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Confidential

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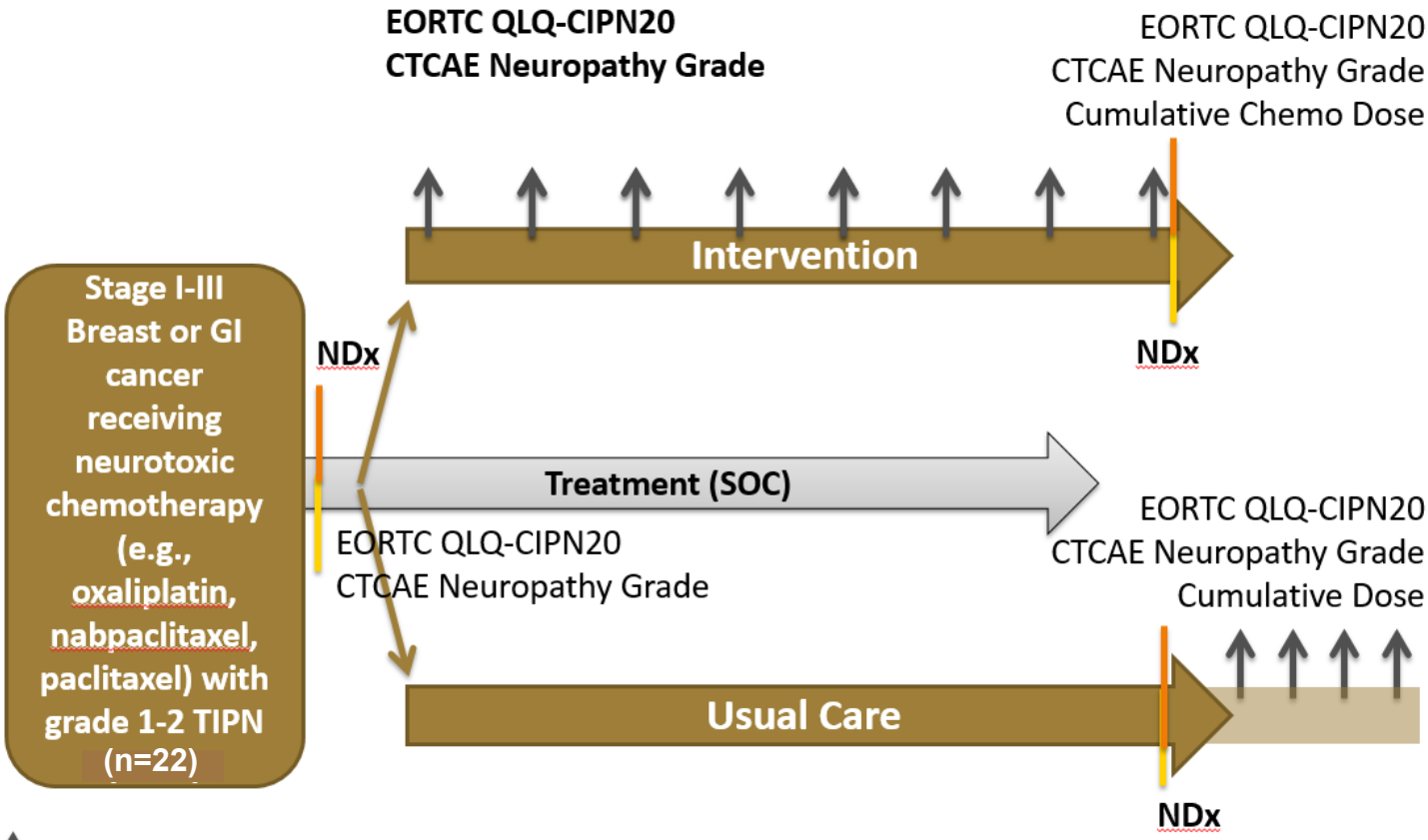
Schema



Acupuncture session performed by WF Integrative Med Clinic

Patient and provider assessment of CIPN via EORTC QLC-CIPN20 (PRO) and blinded clinician grade of Neuropathy by NCI CTCAE

Neurodiagnostic assessment includes standard measures of sensory n. function: nerve conduction, ultrasound, skin biopsy

1.0 Introduction and Background

Peripheral neuropathy (PN) is broadly defined as damage to the peripheral nervous system caused by a primary lesion or dysfunction.[1] Chemotherapy-induced peripheral neuropathy (CIPN) is a common consequence of cytotoxic chemotherapies and results in length-dependent sensory predominant impairments with symptoms of numbness, tingling, burning and pain in hands and feet. CIPN is consistently associated with lower self-reported physical function and quality of life and may contribute to increased cancer mortality as patients often do not complete their full course of chemotherapy due to dose reductions, modifications, or treatment discontinuation. Although the underlying mechanisms of CIPN are only partially understood,[2] CIPN is a small fiber neuropathy that results in reduced nerve fiber density in the skin and can lead to physiologic changes in nerve conduction and anatomic changes in peripheral nerve anatomy. CIPN is more prevalent and more severe in African American (A-A) compared to women of other races, but the reason for this is not understood.[3,4]

CIPN is a significant problem for cancer survivors. Prevalence rates of CIPN vary widely based on different patient populations, different grading systems and symptom assessments, but have been found in up to 80% of patients receiving chemotherapy.[5] In fact, CIPN is the most common reason for dose reduction in breast cancer patients receiving taxane chemotherapy. One study found that 42% of early stage breast cancer survivors had CIPN two years after chemotherapy[6] and another reported that 50% of women cancer survivors reported symptoms of CIPN six years after treatment.[7] Similarly, platinum agents including cisplatin, carboplatin, and oxaliplatin also commonly result in peripheral neurotoxicity. Transient neurotoxic effects are experienced by nearly all patients following oxaliplatin infusion with patients describing cold hypersensitivity within hours of infusion. Chronic peripheral neuropathy is estimated to occur in up to 70% of patients receiving oxaliplatin. Disruption of calcium signaling leads to axonal hyperexcitability and peripheral nerve dysfunction leading to oxaliplatin-induced peripheral neuropathy (OIPN).[8,9]

A recent NCI Symptom Management and Health-related Quality of Life Steering Committee symposium concluded that research was needed to understand the mechanisms of CIPN and to identify therapies to prevent or treat CIPN.[10] This group expressed particular interest in non-drug interventions. The NCI considers the development of adjuncts for the prevention and relief of CIPN as essential for patient care.[11]

Acupuncture has been found to effectively treat other types of pain including chronic low-back pain, migraine and tension headaches, as well as chemotherapy-induced nausea and vomiting.[12,13] Acupuncture is a safe, non-toxic treatment that unlike other pharmacologic agents that target mechanisms of CIPN does not interfere with chemotherapeutic efficacy. A recent systematic review found that acupuncture showed benefit for neuropathy caused by diabetes, Bell's palsy, and carpal tunnel syndrome, and probably for the treatment of HIV-related neuropathy (which also causes a severe sensory-predominant polyneuropathy).[12] The review further concluded that acupuncture appears to improve nerve conduction study parameters in both sensory and motor nerves. There were not enough randomized control trials [RCTs] for cancer-related neuropathy that met the inclusion criteria to review this condition.[12] However, two small nonrandomized pilot studies suggest that acupuncture may be

effective for reducing CIPN.[14,15] These pilot studies support further investigation into how acupuncture works and whether patient-reported symptom improvement is associated with underlying physiologic changes in the nerve.

There are strong mechanistic links between acupuncture and CIPN. The dorsal root ganglion (DRG) is a critical site for peripheral nerve health and plays an important role in mediating the pathologic changes with CIPN and the action of acupuncture. In animal models and human studies, acupuncture has been shown to modulate dorsal horn and DRG neurotransmission including transmission of opioid, norepinephrine, serotonin, and glutamate signals.[16] Cell bodies in the DRG lack a blood-nerve barrier and are thus subject to the toxic effects of most chemotherapy. Taxane chemotherapies disrupt axonal transport from the DRG and perturb normal axonal flow resulting in mitochondrial dysfunction, oxidative stress, and nerve swelling.[17–20] For oxaliplatin, calcium dysregulation leads to a channelopathy in the terminal nerve branches disrupting axoplasmic flow and causing hyperexcitability within the nerve and dorsal root. This results in impaired conduction along peripheral sensory nerves as assessed by nerve conduction studies (NCS), reduced intraepidermal nerve fiber (IENF) density detected by skin biopsy, and emerging evidence of nerve swelling on neuromuscular ultrasound. These standard of care tests provide a window into pathologic changes of CIPN and the potential effect of acupuncture on peripheral neurotoxicity. The results of this pilot study will be applicable to other causes of peripheral neuropathy as there is no compelling reason to believe that acupuncture's mechanisms of action (if proven to be effective) for treating CIPN would be different for other etiologies of peripheral neuropathy.

This pilot study seeks to obtain preliminary evidence for the evaluation of acupuncture in reducing the severity and/or progression of CIPN due to neurotoxic chemotherapy. We hypothesize that acupuncture can improve CIPN and prevent the escalation of CIPN as measured by patient–reported outcomes and the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Neuropathy Sensory Subscale (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50). We also hypothesize that the reduction in CIPN will allow for patients to continue their course of chemotherapy. We will also investigate whether improving CIPN symptoms is associated with improved objective measures of nerve function, which will provide potential mechanisms for how acupuncture works in treating PN. We hypothesize that acupuncture's effect on improving self-reported symptoms will be evidenced by improved objective nerve function as assessed by nerve conduction studies (NCS), intraepidermal nerve fiber (IENF) density, and/or nerve swelling by ultrasound.

Standard of Care, Objective Assessments of Nerve Function

CIPN manifests via several different pathophysiological mechanisms that can be assessed by currently available standard of care methods including physical examination, nerve conduction studies (NCS), skin biopsy to evaluate intraepidermal nerve fiber density (IENF), peripheral nerve ultrasound, and patient-reported outcome measures. Each of these studies are standard of care for the assessment of sensory-predominant neuropathies such as CIPN.

Physical Examination: Physical exam with quantitative sensory testing (QST) uses tuning forks or monofilaments to objectively measure the sensory threshold for proprioception. QST may be a useful addition to self-reported symptoms as it is non-invasive, easily implemented, and well-

correlated with self-reported CIPN symptoms. Although promising, it has not been shown to provide early detection of subclinical taxane-induced CIPN.[22,23]

Patient-Reported Outcome Measures: the European Organization for Research and Treatment of Cancer (EORTC) QLQ-CIPN20 Questionnaire is a 20-item self-reported survey that is easy to administer and was validated across participants in four large cooperative group trials.[24] The QLQ-CIPN20 sensory scale has been studied specifically with TIPN among breast cancer patients and was shown to be correlated with patient-reported symptoms from the Common Toxicity Criteria (0.79, $p < 0.00001$). Since taxanes and oxaliplatin are not associated with hearing loss, that corresponding item was excluded from analysis in that study.[25,26] For normative comparison, non-cancer patients tend to have very low scores on the QLQ-CIPN20 with a sum score average of 3.6 (standard deviation 7.2) and subtotals of 3.2 (7.3) for sensory measures, 3.8 (9.2) for motor, and 4.4 (10.7) for autonomic. The vast majority of non-cancer patients (90.1%) had a sum score of 0-10%; older age and self-reported comorbidities were associated with higher QLQ-CIPN20 scores. Based on the results from that study, age-matched normative data has been generated for the QLQ-CIPN20.[27] PRO-CTCAE is an item library containing 124 items reflecting 78 symptomatic cancer treatment-related symptoms.[28,29] Two PRO-CTCAE items address CIPN concerning the severity of the numbness and tingling and the degree that these symptoms have interfered with usual or daily activities. These items have previously been shown to have good psychometric properties.[30] The two PRO-CTCAE items have the potential of providing a feasible patient-reported measure in a clinic setting.

