Columbia University Medical Center
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TITLE: **Randomized controlled selection trial of cryotherapy vs. compression therapy for the prevention of taxane-induced peripheral neuropathy in breast cancer patients**

Coordinating Center: Columbia University Medical Center

Principal Investigator:
Melissa Accordino
Columbia University
Herbert Irving Pavilion
161 Fort Washington Avenue, HIP 10
New York, NY 10032
Phone: 212-305-1945
FAX: 212-305-0178
E-mail: mkg2134@cumc.columbia.edu

Co-Investigators:
Dawn L. Hershman
Columbia University
Herbert Irving Pavilion
161 Fort Washington Avenue, HIP 10
New York, NY 10032
Phone: 212-305-1945
Fax: 212-305-0178
E-mail: dlh23@cumc.columbia.edu

Katherine Crew
Columbia University
Herbert Irving Pavilion
161 Fort Washington Avenue, HIP 10
New York, NY 10032
Phone: 212-305-1945
Fax: 212-305-0178
E-mail: kd59@cumc.columbia.edu

Kevin Kalinsky
Columbia University
Herbert Irving Pavilion
161 Fort Washington Avenue, HIP 10
New York, NY 10032
Phone: 212-305-1945
FAX: 212-305-0178
E-mail: kk2693@cumc.columbia.edu

Meghna S. Trivedi
Columbia University
Herbert Irving Pavilion
161 Fort Washington Avenue, HIP 10
New York, NY 10032
Phone: 212-305-1945
FAX: 212-305-0178
E-mail: mst2134@cumc.columbia.edu

Statistician:

Shing M. Lee
Department of Biostatistics
Columbia University
722 W 168th St, 6th Floor, Room 645
Phone: 212-342-1266
Email: sml2114@columbia.edu

Cheng-Shiun Leu
Department of Biostatistics
Columbia University
722 W 168th St, 6th Floor, Room 650
Email: cl94@columbia.edu

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Protocol Signature Page

I confirm that I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practices, and the applicable federal, state, and local laws, rules, and regulations relating to the conduct of the protocol. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I will promptly submit the protocol to the applicable IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modification made during the course of the study must first be approved by the IRB, prior to implementation except when such modification is made to remove an immediate hazard to the subject. I certify that I, and the study staff, have received the requisite training to conduct this research protocol. I agree to maintain adequate and accurate records in accordance with Columbia University and Herbert Irving Comprehensive Cancer Center policies, Federal, state and local laws and regulations. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Instructions to Principal Investigator: Sign and Date this signature page and print your name. Return the original, completed and signed to the Clinical Protocol & Data Management Office. Retain a copy in the regulatory binder.

_____ _____
Signature of Principal Investigator Date

_____
Principal Investigator Name (Print)

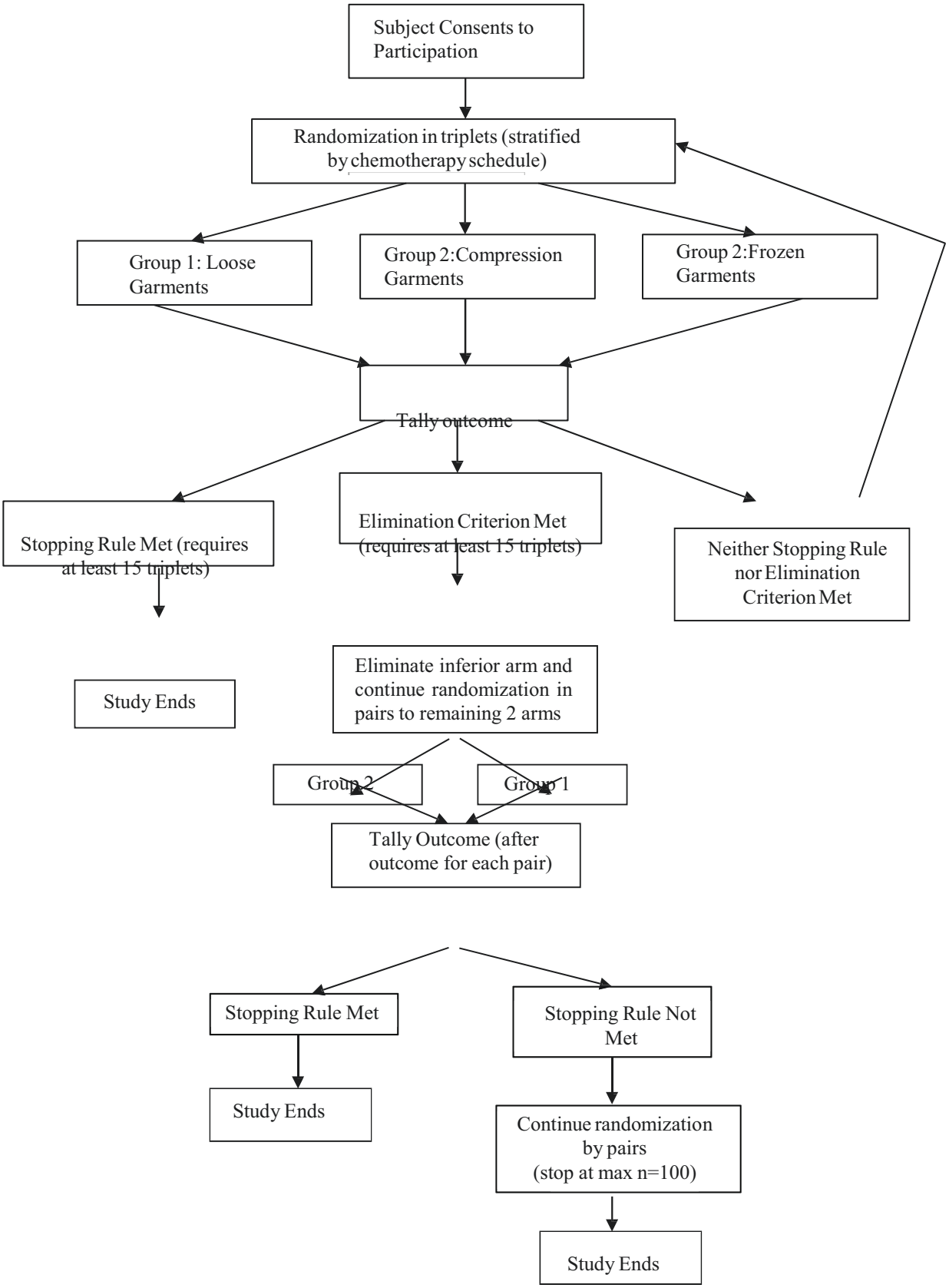
_____
Name of Institution

Protocol Synopsis

Title	Randomized controlled selection trial of cryotherapy vs. compression therapy for the prevention of taxane-induced peripheral neuropathy in breast cancer patients
Short Title	The CONTRoL Trial: **C**ryotherapy vs. c**O**mpression **N**europathy **TR**ia**L**
Protocol Number	AAAR9515
Phase	Phase 2B
Methodology	Randomized, placebo-controlled, clinical selection trial
Study Duration	18 months
Study Center(s)	Single-center - Columbia University Medical Center
Objectives	To select the best intervention from cold therapy, compression therapy and placebo at reducing neuropathic pain as measured by the change in the Neurotoxicity (NTX) component of the Functional Assessment of Cancer Therapy (FACT) -Taxane questionnaire, following 12 weeks of neoadjuvant/adjuvant chemotherapy with paclitaxel or docetaxel among breast cancer patients.
Number of Subjects	Up to 100 subjects
Diagnosis and Main Inclusion Criteria	Stage I-III breast cancer receiving adjuvant or neoadjuvant nab paclitaxel, paclitaxel or docetaxel for at least 12 weeks.
Study Product, Dose, Route, Regimen	Product #1: Frozen garment on hands and feet worn at least 15 minutes before chemotherapy infusion, during infusion and at least 15 minutes after infusion (total time 1.5-2 hours). Product #2: Compression garment for hands/arms and feet/legs worn at least 15 minutes before chemotherapy infusion, during infusion and at least15 minutes after infusion (total time 1.5-2 hours). Product #3: "Loose" garment for hands/arms and feet/legs worn at least 15 minutes before chemotherapy infusion, during infusion and at least 15 minutes after infusion (total time 1.5-2 hours).
Duration of administration	Products will be worn during each chemotherapy infusion for at least 12 weeks of treatment.
Reference therapy	Not applicable

Statistical Methodology	Patients will be randomly assigned in triplets to receive either frozen gloves and socks, compression gloves and socks, or "loose" gloves and socks (placebo arm) during chemotherapy infusion. Randomization will be stratified by chemotherapy schedule (weekly vs q3week). The primary goal of the trial is *to select the best intervention* to be carried forward for further study, with a high probability of *correct* selection if one intervention is truly superior to the other two by a pre-specified effect size. Up to 100 patients will be enrolled in the study, using a novel sequential design based on the Levin-Robbins-Leu family of sequential selection procedures that allows for an early elimination of an apparently inferior arm. The primary endpoint of the study is the change in the neurotoxicity (NTX) component of the Functional Assessment of Cancer Therapy (FACT) -Taxane questionnaire at 12 weeks from baseline, with success being defined as a change in FACT NTX of less than 5 points from baseline. Each time an outcome is observed for all patients in a triplet (or, after elimination of one arm, a pair), those outcomes are added to a running tally of successes for each intervention. Pre-specified criteria for eliminating an inferior arm and for selecting the preferred intervention will be applied starting from the 15th patient. From that point forward, with this sequential procedure, the preferred intervention can be selected during the ongoing enrollment as soon as the pre-specified selection criteria are met, and further enrollment will cease.

Protocol Schema:



Contents

1. INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Columbia University Medical Center institutional research policies and procedures.

2. STUDY OBJECTIVES

2.1 Primary Objective

To select the best intervention from cold therapy, compression therapy and placebo at reducing neuropathic pain as measured by the change in the Neurotoxicity (NTX) component of the Functional Assessment of Cancer Therapy (FACT) -Taxane questionnaire , following 12 weeks of neoadjuvant/adjuvant chemotherapy with paclitaxel or docetaxel among breast cancer patients.

2.2 Secondary Objectives

- To estimate the change in severity of neuropathy as determined by the NCI-CTCAE by therapy.
- To evaluate objective sensory and motor function change from baseline with the Neuropen, tuning fork, timed get up and go test, and tandem/unipedal stance test by therapy.
- To assess cutaneous toxicity and onycholysis using the National Cancer Institute Common Toxicity Criteria (Version 2) by therapy.
- To assess adherence to the intervention by therapy
- To assess patient comfort to the intervention by therapy
- To compare the degree of neuropathy among our intervention arms with historical control data

3. BACKGROUND

Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent side effect resulting from the administration of cytotoxic chemotherapeutic agents. The incidence of CIPN can vary on the type of agent used, the frequency with which it is given, and the cumulative dose. Unfortunately, for some patients, symptoms may persist even after discontinuation of the drug due to irreversible nerve damage [1]. Furthermore, dose reduction or early termination of effective anti-cancer treatment may ultimately affect overall survival. Despite multiple trials investigating various agents for the treatment of established CIPN, only duloxetine is recommended, based on efficacy data from a large randomized placebo-controlled trial [2]. Numerous trials have studied the efficacy of various pharmacologic agents and chemoprotectants in the prevention of CIPN including acetyl-l-carnitine (ALC), amifostine, amitriptyline, calcium and magnesium, diethyldithio-carbamate (DDTC), glutathione (GSH), nimodipine, org 2766, all-*trans*-retinoic acid, rhuLIF, vitamin E, *N*-acetylcysteine, carbamazepine, glutamate, goshajinkigan (GJG), omega-3 fatty acids, and oxycarbazepine. These agents have not shown any consistent and/or

conclusive clinically meaningful benefits when compared with placebo controls. As of now, there are no established agents for CIPN prevention [3].

