Patients can be taken off the study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

6.4.1 Patient voluntarily withdraws;

6.4.2 Patient withdraws consent (termination of study participation);

6.4.3 Patient is unable to comply with protocol requirements;

6.4.4 Treating physician judges continuation on the study would not be in the patient's best interest.

7.0 ADVERSE EVENTS

7.1 Adverse Event Monitoring

Adverse events are extremely unlikely as a result of participation in this study. Patients will be monitored for signs of sock-related skin irritation or discomfort. Only adverse events related to the study intervention will be recorded and reported. Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of Subjects enrolled in the studies as well as those who will enroll in future studies using similar interventions. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

All patients experiencing an adverse event related to the intervention will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- there is a satisfactory explanation other than the study intervention for the changes observed; or
- death.

7.2 Definitions

7.2.1 Definition of Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention. For this study, patients will only be monitored for AEs related to study intervention.

The only expected AEs for this study are:

- Skin irritation on the foot or ankle
- Foot/ankle discomfort
- Temporary mild increase of pain in the foot during the first 3 days of sock wear.

7.2.2 Severity of Adverse Events

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE v5 is available at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

If no CTCAE grading is available, the severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
Moderate (grade 2): the event causes discomfort that affects normal daily activities.
Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
Life-threatening (grade 4): the patient was at risk of death at the time of the event.
Fatal (grade 5): the event caused death.

7.2.3 Serious Adverse Events

A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

7.2.3.1. Results in death.

If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

7.2.3.2. Is life-threatening.

(the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).

7.2.3.3. Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

7.2.3.4 Results in persistent or significant disability or incapacity.

7.2.3.5 Is a congenital anomaly/birth defect

7.2.3.6 Is an important medical event

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event“.
For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.3 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5).

Step 2: Grade the adverse event using the NCI CTCAE v5.

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:
- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed below:
- Skin irritation on the foot or ankle
- Foot/ankle discomfort

7.4 Safety Reporting Requirements

7.4.1 Reporting to the Principal Investigator

The Principal Investigator (PI) must be notified by study staff or co-investigators within 24 hours of learning of any SAEs, regardless of attribution and expectedness, occurring during the study or up until the end of treatment visit.

Contact for Expedited Reporting:

Arash Asher, MD, 310-423-1218, Arash.Asher@cshs.org

Alternate Contact for Expedited Reporting:

Phillip Chang, DO, 310-467-4498, Phillip.Chang@cshs.org

7.4.2 Reporting to DSMC

Serious Adverse Events deemed to be related to the protocol and on-study deaths, including death of a research subject unless the death is expected (e.g. due to disease progression) are to be reported to the DSMC within 24 hours of awareness. Hardcopies or electronic versions of the MedWatch Form 3500A (Mandatory Reporting) or a narrative report, along with any other supporting documentation available, should be submitted to the DSMC Coordinator. The DSMC Coordinator will forward the information to the DSMC Chair, and/or medical monitor. The DSMC Chair will review all documentation upon receipt from the DSMC Coordinator and determination of whether the following actions are required: 1) takes action immediately, 2) convenes a special DSMC session (physical or electronic), or 3) defers the action until a regularly scheduled DSMC meeting. Reports are to be emailed to the DSMC team at GroupSOCCICCTODSMCAdmin@cshs.org.

7.4.3 Reporting to the Device Manufacturer

Serious Adverse Events deemed to be related to the protocol and on-study deaths, including death of a research subject unless the death is expected (e.g. due to disease progression) are to be reported to the Device Manufacturer within 24 hours of awareness. This will be done via a narrative email.

7.4.4 Reporting to the Institutional Review Board (IRB)

As per the Cedars-Sinai IRB Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy, the IRB must be notified of all UPIRSOs as soon as possible, but no later than 10 business days from when the study team learned of any of the following events:

1. Any internal SAE, AE or Research-Related Subject Injury (RRSI), which in the opinion of the Principal Investigator was unanticipated or unexpected, and has a reasonable possibility of relationship to the research.
2. Any actionable external SAE, AE, SUSAR, development safety update report (DSUR), or FDA MEDWATCH report deemed to be a UPIRSO. An event is considered “actionable” if it warrants a change to the conduct of the study.
3. Any internal or external UADE.
4. Any accidental, unintentional protocol or consent/HIPAA related deviation that may impact subjects’ rights, safety, or welfare. See section 10.8.3.
5. Any planned protocol exception or eligibility waiver. See sections 10.8.2 and 10.8.3.
6. Changes to the research or protocol deviations made without prior IRB approval in order to eliminate apparent immediate hazard to a research subject..(Note: These must be reported to the IRB within 5 business days.)
7. Problems, events, unanticipated incidental findings, billing problems, or other events, outcomes, or new information related to the research (e.g., publication, safety monitoring report, interim findings, product labeling changes, findings generated from preclinical, animal studies) that may adversely affect the rights, safety, or welfare of the subjects or others, put subjects or others at increased risk, compromise the research data, or require/recommend changes to the study conduct.
8. Subject complaints or concerns that cannot be resolved by the research staff to the subject’s satisfaction.
9. Breach or potential breach of confidential or sensitive information.
10. Incarceration of a subject who is enrolled in a study that is not approved by the IRB to include prisoners.