Nerve Conduction Studies (NCS): NCS measures impairment of electrical function in large peripheral nerves. NCS measures amplitude and latency of neuronal signaling. Reduction in the conduction velocity within a peripheral nerve indicates damage to the myelin, while reduction in the amplitude indicates axonal damage. Typical NCS findings suggestive of TIPN include slowed conduction velocity at common sites of entrapment (such as the carpal tunnel) and an earlier reduction of sural sensory amplitude relative to the radial nerve.[31] A prospective study of patients receiving paclitaxel and carboplatin found a reduction in sural nerve conduction from baseline in terms of the sensory action potential amplitude (14.5 +/- 9.0 uV to 9.7 +/- 7.1) and the sensory conduction velocity (54.6 +/- 7.7 m/s to 46.3 +/- 8.8).[32] A series of patients who received paclitaxel and cisplatin had a reduction in the sural nerve amplitude of sensory action potential from average 13.7 uV (standard deviation 6.5) to 6.5 (standard deviation 4.1).[33] NCS can be mildly painful for the patient; requires expertise and time to administer, and can only detect CIPN once it has progressed to the point that there is functional impairment of large peripheral nerves.[34] Other functional assays besides NCS have been investigated. Sudomotor testing is a novel technique that uses the topical administration peripheral nerves. Although non-invasive, sudomotor testing tends to have wide variability which can make interpretation difficult and it has not yet been tested in chemotherapy-induced peripheral neuropathy. A nerve excitability study is a novel non-invasive functional assay that detects the threshold of current that is needed to elicit an action potential. Similar to US, this experimental technique has been shown that it can detect oxaliplatin-induced peripheral neuropath.[35]

Skin Biopsy and Intraepidermal Nerve Fiber Density (IENF): skin biopsies are able to detect CIPN with good diagnostic sensitivity that may be superior to NCS in chronic CIPN.[36] Measurement of the IENF density is a standard clinical assessment used in the evaluation of

sensory predominant peripheral neuropathies. Healthy control participants have an average IENF density of 21.1 (standard deviation 10.4) at the thigh and 13.8 (standard deviation 6.7) in the distal leg.[37,38] Typical IENF density findings in CIPN include reduced nerve fiber density that is typically more pronounced distally at the lower leg (mean 3.0, range 0.5-6.3) as compared to the thigh (mean 5.5, range 0.7-13.2).[39] As expected, the IENF density likely continues to decrease with continued exposure to chemotherapy and worsening neuropathy, as a small longitudinal study of patients receiving oxaliplatin found that the distal leg IENF density progressively decreased from baseline 15.39 (6.75) to 12.89 (4.73) at 6 months to 9.45 (3.92) at 12 months.[40] However, IENF density has not been shown to be predictive of chemotherapy-induced peripheral neuropathy.

Peripheral Nerve Ultrasound (US): US is a non-invasive, non-irradiating, emerging imaging modality which can be used to assess peripheral nerves. Nerve fiber cross-sectional area (CSA), echogenicity, and vascularity are assessed and provide an indication of nerve health and potential pathology. The majority of US data have been published on detection of entrapment syndromes such as carpal tunnel syndrome. In these cases the most common US findings include nerve enlargement, decreased echogenicity proximal to the entrapment, and an increase in nerve vascularity.[41] Other studies have found that US can detect other peripheral nerve lesions or neuropathies, with the most reliable finding a change in nerve CSA. Ultrasound measurements of the sensory sural nerve at the distal calf in healthy participants without neuropathy had an average CSA of 5.3 mm^2 with standard deviation 1.8 mm^2 for a normal reference range of 1.7-8.9 mm^2.[42] Another ultrasound study assessed the sural nerve more distally at the ankle and found a smaller CSA which was significantly enlarged ($p < 0.001$) in patients with diabetic polyneuropathy as compared to healthy controls (mean/standard deviation 2.59 / 0.96 mm^2 as compared to 1.40 / 0.59 mm^2).[43]

Each of these assessments including patient-reported outcomes, physical examination, NCS, skin biopsy for IENF, and peripheral nerve ultrasound are standard of care for patients with sensory-predominant neuropathies such as CIPN and will be included in this trial to provide an objective assessment of peripheral nerve function. As standard of care tests, the risks of these studies are not different than those that would be encountered in routine clinical care for a patient undergoing comprehensive eletrophysiological evaluation of peripheral nerve pathology. Since the skin biopsy is an exploratory aim, patients will be allowed to participate in the study even if they are unwilling to have this measure.

2.0 Objectives

The goal of this study is to obtain preliminary evidence of the effect of 8 acupuncture treatments over 10 weeks in breast and GI cancer patients who are currently receiving or recently completed active neurotoxic chemotherapy and have clinically documented grade 1 or 2 neuropathy. Specific objectives for this population and intervention are defined below.

2.1 Primary Objective

2.1.1 To obtain preliminary evidence of the clinical effects of acupuncture compared to usual care on the change in sensory neuropathic pain as measured by the EORTC QLQ-CIPN20 sensory subscale.

2.2. Secondary Objectives

To obtain preliminary evidence of the clinical effects of acupuncture compared to usual care in:

2.2.1 Change in the motor and autonomic neuropathic pain subscores on the EORTC QLQ-CIPN20.

2.2.2 Change in patient-reported assessment of numbness and tingling using the 2-item PRO-CTCAE measure.

2.2.3 Preventing the escalation of CIPN from grade 1 or 2 to a higher grade.

2.2.4 Amount and intensity of planned chemotherapy relative to completed chemotherapy if more chemotherapy is given or planned.

2.2.5 Effect on sensory and motor nerve function via NCS (e.g. conduction velocity, latency, and amplitude).

2.2.6 Effect on peripheral nerve swelling via nerve ultrasound (e.g. cross sectional area, CSA)

2.3. Exploratory Objectives

2.3.1 To obtain preliminary evidence on phenotypic differences between African-American and non A-A (i.e., white, Asian, etc.) with regard to presentation of CIPN as well as response to the intervention.

2.3.2 To obtain preliminary evidence of the effect of acupuncture on intraepidermal nerve fiber density (IENF) via skin biopsy.

2.3.3 To examine the associations among the peripheral nerve assessment measures (nerve conduction, peripheral nerve ultrasound, skin biopsy) and of the peripheral nerve assessment measures with the patient reported outcomes (EORTC QLQ-CIN20, PRO-CTCAE) at baseline, week 12, and for the change from baseline to week 12.

2.3.4 To examine the association between expectations of the effectiveness of acupuncture to reduce peripheral neuropathy and baseline, 12 week, and change in patient-reported outcomes on the EORTC QLQ-CIPN20 and PRO-CTCAE.

3.0 Study Population

This study is designed to enroll breast and GI cancer patients who are currently receiving or recently completed active neurotoxic chemotherapy and have clinically documented grade 1 or 2 neuropathy by CTCAE v5.0 criteria.

3.1 Inclusion Criteria

- Breast or GI cancer stage I-III
- Currently receiving or recently completed neurotoxic chemotherapy (either adjuvant or neoadjuvant). Currently is defined as including up until when the next cycle would be delivered, that is if the patient is getting chemotherapy every week, this would include a week after their last treatment; if the patient is getting treatment every 2 weeks, this would include 2 weeks after their last treatment; if the patient is getting treatment every 3 weeks, this would include 3 weeks after their last treatment, etc. Recently completed is defined as 6 weeks after this time period. For example, if a patient was getting chemotherapy every week, this would include seven weeks after their last treatment; if the patient was getting treatment every 2 weeks, this would include 8 weeks after their last treatment; if the patient were getting treatment every 3 weeks, this would include 9 weeks after their last treatment, etc.
- Clinical symptoms of peripheral neuropathy of grade 1 or grade 2 as measured by the NCI-CTCAE.
- Ability and willingness to understand and sign an informed consent.

3.2 Exclusion Criteria

- Self-reported or documented history of UNRESOLVED pre-existing peripheral neuropathy due to diabetes, HIV, or other conditions.
- Unable to provide medical history.
- Male patients.
- Pregnant
- Unwilling to receive acupuncture or unable to travel for treatments.

3.3 Inclusion of women and minorities

3.3.1 Patients of all races and ethnicity who meet the above-described eligibility criteria are eligible for this trial.

3.3.2 We aim to enroll at least 25% Black or African Americans (N=6). Because of the low incidence of cancer among American Indian/Alaska Native, Asian, and Hispanic/Latinos in our catchment area, we do not expect accruals of individuals of those ancestries; however, no ancestry background is being excluded. Should we not meet or exceed these estimates, the PI will engage the Cancer Center Health Equity Advisory Group to discuss strategies to enhance recruitment in the target populations.

4.0 Methods

4.1 Registration Procedures

All patients entered on any WFBCCC trial, whether treatment, companion, or cancer control trial, **must** be linked to a study protocol in EPIC within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

You must perform the following steps in order to ensure prompt registration of your patient:

1. Complete the Eligibility Checklist (Appendix A)
2. Complete the Protocol Registration Form (Appendix B)
3. Complete the Ethnicity Verification Form (Appendix C)
4. Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

   *Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.

5. Fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

To complete the registration process, the Registrar will:

- assign a patient study number
- register the patient on the study

4.2 Study Activities

Study Calendar*						
	Screening	**Baseline Peripheral Nerve Assessment**	**30 Day Follow-up (+ or – 5 days)**	**Intervention (weeks 2-12)**	**Week 12 End of Treatment Assessment (10 +/2 weeks post baseline)**	**Post Treatment review**
Informed Consent	X					
Randomization[h]		X				
Pregnancy Test for Women of Childbearing Potential	X					
Medical history (Appendix D)	X					
Physician Rated CTCAE (Appendix M)		X			X	
QLQ-CIPN20 (Appendix E)		X			X	
PRO-CTAE (Appendix E)		X			X	
Abbreviated Neurological Examination		X			X	
Nerve Conduction Study[a] (Appendix F)		X			X	
Peripheral Nerve Ultrasound[b] (Appendix G)		X			X	
Skin Biopsy[c] (Appendix H)		X			X	
Acupuncture Expectancy Scale (Appendix P)		X				
Follow-up Form for Skin Biopsy (Appendix J)[g]			X			X
Research Blood Draw[d]		X			X	
Acupuncture treatments (Appendix O)[e]				X		
Post treatment review[f]			X			X
Adverse Events		X	X	X	X	X
Chemotherapy Form (Appendix N)						X

* The Study Calendar represents an ideal schedule for the completion of study related activities; however, depending on patient and physician availability, the completion of these clinical tasks may occur at any clinical encounter. ***The exceptions to this rule are following: the informed consent should be signed before any research activity occurs. While all study related tasks may be completed at a single visit, it is anticipated that due to scheduling, at least 2 study visits will be required.
a. Sural,Tibial, and Median nerve assessments
b. Sural, Tibial, and Median nerve assessments
c. One skin biopsy will be obtained as 4-5mm punch at distal end of leg in sural nerve territory (10cm above lateral malleolus).
d. Green top sodium heparin tube: 8 mL blood sample.
e. Patients assigned to acupuncture will receive 8 treatments over a 10-week period. Appendix O is not required for participants who are randomized to the usual care group.
f. Patients will receive a post biopsy call 30 days after treatment to ensure safety and review adverse events.
g. Appendix J is not required for participants who do not receive a skin biopsy (occurring 30 days after baseline and 30 days after follow-up).
h Randomization is to be done after baseline visit.

4.3 Study setting

Enrollment of participants will be take place at WFBMC Comprehensive Cancer Center (CCC) outpatient clinics.

4.4 Enrollment and Screening

Patients being treated at WFBMC who are identified as having grade 1 or 2 neuropathy will be brought to the attention of the study nurse. Treating clinicians will introduce the study and consent will be obtained by either the clinical or research team.