The taxanes, such as nab paclitaxel, paclitaxel or docetaxel, are effective chemotherapeutic agents used in a variety of malignant diseases such as breast, ovarian, prostate and lung cancer [4]. Clinical trials where patients received taxane-based therapy have reported up to 33% grades 3-4 sensory neuropathy and up to 14% of motor neuropathy [5]. The sensory symptoms associated with taxane-induced peripheral neuropathy often begin in a "stocking-glove" pattern and is characterized by pain, numbness and tingling in the hands and feet. Patients may also experience motor deficits such as weakness, difficulty walking or dropping items [6]. Activities of daily living are often affected and can greatly impair a patient's quality of life [7]. Often patients who experience CIPN require dose reductions or cessation of the offending agent.

Peripheral neuropathy is a disabling adverse effect of taxane therapy and no effective preventative treatment currently exists. The purpose of this study is to directly compare the efficacy of compression therapy and cryotherapy to a control arm for the prevention of CIPN. We hope to overcome some of the study limitations and biases of the prior clinical trials with the current study design. Given the safety and tolerability of cold therapy and compression therapy, it is reasonable to test the efficacy of these non-pharmacological interventions in women with Stage I-III breast cancer receiving adjuvant or neoadjuvant paclitaxel or docetaxel for 12 weeks.

4. INVESTIGATIONAL AGENT

4.1 Preclinical Data - N/A

4.2 Clinical Data to Date

There have been several studies investigating potential pharmaceutical agents, herbal supplements and other modalities for the prevention and treatment of CIPN [8]. Recently, scalp cooling has been shown in a randomized clinical trial to reduce the incidence of chemotherapy-induced alopecia in breast cancer patients receiving taxanes and/or anthracyclines [9]. The rationale behind this therapy is cold temperature causes vasoconstriction, decreasing blood flow to the hair follicles and therefore reducing the amount of drug that reaches the follicles. This concept was applied by Scotté, et al. who evaluated frozen glove use in the prevention of docetaxel-induced nail and skin toxicity. In this case control study, onycholysis and cutaneous toxicity was significantly lower in the hand with the frozen glove compared with the control hand ($P = .0001$). Eleven percent of patients withdrew from the study due to cold intolerance [10].

In another prospective study, forty breast cancer patients were treated with weekly paclitaxel for 12 cycles and wore frozen gloves and socks on the dominant side for 90 minutes [11]. Symptoms on the treated sides were compared to the untreated (non-dominant) side, which served as the control arm. The primary endpoint assessed was tactile disturbance using a monofilament test. Secondary endpoints included thermosensory disturbance, vibration perception, performance speed, patient neurotoxicity questionnaire (PNQ), electrophysiological

signs, and pharmacokinetics. Tactile deterioration was significantly lower for the intervention side compared to the control side (hand: 27.8% vs. 80.6%, P < .001; foot: 25.0% vs. 63.9%, P < .001). In addition, the incidence of severe CIPN (PNQ grades D or E) occurred less with cryotherapy (hand: 2.8% vs. 41.7%, P < .001; foot: 2.8% vs. 36.1%, P = .007). No patients dropped out due to cold intolerance. Limitations of the study included no randomization, each subject acting as their own control, and lack of long term follow-up.

Similar to cryotherapy, compression therapy can also decrease microvascular flow in the extremities. In a self-controlled clinical trial, 42 patients with breast cancer wore two surgical gloves (one size smaller than the size that fit their dominant hand) for 90 minutes while receiving nab-paclitaxel [12]. The rates of grade 2 or higher sensory and motor neuropathy was significantly lower in the hand with the surgical gloves compared to the control hand (sensory neuropathy 21.4 vs. 76.1%; motor neuropathy 26.2 vs. 57.1%). Furthermore, compression gloves significantly decreased the temperature of each fingertip by 1.6-2.2°C (P<.0001). There were no withdrawals from the study due to intolerability of compression gloves. In this trial, peripheral neuropathy was only evaluated using subjective measures (CTCAE, PNQ) and feet were not addressed.

4.3 Other Agent(s)- N/A

5. STUDY DESIGN

5.1 General Design

This is a randomized, placebo-controlled clinical selection trial of interventions for CIPN in patients treated with docetaxel every 3 weeks or paclitaxel on a weekly schedule. Patients will be randomly assigned to receive either frozen gloves and socks, compression gloves and socks, or "loose" gloves and socks (placebo arm) during chemotherapy infusion. The primary goal of the trial is *to select the best intervention* to be carried forward for further study, with a high probability of *correct* selection if one intervention is truly superior to the other two by a pre-specified effect size. Up to 100 patients (with expected sample sizes between 60-70 patients for the most likely scenarios) will be enrolled in the study, using a novel sequential design that allows for an early elimination of an apparently inferior arm. Initially the randomization will be blocked in triplets of patients within chemotherapy strata (every three weeks or weekly). Each time an outcome is observed for all patients in a triplet, those outcomes are added to a running tally of successes for each intervention. There is a pre-specified criterion in terms of the success tallies for eliminating arms as evidence of apparent inferiority accumulates. If and when one arm is eliminated, pairs of patients are thereafter randomly assigned to the two remaining interventions, and the trial continues until one of the remaining interventions is subsequently eliminated, at which time the apparently superior intervention is selected as the preferred intervention. In the event that two arms are simultaneously eliminated at any given examination of triplet tallies, the trial terminates at that time with the selection of the apparently superior intervention. With this sequential procedure, the preferred intervention can be selected during the ongoing enrollment as soon as the pre-specified selection criteria are met, and further enrollment will cease. To ensure that there will be some unbiased estimates of the proportion of patients with a good outcome available for each intervention arm (a secondary goal of the study),

the elimination and selection criteria will not be applied until 15 patients per arm have been observed. Fifteen patients per arm will provide a 95% confidence interval no wider than 0.52 (+/- 0.26) percentage points for the estimate of the proportion of patients with a good outcome based on the Clopper Pearson method.

This novel approach based on the Levin-Robbins-Leu family of sequential selection procedures [18-23] will a) allow a rational selection of the CIPN intervention to be carried forward for confirmatory testing in a future phase 3 trial; b) provide preliminary concurrent control estimates for the placebo arm that can be used for sample size estimation in that future trial; and c) keep the trial small and efficient, consistent with a Phase 2B design, until sufficient evidence of promise accumulates to warrant the major investment in funds, time, and effort to complete the larger Phase 3 study.

Upon enrollment, each study participant will complete a baseline questionnaire assessing demographic information (age, race, and tobacco use). Clinical characteristics (cancer staging, grade, concomitant morbidities, chemotherapy cumulative dose and current medications) will be documented as well. Patients will be able to enroll in the trial and complete the baseline assessment up to the second chemotherapy infusion.

During each study encounter (at baseline, week 12 +/- 14 days, and at week 24 +/- 21 days), study participants will complete a questionnaire assessing pain, severity of CIPN, function, and comfort with the intervention. They will also undergo objective neurological assessments of sensory and motor neuropathy (see below). Further, adherence to the intervention will also be assessed by research staff. Patients will be evaluated at weeks 12 and 24 from baseline to determine clinical benefit of the intervention during treatment and to assess if the benefit is sustained after discontinuation of the intervention. Outcome measures on week 12 from baseline will be evaluated before scheduled chemotherapy infusion. Visits will be conducted within the below specified windows forbidding unexpected circumstances such as missed appointments or loss to follow-up.

MEASURE	**Baseline**	**Week 12** (+/- 14 days)	**Week 24** (+/- 21 days)
History & Physical Exam	X		
Chemotherapy Treatment Schedule	X	X	X
Self-Administered Questionnaires			
Baseline Demographics	X		
FACT NTX	X	X	X
Comfort	X	X	X
PROMIS-29	X	X	X

Staff administered			
History of Falls Assessment	X	X	X
Active Topical Agents, Medications, Supplements, and Interventions	X	X	X
128 Hertz Tuning Fork	X	X	X
Vibration Threshold Test	X	X	X
Neuropen Test (pressure/pain)	X	X	X
NCI-CTCAE	X	X	X
NCI-CTC (V2) (nail changes)	X	X	X
Timed get up and go	X	X	X
Tandem and unipedal stance test	X	X	X
Hand and fingertip color changes	X	X	X
Adherence		X	X

5.2 Dose Limiting Toxicities - N/A

5.3 Number of Patients

Up to 100 patients. The expected sample size is between 60-70 for the most likely scenarios.

6. SUBJECT SELECTION AND WITHDRAWAL

6.1 Inclusion Criteria

- Age ≥18. Because no dosing or adverse event data are currently available on the use of cold therapy and compression therapy in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.
- History of stage I-III breast cancer
- Patient scheduled to be receiving adjuvant or neoadjuvant nab paclitaxel, paclitaxel, or docetaxel for at least 12 weeks
- Signed informed consent
- ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A)

6.2 Exclusion Criteria

- Prior treatment with taxane or platinum based chemotherapy
- Known history of neuropathy
- Raynaud's phenomenon
- Peripheral arterial ischemia
- Cold intolerance
- Current use of duloxetine which may mitigate CIPN

*If a subject has any condition that limits the use of one out of four extremities, i.e. need for peripheral IV, previous amputation, etc, then no device (compression, cryotherapy, or loose

gloves/socks) will be used on that specific extremity.

6.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial. As most patients diagnosed with breast cancer are women, there will be more women accrued in the trial.

Accrual Targets								
Ethnic Category	**Sex/Gender**							
	Females			**Males**			**Total**	
Hispanic or Latino	30		+	0		=		
Not Hispanic or Latino	70		+	0		=		
Ethnic Category: Total of all subjects	100	(A1)	+	0	(B1)	=	100	(C1)
Racial Category								
American Indian or Alaskan Native	0		+	0		=		
Asian	5		+	0		=		
Black or African American	5		+	0		=		
Native Hawaiian or other Pacific Islander	0		+	0		=		
White	90		+	0		=		
Racial Category: Total of all subjects	100	(A2)	+	0	(B2)	=	100	(C2)
	(A1 = A2)			(B1 = B2)			(C1 = C2)	

6.4 Subject Recruitment

Patients will be recruited by their medical oncologist from the Breast Oncology Clinic of Columbia University Medical Center (CUMC). The estimated accrual is 6 patients per month for a period of 18 months. The CUMC Breast Oncology clinic sees approximately 100 breast cancer patients each week. Approximately 8-12 patients per month are generally scheduled to receive adjuvant or neoadjuvant paclitaxel or docetaxel. Therefore, an accrual of up to 100 participants, with an expected accrual of 60-70 participants, is feasible.

6.5 Early Withdrawal of Subjects

6.5.1 When and How to Withdraw Subjects

- Patients are not expected to develop progressive disease while receiving neoadjuvant or adjuvant therapy. However, if at any time the patient develops progressive disease, he/she
  will be referred for alternative therapy. He/she will continue to be followed for the primary endpoint.

- If at any time the patient develops unacceptable neuropathy from the chemotherapy that leads to dose reduction/modification or treatment discontinuation, he/she will be counted as having a "poor" outcome for the primary endpoint.
- If at any time the patient develops unacceptable toxicity from the chemotherapy unrelated to neuropathy, and needs to stop treatment, he/she will continue to be followed for the primary endpoint.
- If at any time the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (*i.e.*, a change in diagnosis), the patient will be removed from study.
- If the patient withdraws consent for continued participation, he/she will be removed from study

6.5.2 Data Collection and Follow-up for Withdrawn Subjects

Even though subjects may be withdrawn prematurely from the study, it is imperative to collect at least efficacy data on such subjects throughout the protocol defined follow-up period for that subject. Such data are important to the integrity of the final study analysis since early withdrawal could be related to the safety profile of the study products. If a subject withdraws consent to participate in the study, attempts will be made to obtain consent from the subject to record at least efficacy data up to the protocol-described end of subject follow-up period. It must be a high priority to try to obtain at least efficacy data on all subjects lost to follow-up and to note what methods should be used before one can state the subject is truly lost to follow-up (e.g. number of phone calls to subject, phone calls to next-of-kin if possible, certified letters, etc.). Subjects withdrawn because of unacceptable adverse events will be followed for the primary endpoint and/or until resolution or stabilization of the adverse event. In order to preserve the intent-to-treat principle ("once randomized then analyzed") we will impute a "poor" outcome for any patient who withdraws from the study and cannot or will not be evaluated at 12 weeks from baseline.