7.5 Unblinding Procedures

Unblinding will occur when all data has been entered into the database for all participants and the team has declared the study dataset to be complete. Emergency unblinding will only occur when knowledge of the investigational product is essential for the safety of the patient. The investigator will document in the patient’s source document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to serious adverse event). Unblinding will be reported to the IRB at the time of annual Continuing Review unless it occurs as part of managing a UPIRSO and then will be reported along the same timelines as the UPIRSO.

8.0 STATISTICAL CONSIDERATIONS

Sample size and randomization: This is a pilot crossover study to collect data on effect sizes for the outcomes. Patients will be randomized to one of two treatment sequences as Voxx socks then placebo socks, or placebo socks then Voxx socks. We will enroll 30 patients to allow for dropout to obtain 20 evaluable patients.

Statistical Methods: The fundamental analytic approach will be based on a within-subjects comparison of the main outcome measured with Voxx socks versus that measured on placebo in this crossover trial. The primary approach will used linear mixed models with time and treatment effects, adjusted for the repeated measures of subjects nested within sequence in the correlation structure. Carry-over effects will be tested by examining the interaction between treatment and period. In the unlikely event of a statistically significant carry over effect, only data from the first period will be used for the analysis. The overall type I error rate for the primary outcome measure will be controlled at 5%. The main outcome is the score on the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity (FACT/GOG-NTX) Neurotoxicity Subscale.

Data will first be assessed for reliability and general integrity (e.g., distribution characteristics) to ensure that appropriate statistical techniques are applied. Our basic approach to the analysis assumes there are no carry-over effects between the two treatment periods. All subjects entered into the trial will be included in the analysis. Strictly speaking, this is not an “intent-to-treat” policy because the crossover design should assure that each participant receives both Voxx socks as well as placebo in the appropriate treatment periods. If a study participant did not receive one or both treatments, they cannot be included in the primary analysis because that analysis relies on within-subject differences between the treatments. The status of all participants will be reported in the analysis as in the CONSORT recommendations. The fundamental analytic approach will be based on a within-subjects comparison of the relevant outcome measured on Voxx socks versus that measured on placebo. Secondary endpoints will be analyzed the same way as the primary endpoint.

For all secondary objectives, a significance level of 0.05 will be used. A patient will be considered to have completed treatment if they have completed FACT/GOG-NTX at baseline, both treatment periods, and at least 50% compliance for both treatment periods. Compliance will be defined as wearing the socks for at least 16 hours per day.

9.0 STUDY MANAGEMENT

9.1 Conflict of Interest

Any reportable conflict of interest will be disclosed to the local IRB and will be outlined in the Informed Consent Form.

9.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s),and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA

Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

9.3 Registration Procedures

All subjects that sign informed consent will be assigned a subject number sequentially by their date of consent. Those subjects that do not pass the screening phase will be listed as screen failures on the master list of consented subjects. Eligible subjects, as determined by screening procedures and verified by a treating investigator, will be registered on study at Cedars Sinai Medical Center by the Study Coordinator.

Issues that would cause study participation delays after registration should be discussed with the Principal Investigator (PI). If a patient does not begin on-study procedures following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Assignment of Subject ID: The study team will track all subjects who sign consent on a subject screening/enrollment log using a unique ID. Subjects found to be ineligible will be recorded as screen failures. Subjects found to be eligible will be registered using only the three-digit numeric ID assigned at screening that follows the standard SOCCI format.

A) Eligibility Verification

Prior to registration, subject eligibility must be verified by the Principal Investigator or Treating Investigator and Study Coordinator.

B) Registration

After eligibility is verified, registration is completed as follows:

- Assign a patient study number
- Enter the patient in OnCore
- Mark the patient as on-study in OnCore

9.4 Data Management and Quality Control and Reporting

The data will be entered into a validated database. The study team will manage the database development, data collection, and data entry. The data will be monitored by the study team and the PI. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

9.5 Data and Safety Monitoring

9.5.1 Data Monitoring and Quality Assurance

Adherence to the protocol, Good Clinical Practices (GCP), and institutional policy will be monitored by the PI during the course of the study through routine departmental/study staff or Survivorship, Lifestyle, and Supportive Health (SLASH) meetings as applicable.). In addition, the SOCCI Cancer Clinical Trials Office (CCTO) Quality Management Core (QMC) will conduct a focused internal monitoring visits and audits for data quality and protocol adherence. For any protocol, QMC has the authority to request more frequent reviews or closer safety monitoring if it is deemed appropriate for any reason.