Non-WFBMC patients who respond to posted flyers will be directed to call a project specific phone line. The eligibility of non-WFBMC patients will be initially assessed via a brief telephone screen (Appendix Q) conducted by the Study in which study components and eligibility criteria are reviewed. If the patient is eligible and expresses interest in participating, a subsequent in-person appointment at Clinical Research Unit (CRU) Services facility will be scheduled with a study investigator who will review the patient's EHR and conduct a physical exam of the patient's nerve sensations. If the patient is still eligible and expresses interest in participating, consent will be obtained and a study visit will be scheduled at WFBMC to complete the clinical assessments outlined below.

Clinical assessment will take place in the CCC outpatient clinic and will include a focused history by one of the study investigators or research employees. The medical record will also be reviewed to confirm details of the medical history. The focused history will assess age, body-mass index (BMI), cancer staging, types and dosages of chemotherapy received, corticosteroid and analgesic use, and presence of comorbidities (diabetes, B12 deficiency, thyroid disorders, alcoholism, depression, carpal tunnel syndrome, sciatica). A physical examination will occur and will also assess peripheral pulses and peripheral sensation. Clinical symptoms of peripheral neuropathy of grade 1 or grade 2 as measured by the NCI-CTCAE will be verified. The QLQ-CIPN20 questionnaire and Pro-CTCAE will also be administered at this encounter.

Participants will be scheduled for the NCS, ultrasound, and skin biopsy (approximately 2-2.5 hours) . Patients will receive a $25.00 gift card upon completion of the baseline peripheral nerve assessment and a $75 gift card upon completion of the follow-up assessment. Patients that live 60 miles or more from WFBMC will receive an additional

$50 gift card upon completion of the baseline peripheral nerve assessment and an additional $50 gift card upon completion of the follow-up assessment.

4.5 Peripheral Nerve Assessment

Peripheral nerve evaluation will be performed in the Diagnostic Neurology clinic at the WFBMC. Patients will undergo abbreviated neurological exam to assess strength of the tibialis anterior and gastrocnemius and deep tendon reflex exam of the Achilles tendon. Nerve conduction studies, nerve ultrasound and skin biopsies will be performed per standard of care on the affected lower limb and completed at a single visit. As standard of care tests, these tests results will be reported in the medical record for review by the patient's treating oncologist. Skin biopsy tissue that remains after clinical assessment of IENF will be sent to Dr. Shiozawa's lab for storage and exploratory assessment (see Section 4.5.4).

4.5.1 Nerve Conduction Study

CS technique and reference values for the sural and tibial nerves among healthy adults are based on data from Chen et al.[44] and standard institutional practice.[44] NCS assessment of the sural sensory nerve involves electrode placement at the ankle (posteroinferior to the lateral malleolus) and more distally with a 3cm bar for a distance of approximately 14cm; the nerve is stimulated at the calf midline with a display sensitivity 2-5 uV/div and sweep of 1 ms/div. The sural sensory nerve reference values for amplitude is a lower limit (3rd percentile) of 4 uV (onset-to-peak) and 4 uV (peak-to-peak); and for latency is an upper limit (97th percentile) of 3.6 ms (onset) and 4.5 ms (peak). NCS assessment of the tibial motor nerve involves electrode placement at the medial foot (slightly anterior/inferior to the navicular tubercle) and more distally at the first metatarsophalangeal (MTP) joint for a distance of approximately 8cm; the nerve is stimulated at the ankle (posterior to the medial malleolus) and knee (at the midpopliteal fossa) with a display sensitivity 5 mV/div and sweep of 5 ms/div. The tibial motor nerve reference values for distal amplitude is a lower limit (3rd percentile) of 4.4 mV across all ages; and for distal latency is an upper limit (97th percentile) of 6.1 ms.

4.5.2 Skin Biopsy

One skin biopsy will be obtained as 4-5mm punch biopsy at distal end of leg in sural nerve territory (10cm above lateral malleolus). As described in a review by Lauria and Devigili[45], biopsied tissue will be cut into 50 uM sections which will be hematoxylin and eosin stained and also immunostained with an antibody to PGP (protein gene product) 9.5, a neuron- and neuroendocrine cell-specific ubiquitin carboxy-termiForm Onal hydrolase expressed throughout the peripheral nervous system. Slides will be reviewed by Dermatopathology (Dr. Sangueza) in order to count PGP9.5-positive fibers as they cross the dermal-epidermal junction to calculate linear density of IENF (IENF/mm). Additional staining will be done as indicated. Routine processing of specimens and comparison to standardized values (similar to those described by McArthur et al.[37] will be done by Dermatopathology as per their institutional guidelines. These methods are standard clinical procedures for the routine assessment of IENF density. Dermatopathology will also obtain descriptive measures of morphologic changes that will be analyzed as an exploratory outcome. Additional unstained slides or blocks will be

stored. Patients who are eligible to participate in the study, but unwilling to have a skin biopsy will be allowed to participate.

4.5.3 Nerve Ultrasound

Peripheral nerve US technique and reference values for the sural sensory (measured at the ankle) and tibial motor nerves are based on institutional data and standard institutional practice. These reference values were de-identified historical data which have also been published by Cartwright et al.[42] as noted in the Introduction and Background section. Peripheral nerves will be assessed at non-compressive sites with a routine 15Hz linear probe. If available, a higher resolution 70Hz linear probe may be used – this would allow for descriptive characterization of nerve changes and would not be anticipated to cause variability in terms of CSA measurement as compared to the standard 15Hz US.

4.5.4 Storage of Serum and Skin Biopsy Material

Venous blood will be sampled at the time of peripheral nerve assessment (e.g. pre-treatment and end-of-treatment) to explore potential circulating markers of peripheral nerve health.

If the patient will undergo regularly scheduled phlebotomy on the day of peripheral nerve assessment, this blood draw will be preferentially added to the routinely collected specimens. Some participants may require an additional blood draw if insufficient blood samples were collected or regularly scheduled blood draw is not planned on the date of peripheral nerve assessment. For the purposes of this study, 16 mL of venous blood (8mL at each of two draws) will be collected in (2) 4mL (green-top) collection tubes and then transferred directly to Dr. Shiozawa's lab for processing. Serum will be stored in Dr. Shiozawa's lab.

Blood Sample Preparation

1. Email notification will be sent to Matt Eber (meber@wakehealth.edu), Sun Park (shpark@wakehealth.edu) and Yusuke Shiozawa (yshiozaw@wakehealth.edu) the day before the blood collection.

2. Blood will be collected in a green-top vacutainer tube containing heparin (60 USP Units of Lithium Heparin/4 mL tube), and immediately inverted 8-10 times to prevent coagulation. **Attention: Protocol #: CCCWFU # (97118) and the OnCore PID in addition to the other standard information should be on the tube.**

3. Samples will then be transported from the Cancer Center to the Shiozawa lab (Lab: 3-6624, 3-5119, Office: 6-8743).

4.6 Randomization

Following completion of the baseline visit, participants will be randomized to receive acupuncture immediately (acupuncture group) or to a usual care control group using a

randomized block design developed by Dr. Tooze. The randomization will be stratified by cancer type and race (AA, non-AA) to ensure balance within each race strata. Block sizes will be chosen randomly to ensure that future assignments cannot be inferred from previous ones.

4.7 Intervention: Acupuncture Treatments

Participants randomized to the acupuncture group will be scheduled to receive 8 acupuncture treatments over a 10-week period. All treatments will be conducted by a licensed acupuncturist at the Wake Forest Baptist Health Integrative Medicine Clinic Center. The first acupuncture treatment will be scheduled by the Study Coordinator. Future appointments will be scheduled by the participant and the Center.

Up to 20 acupuncture points (bodily locations where acupuncture needles are inserted) will be selected for needling. We will use a standardized treatment plan rather than a personalized treatment plan given that the etiology of the symptoms is presumably the chemotherapy and that a procedure-based approach is more appropriate for CIPN than a diagnostic approach. In the case that a patient has a comorbidity effecting a specific area of the body, study investigators may allow for a deviation to the standardized acupuncture treatment plan as appropriate.

Week 12 End of Treatment Assessment

All patients will be scheduled for a follow-up assessment to occur 10 (+2) weeks after baseline (referred to as Week 12 assessment), regardless of whether they have completed all acupuncture treatments. The same protocol will be performed as described in Section 4.5 with addition of the QLQ-CIPN20 and PRO-CTCAE as described in Section 4.4. Peripheral neuropathy grade, as measured by the NCI-CTCAE, will be assessed at this time by a clinician who is blinded as to the patient's group (acupuncture vs. usual care) assignment. Participants who complete this assessment will receive a $75 gift card. If the patient lives 60 miles or more from WFBMC will receive an additional $50 gift card upon completion of the follow-up assessment.

4.8 Acupuncture for Usual Care Control Group

Following completion of all measures, patients in the usual care group will be scheduled for their acupuncture visits. They will be instructed to contact the Wake Forest Baptist Health Integrative Medicine Clinic Center and provided up to 4 acupuncture treatments. These treatments are being provided as an incentive for patients to remain in the study to receive the end of treatment assessment.

5.0 Adverse Events List and Reporting Requirements

5.1 Adverse Event List for Acupuncture

5.1.1 Acupuncture may sometimes cause temporary discomfort or pain, bleeding, bruising, or soreness.

5.1.2 There have been very rare reports of acupuncture causing minor nerve damage, hematomas (bleeding under the skin or inside your body), infections, or pneumothorax (puncture of a lung).

5.2 Adverse Event List for Nerve Conduction Studies

5.2.1 Standard risks include discomfort or pain from the procedure.

5.3 Adverse Event List for Biopsies

5.3.1 Risks associated with skin biopsies may include brief pain (common), bleeding or bruising (uncommon), or in rare instances, infection (rare). Standard precautions will be used for these tests. The risks are not expected to be different from routine clinical procedures. We do not expect any long-term, or life-threatening risks.

5.4 Adverse Event List for Ultrasound

5.4.1 Ultrasound is a safe procedure. Patients may experience a slight warming and coldness from the gel.

5.5 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only.

- **Attribution** of the AE:

  Definite – The AE **is clearly related** to the study treatment.
  Probable – The AE **is likely related** to the study treatment.
  Possible – The AE **may be related** to the study treatment.
  Unlikely – The AE **is doubtfully related** to the study treatment.
  Unrelated – The AE **is clearly NOT related** to the study treatment.

5.6 STRC SAE Reporting Requirements

The Safety and Toxicity Reporting Committee (STRC) is responsible for reviewing SAEs for WFBCCC Institutional studies as outlined in.
The Safety and Toxicity Reporting Committee (STRC) is responsible for reviewing SAEs for WFBCCC Institutional studies as outlined in Appendix K. **All Adverse Events that occur during protocol intervention and are coded as either 1) unexpected grade 4, 2) unplanned inpatient hospitalization > 24 hours (regardless of grade), or grade 5 (death)**

must be reported to the STRC using the using the SAE console in WISER. All WFBCCC Clinical Protocol and Data Management (CPDM) staff members assisting a Principal Investigator in investigating, documenting and reporting an SAE qualifying for STRC reporting are responsible for informing a clinical member of the STRC as well as the entire committee via the email notification procedure of the occurrence of an SAE.

5.7 WFUHS IRB AE Reporting Requirements

Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The Principal Investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS IRB (external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or informed consent process/document in order to insure the safety, rights or welfare of research subjects.

6.0 Duration of Follow-up

Following recruitment, patients will be scheduled for neurodiagnostic assessments with 2 weeks. Acupuncture treatments will occur over 10 weeks, after which, patients will return to neurology for follow-up assessment within 2 weeks. Patients randomized to usual care will have the opportunity to receive four acupuncture treatments . All patient will receive a telephone foll-up call 30 days (+ or – 5 days) after their follow-up neurodiagnositc assessments to identify whether any adverse events have occurred.