6.6 CUMC Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures, along with applicable institutional policies and federal regulations.

Only Investigators/Research personnel properly trained and delegated to consent subjects for this protocol will participate in the consenting process. Furthermore, properly delegated/trained Physician Investigators (e.g., MD, MD PhD) are required to sign/verify a protocol specific Eligibility Checklist for each subject enrolled on the study, in addition to providing the relevant source documentation confirmation subject eligibility.

All participants must be centrally registered through the Central Registration Office within Herbert Irving Comprehensive Cancer Center at CUMC prior to initiation of study treatment.

Registration hours are available Monday through Friday from 9:00am – 5:00pm EST (excluding holidays and weekends). Same day patient registrations (and after hour registrations) will be accommodated on a case by case basis provided that the study team has expressed all time sensitive registration concerns/cases in a timely manner to the Central Registration Office.

CPDM Central Registration Procedures:

Within 48 hours of obtaining consent (excluding holidays and weekends), a completed/signed IRB approved informed consent HIPAA form, and demographics forms must be submitted to the CPDM Central Registration Office via an email to CPDMRegistration@columbia.edu or fax to 212.305.5292, with the subject line "AAAR9515 Pending Subject Registration Request (PHI)". Upon receipt, applicable subject information as well as a "pending eligibility" status will be entered into HICCC's institutional database. This status will remain until further source documentation is made available to confirm overall patient eligibility. Required materials for all pending registration submissions are as follows:

- Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable.
- The completed/signed IRB approved HIPAA Authorization form
- Completed/signed CPDM ICF checklist
- Completed/signed HICCC personal census form
- Completed/signed CPDM Demographics Note to File

In order to confirm eligibility status, Investigators/designees (e.g., study specific Clinical Research Coordinator/Research Nurse, etc.) must submit the following documentation to the Central Registration Office via email or fax:

- The completed/signed study specific Eligibility Checklist (signed by an Physician level Investigator)
- Copies of source documentation necessary for each item to be verified on the CPDM specific Eligibility Checklist, including but not limited to:
    - Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)
    - Copy of pathology and surgical reports
    - Copy of clinic note(s) or other appropriate medical records capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms (e.g., positive

investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)

- Protocol deviation/waiver approvals (if applicable)

- **Please note**: subject line of email or fax should include the following: "AAAR9515 Complete Subject Registration Request (PHI)".

Upon receipt of the above mentioned documentation, participant eligibility information will be verified by a qualified Central Registration Registrar. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable study team personnel for clarification prior to enrollment. All applicable finalized registration/eligibility information will then be entered into HICCC's institutional CTMS database by the Central Registration Registrar. Upon completion, an official subject registration notification email will be sent to the PI/research team which will include eligibility/enrollment status, as well as subject ID information. Protocol therapy may not be initiated prior to receipt of this notification from the Central Registration Office.

All screen fail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

7. TREATMENT PLAN

7.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for frozen mittens/socks and compression garments are described in Section 10. There are no dose modifications for the products.

Cryotherapy: Study subjects will wear NatraCure flexible socks on bilateral hands and feet. The garments will be available in 3 sizes: small, medium, large. The correct size will be determined during the initial visit and the same size used during each chemotherapy infusion. The sock will act as a mitten and covers the entire hand until past the wrist. There are 2 gel packs inserted into the sock, to provide cooling to the dorsal and frontal aspect of the hand. For the feet, the sock will cover the entire foot until above the ankle. Garments will be refrigerated for at least 3 hours at -25 to -30°C prior to use. With each infusion, patients will wear the frozen garments on their hands and feet for a total of 90-120 minutes, beginning at least 15 minutes (with the window being within 30 minutes prior to start) before the start of the infusion and until at least 15 minutes after the end of the infusion. Two sets of socks will be used during each session for 45-60 minutes each to maintain a consistently low temperatures of the extremities. Patients may remove the garments for up to 10 minutes during treatment if they need to use the restroom.

Compression therapy: Study participants will wear Sigvaris Secure Arm Sleeves and Gloves on bilateral upper extremities. The sleeves and gloves provide 20-30mmHg of compression. The

arm sleeves will be available in several sizes. Subjects will wear Sigvaris CompreFlex Lite compression garments on the lower extremities which includes a transition liner with a compressive foot, providing 20-30mmHg of compression on the lower leg and 15mmHg on the toes and feet. AccuTabs will be placed along the CompreFlex Lite to easily and accurately set the compression level at 20-30mmHg. For the compression garments, the correct size will be determined during the initial visit and the same size and products used during each chemotherapy infusion. With each chemotherapy infusion, patients will wear the sleeves/gloves and socks for a total of 90-120 minutes, beginning at least 15 minutes before the start of the infusion (with the window being within 30 minutes prior to start) and until at least 15 minutes after the end of the infusion.

Control arm (Loose glove/sock): To minimize potential biases of patients receiving treatment in the intervention arms, we will have a control arm where patients will wear loose or comfortably fitting gloves/sleeves and socks on their hands and feet.

Study subjects will wear a non-compressive sleeve and loosely fitting glove on bilateral arms and hands. They will also wear a non-compressive Sigvaris Basic Liner with the CompreFlex Lite loosely applied over it. We will verify that no compression is applied via using an interface pressure sensor (PicoPress). The maximum level of allowed pressure for garments on the upper and lower extremities will be 3mmHg. If the pressure reading is >3mmHg, then a larger garment size will be used. For the loose garments, the correct size will be determined during the initial visit and the same size and products used during each chemotherapy infusion. If weight gain or swelling is noticed, then the patient may need to be refitted to ensure the correct placebo pressure is applied. Measurements with the pressure sensor will be repeated as needed to ensure a low pressure level of less than 3mmHg. With each chemotherapy infusion, patients will wear the gloves/sleeves and socks for a total of 90-120 minutes, beginning 15 minutes before the start of the infusion and until 15 minutes after the end of the infusion.

8.1.1 Investigational Agent(s) - N/A
8.1.2 Other Agent(s)- N/A
7.1.3 Other Modality(ies) or Procedures -N/A
7.2 General Concomitant Medication and Supportive Care Guidelines- N/A

7.3 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for until completion of all cycles or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events(s) such as frostbite or cold intolerance
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

7.4 Duration of Follow Up

Patients will be followed for 24 weeks after completion or removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

7.5 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 8.5 applies. The reason for study removal and the date the patient was removed will be documented in the Case Report Form.

8. DOSING DELAYS/DOSE MODIFICATIONS - N/A

9. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

9.1 Adverse Events

Risk associated with frozen mitten and sock
Very Likely
-feeling cold
Less Likely
-sensory abnormalities including numbness and tingling
-mild pain
Very unlikely
-frostbite

Risk associated with compression therapy
Less likely
-sensory abnormalities including numbness and tingling
Very unlikely
-pain
-skin changes

Risk associated with control arm
-none

Patients will be assessed at baseline, 12 weeks and 24 weeks from baseline with an assessment of any skin color changes to evaluate for any signs of frostbite.

9.2 Definitions

Adverse Event:

An adverse event (AE) is any untoward or unfavorable medical occurrence in a human subject, including abnormal sign, symptom or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event:
Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires inpatient hospitalization/prolongation of existing hospitalization, unless
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above/below and not resulting in hospital administrations
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious events should be regarded as non-serious adverse events.

Unanticipated Problem:
An unanticipated problem is any incident, experience or outcome involving risks to subjects or others in any human subjects research that meets all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approval protocol and informed consent document, and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in such research (e.g., there is a reasonable

possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and

- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures (e.g., after the first dose of study treatment) to the end of the study treatment (e.g., last dose of study treatment) and/or follow-up. For this study, the study treatment follow-up is defined as 21 days following 24 weeks after baseline visit, **or 30 days following the decision to remove the subject from study treatment, whichever is earliest.**

Baseline/Preexisting Condition

A baseline/preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or if the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management (e.g., change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.).

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an

adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

9.3 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

9.4 Reporting of Serious Adverse Events

9.4.1 IRB Notification by Sponsor-Investigator

Reports of all events (including follow-up information) that meet the definition of an unanticipated problem posing risk to subjects or others must be submitted to the IRB within one week (5 business days) following the occurrence of the unanticipated problem or the principal investigator's acquiring knowledge of the unanticipated problem in accordance with IRB policy. Additionally, the sponsor-investigator will submit a summary of all Unanticipated problems that occurred since the beginning of the study at the time of continuing review. Copies of each report and documentation of IRB notification and receipt will be kept in the Regulatory binder.

9.4.3FDA Notification by Sponsor-Investigator- N/A

9.4.4DSMC Reporting by the Sponsor Investigator

Serious adverse events not constituting unanticipated problems are to be reported to the HICCC DSMC. Reporting should occur within 24 hours of knowledge of the SAE occurring at our institution or affiliate sites.

9.4.5Reporting to Drug Manufacturer by Sponsor-Investigator

The Sponsor-Investigator will report to investigational agent manufacturer any serious adverse events that meet the reporting criteria to the Institutional Review Board as described in section

9.4 and/or to the FDA as described in section 9.4 within 24 hours of becoming aware of it, so that these reports can be evaluated and included in the Investigator's Brochure and for IND safety submissions per regulations. Reporting will occur by sending the reporting form along with any additional documentation sent to the regulatory authorities.

At the time of IRB renewal or at the request of the manufacturer, the Sponsor- Investigator will submit a summary of all Serious Adverse Events that have occurred inclusive of all sites to manufacturer.

9.5 Reporting Process

Adverse events may be submitted on FDA Form 3500A, the HICCC DSMC Serious Adverse Event Reporting Form, or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 10.

Study Products

9.6 Description

Cryotherapy: Study subjects will wear NatraCure flexible socks on bilateral hands and feet. The garments will be available in 3 sizes: small, medium, large. The correct size will be determined during the initial visit and the same size used during each chemotherapy infusion. The sock will act as a mitten and covers the entire hand until past the wrist. There are 2 gel packs inserted into the sock, to provide cooling to the dorsal and frontal aspect of the hand. For the feet, the sock will cover the entire foot until above the ankle.

Compression therapy: Study participants will wear Sigvaris Secure Arm Sleeves and Gloves on bilateral upper extremities. The sleeves and gloves provide 20-30mmHg of compression. The arm sleeves will be available in several sizes. Subjects will wear Sigvaris CompreFlex Lite compression garments on the lower extremities which includes a transition liner with a compressive foot, providing 20-30mmHg of compression on the lower leg and 15mmHg on the toes and feet. AccuTabs will be placed along the CompreFlex Lite to easily and accurately set the compression level at 20-30mmHg. For the compression garments, the correct size will be determined during the initial visit and the same size and products used during each chemotherapy infusion.

Control arm (Loose glove/sock): Study subjects will wear a non-compressive sleeve and loosely fitting glove on bilateral arms and hands. The will also wear a non-compressive Sigvaris Basic Liner with the CompreFlex Lite loosely applied over it. We will verify that no compression is applied via using an interface pressure sensor (PicoPress). The maximum level of allowed pressure for garments on the upper and lower extremities will be 3mmHg. If the pressure reading is >3mmHg, then a larger garment size will be used. For the loose garments, the correct size will be determined during the initial visit and the same size and products used during each chemotherapy infusion.

9.7 Treatment Regimen

Cryotherapy: Products will be refrigerated for at least 3 hours at -25 to -30°C prior to use. With each infusion, patients will wear the frozen socks on both hands and feet for a total of 90-120

minutes, beginning at least 15 minutes before the start of the infusion (with a window of 30 minutes prior to infusion) and until at least 15 minutes after the end of the infusion. Two sets of socks will be used during each session for 45-60 minutes each to maintain a consistently low temperature of the extremities.