9.5.2 Safety Monitoring

As a single-site study, oversight of the progress and safety of the study will be provided by the PI. The PI will maintain continuous safety monitoring for the duration of the study by reviewing subject/study data. Adverse events and unanticipated problems not expected, but if they occur, they will be documented and reported according to CSMC IRB policies and procedures. If the PI becomes aware of any new safety information that may place subjects at increased risk than what was previously known the IRB will be promptly notified and if warranted, enrollment may be held until the PI determines whether a modification to the study is necessary and/or the informed consent documents are updated accordingly.

In addition, this protocol will utilize the SOCCI Data and Safety Monitoring Committee will provide another layer of data and safety oversight. Committee membership includes experts in the field of oncology, nursing, pharmacy, and biostatistics in reviewing the over data, safety, quality, and study integrity of SOCCI interventional IITs. DSMC membership and responsibilities are governed by the committee charter. The DSMC findings and recommendations will be reported in writing to the Principal Investigator. A summary letter will be forwarded by the Principal Investigator or his/her designee to the Cedars-Sinai Medical Center IRB. Refer to the DSMC Charter for details of the DSMC review.

9.6 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the study. Study documents should be kept on file per institutional guidelines.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. Study documents should be kept on file until three years after the completion and final study report of this investigational study or as required by institutional guidelines.

9.7 Adherence to Protocol

It is the responsibility of the Investigator-sponsor to ensure that patient recruitment and enrollment, treatment, follow-up for toxicities and response, and documentation and reporting at SOCCI are all performed as specified in the protocol. Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, or a protocol exception request approved by the SOCCI Medical Director and CSMC IRB, the study shall be conducted exactly as described in the approved protocol.

9.7.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval. For any such emergency modification implemented, the IRB must be notified as soon as possible, but no more than 10 days from the investigator's awareness of the event.

9.7.2 Protocol Exceptions and Eligibility Waivers

An exception is an anticipated or planned deviation from the IRB-approved research protocol, as described in the IRB Policy*, Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement.*

A protocol exception most often involves a single subject and is not a permanent revision to the research protocol. Protocol exceptions that extend beyond a single subject should result in a protocol amendment to avoid serial violations.

Planned exceptions to the protocol that are more than logistical in nature and/or impact an eligibility criterion, affect timing of study drug administration, or the investigator assesses the event may impact subject safety and/or study integrity, may not be implemented without prior IRB approval. The PI or her/his designee is responsible for submitting a protocol exception request and its supporting documents to the CSMC IRB if it meets the CS-IRB UPIRSO policy guidelines of a reportable exception/waiver. Study team should also refer to the IRB Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement guidelines to determine which deviations and exception requests require IRB reporting. Once IRB approved, the deviation or exception can be implemented.

Special considerations for Eligibility Waivers (EW)
In general, subjects who do not meet the eligibility requirements should not be enrolled. In the rare event that it is appropriate for subject inclusion, the rationale/justification and subject case history should be submitted to the IRB for approval. Such requests for minimal risk studies do not require prior review by the CCTO Medical Director.

9.7.3 Other Protocol Deviations

Logistical deviations from the protocol (e.g., minor changes to the study schedule for an individual subject) do not require prior IRB approval unless the deviation has the potential to affect the subject's safety or study integrity. Such planned deviations that do meet this definition and do not affect the subject's safety should be noted in the subject's research record or deviation log as described in the SOCCI CCTO's Standard Operating Procedure 12: Deviation and Noncompliance Reporting.

Unintentional deviations from the protocol that might affect subject safety or study integrity should be reported to the IRB within 10 days from when the investigator becomes aware that such a deviation has occurred, as outlined in the SOCCI Clinical Research Office's Working Instruction 11: Deviation and Noncompliance Reporting. In this case, a Protocol Deviation report must be submitted in CSIRB, per IRB policy, Reporting Possible Unanticipated Problems Involving Risks to Subject or Others (UPIRSO) Policy: Institutional Review Board/Research Compliance and Quality Improvement. All submissions should include a description of the plan to avoid similar

deviations or exceptions in the future.

9.7.4 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation. Repeat exceptions or deviations to the protocol may suggest a protocol amendment is needed.

9.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms and/or into a HIPAA-compliant study database. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

10.9 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the sponsor-investigator and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

10.0 REFERENCES

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APPENDIX 1

Concomitant Medications of Interest (Analgesics)

- Cymbalta (Duloxetine)
- Effexor (Venlafaxine)
- Neurontin (Gabapentin)
- Lyrica (Pregabalin)
- Topamax (Topiramate)
- Amitriptyline
- Nortriptyline
- Cannabis/CBD