7.0 Outcome Measures

Listed below are the primary, secondary and exploratory outcomes. Given that this is a pilot study, other parameters associated with nerve conduction and ultrasound studies will be captured and may be used for exploratory analyses and will include, but will not be limited to latency for nerve conduction studies and for ultrasound, echogenicity, vascularity, fascicle concentration, other qualitative descriptions of nerve changes, and other skin biopsy markers (e.g. macrophage infiltration, mast cell concentration, tryptase, chymase and histamine, etc).

7.1 Primary Outcome

5.1.1 Change in the sensory neuropathic pain score as measured by the EORTC QLQ CIPN20.

7.2 Secondary Outcomes

7.2.1 Motor and autonomic pain subscores on the EORTC QLQ-CIPN20.

7.2.2 PRO-CTCAE measure of numbness and tingling.

7.2.3 CIPN as measured by NCI-CTCAE 5.0.

7.2.4 Dose and number of cycles of planned chemotherapy and completed chemotherapy.

7.2.5 Cross sectional area (CSA) of peripheral nerves as determined by ultrasound (sural CSA and median CSA).

7.2.6 Amplitude, distal latency, and conduction velocity of nerve response derived from NCS (sural, tibial, and median).

7.2.7 Nerve fiber density in the skin (IENF/mm)

7.3 Covariates

7.3.1 BMI

7.3.2 Age

7.3.3 Cancer staging

7.3.4 Types/dosages of systemic therapy

7.3.5 Race (white/non-white)

7.3.6 Use of analgesics or treatments for neuropathy

7.3.7 Cancer Type

7.3.8 Sex

7.3.9 Neurotoxic chemotherapy

8.0 Statistical Considerations

8.1 Sample Size and Power

The primary goal of this study is to provide preliminary data for future studies including estimating the variance of the sensory neuropathic pain patient-reported measures. There is an asymptote for the gain in the precision to estimate the variance with 20 degrees of freedom. With a sample size of 22, the probability is 0.80 (80% confidence) that the estimate of the SD will be no more than 14% of the true population SD below the true population SD.

8.2 Analysis of Primary Objective

Because this is a pilot study, analyses will be primarily descriptive to estimate variances and effect sizes for future work. Therefore, we will estimate means and standard deviations by group for the EORTC QLQ-CIPN20 sensory subscale at baseline and week 12, the correlation between the two measures, and the within-person change from baseline to week 12. To estimate effect size, we will use an ANCOVA model at week 12, which will include the group and the baseline value. The estimated difference between the groups and the variance will inform sample size calculations for future studies. The ANCOVA approach is the most efficient method comparing change of an outcome between two groups. We will estimate means by cancer type, treatment received, gender, and overall.

8.3 Analysis of Secondary Objectives

Because the primary goals of the secondary objectives are to provide preliminary data on the effect of the intervention on the secondary outcomes of interest, we will use the same general approach as outlined above for the continuous variables (Objective 2.2.1, EORTC QLQ-CIPN20 motor and autonomic neuropathic pain subscale; Objective 2.2.2, PRO-CTCAE Numbness and Tingling; Objective 2.2.4, Dose and number of cycles of chemotherapy; Objectives 2.2.4, 2.2.5, and 2.2.6, Peripheral Nerve Assessments), i.e., means and standard deviations will be computed at baseline and week 12 by group, and for the change in the measures, and we will also estimate the correlation between the measures at the two time points, and fit ANCOVA models for each outcome of interest. Because the primary interest in the measure of the CTCAE measure of CIPN is in the time to change of this categorical outcome, it will be assessed using frequencies of grade by time point (baseline, week 12), as well as whether the grade of CIPN increased, decreased or remained stable from baseline to week 12. A Fisher's Exact test will be used to compare the groups at each time point and for the change

during the study period. We will estimate means by cancer type, treatment received, gender, and overall.

8.4 Analyses of Exploratory Outcome

To meet objective 2.3.1, all of the descriptive statistics for the primary and secondary objectives will be computed by race subgroup (A-A, non-A-A), and ANCOVA models will be run including baseline value, group, race, and the interaction with race.

To meet objective 2.3.2 (to obtain preliminary evidence of the effect of acupuncture on intraepidermal nerve fiber density (IENF) via skin biopsy, means and standard deviations will be computed at baseline and week 12 by group and for the change in measures. We will estimate the correlation between the measures at the two time points.

Objective 2.3.3 will be analyzed through calculating Pearson correlations of the association of the peripheral nerve assessments with each other and with the patient reported outcomes at each visit; change in the measures over the study will also be correlated.

Objective 2.3.4. will be analyzed by correlating the expectancy rating scale score with baseline, 12 week, and changes in the EORTC QLQ-CIPN20 and PRO-CTCAE overall and by arm. We will also classify participants into expectancy categories, and compare baseline, 12 week, and changes in EORTC QLQ-CIPN20 and PRO-CTCAE overall and by arm using an ANOVA. If expectancy is related to baseline scores, we may use a mixed effects model to examine the trajectory of change related to expectancy, including arm in the model.

8.5 Accrual Rate

4 participants per month.

8.6 Length of Study

12 months

9.0 Data Management

Informed consent document	EPIC
Protocol Registration Form (Appendix B)	EPIC
Clinical Evaluation from History/Exam (Appendix D)	WISER/OnCore
EORTC QLQ-CIPN20 (neuropathy scale) (Appendix E)	REDCap
PRO-CTCAE Numbness and Tingling (Appendix E)	REDCap
Nerve Conduction Study Data Collection Form (Appendix F)	WISER/OnCore
Ultrasound Nerve Diameter Data Form (Appendix G)	WISER/OnCore
Nerve Fiber Density Data Collection Form (Appendix H)	WISER/OnCore
Adverse Events Log (Appendix I)	WISER/OnCore

Follow-up Form for Skin Biopsy (Appendix J)	WISER/OnCore
CTCAE Neuropathy Grading Form (Appendix M)	WISER/OnCore
Chemotherapy Form (Appendix N)	WISER/OnCore
Acupuncture Treatment Form (Appendix O)	WISER/OnCore

10.0 Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

11.0 Data Safety and Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

12.0 Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

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Appendix A: Subject Eligibility Checklist

IRB Protocol No. 00049061	**CCCWFU Protocol No.** 97118
Study Title: Acupuncture for Chemotherapy-Induced Peripheral Neuropathy Among Cancer Patients	
Principal Investigators: Nancy E. Avis, PhD	

Inclusion Criteria (as outlined in study protocol)	**Criteria is met**	**Criteria is NOT met**	**Source Used to Confirm * (Please document dates and lab results)**
Breast or GI cancer	☐	☐	
Cancer stage I-III	☐	☐	
Currently receiving or recently completed neurotoxic chemotherapy (either adjuvant or neoadjuvant). Currently is defined as including up until when the next cycle would be delivered, that is if the patient is getting chemotherapy every week, this would include a week after their last treatment; if the patient is getting treatment every 2 weeks, this would include 2 weeks after their last treatment; if the patient is getting treatment every 3 weeks, this would include 3 weeks after their last treatment, etc. Recently completed is defined as 6 weeks after this time period. For example, if a patient was getting chemotherapy every week, this would include seven weeks after their last treatment; if the patient was getting treatment every 2 weeks, this would include 8 weeks after their last treatment; if the patient were getting treatment every 3 weeks, this would include 9 weeks after their last treatment, etc	☐	☐	
Clinical symptoms of peripheral neuropathy of grade 1 or grade 2 as measured by the NCI-CTCAE. Grade: _____	☐	☐	
Ability and willingness to understand and sign an informed consent	☐	☐	

Exclusion Criteria (as outlined in study protocol)	**Criteria NOT present**	**Criteria is present**	**Source Used to Confirm * (Please document dates and lab results)**
Self-reported or documented history of UNRESOLVED pre-existing peripheral neuropathy due to diabetes, HIV, or other conditions.	☐	☐	
Unable to provide history	☐	☐	
Male patients	☐	☐	
Pregnant	☐	☐	
Unwilling to receive acupuncture or unable to travel for treatments.	☐	☐	

This subject is ☐ eligible / ☐ ineligible for participation in this study.

OnCore Assigned PID: __ __ __ __ __ __ __ __

Signature of research professional confirming eligibility:_____
Date (mm/dd/yy): __ __/__ __/__ __

Signature of Treating Physician: _____Date (mm/dd/yy): __ __/__ __/__ __

Signature of Principal Investigator**: _____ Date (mm/dd/yy): __ __/__ __/__ __
* Examples of source documents include clinic note, pathology report, laboratory results, etc. When listing the source, specifically state which document in the medical record was used to assess eligibility. Also include the date on the document. Example: “Pathology report, 01/01/14” or “Clinic note, 01/01/14”

**Principal Investigator signature can be obtained following registration if needed

Appendix B: Protocol Registration Form

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

MRN: ___ ___ ___ ___ ___ ___ ___ ___ DOB (mm/dd/yy): ___ ___ / ___ ___ / ___ ___

ZIPCODE: ___ ___ ___ ___ ___

SEX: ☐ Male ☐ Female Ethnicity (choose one): ☐ Hispanic

☐Non-Hispanic

Race (choose all that apply): ☐ WHITE ☐BLACK ☐ ASIAN ☐ PACIFIC ISLANDER ☐ NATIVE AMERICAN

Height: ___ ___.___ inches Weight: ___ ___ ___.___lbs.(actual)

Surface Area: ___ ___.___m^2 BMI: ___ ___.___kg/m2

Primary Diagnosis: _____

Date of Diagnosis(mm/dd/yy): ___ ___ /___ ___/___ ___

Performance Status: ___ ☐ ECOG

PROTOCOL INFORMATION

Date of Registration(mm/dd/yy): ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started(mm/dd/yy): ___ ___ / ___ ___ / ___ ___

Informed written consent: ☐ YES ☐ NO

(consent must be signed prior to registration)

Date Consent Signed(mm/dd/yy): ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by OnCore): ___ ___ ___ ___ ___ ___ ___ ___

Protocol Registrar can be contact by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday.

Completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at 336-7136772 or registra@wakehealth.edu.

Appendix C - Race & Ethnicity Verification Form

Thank you so much for helping us to verify your race and ethnicity to ensure the quality of our information. As a brief reminder, the information you provide today will be kept confidential.

1. Are you:
   - ☐ Hispanic or Latina
   - ☐ Not Hispanic or Latina

2. What is your race? One or more categories may be selected.
   - ☐ White or Caucasian
   - ☐ Black or African American
   - ☐ American Indian or Alaskan Native
   - ☐ Asian
   - ☐ Native Hawaiian or Other Pacific Islander
   - ☐ Other, Please Specify: _____

Internal use only:

Name: _____ MRN#: ___ ___ ___ ___ ___ ___ ___ ___

Was the self-reported race and ethnicity of the participant verified at the time of consent?
☐ **Yes** ☐ **No**

Was a discrepancy found? **Yes** ☐ **No** ☐
If yes, please provide what is currently indicated in the EMR:
Ethnicity: _____ Race: _____

Additional comments: _____
_____
_____

Appendix D: Clinical Evaluation from History/Exam

OnCore PID: __ __ __ __ __ __ __ __ **Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __

PI: Nancy E. Avis, PhD **Study Number:** CCCWFU 97118

Instructions: To be filled out by medical staff.