Compression therapy/Control arm: With each chemotherapy infusion, patients will wear the gloves/sleeves and socks for a total of 90-120 minutes, beginning at least 15 minutes before the start of the infusion (with a window of 30 minutes prior to infusion and until at least 15 minutes after the end of the infusion.

Control arm (Loose glove/sock): With each chemotherapy infusion, patients will wear the gloves/sleeves and socks for a total of 90-120 minutes, beginning at least 15 minutes before the start of the infusion (with a window of 30 minutes prior to infusion and until at least 15 minutes after the end of the infusion.

9.8 Method for Assigning Subjects to Treatment Groups

Randomization will be centralized by the CPDM. Randomization will be stratified by the chemotherapy intervention schedule (every 3 weeks versus weekly). Patients will be randomized in triplets at the start of the trial until the outcomes of 15 triplets have been observed. If and when one arm is eliminated, the randomization will proceed in pairs until a terminal decision is reached or enrollment is truncated at 99 or 100 patients.

9.9 Preparation and Administration of Study Drug

The study coordinator will assist patients in wearing the cold therapy, compression, and loose, garments.

9.10 Subject Compliance Monitoring

The study team will track subject compliance with the frozen, compression and placebo products during each treatment. Subjects who are significantly non-compliant with the study treatment regimen will be asked to withdraw from the study.

9.11 Prior and Concomitant Therapy

- Concomitant chemotherapy or antibody therapy is permitted during the study with taxane drug
- Prior taxane or platinum therapy is not permitted during the study

9.12 Packaging

CompreFlex Lite compression garments including Transition Liners will be packaged in lot traceable units. Secure Arm Sleeves and Gloves will be packaged in lot traceable units. Medical device labeling and instructions for use are provided within the packaging of each device. These are Class 1 registered devices. Devices are shipped in bulk and may be used for up to 6 months.

9.13 Blinding of Study Drug

Participants will not be blinded if they are assigned to the cryotherapy. However, if randomized to the compression versus loose gloves group they will be blinded to their assignment.

9.14 Receiving, Storage, Dispensing and Return

9.14.1 Receipt of Product Supplies

PolyGel and Sigvaris will directly ship the products to the Herbert Irving Pavilion. Upon receipt of the study treatment supplies, an inventory will be performed and a device receipt log filled out and signed by the person accepting the shipment. The designated study staff will count and verify that the shipment contains all items noted in the shipment inventory. Any damaged or unusable devices in a given shipment will be documented in the study files. The study team will notify device manufacturer of any damaged or unusable devices that were supplied to the study site.

9.14.2 Storage

All products will be stored in a locked and secure location on the 10th floor of Herbert Irving Pavilion. Each subject's frozen garments, compression garments or loose gloves and socks will be placed in a bag marked with the patient's study ID number and then placed in a locked and secure storage area on the 10th floor of Herbert Irving Pavilion.

9.14.3 Dispensing of Study Products

The study coordinator will assist patients in wearing the compression, loose, cold therapy garments.

9.14.4 Return or Destruction of Study Products

At the completion of the study, the used and unused products will be discarded appropriately.

9.15 Other Agent(s)- N/A

10. STUDY CALENDAR

Study protocol and schedule of evaluation: Upon enrollment, each study participant will complete a baseline questionnaire assessing demographic information (age, race, and tobacco use). Clinical characteristics (cancer staging, grade, concomitant morbidities, chemotherapy cumulative dose and current medications) will be documented as well. Patients will be able to enroll in the trial and complete the baseline assessment up to the second chemotherapy infusion. During each encounter, study participants will complete a questionnaire assessing pain, severity of CIPN and function, and self-reported comfort with the study intervention. They will also undergo objective neurological assessments of sensory and motor neuropathy (see below). Further, research staff will assess adherence to the treatment intervention. Patients will be evaluated at weeks 12 and 24 from baseline to determine clinical benefit of the intervention during treatment and to assess if the benefit is sustained after discontinuation of the intervention. Outcome measures on week 12 from baseline will be evaluated before scheduled chemotherapy infusion. Visits will be conducted within the below specified windows

forbidding unexpected circumstances such as missed appointments or loss to follow-up.

MEASURE	**Baseline**	**Week 12** (+/- 14 days)	**Week 24** (+/- 21 days)
History & Physical Exam	X		
Chemotherapy Treatment Schedule	X	X	X
Self-Administered Questionnaires			
Baseline Demographics	X		
FACT NTX	X	X	X
Comfort	X	X	X
PROMIS-29	X	X	X
Staff administered			
History of Falls Assessment	X	X	X
Active Topical Agents, Medications, Supplements, and Interventions	X	X	X
128 Hertz Tuning Fork	X	X	X
Vibration Threshold Test	X	X	X
Neuropen Test (pressure/pain)	X	X	X
NCI-CTCAE	X	X	X
NCI-CTC (V2) (nail changes)	X	X	X
Timed get up and go	X	X	X
Tandem and unipedal stance test	X	X	X
Hand and fingertip color changes	X	X	X
Adherence		X	X

11. MEASUREMENT OF EFFECT -

Primary endpoint:

Functional Assessment of Cancer Therapy-Taxane (FACT-Taxane) Neurotoxicity (NTX): We will assess neurotoxicity using the 11-item neurotoxicity component of the Functional Assessment of Cancer Therapy- Taxane symptom module. Each item is measured on a 0-4 scale (1, not at all; 4, very much). Questions pertain to sensory neuropathy, motor neuropathy, hearing neuropathy, and dysfunction associated with neuropathy. The FACT NTX was initially developed with input of expert clinicians and patients who reported symptoms of CIPN within the past month.[13] The questionnaire was validated in patients with cancer who received taxane and platinum chemotherapy, drugs known to cause CIPN.[14, 15]. The FACT NTX has been shown to have internal consistency reliability on the basis of Cronbach α coefficients of 0.84-0.88 and the scale is also responsive to changes

in patient reported CIPN over time [15]. The FACT NTX has been used in prior clinical trials evaluating intervention for treatment and prevention of CIPN.[16-19]

The primary endpoint is the change in FACT NTX at 12 weeks from baseline from the start of chemotherapy. The change in FACT NTX will be dichotomized into a good outcome (change in FACT NTX<5 from baseline to week 12) versus a poor outcome (change in FACT NTX≥5 from baseline to week 12).[16] This dichotomy will be the primary outcome for monitoring in the selection procedure. Patients who experience dose reductions/modifications and/or treatment discontinuation for their chemotherapy treatment due to neuropathy are considered to have a ”poor” outcome.

Secondary endpoints:

National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading scale*:* The NCI-CTCAE is a subjective method to evaluate CIPN which is performed by a healthcare professional. The patient's peripheral sensory neuropathy, peripheral motor neuropathy, dysestheia, paresthesia and neuralgia will be graded on a scale of 1 to 5 depending on severity [20].

Skin/nail toxicity: Cutaneous toxicity and onycholysis will be assessed by a healthcare professional using the National Cancer Institute Common Toxicity Criteria (Version 2), specifically nail changes. Grade 1 includes discoloration, ridging (koilonychia), or pitting of the nails and Grade 2 is partial or complete loss of nail(s) or pain in the nail beds.

Comfort with Intervention: Comfort with the study intervention will be assessed on a 4-point scale, (0=dissatisfied; 1=not satisfied; 2=satisfied; 3=very satisfied). This scale was used to assess comfort of cryotherapy previously, comfort to compression therapy was not previously assessed.[10]

Tuning fork (vibration): Study participants will be assessed for development of sensory neurological dysfunction. Vibration perception will be assessed using a tuning fork [21].

Vibration threshold will be tested on the bilateral dorsum of the distal interphalangeal joint of the index finger and dorsum of the interphalangeal joint of the hallux. Subjects will be asked to indicate when the vibration stimulus is initially felt (perception threshold) and when the stimulus disappears (disappearance threshold.) The vibration perception threshold is the average of three paired measurements.

Neuropen (pressure/pain): Evaluation of other sensory endpoints including touch, pressure and pain will be evaluated using a Neuropen. Touch and pressure sensation will be assessed using a 10-g monofilament on the subject's dominant foot. Pain and subjective sharpness sensation will be assessed using the Neuropen on the dominant foot. The spring mechanism is calibrated to exert a force of 40 grams to help identify subjects with loss of pain sensation.

Timed get up and go: The ‘timed get up and go’ test is a rapid and widely used clinical performance-based measure of lower extremity function, mobility, and fall risk [22]. Subjects are asked to stand up from a standard chair (seat height between 44 and 47 cm), walk a distance of 3 m (marked on the floor) at a comfortable pace, turn, walk back and sit down. Subjects are permitted to use routine walking aids and are instructed not to use their arms to

stand up. No physical assistance is given. The time to complete the task is measured with a stopwatch. Timing commences on the command 'go' and stops when the subject's back is positioned against the back of the chair after sitting down. Shorter times indicate better performance. Patients who are wheelchair-bound will not be required to complete this assessment. Training on the use of this tool is available online (https://www.youtube.com/watch?v=grrYoBucNPE).

Tandem and Unipedal stance test: Balance will be assessed using the tandem and unipedal stance test [23]. In this assessment, the subject stands with one foot in front of the other (heel to toe) (30 seconds), then on one leg with: eyes open (60 seconds), eyes closed (30 seconds), and eyes open with head rotation (30 seconds) with arms held comfortably at the side. Participants are allowed one practice trial for each of the balance tests. Tests are recorded as achieved or not. The test was accepted failure when the stance foot shifted in any way or the nonstance foot touched the ground. If the subject did not reach the maximum time, the best time was recorded.

Adherence to the Study Intervention: Adherence will be defined as wearing the assigned gloves and socks for ≥ 80% of infusions

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10.0 (Adverse Events: List and Reporting Requirements). The Data Safety Monitoring Plan is described in Section 12.2.

12.1 Data Collection

The Herbert Irving Comprehensive Cancer Center has an electronic clinical trials and data management system (CTMS) that will be used for data collection. CRFs for the study will be built into the CTMS for data entry. The system has full auditing capabilities which is web-based and housed on a server in a fully HIPAA compliant server room with restricted access and video camera monitoring. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials. Users are only able to see study information if they are indicated as study personnel in our electronic IRB system. Users are limited to access based on the role assigned in their corresponding protocol. Subject data is entered directly into the system, which (in the case of Columbia subjects) confirms the correct identity of patients via an interface with the electronic medical patient index. Staff with the appropriate IRB defined roles can run reports within the system for reporting purposes.

12.2 Data Reporting

Case Report Forms will be completed for each subject enrolled into the clinical study through the CTMS. It is the investigator's responsibility for ensuring that all clinical and laboratory data entered on the corresponding CRFs are complete, accurate and authentic.

12.3 Data and Safety Monitoring Committee

The NCI-approved Data Safety and Monitoring Committee (DSMC) of the Herbert Irving Comprehensive Cancer Center (HICCC) will monitor every subject who receives treatment on this protocol for toxicity. This protocol will adhere to the policies of the currently approved HICCC Data and Safety Monitoring Plan (DSMP), which is in accordance with NCI and CUMC-IRB policy and guidelines. The committee is chair is appointed by the HICCC Director. The committee consists of HICCC faculty and staff with expertise in oncology, research pharmacy, research nursing, and data management. The DSMC convenes twice a month to review patient safety and the conduct of the trial. The PI will submit data and safety monitoring reports to the DSMC at a frequency to be determined by the DSMC based on risk to the subjects.

At the time of renewal, the study team will submit the most recent DSMC approval letter for safety review to the CUMC IRB. Any modifications that are required by the DSMC to ensure patient safety will be submitted to the IRB. All protocol deviations, violations, and eligibility waivers will be submitted to and approved by the DSMC prior to being reported to the IRB. All study data reviewed and discussed during these meetings will be kept confidential.

12.4 Quality Control and Quality Assurance

Independent monitoring of the clinical study for protocol and GCP compliance will be conducted periodically by the CPDM Compliance Core on behalf of the HICCC DSMC. Additionally, the Compliance Oversight Committee of the IRB at Columbia University Medical Center may audit the study at any time per institutional policies and procedures. The investigator-sponsor and Columbia University Medical Center will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

A risk-based approach will be used by the Compliance Core to determine the frequency, number of subject charts, and data elements to be monitored. The Compliance Coordinator will review the study status and summarize enrollment, toxicities, SAEs/UPs, dose escalation, statistical endpoints (e.g., stopping rules), etc. for the full DSMC membership at the regularly scheduled meetings.

Internal On-site Monitoring:

- Initial, recurrent, and close-out on-site monitoring visits will also be conducted at remote clinical sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).

- The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.

- The Compliance Coordinator will communicate with the site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.

- The assigned Compliance Coordinator will monitor IIT trials within 1 month after the

first subject is enrolled and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source documents, that all toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

12.5 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (e.g., that the subject is alive) at the end of their scheduled study period.

The subject binders will be maintained with in the CPDM offices, a secured floor within the Herbert Irving Pavilion and only the investigator and study staff will have access to the file.

12.6 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or 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.

12.7 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the

CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A".

12.8 Records Retention

Records relating to a specific research activity, including research records collected by investigators, must be maintained for at least three years after completion of the research (45 CFR 46.115(b); 21 CFR 56.115(b); 21 CFR 312.62). This minimum retention period applies whether or not any subjects were enrolled in the study.
If the research is FDA regulated, records should be retained for at least two years after approval of the investigational agent by FDA; if it is not approved, records should be retained at least two years after the study is terminated and FDA is notified (note the additional requirement below for clinical research studies);
Clinical records, including consent forms that document clinical intervention or clinical diagnostic procedure research-related procedures, must be retained in medical records by the institution for at least seven years, per CUMC and NYP policy which is based on state law.

13. STATISTICAL CONSIDERATIONS

13.1 Study Implementation:

This is a randomized, placebo-controlled clinical selection trial of interventions for CIPN in patients treated with paclitaxel or docetaxel every 3 weeks or on a weekly schedule. The study design is described in detail in section 5.1.

The identification of a preferred treatment will be done using an innovative sequential selection procedure, which will substantially reduce the number of patients in comparison to a hypothesis test procedure. The data will be examined each time a triplet (or, after elimination of one arm, a pair) of randomized patients completes follow-up.

The goal of the procedure is to make a correct selection, i.e. to select the intervention that yields the greatest true probability of change in FACT NTX<5, assuming one exists, with high probability. The procedure follows the preference zone / indifference zone approach, wherein we require the selection procedure to guarantee a probability of at least 80% *correct* selection (of the truly best intervention), assuming that one is truly superior to the others by a pre-specified amount. This pre-specification defines a region in the parameter space called the *preference zone*. If the best intervention does not exceed the next best by the pre-specified amount, the success probabilities are said to lie in the *indifference zone*, where we shall be indifferent to the fact that the probability of correct selection may be less than 80%. For this trial, the preference zone consists of all parameter vectors (p_1, p_2, p_3) of success probabilities where the odds ratio comparing the largest to the next largest is greater than or equal to 2.0.

The selection procedure is specified by the sampling rule, the elimination rule, the stopping rule, and the terminal decision rule, as follows.

Sampling rule:
Vector-at-a-time sampling will be used. Patients will be randomized in triplets within

chemotherapy strata to one of the three intervention arms. If and when one arm is eliminated, patients will be randomized in pairs to the remaining interventions.

Success tallies:
Each time the follow-up for each patient in a triplet is complete and a "good" or "poor" outcome is determined for each (change in FACT NTX<5 or >=5, respectively), the triplet becomes "observed" and is available for sequential monitoring by adding to a running tally of the "good" outcomes for each intervention. These *success tallies* are used for the elimination criterion.

Elimination criterion:
The criterion for elimination of an intervention is a *difference of 4 between the currently greatest and smallest success tallies*. That is, the first time that the success tally for the intervention (or interventions) with the largest tally exceeds the success tally of the intervention (or interventions) with the smallest tally, we *eliminate* the intervention (or interventions) with that smallest tally. By "elimination" of an intervention arm we mean that no further patients will be randomized to such an arm. Thereafter, the trial continues with the remaining interventions whose success tallies resume at their current values. The trial then continues randomizing additional *pairs* of patients until the difference in success tallies again equals 4, at which time the intervention with the smaller success tally is eliminated. If at any time two arms should happen to be tied with 4 fewer successes than the intervention currently in the lead, then both trailing interventions are eliminated at that time.

Stopping rule:
Stop the first time two intervention arms have been eliminated, if this occurs at or before 100 patients' outcomes have been observed. If the criterion for the second elimination has not been reached at or before 100 outcomes have been observed, the trial will stop by *truncation*. The maximum number of triplets or pairs at time of truncation is determined as follows. If no early elimination occurs, a total of 99 patients in 33 triplets will be randomized. If an early elimination of one intervention occurs after N triplets have been observed, the maximum number of subsequent pairs will be $(100-3N)/2$ if N is even or $(99-3N)/2$ if N is odd. (There is no truncation if an early elimination of two interventions occurs at or before 33 triplets have been observed because the trial stops in that case with a criterion decision.)

Decision rule:
If the second elimination criterion is reached, the remaining intervention with the largest success tally is selected as the preferred intervention. If the trial stops by truncation, the intervention with the largest success tally among the remaining competitors is selected. If there are ties for the largest success tally at time of truncation, we will select the intervention according to other considerations (safety, ease of compliance, etc.). By construction of the elimination rule, there can be no ties for best success tally if the trial stops before truncation.

Incomplete triplets and overrunning:
If at the time of first elimination there are partially filled or partially observed triplets of patients that have been randomized and have started their intervention, we will allow each patient in each such triplet to complete their follow-up even if the arm to which they were randomized is

eliminated. Outcomes collected from these *incomplete triplets* will contribute to the secondary goal of obtaining unbiased estimates of the success probabilities and in interpreting the results of the study as explained below. However, the data from patients in incomplete triplets randomized to eliminated arms will not be considered in applying the criterion to eliminate a subsequent intervention, in order to preserve the validity of the sequential stopping procedure.

Similarly, if there are partially observed triplets or pairs of patients at the stopping time with a selection decision prior to truncation, we will allow the patients to complete their follow-up in order to observe their outcomes. As for incomplete triplets at time of first elimination, data from such *overrun* triplets or pairs will be used to weigh the evidence concerning success probabilities, but they will not be used to alter the stopping time and terminal selection decision, in order to preserve the validity of the sequential stopping procedure.

Operating characteristics of the Study Design:
The elimination criterion of a lead of 4 between largest and smallest success tallies was chosen to achieve a probability of correct selection of at least 80% for any true success probabilities lying in the preference zone characterized by an odds ratio of 2.0 or greater between the true success probabilities of the best two interventions. For example, true success probabilities of 26/33 (approximately 0.79), 0.65, and 0.65 with an odds ratio of 2.0 comparing 26/33 and 0.65 is a *least favorable configuration* lying on the boundary between the preference and indifference zones. For any such least favorable configuration with $p_1 > p_2 = p_3$ and $\{p_1/(1-p_1)\}/\{p_2/(1-p_2)\} = 2.0$, the selection procedure will result in a correct selection with at least 80% probability. Based on published studies [12,13] [12] [12] evaluating frozen and compression gloves, the observed rates were 72% and 79%, respectively, and experience suggests a 40% success rate for the control arm is plausible. We shall refer to the configuration of success probabilities of 79%, 65% and 40% as the *design alternative* and it too is inside the preference zone. Under the design alternative, the probability of correct selection is over 90%. Table 1 shows the operating characteristics of the selection procedure under various scenarios of true success probability configurations for the three arms.

TABLE 1
Operating characteristics of the selection procedure

	Scenario 1 0.79, 0.65, 0.65	**Scenario 2** 0.79, 0.65, 0.40	**Scenario 3** 0.75, 0.65, 0.40	**Scenario 4** 0.65, 0.65, 0.40	**Scenario5** 0.65, 0.65, 0.65
P[*cs*]	83.8%	91.2%	83.1%	49.8%	33.6%
P[*as*]	83.8%	91.2%	99.9%	99.7%	100%
Mean[*N*]	75.2	65.7	69.8	74.8	83.1
Median[*N*]	76	59	65	75	99
Mean[*N at first elim*	57.4	46.5	47.2	49.6	63.2
P[*truncation*]	30.3%	16.3%	23.1%	32.4%	48.9%
P[*cs at N=45*]	68.1%	79.2%	71.7%	48.7%	33.7%
P[*as at N=45*]	68.1%	79.2%	86.3%	83.2%	100%
P[*N=45*]	13.4%	27.2%	21.4%	15.3%	7.5%
P[N<80]	53.4%	71.9%	63.8%	53.7%	36.2%
P[*N<60*]	32.2%	51.4%	43.5%	34.3%	20.1%

P[*cs*] is the probability of correct selection overall, either by reaching the criterion difference at or before 100 patients, or at the 100th patient without having reached the early stopping criterion.

P[*as*] is the probability of an *acceptable* selection overall, either by reaching the criterion difference at or before 100 patients, or at the 100th patient without having reached the early stopping criterion.

Mean[*N*] is the mean of the distribution of the (random) total number of patients.

Median[*N*] is the median of the distribution of the total number of patients.

Mean[*N at first elim*] is the mean number of outcomes observed at time of first elimination. If no arms are eliminated, the number at first elimination is the number at truncation (i.e. 99).

P[*truncation*] is the probability that the trial will be truncated before the second elimination time.

P[*cs at N=45*] is the probability of correct selection after 45 patients have been randomized (15 patients in each of the three arms).

P[*as at N=45*] is the probability of acceptable selection after 45 patients have been randomized (15 patients in each of the three arms).
P(N=45) is the probability of reaching a decision after exactly 45 patients have been randomized. We are evaluating the operating characteristic at this point given that this is the point from which we will start to compare the tallies and represents the earliest stopping time with the minimum number of outcome observations.
P(N<80] is the probability that the total number of patients is less than 80
P(N<60] is the probability that the total number of patients is less than 60

The first scenario corresponds to success probabilities in the *least favorable configuration* in the preference zone with an odds ratio of 2.0. The second scenario corresponds to the abovementioned design alternative based on the observed rates from previously conducted studies (where we have adjusted those rates to have more conservative effect sizes to account for a potential placebo effect). The third and fourth scenarios describe the operating characteristics of the selection procedure inside the indifference zone, assuming smaller differences in the success rates for the two interventions. The third scenario assumes that both interventions are superior to the placebo with a smaller difference between them (such that the odds ratio between the best and second best intervention is less than 2.0). The fourth scenario

assumes that both interventions are superior to the placebo with no difference between them (an odds ratio of 1.0). The fifth scenario illustrates a case where there is no true difference in the rates for all three arms. The first row displays the probability of selecting the first intervention (which is the best in scenarios 1-3, and tied for the best in scenarios 4-5). The second row of the table shows the probability of an *acceptable* selection. For parameter values inside the indifference zone, it is deemed *acceptable* to select any intervention whose success probability has an odds ratio compared to the best treatment no less than 1/2.0 = 0.5. Thus in the third and fourth scenarios, it is acceptable to select either of the first two interventions. In the fifth scenario, it is acceptable to select any of the three interventions. For configurations in the preference zone, only correct selections are deemed acceptable.

In scenarios 1-3 where there is a superior arm, the design chooses the superior arm over 83% of the time across these scenarios with average sample sizes between 65.7 and 75.2 (median of 59 to 76). The average time to first elimination ranges from 46.5 to 57.4. At least 45 patients are required to ensure at least 15 patients per arm. Under the design alternative, there is 27.2% probability that we will stop the trial with 15 patients per arm. The probability of having to truncate the study ranges from 16.3% to 30.3%, with the lowest probability for our design alternative. The probability of selecting the superior arm after 45 patients are enrolled is between 68.1% and 79.2% in these scenarios, which explains the need to continue enrollment to ensure that the correct dose is selected with high probability.