1. Oncologic history

a. Stage: ☐clinical ☐pathologic

T: ☐ 0 ☐ is ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐X

N: ☐ 0 ☐1 ☐ 2 ☐ 3 ☐X

M: ☐0 ☐1 ☐X

b. Current neurotoxic chemotherapy (if recently completed neurotoxic chemotherapy, skip b and continue with c):

Name		Neurotoxic Dose	Start Date of regimen (mm/dd/yy)	Current cycle number	Current week of P, C, NP	Standard neurotoxic dose? (circle)
☐AC-T	Doxorubicin/ cyclophosphamide followed by weekly paclitaxel (12 wk)	80 mg/m^2				Yes No*
☐TC	Docetaxel and cyclophosphamide	75 mg/m^2				Yes No*
☐TCH	Docetaxel/carboplatin/ trastuzumab	75 mg/m^2				Yes No*
☐TCHP	Docetaxel/carboplatin/ trastuzumab +pertuzumab	75 mg/m^2				Yes No*
☐TH	Paclitaxel (12 weeks) + trastuzumab	80 mg/m^2				Yes No*
☐mFFX6	mFOLFOX6	O-85 mg mg/m^2				Yes No*
☐mFFX4	FOLFOX 4	O-85 mg mg/m^2				Yes No*
☐FFXI	FOLFOXIRI	O-85 mg mg/m^2				Yes No*
☐FFIX	FOLFIRINOX	O-85 mg mg/m^2				Yes No*
☐mFFIX	mFOLFORINOX	O-85 mg mg/m^2				Yes No*
☐FLOT	FLOT	T-50 mg/m^2 O-85 mg mg/m^2				Yes No*
☐NG	Nabpaclitaxel and Gemcitabibe	NP- 125 mg/m^2				Yes No*
☐CP	Carboplatin and Paclitaxel (CROSS regimen)	C- AUC2 P- 50 mg/m^2				Yes No*

☐ Oth	Other (specify):				Yes No*

*If reduced, is CIPN reason for reduction? ☐Yes ☐No ☐Other:_____

c. Previous neurotoxic chemotherapy (if, currently receiving neurotoxic chemotherapy. Skip c and continue with d):

Name		Neurotoxic Dose	Start Date of regimen (mm/dd/yy)	Current cycle number	Current week of P, C, NP	Standard neurotoxic dose? (circle)
☐AC-T	Doxorubicin/ cyclophosphamide followed by weekly paclitaxel (12 wk)	80 mg/m^2				Yes No*
☐TC	Docetaxel and cyclophosphamide	75 mg/m^2				Yes No*
☐TCH	Docetaxel/carboplatin/ trastuzumab	75 mg/m^2				Yes No*
☐TCHP	Docetaxel/carboplatin/ trastuzumab +pertuzumab	75 mg/m^2				Yes No*
☐TH	Paclitaxel (12 weeks) + trastuzumab	80 mg/m^2				Yes No*
☐mFFX6	mFOLFOX6	O-85 mg mg/m^2				Yes No*
☐mFFX4	FOLFOX 4	O-85 mg mg/m^2				Yes No*
☐FFXI	FOLFOXIRI	O-85 mg mg/m^2				Yes No*
☐FFIX	FOLFIRINOX	O-85 mg mg/m^2				Yes No*
☐mFFIX	mFOLFORINOX	O-85 mg mg/m^2				Yes No*
☐FLOT	FLOT	T-50 mg/m^2 O-85 mg mg/m^2				Yes No*
☐NG	Nabpaclitaxel and Gemcitabibe	NP- 125 mg/m^2				Yes No*
☐CP	Carboplatin and Paclitaxel (CROSS regimen)	C- AUC2 P- 50 mg/m^2				Yes No*
☐ Oth	Other (specify):					Yes No*

*If reduced, was CIPN reason for reduction? ☐Yes ☐No ☐Other:_____

d. Other current cancer therapy: ☐ hormone ☐ other: _____

e. Other prior cancer therapies (excluding 1c.) for most recent cancer. Mark all that apply:

☐ Chemotherapy ☐ Radiation ☐ Surgery ☐ Hormone therapy
☐ Other: _____ ☐ None

2. Date of onset of CIPN (mm/dd/yy): __ __/__ __/__ __

OnCore PID: __ __ __ __ __ __ __ __ **Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __

PI: Nancy E. Avis, PhD **Study Number:** CCCWFU 97118

3. Medical history (check all that apply, if unknown can be left unchecked):
   - ☐ Thyroid Disorder:
     If yes: ☐ Hyperthyroidism ☐Hypothyroidism ☐Other; specify: _____
   - ☐ Vitamin B12 deficiency
   - ☐ Peripheral vascular disease (claudication, arterial bypass, untreated aneurysm ≥6cm)
   - ☐ Cerebrovascular disease (history of TIA or CVA)
   - ☐ Alcoholism
   - ☐ Carpal tunnel syndrome
   - ☐ Sciatica
   - ☐ Diabetes: If yes, end organ damage? Yes ☐ No ☐
   - ☐ AIDS
   - ☐ Depression
   - ☐ Other major medical condition; specify_____

4. List all prescription and over-the-counter medications (includes prescription supplements)

Medication Name	Is it PRN?		Medication Name	Is it PRN?	
1.	yes	no	11.	yes	no
2.	yes	no	12.	yes	no
3.	yes	no	13.	yes	no
4.	yes	no	14.	yes	no
5.	yes	no	15.	yes	no
6.	yes	no	16.	yes	no
7.	yes	no	17.	yes	no
8.	yes	no	18.	yes	no
9.	yes	no	19.	yes	no
10.	yes	no	20.	yes	no

5. List all supplements

Supplement Name	Taking?		If yes - taken for neuropathy?		If yes - PRN?	
Multivitamin	yes	no	yes	no	yes	no
B12	yes	no	yes	no	yes	no
B vitamin complex	yes	no	yes	no	yes	no
Vitamin C	yes	no	yes	no	yes	no
Vitamin E	yes	no	yes	no	yes	no
Vitamin D	yes	no	yes	no	yes	no
Calcium	yes	no	yes	no	yes	no
Iron	yes	no	yes	no	yes	no
Probiotics	yes	no	yes	no	yes	no
Fiber	yes	no	yes	no	yes	no
Tumeric	yes	no	yes	no	yes	no
Fish oil/omega-3/flaxseed	yes	no	yes	no	yes	no
Other:_____	yes	no	yes	no	yes	no
Other:_____	yes	no	yes	no	yes	no
Other:_____	yes	no	yes	no	yes	no
Other:_____	yes	no	yes	no	yes	no
Other:_____	yes	no	yes	no	yes	no
Other:_____	yes	no	yes	no	yes	no

Appendix E Patient Reported Outcomes: EORTC QLQ-CIPN20 and PRO-CTCAE

OnCore PID: __ __ __ __ __ __ __ __ __ Date Completed (mm/dd/yy)**:** __ __ / __ __ / __ __
PI: Nancy E. Avis, PhD **Study Number:** CCCWFU 97118

Visit: ☐Baseline
☐12 week

EORTC QLQ-CIPN20

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

DURING THE PAST WEEK	Not at all	A little	Quite a bit	Very much
1) Did you have tingling fingers or hands?	1	2	3	4
2) Did you have tingling toes or feet?	1	2	3	4
3) Did you have numbness in your fingers or hands?	1	2	3	4
4) Did you have numbness in your toes or feet?	1	2	3	4
5) Did you have shooting or burning pain in your fingers or hands?	1	2	3	4
6) Did you have shooting or burning pain in your toes or feet?	1	2	3	4
7) Did you have cramps in your hands?	1	2	3	4
8) Did you have cramps in your feet?	1	2	3	4
9) Did you have problems standing or walking because of difficulty feeling the ground under your feet?	1	2	3	4
10) Did you have difficulty in distinguishing between hot and cold water?	1	2	3	4
11) Did you have a problem holding a pen, which made writing difficult?	1	2	3	4
12) Did you have difficulty in manipulating small objects with your fingers (for example, fastening small buttons)?	1	2	3	4
13) Did you have difficulty in opening a jar or bottle because of weakness in your hands?	1	2	3	4
14) Did you have difficulty walking because your feet dropped downwards?	1	2	3	4
15) Did you have difficulty in climbing stairs or getting up out of a chair because of weakness in your legs?	1	2	3	4

DURING THE PAST WEEK	Not at all	A little	Quite a bit	Very much
16) Were you dizzy when standing up from a sitting or lying position?	1	2	3	4
17) Did you have blurred vision?	1	2	3	4
18) Did you have difficulty in hearing?	1	2	3	4
Please answer the following question only if you drive a car: **19) Did you have difficulty using the pedals?** **Or mark: ☐ Not applicable: I do not drive a car**	1	2	3	4

PRO-CTCAE
As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please mark the one box that best describes your experiences over the past 7 days.

PRO-CTCAE™ Symptom Term: Numbness & tingling				
a. In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
○ None	○ Mild	○ Moderate	○ Severe	○ Very Severe
b. In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

The PRO-CTCAE™ items and information herein were developed by the Division of Cancer Control and Population Sciences in the NATIONAL CANCER INSTITUTE at the NATIONAL INSTITUTES OF HEALTH, in Bethesda, Maryland, U.S.A. Use of the PRO- CTCAE™ is subject to NCI's Terms of Use

1. Are you currently taking any medications or supplements (such as gabapentin/Neurontin, amitriptyline/Elavil, nortriptyline/Pamelor, vitamin B12, pain medications) for your neuropathy?

☐ No

☐ Yes

1a. What are you taking? _____

1b. When did you start taking this? _____

2. Are you currently doing anything else to treat your neuropathy (such as meditation, massage, yoga)?

☐ No

☐ Yes

2a. What are you doing? _____

2b. When did you start doing this? _____

Appendix F: Nerve Conduction Study Data Collection Form

OnCore PID: __ __ __ __ __ __ __ __ **Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __

PI: Nancy E. Avis, PhD **Study Number:** CCCWFU 97118

Visit: ☐Baseline
☐12 week

Instructions

- Use the OnCore PID and visit to Identify the Sample
- Date is the date of experimentation and listed before the technique. Use the following format (mm/dd/yy)
- Do not erase entries. If an entry is incorrect, cross the entry out, initial, and write in the correct entry. Please write neatly.

Nerve Conduction Worksheet

Date of Nerve Conduction Study: __ __/__ __/__ __

Conduction studies

Tibial				**Sural**			**Median**			
☐Done ☐Not Done				☐Done ☐Not Done			☐Done ☐Not Done			
	Amplitude	Latency	Conduction Velocity	Amplitude	Latency	Conduction Velocity		Amplitude	Latency	Conduction Velocity
Ankle							Wrist			
Pop Fossa							Elbow			

Appendix G: Ultrasound Nerve Diameter Data Form

OnCore PID: __ __ __ __ __ __ __ __ **Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __

PI: Nancy E. Avis, PhD **Study Number:** CCCWFU 97118

Visit: ☐Baseline
☐12 week

To be used for determination of tibial, sural and median nerve diameters.

Date of Procedure (mm/dd/yy): __ __/__ __/__ __

Nerve	**Probe Location and Landmark**	**Side (circle)**	**Area (mm^2)**	**Fascicles**	**Vascularity**	**Mobility**
Sural		left right				
Superficial peroneal		left right				
Median		left right				N INC DEC A NA
Other: _____						

Person recording information: _____

Appendix H: Nerve Fiber Density Data Collection Form

OnCore PID: __ __ __ __ __ __ __ __ **Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __

PI: Nancy E. Avis, PhD **Study Number:** CCCWFU 97118

Visit: ☐ Baseline
☐12 week

Instructions

- Use the OnCore PID to Identify the Sample
- Date is the date of experimentation and listed before the technique. Use the following format(mm/dd/yy)
- Initials of person performing the assay.
- Do not erase entries. If an entry is incorrect, cross the entry out, initial, and write in the correct entry. Please write neatly.