In scenario 4, both interventions are equally efficacious and superior to the placebo. In that setting there is not a single superior treatment and selecting either one of the superior interventions would be acceptable. In that scenario, the probability of selecting either of the superior interventions is 99.7%. The average total sample size is similar to that under the least favorable configuration and the probability of truncation is slightly larger because there is no superior arm after a first elimination of the placebo arm.

In scenario 5, there is no difference among the three arms. Thus, the design randomly selects one of them with a probability of 0.33. However, given that they are all the same, it is acceptable to select any of them and thus the probability of selecting an acceptable intervention is 100%. Because there is no superior intervention in this scenario, evidence of an apparent advantage accumulates more slowly than under other scenarios and thus the procedure incurs a larger average sample size, average sample size to first elimination, and probability of truncation.

Thus, under the design alternative the average sample size is 66 (median is 59), and it is more likely than not that the sample size is under 60. Under scenario 3, which assumes a smaller difference, the average sample size is 70 and the median is 65. Under all scenarios considered except scenario 5 in which there is no difference among the three arms, it is more likely than not to have a sample size of 80 or less.

Analysis of the Primary Endpoint:

For reporting purposes, we will calculate the sample proportion of patients along with the corresponding exact binomial 95% confidence interval after 15 patients have been randomized to each arm. The final sample proportion with a change in FACT NTX<5from baseline to week 12 for each arm will also be reported. In general, a selection procedure, unlike a hypothesis test procedure, is not specifically designed to provide a *p*-value below a conventional level of significance. Indeed, in this phase 2 trial, we will *not* be declaring any differences statistically significant, as that is explicitly *not* the goal of the present selection trial, i.e., we are explicitly *not interested* in testing the null hypothesis of no differences between the three interventions. Instead, because the adaptive sequential selection procedure can be described as a procedure that samples until there is a pre-specified *weight of evidence* for making correct selections, assuming there is a minimum true degree of superiority as measured by the design odds ratio, we will quote the *likelihood ratio (LR) measure of weight of evidence* in various ways as follows.

At the end of the trial, we will calculate the likelihood of the success tallies for the intervention selected together with the first runner-up. This likelihood is given by

$$L(p_i, p_j \mid X_i^{(n)}, X_j^{(n)}) = p_i^{X_i^{(n)}} (1-p_i)^{n-X_{i(n)}} p_j^{X_j^{(n)}} (1-p_j)^{n-X_{j(n)}},$$

where $X_i^{(n)}$ and $X_j^{(n)}$ are the observed success tallies for the selected and first runner-up intervention and where p_i and p_j are the respective true success probabilities. We will also calculate the likelihood of the observed success tallies under the assumption that we erred in our selection and that the true success probabilities are those for the two interventions *transposed*, namely, $L(p_j, p_i \mid X_i^{(n)}, X_j^{(n)})$. The *likelihood ratio LR* is the ratio of these two likelihoods. It can be shown that *LR*, equals the true odds ratio raised to the fourth power,

$$LR = \frac{L(p_i, p_j \mid X_i^{(n)}, X_j^{(n)})}{L(p_j, p_i \mid X_i^{(n)}, X_j^{(n)})} = \left\{ \frac{p_i/(1-p_i)}{p_j/(1-p_j)} \right\}^4,$$

in the case where the trial ends meeting the selection criterion. In the case of truncation, the exponent 4 is replaced by $X_i^{(n)} - X_j^{(n)}$. We will evaluate *LR* at the maximum likelihood estimates of p_i and p_j, which are the adjusted sample proportions $(X_i^{(n)} + 0.5)/(n+1)$ and $(X_j^{(n)} + 0.5)/(n+1)$.

The values of success tallies used in *LR* are those used in the elimination and selection criteria, i.e., without follow-up data from incomplete triplets or overrun triplets or pairs. However, for the values of p_i and p_j used in *LR*, we will use the corresponding sample proportions using *all* of the available outcome data including data from incomplete triplets and overrun triplets or pairs.

For example, suppose after an early elimination of the placebo arm, the success tally for the frozen gloves and socks is 18 and that of the compression gloves and socks is 14, each with 27 patients observed at stopping time. Then the maximum likelihood estimate of the true odds ratio comparing the two interventions (adding one-half to each frequency) is (18.5/9.5) / (14.5/13.5) = 1.813, so that the likelihood ratio weight of evidence is 1.813 raised to the fourth power which is

10.8. Likelihood ratios in excess of 8 or 10 are generally considered to be moderate to strong evidence [24]. For example, the usual "significant at $p<0.05$" corresponds to a LR of only 6.8 in large samples.

We will also report the *LR* at the time of first elimination, measuring the weight of evidence that the intervention eliminated by the leading success tally was correctly eliminated as opposed to mistakenly eliminated with transposed true success probabilities. In the above example, suppose that the placebo was eliminated after 20 triplets with a success tally of 7 compared with the other two interventions' tallies tied at 11 successes each. Then the odds ratio comparing the leading tally to the trailing tally is (11.5/9.5) / (7.5/13.5) = 2.179. Then the *LR* is 2.179 raised to the fourth power, which is 22.5. Thus, we would have strong evidence that the placebo was correctly eliminated at that time.

As a sensitivity analysis we will restrict the sample proportions used in *LR* to the same success tallies used in *LR*, i.e., excluding data from incomplete triplets or overrun triplets or pairs.

The *LR* may offer strong evidence of correct selection (if *LR*>10) or only weak evidence, and the *LR* weight of evidence will be taken account of in evaluating whether or not to mount a subsequent phase 3 trial. If, for example, the *placebo* arm should be the selected intervention arm, there would presumably be either weak or even strong evidence *against* either active intervention being the best.

13.2 Size/Accrual Rate

Patients will be recruited by their medical oncologist from the Breast Oncology Clinic of Columbia University Medical Center (CUMC). The estimated accrual is 6 patients per month for a period of 18 months. The CUMC Breast Oncology clinic sees approximately 100 breast cancer patients each week. Approximately 8-12 patients per month are scheduled to receive adjuvant or neoadjuvant paclitaxel or docetaxel. Therefore, an accrual of 100 patients, expected to be around 60 to 70, is feasible.

13.3 Stratification Factors

Randomization will be stratified by the chemotherapy intervention schedule (every 3 weeks versus weekly).

13.4 Analysis of Secondary Endpoints

Proportions of patients with a change in FACT NTX of less than 5 and a worsening in neuropathy as determined by the NCI-CTCAE grading, who reported satisfied or very satisfied in the comfort scale, who discontinued intervention will be reported by type of therapy. Moreover, we will report the descriptive statistics (mean, median, interquartile range) for the changes from baseline with the Neuropen, tuning fork, timed get up and go test, and tandem/unipedal stance test by therapy, as well as, changes in FACT NTX,. The proportion of patients with cutaneous toxicity and onycholysis using the National Cancer Institute Common Toxicity Criteria (Version 2) will also be estimated by therapy. Graphical display of the data will also be done.

13.5 Reporting and Exclusions

If at the time of first elimination there are partially filled or partially observed triplets of patients that have been randomized and have started their intervention, we will allow each patient in each such triplet to complete their follow-up even if the arm to which they were randomized is eliminated. Outcomes collected from these *incomplete triplets* will contribute to the secondary goal of obtaining unbiased estimates of the success probabilities and in interpreting the results of the study as explained below. However, the data from patients in incomplete triplets randomized to eliminated arms will not be considered in applying the criterion to eliminate a subsequent intervention, in order to preserve the validity of the sequential stopping procedure.

Similarly, if there are partially observed triplets or pairs of patients at the stopping time with a selection decision prior to truncation, we will allow the patients to complete their follow-up in order to observe their outcomes. As for incomplete triplets at time of first elimination, data from such *overrun* triplets or pairs will be used to weigh the evidence concerning success probabilities, but they will not be used to alter the stopping time and terminal selection decision, in order to preserve the validity of the sequential stopping procedure.

13.5.1 Evaluation of toxicity

All patients will be evaluable for toxicity from the time of their first treatment with the study products.

Evaluable for primary endpoint

All patients randomized will be evaluable for the primary endpoint. Patients who progress or stop chemotherapy due to toxicity should continue to be followed for the primary endpoint.

14. PROTECTION OF HUMAN SUBJECTS

This study is to be conducted in accordance with applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be obtained before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, as outlined in the IRB approved protocol, and the investigator-designated research professional obtaining the consent.

15. STUDY FINANCES

15.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or

financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the Columbia University Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved prior to participation in this study. All CUMC investigators will follow the University conflict of interest policy.

15.2 Subject Stipends or Payments

There are no subject payments or stipends.

16. PUBLICATION PLAN

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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AAAR9515
ON STUDY FORM 1

Patient Identifier | | | | | | | **Study Identifier** | R | 9 | 5 | 1 | 5 | **Registration Step** |

Patient Initials_____(L, F M)

Time point: ☐ Baseline ☐ 12 Weeks ☐ 24 Weeks

Instructions: Submit this form at the time points listed above. All dates are **MONTH, DAY, YEAR**. Explain any blank dates or fields in the **Comments** section. Place an **X** in appropriate boxes.

VITAL STATUS

Vital status: ☐ Alive ☐ Dead *(submit Notice of Death)* **Date of last contact:** / /

If dead, date of death: / /

TREATMENT RECEIVED FOR THIS TIME PERIOD

Date of assessment: / /

Were there any treatment delays since the previous time point?

☐ No ☐ Yes ☐ Unknown, no contact with patient

If yes, indicate reasons for treatment delays *(select all that apply)*:

Scheduling problems

CIPN symptoms

Neutropenia

Other toxicities/side effects

Patient refusal (not due to toxicity)

Other, specify:_____

Is the patient still receiving the planned therapy as described at the previous time point?

Yes, planned treatment ongoing

No, treatment complete

Unknown, no contact with patient

No, change in treatment dose or frequency *(select patient's treatment below and describe any modifications to standard dose and frequency)*

No, change in treatment type *(select patient's treatment below and describe any modifications to standard dose and frequency)*

Patient Initials_____(L, F M)

TREATMENT REGIMEN

BREAST

Using or Planned?	Regimen	Standard Taxane Dose	Frequency
☐	P x 4	Paclitaxel 175 mg/m^2	Every 2 weeks for 4 cycles
☐	P x 12 +/- Carboplatin (AUC 2 for weekly or AUC 5-6 for every 3 weeks)	Paclitaxel 80 mg/m^2	Every week for 12 cycles
☐	TC x 4 or TC x 6	Docetaxel 75 mg/m^2	Every 3 weeks for 4 or 6 cycles
☐	TAC x 6	Docetaxel 75 mg/m^2	Every 3 weeks for 6 cycles
☐	T x 4	Docetaxel 100 mg/m^2	Every 3 weeks for 4 cycles
☐	T/Carboplatin (AUC6)	Docetaxel 75 mg/m^2	Every 3 weeks for 6 cycles
☐	Other, specify:_____	Taxane: Docetaxel/Paclitaxel Dose:_____mg/m^2	Every_____weeks for_____cycles

Abbreviations: dd, dose-dense; A, doxorubicin; C, cyclophosphamide; P, paclitaxel; T, docetaxel
Trastuzumab and/or pertuzumab may be added to any of the regimens.

AAAR9515
ON STUDY FORM 2

Patient Initials _____(L, F M) **Date of Assessment**: ☐☐ / ☐☐ /☐☐☐☐

Instructions: Submit this form within 7 days after initial registration. All dates are MONTH, DAY YEAR. Explain any blank fields or blank dates in the **Comments** section. Place an **X** in appropriate boxes.

PATIENT AND DISEASE DESCRIPTION

Performance status (Zubrod): ☐ **Height:** ☐☐☐ **cm** **Weight:** ☐☐☐ . ☐ **Kg**

Does the patient have a history of falls within the 6 months prior to registration?

☐No ☐Yes

Has the patient been diagnosed with the following diseases or conditions?