Date of Biopsy(mm/dd/yy): __ __/__ __/__ __

Nerve Fiber Density Form		
Location of Biopsy	Side (circle)	Nerve Fiber Density (IENF/mm)
☐ Distal leg	left right	
☐ Other: _____		

Appendix I: Adverse Events Log

WFBCCC Adverse Event (AE) Log

PI: _____	**Subject PID:** ___ ___ ___ ___ ___ ___ ___ ___	**MRN:** ___ ___ ___ ___ ___ ___ ___ ___

Cycle #: ____	**Cycle Start Date(mm/dd/yyyy):** ___ ___/___ ___/___ ___ ___ ___	**Cycle Start Time:** ___ ___:___ __	**Cycle End Date(mm/dd/yyyy):** ___ ___/___ ___/___ ___ ___ ___	**Cycle End Time:** ___ ___:___ ___

Adverse Event CTC Term	**Lab Value**	**Grade** (1-5) per CTC	**Start Date**	**Attribution** DEF=Definite PROB=Probable POSS=Possible UNLK=Unlikely UNRL=Unrelated	**Treating MD Initials/Date**	**End Date**	**Expected** N=No Y=Yes	**Serious Adverse Event Detail** NO=No LT=Life Threatening DTH=Death DIS=Disability HOS=Hospitalization CA=Caused congenital anomaly RI=Required intervention to prevent impairment	**Dose Limiting Toxitity (DLT)** N=No Y=Yes	**Action Taken** NO=None DR=Dose Reduced RI=Regimen Interrupted TD=Therapy discontinued INTR=Interrupted then reduced	**Therapy Given** NO=None SYM=Symptomatic SUP= Supportive VSUP=Vigorous supportive	**Reportable?** IRB-IRB STRC-STRC FDA-FDA SPON-Sponsor (Mark all that apply)	**Adverse Event Report (AER) Filed** N=No Y=Yes	**Outcome** R=Recovered TX=Still under treatment/ observation A=Alive with sequalae D=Died

Serious Adverse Event: Hospitalization; Disability; Birth Defect; Life-threatening; Death.

CTCAE Version 4 - http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

STRC- Safety and Toxicity Review Committee — Version 10/30/17

Appendix J: Follow-up Form for Skin Biopsy

OnCore PID: __ __ __ __ __ __ __ __ **Date Completed**(mm/dd/yy)**:** __ __ / __ __ / __ __

PI: . Nancy E. Avis, PhD **Study Number:** CCCWFU 97118

Instructions: Use this form as follow-up after the skin biopsies to record any complications related to the skin biopsy. If any problems are reported, complete the AE log. **Appendix J is not required for participants who do not receive a skin biopsy (occurring 30 days after baseline and 30 days after follow-up).**

Visit: ☐Baseline
☐12 week

Date of Skin Biopsy (mm/dd/yy)	Date of Phone / In-person assessment (mm/dd/yy)	Phone / In-person assessment completed within 30 days? (circle one)	Any skin biopsy problems reported by participant? (circle one)
__ __/__ __/__ __	__ __/__ __/__ __	Yes / No* *If no, describe reason below	Yes** / No **If yes, describe problems below and complete AE log

* Reason assessment not completed within 30 days:_____

_____

_____

** Skin biopsy problems reported by participant:_____

_____

_____

** Date AE log completed: __ __/__ __/__ __

Appendix K: Mandatory STRC SAE Reporting Requirements

Safety and Toxicity Review Committee (STRC; previously known as CROC) Serious Adverse Event (SAE) Notification SOP	**Date: 7/10/2019**

Mandatory STRC SAE Reporting Requirements in WISER

This document describes reporting requirements of adverse events from **WFBCCC Investigator Initiated interventional trials to the Safety and Toxicity Review Committee (STRC).** A trial is considered a **WFBCCC Investigator Initiated interventional trial** if the following criteria are met:

1. The Principal Investigator (PI) of the trial is a member of a department at the Wake Forest University Baptist Medical Center.
2. WFBCCC is considered as the primary contributor to the design, implementation and/or monitoring of the trial.
3. The trial is designated as "Interventional" using the Clinical Research Categories definitions provided by the NCI in the Data Table 4 documentation. (https://cancercenters.cancer.gov/GrantsFunding/DataGuide#dt4)

There are two distinct types of WFBCCC Investigator Initiated interventional trials based on where patient enrollment occurs. These include:

1. Local WFBCCC Investigator Initiated interventional trials defined as trials where **all patients are enrolled from one of the WFBCCC sites.** These include the main outpatient Cancer Center clinics (located in Winston-Salem) as well as WFBCCC affiliate sites located in Bermuda Run (Davie Medical Center), Clemmons, Lexington, High Point, or Wilkesboro.
2. Multi-Center WFBCCC Investigator Initiated interventional trials defined as trials where patients are enrolled from other sites in addition to WFBCCC sites.

   There are three types of trials that are included in this category:

   a. Trials sponsored by the NCI Community Oncology Research Program (NCORP) that are conducted at multiple sites where the PI is a member of a department at the Wake Forest University Baptist Medical Center.
   b. Trials sponsored by Industry that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.
   c. Trials sponsored by WFBCCC that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.

All Adverse Events (AEs) and Serious Adverse Events (SAEs) that occur on any patients enrolled on WFBCCC Investigator Initiated Interventional trials must be entered

into the WISER system. The only exception to this requirement is for patients enrolled on NCORP trials at non- WFBCCC sites. AEs and SAEs for NCORP patients enrolled at WFBCCC sites must be entered into the WISER system. Once these AEs and SAEs are entered in WISER, certain actions must be taken regarding the reporting of specific Adverse Events to the STRC.

All Adverse Events that occur during protocol intervention (defined below) and are coded as either 1) **unexpected grade 4,** 2) **unplanned inpatient hospitalization > 24 hours (regardless of grade)**, or **grade 5 (death)** must be reported to the STRC using the using the SAE console in WISER.

A research nurse or clinical research coordinator when made aware that an adverse event meets one of the above criteria has occurred on a WFBCCC Investigator Initiated interventional trial, is responsible for informing a clinical member of the STRC by phone (or in-person) about the adverse event. The nurse/coordinator should contact the treating physician prior to calling the STRC clinical member to obtain all details of the SAE, as well as all associated toxicities to be recorded along with the SAE. In addition, this nurse or coordinator is responsible for entering the adverse event information into the SAE console in WISER. Once the adverse event has been entered into the SAE console an email informing the entire STRC committee will be generated.

THESE REPORTING REQUIREMENTS APPLY TO any staff member on the study team for a WFBCCC Institutional Interventional trial. Ultimately, the protocol PI has the primary responsibility for AE identification, documentation, grading and assignment of att ribution to the investigational agent/intervention. However, when an AE event as described above is observed, it is the responsibility of the person who observed the event to be sure that it is reported to the STRC.

What is considered during protocol intervention?

During protocol intervention is considered to be the time period while a patient is on study treatment or during the time period within 30 days of last study treatment (even if patient begins a new (non-study) treatment during the 30 days). This window of 30 days should be the standard window to be used in all protocols unless a specific scientific rationale is presented to suggest that a shorter window can be used to identify events. If it is a trial sponsored by Industry and the sponsor requires a longer window for monitoring of SAEs, then the longer window of time specified by the sponsor should be followed.

What is considered as an Unexpected Grade 4 event?

Any grade 4 event that was not specifically listed as an expected adverse event in the protocol should be considered as unexpected. A grade 4 adverse event can be considered to be unexpected if it is an event that would not be expected based on the treatment being received or if it is unexpected based on the health of the patient. In either case, if there is any uncertainty about whether a grade 4 adverse event is expected or unexpected it should be reported to STRC.

STRC notification responsibilities of the person (e.g., nurse) handling the reporting/documenting of the SAE in WISER:

1. Make a phone call (or speak in person) to the appropriate clinical member of the STRC as listed below (page if necessary)
2. Enter a new SAE into the SAE module that is located in the Subject>> CRA Console in WISER WITHIN 24 HOURS of first knowledge of the event. Information can be entered and saved, but the STRC members will not be notified until a date is entered into the STRC Notification Date Field. This will ensure that all persons that need to be made aware of the event (i.e., study team members and STRC members) will be notified; remember to file a copy of the confirmation.
3. Document that the appropriate person(s) on the STRC has been contacted. Indicate the name of the STRC clinician that was contacted in the Event Narrative field in the SAE console of the particular subject.
4. Document whether or not the protocol should be suspended based on the discussion with the STRC clinician. This is the major function of the email notification. Enter whether the protocol should be suspended in the Event Narrative Field.
5. Follow up/update the clinical member(s) of STRC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

Elements needed to complete the SAE form in the Subject Console in WISER (see Screen Shot 3):

1. Event Date
2. Reported Date
3. Reported by
4. If Grade 5, enter Death Date
5. If Grade 5, enter Death occurred: within 30 days
6. Event Narrative: Brief description (include brief clinical history relevant to this event, including therapies believed related to event). Begin narrative with the STRC clinician who was notified and Date/Time notified. In addition, state attribution by STRC clinician as either “Unrelated”, “Unlikely”, “Possibly”, “Probably”, or “Definitely”. Always include the following here:
    i. STRC clinician name and comments
    ii. Date of last dose before the event
    iii. Is suspension of the protocol needed? Y/N
7. Treating Physician comments
8. PI comments, if available
9. Protocol Attribution after discussion with STRC clinician
10. Outcome (Fatal/Died, Intervention for AE Continues, Migrated AE, Not Recovered/Not Resolved, Recovered/Resolved with Sequelae, Recovered/Resolved without Sequelae, Recovering and Resolving)
11. Consent form Change Required? Y/N

12. SAE Classification *This is required in order for the email notification to be sent*
13. Adverse Event Details – Enter all details for each AE associated with the SAE.
    a. Course start date
    b. Category
    c. AE Detail
    d. Comments
    e. Grade/Severity
    f. Unexpected Y/N
    g. DLT Y/N
    h. Attributions
    i. Action
    j. Therapy
    k. Click ADD to attach the AE Detail to the SAE.
14. Enter Date Notified STRC -- *This is required for the email notification to be sent*
15. Click Submit. The auto-generated notification email will disseminate within 5 minutes. If you do not receive an email within 5 minutes, check that you have entered the "Date Notified STRC" and the "SAE Classification". If these have been entered and the email still has not been received, take a screen shot of the SAE in WISER and immediately email it out to all of the STRC members listed in this SOP. In the subject line, indicate that this is a manual transmission of the SAE in lieu of the auto-generated email. It is required that a notification goes to the STRC members immediately so that their assessment can be obtained within the 24 hour time frame requirement. Contact the Cancer Center Programmer/Analyst to alert that there is an issue with the auto-generated email.

The Clinical Members of STRC to Notify by Phone or Page:

Bayard Powell, MD –
Glenn Lesser, MD –**Stefan Grant, MD, JD**
Jimmy Ruiz, MD-
Mercedes Porosnicu, MD-
Michael Farris, MD –

Definition of Unavailable:

As a general guideline if the first clinician that is contacted does not respond to the phone call or page within 30 minutes, then initiate contact with a different STRC clinician. Allow up to 30 minutes for the new STRC clinician to respond to a phone call or page before contacting another member. These times (30 minutes) are a general guideline. Best judgment as a clinical research professional should be used giving considerations of the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting the STRC notification form. It is important

to take reasonable steps and to document that some type of contact has been initiated to one or more of the clinical members of STRC.

STRC CLINICAN RESPONSIBILITY:

It is the responsibility of the STRC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of STRC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made and further communication directly with the investigator may be warranted. STRC reserves the right to disagree with the Investigator's assessment. If STRC does not agree with the
Investigator, STRC reserves the right to suspend the trial pending further investigation. If ther e is any immediate danger or harm that could be present for a future patient based on the information provided in the STRC report then an immediate suspension of enrollment should be considered.

AMENDMENTS TO PREVIOUS REPORTS

If all pertinent information is unavailable with the initial submission, once the additional information is available **do not submit a new report**. Rather, go to the original email that was sent to the STRC and using that email "reply to all". Entitle this new email "**Amendment** for (list date of event and patient ID)" this will avoid duplications of the same event. List the additional information being reported. This information needs to be entered into WISER as well. To do this, go to the Subject console and click SAEs on the left column. Click on the
appropriate SAE number that needs updating. Then click update. This will allow additional in formation to be added

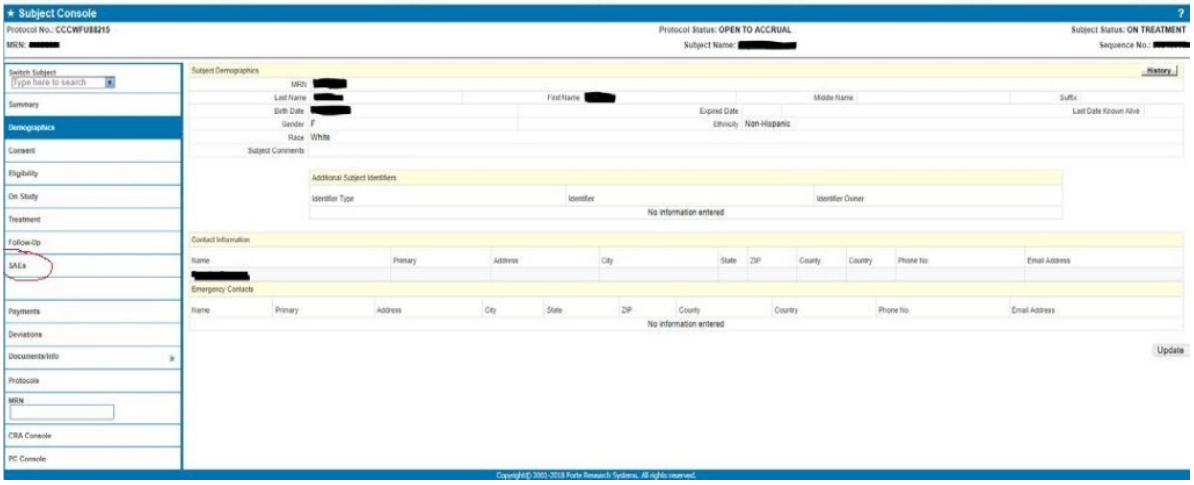
Acronyms

AE – Adverse Event
STRC-Safety and Toxicity Review Committee
SAE-Serious Adverse Event
WFBCCC – Wake Forest Baptist Comprehensive Cancer Center
NCI-National Cancer Institute
WISER –Wake Integrated Solution for Enterprise Research

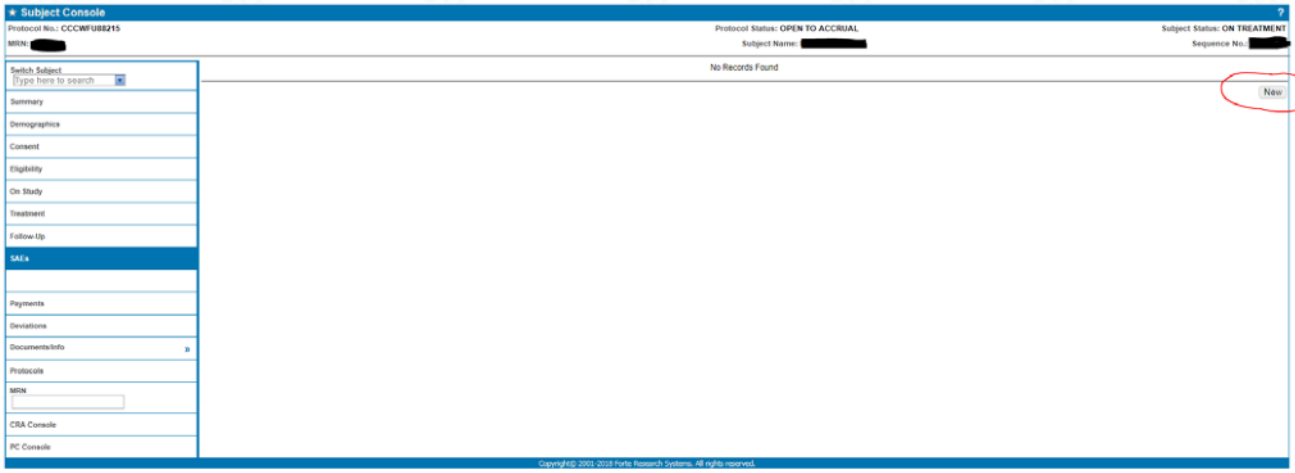
Screen Shots:

The following screen shots come from the SAE Console within the Subject Console in WISER.

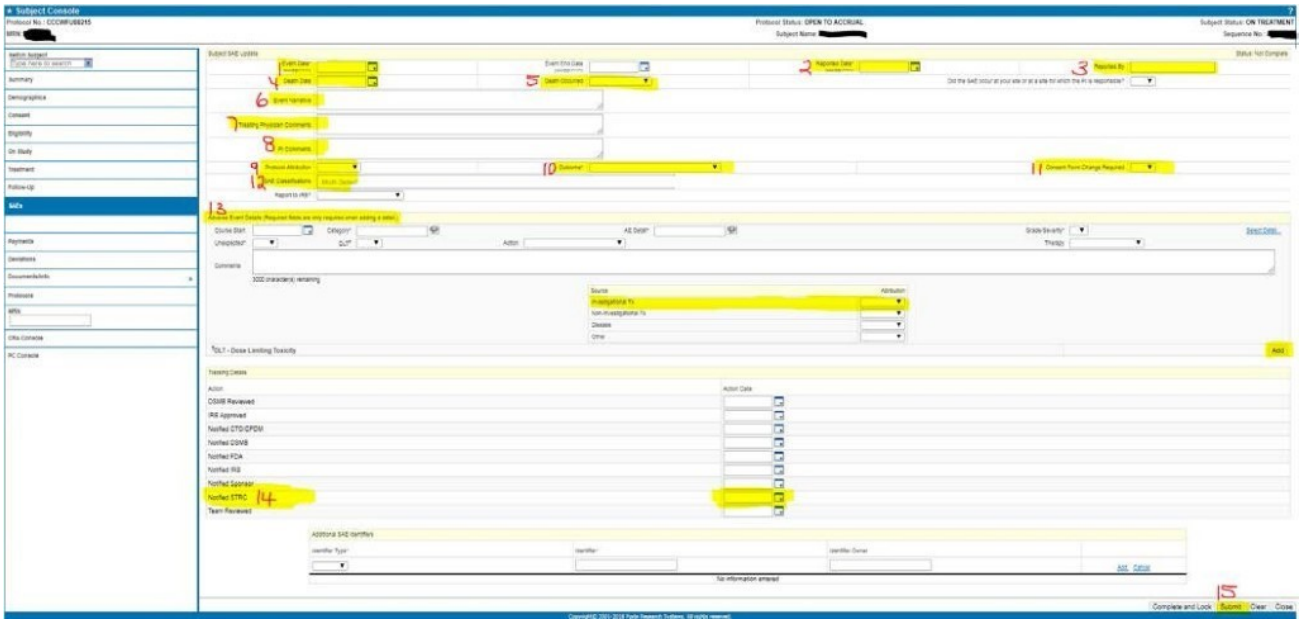
Screen Shot 1:



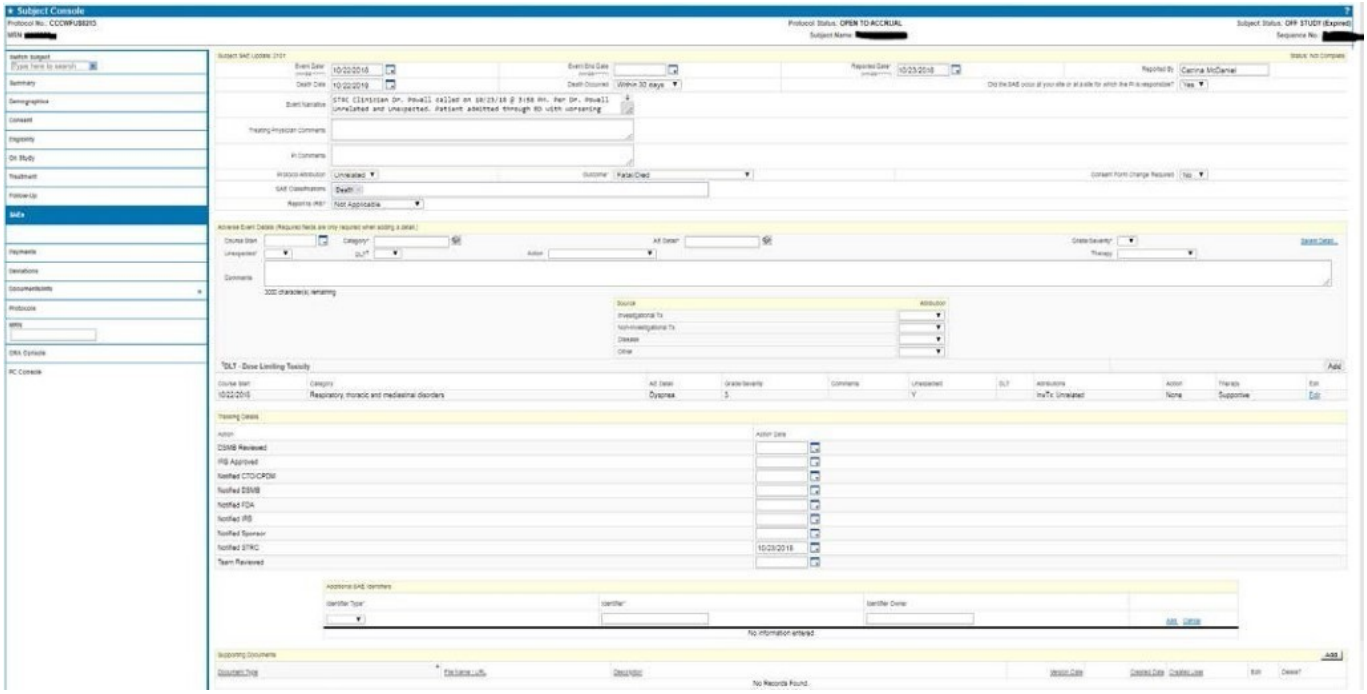
Screen Shot 2:



Screen Shot 3:



Screen Shot 4:



Appendix L: Patient Pre-Neuropathy Grading Instructions Card

The following information card will be handed to the patient at the end of treatment assessment encounter by the nurse, technologist, or coordinator prior to clinical assessment of neuropathy grade. End of treatment neuropathy grading will occur by one of the neurologists on the study team who will be blinded to the patient's randomization and treatment allocation at the time of the assessment.

Thank you for participating in this study. A doctor will be coming in to ask you some questions about your neuropathy. The doctor will use this information to grade your neuropathy. This doctor will not know whether you have been receiving acupuncture or not. You may answer all questions. Please do not provide any information about whether you have been receiving acupuncture treatments or not until the doctor has completed his/her assessment. Thank you.

Appendix M: CTCAE Neuropathy Grading Form

OnCore PID: __ __ __ __ __ __ __ __ **Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __

PI: Nancy E. Avis, PhD **Study Number:** CCCWFU 97118

Visit: ☐Baseline Date: (mm/dd/yy) __ __/__ __/__ __
☐12 week Date: (mm/dd/yy) __ __/__ __/__ __

As the clinician grading this patient's neuropathy, you are blinded from the patient's treatment allocation. You may ask the patient questions to understand the grade of their neuropathy but should not ask the patient to reveal their treatment arm.

Please select the appropriate grade of the patient's neuropathy based on your assessment today.

After you have selected the neuropathy grade, you may discuss the patient's prior treatment and prior randomization but do not change your selection.