Diabetes:	☐No	☐Yes
Hypothyroidism:	☐No	☐Yes
Hyperthyroidism:	☐No	☐Yes
Parkinson's disease:	☐No	☐Yes
Other neurologic disease or condition:	☐No	☐Yes
Vitamin B12 deficiency:	☐No	☐Yes
Vitamin D deficiency:	☐No	☐Yes
Multiple sclerosis:	☐No	☐Yes
Other autoimmune disease:	☐No	☐Yes

If yes, please specify:_____

Has the patient smoked > 100 cigarettes in his/her lifetime?

☐No ☐Yes ☐Unknown

If yes, respond to the following questions:

Smoking Status

☐Former: No smoking for 1 year or more

☐Recent: Quit less than 1 year ago

☐Current: Smoke now

During the years the patient smoked, how many cigarettes did the patient usually smoke each day?

☐1-4 ☐5-14 ☐15-24 ☐25-34 ☐35-44

☐45-54 ☐55 or more

How many years has the patient been (was the patient) a regular smoker? Do not count years the patient did not smoke.

☐1-4 ☐5-9 ☐10-19 ☐20-29 ☐30-39

☐40-49 ☐50 or more

(continued on next page)

Patient Initials _____(L, F M)

CAUSES OF NEUROPATHY

Does the patient currently have neuropathy? ☐No ☐Yes

If yes, select all causes that apply:

- ☐ Diabetic neuropathy
- ☐ Idiopathic neuropathy (also called cryptogenic neuropathy)
- ☐ Chronic inflammatory demyelinating polyradiculoneuropathy
- ☐ Neuropathy associated with B12 deficiency
- ☐ Neuropathy associated with other vitamin or mineral deficiency (*e.g.* Niacin deficiency (pellagra), B1 deficiency, B6 deficiency, Copper deficiency, Vitamin E deficiency)
- ☐ Neuropathy associated with alcohol abuse
- ☐ Charcot Marie Tooth
- ☐ Hereditary neuropathy (sensory and autonomic neuropathy, motor neuropathy, or with tendency to pressure palsy)
- ☐ Neuropathy associated with a genetic disorder (Adrenomyeloneuropathy, MNGIE [mitochondrial neuropathy, with gastrointestinal symptoms and encephalopathy], NARP [neuropathy ataxia retinal pigmentosa], CANOMAD [chronic ataxic neuropathy, with ophthalmoplegia, monoclonal protein, cold agglutins and disialosyl antibodies])
- ☐ Amyloid associated neuropathy (Transthyretin familial amyloid polyneuropathy, AL amyloidosis, POEMS (polyneuropathy, organomegaly, endocrinopathy, m protein, skin changes))
- ☐ Neuropathy associated with other autoimmune disorder (*e.g.* Anti myelin associated glycoprotein (MAG) neuropathy, Anti-sulfatide antibody neuropathy, Multifocal motor neuropathy, Guillain barre syndrome, Celiac disease)
- ☐ Neuropathy associated with rheumatologic autoimmune disease (*e.g.* Systemic lupus erythematosus, Vasculitis, Sjogren's disease, Wegener's granulomatosus, Churg-Straus, cryoglobulinemia, Sarcoidosis, Rheumatoid arthritis)
- ☐ Toxic neuropathy (*e.g.* Pyridoxine (B6) toxicity, Amiodarone, Colchicine, Isoniazid, Dapsone, Phenytoin, disulfiram, Dideoxynucletides, Metronidazole, Nitrofurantoin, Arsenic, Lead, Mercury, Thallium, Acrylamide, N-hexane)
- ☐ Neuropathy associated with infectious etiology (*e.g.* HIV, Leprosy, Lyme disease, Hepatitis C, Diphtheria)
- ☐ Paraneoplastic neuropathy (*e.g.* associated with Anti-hu antibodies or Anti-CV2 (crmp5) antibodies)
- ☐ Critical illness neuropathy
- ☐ Uremic Neuropathy
- ☐ Neuropathy associated with thyroid disease (Hyperthyroidism or Hypothyroidism)
- ☐ Other cause of neuropathy, specify:_____
- ☐ Unknown cause of neuropathy

(continued on next page)

Patient Initials_____(L, F M)

ALCOHOL USE

PRIOR TREATMENT

Has the patient ever received the following therapies?

Taxane	☐ No	☐ Yes
Platinum agent	☐ No	☐ Yes
Vinca alkaloid	☐ No	☐ Yes
Bortezomib-based chemotherapy	☐ No	☐ Yes

Has the patient received any prior oncologic treatment for this cancer?

Chemotherapy *(e.g., adriamycin, cyclophosphamide, ifosfamide,*		
Hormonal therapy *(e.g., anastrozole, letrozole, exemestane, tamoxifen)*	☐ No	☐ Yes
Biologic therapy *(e.g., trastuzumab, pertuzumab, bevacizumab)*	☐ No	☐ Yes
Immunotherapy *(e.g., pembrolizumab, nivolumab, ipilimumab)*	☐ No	☐ Yes
Molecular therapy *(e.g., palbociclib, ribociclib, erlotinib)*	☐ No	☐ Yes
Surgery	☐ No	☐ Yes
Radiation therapy	☐ No	☐ Yes
Other	☐ No	☐ Yes

If yes, specify:_____

Comments:

AAAR9515
SUPPLEMENTS, TOPICAL AGENTS, AND OTHER TREATMENTS FORM

Patient Initials_____(L, F M) **Date of Assessment**: ☐☐ / ☐☐ / ☐☐☐☐

Time point: ☐ Baseline ☐ 12 Weeks ☐ 24 Weeks

Instructions: Submit this form at the time points listed above. All dates are **MONTH, DAY, YEAR**. Explain any blank dates or fields in the **Comments** section. Place an **X** in appropriate boxes.

MEDICATIONS

Indicate whether the patient took each prescription or over-the-counter medication since the last time point (Baseline only: indicate whether the patient is currently taking these prescription or over-the-counter medications). Also indicate dosage per pill and frequency, using the frequency codes below.

Medication	Taken	Dosage (per pill)	Frequency Code	Taken for neuropathy symptoms?
Anti-depressants (specify in comments)	Yes ☐ No	☐☐☐ mg	☐	☐ Yes ☐ No
Gabapentin	Yes ☐ No	☐☐☐ mg	☐	☐ Yes ☐ No
Narcotics (specify in comments)	Yes ☐ No	☐☐☐ mg	☐	☐ Yes ☐ No
Tramadol	Yes ☐ No	☐☐☐ mg	☐	☐ Yes ☐ No
Duloxetine	Yes ☐ No	☐☐☐ mg	☐	☐ Yes ☐ No
Acetaminophen (e.g., Tylenol)	Yes ☐ No	☐☐☐ mg	☐	☐ Yes ☐ No
Ibuprofen (e.g., Advil)	Yes ☐ No	☐☐☐ mg	☐	☐ Yes ☐ No

Frequency codes:

Code	Pills
1	< 1 pill per week
2	2-3 pills per week
3	4-6 pills per week
4	1 pill per day
5	> 1 pill per day

(continued on next page)

SUPPLEMENTS, TOPICAL AGENTS, AND OTHER TREATMENTS FORM

Patient Initials _____(L, F M) Date of Assessment: / / ☐☐☐☐

VITAMINS AND SUPPLEMENTS

Indicate whether the patient took each vitamin or supplement since the last time point (Baseline only: indicate whether the patient is currently taking each vitamin or supplement). Also indicate dosage per pill and frequency, using the frequency codes below. If vitamins or supplements were not taken in pill form, explain in comments.

Vitamin or Supplement	Taken	Dosage (per pill)	Frequency Code	Taken for neuropathy symptoms?
Vitamin E	☐ Yes ☐ No	☐☐☐ IU	☐	☐ Yes ☐ No
Glutamine	☐ Yes ☐ No	☐☐☐ mg	☐	☐ Yes ☐ No
Vitamin B6	☐ Yes ☐ No	☐☐☐ mg	☐	☐ Yes ☐ No
Fish Oil	☐ Yes ☐ No	☐☐☐ mg	☐	☐ Yes ☐ No

TOPICAL AGENTS

Topical Agent	Used	Application Site (check all that apply)	Frequency Code	Used for neuropathy symptoms?
Menthol	☐ Yes ☐ No	☐ Upper extremity (ies) ☐ Lower extremity (ies)	☐	☐ Yes ☐ No
Other topical agent, specify:	☐ Yes ☐ No	Upper extremity (ies) Lower extremity (ies)	☐	☐ Yes ☐ No

Frequency codes:

Code	Pills	Topical Agents, 1 application:
1	< 1 pill per week	1-3 times per week (or fewer)
2	2-3 pills per week	4-6 times per week
3	4-6 pills per week	Daily
4	1 pill per day	Twice daily
5	> 1 pill per day	> Twice daily

(continued on next page)

Patient Initials_____(L, F M) Date of Assessment: ☐☐ / ☐☐ / ☐☐☐☐

COMPLEMENTARY AND ALTERNATIVE MEDICINES

Since last contact, has the patient used acupuncture (Baseline: has the patient ever used acupuncture)**?**

☐ Yes ☐ No

If yes, did the patient use acupuncture for neuropathy symptoms?

☐ Yes ☐ No

Since last contact, has as the patient used cooling gloves or socks (Baseline: has the patient ever used cooling gloves or socks)**?**

☐ Yes ☐ No

If yes, did the patient use cooling gloves or socks for neuropathy symptoms?

☐ Yes ☐ No

Since last contact, has as the patient used compression gloves or socks (Baseline: has the patient ever used com- pression gloves or socks)**?**

☐ Yes ☐ No

If yes, did the patient use compression gloves or socks for neuropathy symptoms?

☐ Yes ☐ No

Since last contact, has the patient used any other complementary or alternative therapies for neuropathy symptoms (Baseline: has the patient ever used any other complementary or alternative therapies for neuropathy symptoms)**?**

☐ Yes ☐ No

If yes, specify:_____

Did the patient feel these therapies improved their symptoms?

☐ Yes ☐ No

Comments

AAAR9515
NEUROPATHY ASSESSMENT FORM

Patient Initials_____(L, F M) **Date of Assessment**: ☐☐ / ☐☐ / ☐☐☐☐

Time point: ☐ Baseline ☐ 12 Weeks ☐ 24 Weeks

Instructions: Submit this form at the time points listed above. All dates are **MONTH, DAY, YEAR**. Explain any blank dates or fields in the **Comments** section. Place an **X** in appropriate boxes.

Test Performed by:_____Signature: x_____

TIMED GET UP AND GO

Baseline, 24 weeks, and 52 weeks only.

Timed Get Up and Go: ☐☐☐.☐ sec

FALLS

Baseline, 24 weeks, and 52 weeks only.

Did the patient have a history of falls within the past six months? ☐ Yes ☐ No

DOMINANT SIDE

Dominant hand/arm *(side with which patient writes):* ☐ Left ☐ Right

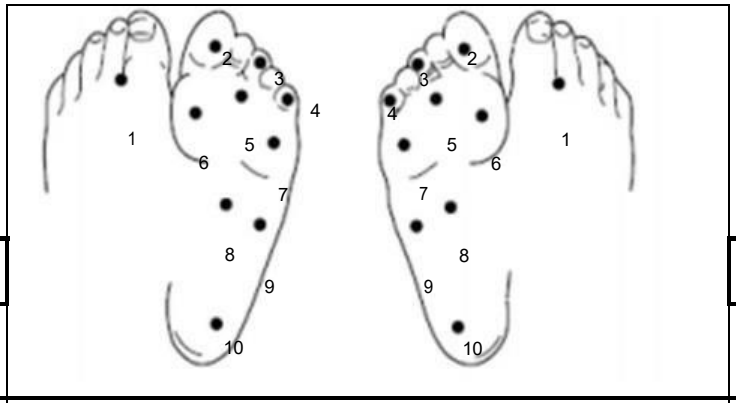
Dominant foot *(side with which patient kicks a ball):* ☐ Left ☐ Right

NEUROPEN

All time points.
Indicate whether sensation is detected at the following sites on the patient's dominant foot.