CTCAE Grade of neuropathy	Description of CTCAE grade	Question you may consider asking:	Check the box that corresponds to neuropathy grade
Grade 1	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Do you have any numbness or tingling in your hands, fingers, feet or toes?	
Grade 2	Moderate symptoms; limiting instrumental ADL	Because of your neuropathy, are you not able to clean your home, cook meals, shop for groceries, or use your telephone?	
Grade 3	Severe symptoms; limiting self-care ADL; assistive device indicated	Because of your neuropathy, are you not able to dress yourself, button your shirt or pants, bath or shower, cut your food or eat?	
Grade 4	Life-threatening consequences; urgent intervention indicated		
Grade 5	Death		

Appendix N: Chemotherapy Form

OnCore PID: __ __ __ __ __ __ __ __ **Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __

PI:. Nancy E. Avis, PhD **Study Number:** CCCWFU 97118

INSTRUCTIONS: To be completed at the post treatment visit. Use this form to summarize regimen type and changes in regimen during the study

Total chemotherapy cycles completed: ☐1 ☐2 ☐3 ☐4 ☐5 ☐6

Weeks completed (paclitaxel): ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 ☐11 ☐12

Was the chemotherapy regimen changed during treatment? ☐Yes ☐No

If yes, was it due to CIPN? ☐Yes ☐No ☐Partly (explain):_____

Name		Neurotoxic Dose	Start Date of regimen (mm/dd/yy)	Current cycle number	Current week of P, C, NP	Standard neurotoxic dose? (circle)
☐AC-T	Doxorubicin/ cyclophosphamide followed by weekly paclitaxel (12 wk)	80 mg/m^2				Yes No*
☐TC	Docetaxel and cyclophosphamide	75 mg/m^2				Yes No*
☐TCH	Docetaxel/carboplatin/ trastuzumab	75 mg/m^2				Yes No*
☐TCHP	Docetaxel/carboplatin/ trastuzumab +pertuzumab	75 mg/m^2				Yes No*
☐TH	Paclitaxel (12 weeks) + trastuzumab	80 mg/m^2				Yes No*
☐mFFX6	mFOLFOX6	O-85 mg mg/m^2				Yes No*
☐mFFX4	FOLFOX 4	O-85 mg mg/m^2				Yes No*
☐FFXI	FOLFOXIRI	O-85 mg mg/m^2				Yes No*
☐FFIX	FOLFIRINOX	O-85 mg mg/m^2				Yes No*
☐mFFIX	mFOLFORINOX	O-85 mg mg/m^2				Yes No*
☐FLOT	FLOT	T-50 mg/m^2 O-85 mg mg/m^2				Yes No*
☐NG	Nabpaclitaxel and Gemcitabibe	NP- 125 mg/m^2				Yes No*
☐CP	Carboplatin and Paclitaxel (CROSS regimen)	C- AUC2 P- 50 mg/m^2				Yes No*
☐ Oth	Other (specify):					Yes No*

*If standard dose was not given during all cycles, complete the table below for all cycles/weeks of regimen given:

Dose Reductions During Chemotherapy Treatment				
Regimen (use abbreviation above)	**Cycle**	**Week**	**Taxane Dose (mg/m^2)**	**Reduction due to CIPN?**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**
				Yes No Other**

** If other, please explain: _____

_____

_____

Person filling out form: _____

Date (mm/dd/yy): ___ ___/___ ___/___ ___

Appendix O: Acupuncture Treatment Summary Form

OnCore PID: __ __ __ __ __ __ __ __ **Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __

PI:. Nancy E. Avis, PhD **Study Number:** CCCWFU 97118

Instructions: Complete this form to summarize the acupuncture treatment. **Appendix O does not need to be filled out for participants in the control group.**

Session Number	Completed	Date Completed	Session Duration (min)	Number of Needles Used	Were any side effects reported?
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

*If Yes, Please describe any side effects in the table below (and report as an adverse event):

Session Number	Description of symptoms	Did/Will side effects necessitate a treatment change?
		Yes No
		Yes No
		Yes No
		Yes No
		Yes No
		Yes No
		Yes No
		Yes No

		Yes No

Comments:

_____

_____

_____

_____

_____

_____

Acupuncturist signature: _____

Date (mm/dd/yy): __ __/__ __/__ __

Appendix P: Acupuncture Expectancy Scale

OnCore PID: __ __ __ __ __ __ __ __ **Date Completed** (mm/dd/yy)**:** __ __ / __ __ / __ __

PI:. Nancy E. Avis, PhD **Study Number:** CCCWFU 97118

Every individual may have different expectations for the effects of acupuncture. If we use the following sentences to describe your expectation of acupuncture's effect on your neuropathy after the entire course of acupuncture therapy, how much do you agree? For each statement, please circle the closest answer.

	Not at All Agree	A Little Agree	Moderately Agree	Mostly Agree	Completely Agree
1) My neuropathy will improve a lot	1	2	3	4	5
2) I will be able to cope with my neuropathy better	1	2	3	4	5
3) The symptoms of my neuropathy will disappear	1	2	3	4	5
4) My energy level will increase	1	2	3	4	5

1. Have you ever had previous experience with acupuncture?

☐ No

☐ Yes

2a. What was your acupuncture for? _____

2b. When did you last engage in acupuncture? _____

Appendix Q: Telephone Screening Form

Date Completed (mm/dd/yy)**:** __ __ / __ __ / __ __

PI:. Nancy E. Avis, PhD **Study Number:** CCCWFU 97118

Personal Identifiers are **NOT** to be written on this sheet

Hello, my name is _____ and I am calling from the Wake Forest School of Medicine for the Acupuncture for Chemotherapy Induced Peripheral Neuropathy study. I am a research assistant who is helping to enroll subjects in clinical studies.

If not home/answering machine:
You called requesting information about our study and I am sorry you are not at home. I would like to speak to you about the study in more detail. Please call me at _____/ or I will try you again later. Thank you.

If home:
You called requesting information about our study.

You may be eligible to participate in this study, but I will first need to ask you some questions now on the telephone to find out if you are likely to be eligible.

First, could you tell me how you found out about the study? [Check all that apply]

_____newspaper/magazine
_____friend/acquaintance
_____flyer/poster
_____clinic/MD
_____online
_____other, specify
_____

Let me give you some more information about the study itself. This is approximately a 12 week study to see what effects (good and bad) acupuncture has on neuropathy (nerve pain or tingling in hands or feet). We are recruiting 22 participants with breast or GI cancer for this study. Some participants will get acupuncture right away and others will wait 10 weeks to get acupuncture. All participants will get some acupuncture. Whether you get acupuncture now or later will be randomly determined. I am going to

ask you some questions today to see if you meet initial eligibility for the study. If you are eligible, you will be asked to come into the clinic for an initial visit where you will receive a physical exam of your nerve sensations and your medical history will be reviewed. If you are still eligible for our study, you will be asked to complete a questionnaire about your neuropathy pain. You will also be scheduled for your next study visit that will take place in approximately 1-2 weeks.

At your second study visit, you will receive a standard evaluation of your neuropathy. This will take place at the Wake Forest Baptist Health Neurology Clinic. This will involve a nerve conduction test, ultrasound imaging, skin biopsy, and blood draw. This will last approximately 1.5 hours.

After your second visit, you will be randomized into one of two study groups. You will have an equal chance of being placed in either group. The two study groups include an acupuncture group and a waitlist group. If you are randomized to the acupuncture group, your first acupuncture visit will be scheduled by the Study Coordinator to take place within 2 weeks. Acupuncture treatments will take place at the Wake Forest Baptist Health Integrative Medicine Clinic Center at 755 Highland Oaks Drive in Winston-Salem, NC. You will then receive 8 acupuncture treatments (approximately 1x/week) over a period of 10 weeks. These can be scheduled at your convenience.

If you are randomized to the waitlist group, you will continue to receive your usual medical care and treatments with your clinical providers, but you will not receive any acupuncture treatments. After your third study visit, which will be 10-12 weeks from the second study visit, you will be offered up to 4 acupuncture treatments at the Wake Forest Baptist Health Integrative Medicine Clinic.

You will be provided with parking passes for all study visits. You will also receive a $25 gift card at study visit 2 and a $75 gift card at study visit 3. These are the two visits that involve clinical measures. If you live 60 miles or more from WFBMC, you will receive an additional $50 gift card upon completion of the baseline peripheral nerve assessment and an additional $50 gift card upon completion of the follow-up assessment.

Now, I need to ask you some questions to find out if you might be eligible to participate.

1. Are you willing to receive acupuncture?

   ____ No (**not eligible**)

   ____Yes

2. Are you able to travel to the Center for Integrative Medicine Clinic for treatments?

____ No (**not eligible**)

____Yes

3. Do you have breast or GI cancer?

____ No (**not eligible**)

____Yes

4. Do you know the stage of your breast or GI cancer? (check one and confirm that it is not currently metastatic)

____ I

____ II

____ III

____ IV (**not eligible**)

____ Unknown

5. Did you complete or are you receiving chemotherapy?

____ No (**not eligible**)

____ Yes, currently (go to a)

____ Yes, completed (go to b)

   a. For patients that are currently receiving chemotherapy:
      i. How many cycles are you supposed to receive?_____
      ii. How frequently do you receive tx?_____

   b. For patients who have recently completed chemotherapy:
      i. What day did you complete tx? __/__/__
      ii. How many weeks was it between each tx? _____

6. What kind of chemotherapy have you received/are you receiving? [Note: If respondant says paclitaxel, docetaxel, or b=nabpaclitaxel, she is eligible. If she says “other” the treatment eligibility will need to be checked by Dr. Thomas].

____ Paclitaxel

____ Docetaxel

____ Nabpaclitaxel

____ Other (please specify): _____

____ Unknown

7. Are you experiencing numbness and tingling in your hands and feet?

____ No (**not eligible**)

____Yes

8. Do you have a history of history of UNRESOLVED pre-existing peripheral neuropathy due to diabetes, HIV, or other conditions?

____ No

____Yes (**not eligible**)

9. Are you pregnant?

____ No

____Yes (**not eligible**)

10. Is the patient eligible?

____ No, refused to complete screener

____ No, did not meet eligibility criteria. EXPLAIN

It looks as though you meet initial eligibility for our study. We will need for you to come to the medical where your medical history will be reviewed and your eligibility confirmed. If you are still eligible for our study, you will be scheduled for your next study visit that will take place in approximately 1-2 weeks. At that visit, you will be asked to completed the consent process, complete a questionnaire, receive a standard evaluation of your neuropathy (including a nerve conduction test, ultrasound imaging, skin biopsy and blood draw) and be told whether you are in the waitlist group or will start acupuncture right away. The first acupuncture treatment will last approximately 1 hour and subsequent visits will last approximately 30 minutes. If you are in the waitlist group, you will wait approximately 10 weeks before

having another neuropathy assessment and being offered 4 acupuncture treatments and during this time we request that you do not receive any acupuncture at all.

11. Are you willing to participate in this study?

____ No (If no, go to question a)

____ Yes (If yes, go to question 12)

a. If no, why not? **(Check all that apply)**

____not interested

____not enough time

____don't want to be randomized

____too many visits

____no transportation

____call back – need time….

____other, specify _____

Thank patient for their time and end interview

12. If you qualify for the study, are you willing to accept random assignment to one of the 2 groups?

____ No (**STOP**, thank woman)

____Yes

SCHEDULE BASELINE VISIT:

Schedule a baseline visit date and time with woman:

Baseline visit: ____ ____ - ____ ____ - ____ ____ ____ ____
Month Day Year

Visit time: ____ ____: ____ ____ AM ____
Hour Min PM ____

Your first visit will include a meeting with the study coordinator who will tell you all about the study, review the study risks and procedures, and confirm additional eligibility. Should you have any questions, feel free to call Kelsey Shore and she will assist you in any way that she can.

We look forward to seeing you for your first study visit.

Thank you for your time.

Clinic Staff: _____

MAKE SURE YOU OBTAIN PATIENT'S ADDRESS AND COMPLETE CONTACT RECORD
PLEASE VERIFY THAT STUDY ID ON SCREENER AND CONTACT RECORD MATCH