Site	Touch and pressure (Monofilament): Sensation detected?		ess cted?	
1.	☐ Yes	☐ No	☐ Yes	☐ No
2.	☐ Yes	☐ No	☐ Yes	☐ No
3.	☐ Yes	☐ No	☐ Yes	☐ No
4.	☐ Yes	☐ No	☐ Yes	☐ No
5.	☐ Yes	☐ No	☐ Yes	☐ No
6.	☐ Yes	☐ No	☐ Yes	☐ No
7.	☐ Yes	☐ No	☐ Yes	☐ No
8.	☐ Yes	☐ No	☐ Yes	☐ No
9.	☐ Yes	☐ No	☐ Yes	☐ No
10.	☐ Yes	☐ No	☐ Yes	☐ No

Sites:



Left foot

Right foot

Patient Initials_____(L, F M) Date of Assessment: ☐☐ / ☐☐ / ☐☐☐☐

128 Hz TUNING FORK

All time points. Report time, in seconds, until vibration is no longer felt at each of the following

sites: Lower extremity testing

	Dominant side	Normal value
Interphalangeal joint of the great toe	☐☐☐.☐ sec	> 15 sec
Middorsal foot*	☐☐☐.☐ sec OR ☐ N/A	> 15 sec
Medial Mallelolus*	☐☐☐.☐ sec OR ☐ N/A	> 15 sec
Midfibular region*	☐☐☐.☐ sec OR ☐ N/A	> 15 sec
Patellar region*	☐☐☐.☐ sec OR N/A	> 15 sec

*Complete only if measurement of interphalangeal joint of the great toe < 15 sec.

Upper extremity testing

	Dominant side	Normal value
Distal interphalangeal joint of the index finger	☐☐☐.☐ sec	> 25 sec
Ulnar styloid of wrist	☐☐☐.☐ sec	> 15 sec
Lateral epicondyle of elbow	☐☐☐.☐ sec	> 15 sec

Comments

AAAR9515
SOLICITED NEUROPATHY FORM

Patient Initials_____(L, F M) **Date of Assessment** ☐☐ / ☐☐ / ☐☐☐☐

Time point: ☐ 12 Weeks ☐ 24 Weeks

Instructions: Submit this form at the time points listed above. Using CTCAE 5.0 Grade definitions, please grade abnormalities or conditions present PRIOR to taxane administration for this time point (if applicable. If the condition is not present, enter grade 0. Do not code a condition existing prior to registration as an adverse event unless it worsens. Indicate if the adverse event results in inpatient hospitalization or prolongation of existing hospitalization for 24 hours. Follow instructions in Section 16.0 of the protocol for expedited reporting requirements on this study. Category lists may not include all adverse events from that category. All dates are **MONTH, DAY, YEAR.** Explain any blank dates or fields in the **Comments** section. Place an **X** in appropriate boxes.

Were solicited events assessed during most recent period? ☐ Yes ☐ No

Solicited event term (CTCAE v5.0)	Solicited event grade (0-5)	Attribution to study intervention*	Hospitalization (at least 24 hours)
Dysesthesia	☐	☐	☐
Neuralgia	☐	☐	☐
Paresthesia	☐	☐	☐
Peripheral motor neuropathy	☐	☐	☐
Peripheral sensory neuropathy	☐	☐	☐

***Attribution codes:** 1 - unrelated 2 - unlikely 3 - possible 4 - probable 5 - definite

Comments

AAAR9515
OFF PROTCOL NOTICE

Patient Initials_____(L, F M)

Instructions: Submit this form within 14 days after completion (or discontinuation) of protocol participation as outlined in Section 7.0 of the S1714 Protocol. All dates are **MONTH**, **DAY**, **YEAR**. Explain any blank fields or blank dates in the **Comments** section. Place an **X** in appropriate boxes.

VITAL STATUS

Vital Status: ☐ Alive ☐ Dead *(submit Notice of Death form)*

Date of last contact: ☐☐ / ☐☐ / ☐☐☐☐

If dead, date of death: ☐☐ / ☐☐ / ☐☐☐☐

OFF PROTOCOL

Off protocol reason *(select one)*:

☐ Completion of 52 weeks of protocol participation

☐ Patient did not receive at least one cycle of taxane-containing chemotherapy within 30 days after registration

☐ Patient received another chemotherapy regimen containing neurotoxic agents

☐ Patient refusal

☐ Death

Off protocol date (date of completion, death, or decision to discontinue participation):

☐☐ / ☐☐ / ☐☐☐☐

Comments:

AAAR9515
OFF-TREATMENT FOLLOW UP FORM

Patient Initials_____(L, F M)

Time point: ☐ Baseline ☐ 12 Weeks ☐ 24 Weeks

Instructions: Submit this form at the time points listed above. All dates are **MONTH, DAY, YEAR**. Explain any blank dates or fields in the **Comments** section. Place an **X** in appropriate boxes.

VITAL STATUS

Vital status: ☐ Alive ☐ Dead *(submit Notice of Death)*

Date of last contact: ☐☐ / ☐☐ / ☐☐☐☐

If dead, date of death: ☐☐ / ☐☐ / ☐☐☐☐

Comments:

AAAR9515
CIPN FORM

Participant ID_____ Visit Date (*MM/DD/YYYY*) _____

Visit: BASELINE / 12 WEEKS / 24 WEEKS

Vibration Perception Threshold Test
Perception Threshold: when vibration stimulus is initially felt
Disappearance Threshold: when the stimulus disappears

Distal Index Finger

Trial	Right Hand		Left Hand	
	Perception Threshold	Disappearance Threshold	Perception Threshold	Disappearance Threshold
1st				
2nd				
3rd				
Avg				

[Normal Finger Tip: 0.420]

Big Toe

Trial	Right Foot		Left Foot	
	Perception Threshold	Disappearance Threshold	Perception Threshold	Disappearance Threshold
1st				
2nd				
3rd				
Avg				

[Normal Toe Base: 0.616]

AAAR9515
CIPN FORM

Participant ID_____Visit #:_____

TANDEM AND UNIPEDAL STANCE TEST

		Successfullycompleted?	
Test	Max time	YES	NO, (seconds)
Tandem (heel to toe)	30 sec	☐	☐ (_____.)
One leg (eyes open)	60 sec	☐	☐ (_____.)
One leg (eyes closed)	30 sec	☐	☐ (_____.)
One leg (eyes open, head rotated)	30 sec	☐	☐ (_____.)

HANDS AND FEET COLOR CHANGES

NORMAL	RED	WHITE	BLUE	BLACK

ADHERENCE WITH STUDY INTEVERNTION

Cycle 1	Yes	No	N/A
Cycle 2			
Cycle 3			
Cycle 4			
Cycle 5			
Cycle 6			
Cycle 7			
Cycle 8			
Cycle 9			
Cycle 10			
Cycle 11			
Cycle 12			

Performed by: _____

AAAR9515
BASELINE TUMOR DESCRIPTION (BREAST CANCER)

Participant ID_____ Visit Date (*MM/DD/YYYY*) _____

Instructions: Submit this form within 7 days after initial registration. Explain any blank fields or blank dates in the **Comments** section. Place an **X** in appropriate boxes.

Date of current pathologic diagnosis: ☐☐/ ☐☐/ ☐☐☐☐

Primary tumor size at diagnosis: ☐☐.☐cm

AJCC clinical stage:

T: ☐T1 ☐T1mi ☐T1a ☐T1b ☐T1c ☐T2 ☐T3 ☐T4 ☐T4a ☐T4b ☐T4c ☐T4d

N: ☐cN0 ☐cN1 ☐cN1mi ☐cN2 ☐cN2a ☐cN2b ☐cN3 ☐cN3a ☐cN3b ☐cN3c ☐cNX

M: ☐cM0 ☐cM1 ☐pM1

ER status: ☐Positive ☐Negative

PgR status: ☐Positive ☐Negative

HER-2 status: ☐Positive ☐Negative ☐Equivocal

Clinical Prognostic Stage group: ☐IA ☐IB ☐IIA ☐IIB ☐IIIA ☐IIIB ☐IIIC ☐IV

Pathological Prognostic Stage group: ☐IA ☐IB ☐IIA ☐IIB ☐IIIA ☐IIIB ☐IIIC ☐IV

Select planned taxane-containing treatment regimen (if dose or frequency varies from standard, select closest regimen and indicate dose and frequency below)**:**

Using or Planned	Regimen	Standard Taxane Dose	Frequency
☐	P x 4	Paclitaxel 175 mg/m^2	Every 2 weeks for 4 cycles
☐	P x 12 +/- Carboplatin (AUC 2 for weekly or AUC 5-6 for every 3 weeks)	Paclitaxel 80 mg/m^2	Every week for 12 cycles
☐	TC x 4 or TC x 6	Docetaxel 75 mg/m^2	Every 3 weeks for 4 or 6 cycles
☐	TAC x 6	Docetaxel 75 mg/m^2	Every 3 weeks for 6 cycles
☐	T x 4	Docetaxel 100 mg/m^2	Every 3 weeks for 4 cycles
☐	T/Carboplatin (AUC6)	Docetaxel 75 mg/m^2	Every 3 weeks for 6 cycles
☐	Other, specify:_____	Taxane: Docetaxel/Paclitaxel Dose:_____mg/m^2	Every_____weeks for_____cycles

Abbreviations: dd, dose-dense; A, doxorubicin; C, cyclophosphamide; P, paclitaxel; T, docetaxel

Is taxane planned to be delivered at the standard dose for the regimen shown in the table above?

☐Yes ☐No, reduced dose

If no, specify dose: ☐☐☐ mg/m^2

Is taxane planned to be delivered at the standard frequency for the regimen shown in the table above?

☐Yes ☐No

If no, indicate frequency:

☐Weekly ☐Biweekly ☐Triweekly ☐ > Triweekly

Will patient be taking HER-2 targeted therapy?

☐Yes ☐No

Will the platinum agent be delivered at the standard dose?

☐Yes ☐No, reduced dose ☐Not Applicable (regimen does not contain a platinum agent)

Comments:

AAAR9515
SOLICITED NEUROPATHY EVENTS FORM

Patient Initials_____(L, F M) Date of Assessment ☐☐/☐☐/☐☐☐☐

Time point: ☐ 12 Weeks ☐ 24 Weeks

Instructions: Submit this form at the time points listed above. Using CTCAE 5.0 Grade definitions, please grade abnormalities or conditions present PRIOR to taxane administration for this time point (if applicable. If the condition is not present, enter grade 0. Do not code a condition existing prior to registration as an adverse event unless it worsens. Indicate if the adverse event results in inpatient hospitalization or prolongation of existing hospitalization for 24 hours. Follow instructions in Section 16.0 of the protocol for expedited reporting requirements on this study. Category lists may not include all adverse events from that category. All dates are **MONTH, DAY, YEAR.** Explain any blank dates or fields in the **Comments** section. Place an [X] in appropriate boxes.

Were solicited events assessed during most recent period? ☐ Yes ☐ No

Solicited Event Term (CTCAE v5.0)	Solicited Event Grade (0-5)	Attribution to Study Intervention	Attribution to Chemotherapy	Hospitalization (at least 24hrs)	Hands uni or bilateral		Feet uni or bilateral	
Dysesthesia	☐	☐	☐	☐	unilateral side:	bilateral	unilateral side:	bilateral
Neuralgia	☐	☐	☐	☐	unilateral side:	bilateral	unilateral side:	bilateral
Paresthesia	☐	☐	☐	☐	unilateral side:	bilateral	unilateral side:	bilateral
Peripheral motor neuropathy	☐	☐	☐	☐	unilateral side:	bilateral	unilateral side:	bilateral
Peripheral sensory neuropathy	☐	☐	☐	☐	unilateral side:	bilateral	unilateral side:	bilateral

***Attribution codes:** 1 - unrelated 2 - unlikely 3 - possible 4 - probable 5 - definite

Comments