A Pilot Study Using Ultrasound for the Detection of Taxane-Induced Peripheral Neuropathy
Wake Forest Baptist Comprehensive Cancer Center (WFBCCC)
CCCWFU # 97217

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1.0 Introduction and Background

Taxane chemotherapies such as paclitaxel and docetaxel have had an increasing role in the treatment of breast cancer and are now used in the majority of patients receiving perioperative chemotherapy.[1] Taxanes exert their effect by excess stabilization of microtubules which disrupts the mitotic spindle of dividing cancer cells. However, healthy neuronal cells also rely on functional mitrotubules in their axons and dendrites for both structural support and transport of intracellular products. Disruption of these neuronal microtubules leads to a dose-dependent peripheral neuropathy that is the dose-limiting toxicity of taxanes.[2] Taxane-induced peripheral neuropathy (TIPN) initially tends to manifest as a progressively worsening sensory impairment which is often felt as painful paresthesias with decreased deep tendon reflexes; this may be followed by a delayed motor deficit causing distal weakness.[3] TIPN is often reversible if it is intervened upon early enough with dose reduction or discontinuation of taxane treatments; if treatment is continued there is higher risk of irreversible symptoms.[4] A retrospective clinical practice study of early-stage taxane-treated breast cancer patients found that 10% of them had dose-limiting TIPN; roughly half of whom had early discontinuation of treatment with an average 28% lower cumulative taxane dose than planned.[5] When chemotherapy cannot be given as intended due to dose reductions it is generally associated with worse outcomes,[6] suggesting that TIPN may have an indirect effect upon overall survival in some breast cancer patients.

TIPN manifests via several different pathophysiological mechanisms that can be assessed by current modalities; none of which have yet emerged as a widely-adopted standardized approach. Taxane disruption of microtubules impairs the normal self-maintenance of neurons which is evident structurally as the degeneration of distal axons and nerve terminals. Inflammatory changes occur as the innate immune system responds to these damaged and leaking organelles. Genetic polymorphisms in neuronal and inflammatory cells contribute to individual variability in TIPN vulnerability. Functionally, as a neuronal myelin sheath deteriorates it increases the membrane surface area through which current must flow, slowing electrical conduction velocity and weakening its signal amplitude. Finally, as a result of the above mechanisms, degradation and inflammation can alter large peripheral nerves to the point that gross anatomic changes are evident on imaging.

Ultrasound (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.[7] 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.[8] 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).[9]

To date, there has only been one small study assessing US detection of chemotherapy-induced peripheral neuropathy; this was done among colorectal cancer patients who had received oxaliplatin. Similar to several other etiologies of nerve lesions/neuropathies, this study also found an increased peripheral nerve CSA compared to reference values. Interestingly, although the patients had denied symptoms of neuropathies at time of recruitment, this study found areas of increased peripheral nerve CSA at upper extremity sites of entrapment such as the carpal tunnel and ulnar groove; it did not find US abnormalities in terms of CSA or echogenicity at the sural nerve or other sites.[10] Oxaliplatin has a much different mechanism of action from the taxanes; as a platinum-based agent it causes DNA cross-linking which inhibits cancer cell growth. Oxaliplatin-induced neuropathy is also a distinct entity that is characterized by cold sensitivity and mediated by prolonged opening of sodium ion channels along neuronal axons.[11] On a review of publications in the MEDLINE database as well as abstracts from the American Society of Clinical Oncology, we did not find any other prior studies that focused on the use of US to detect chemotherapy-induced peripheral neuropathy, and none for TIPN.

As noted above, there are currently several different diagnostic modalities that can assess TIPN, including self-reported symptoms, physical examination, nerve conduction study, sudometer testing, and skin biopsies. But each have limitations so that none have emerged as a widely-adopted standardized approach.

In routine practice, most clinicians rely on patients' self-reported symptoms alone for TIPN detection. These symptoms can be measured on one of several clinician-administered grading scales, although these have inter-scale and inter-observer variability.[12] 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.[13] Furthermore, although in many patients the development of acute TIPN symptoms is predictive of eventual chronic TIPN,[14] some patients develop a disproportionately delayed TIPN that is not able to be self-reported early enough to allow for intervention.

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.[13] 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 are not associated with hearing loss, that corresponding item was excluded from analysis in that study.[15] 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.[16]

Physical examination 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 TIPN symptoms. Although promising, it has not been shown to provide early detection of subclinical TIPN.[17,18]

Nerve conduction studies (NCS) measure impairment of electrical function in large peripheral nerves and are thought to be a sensitive and specific measure of TIPN. 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.[19] 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).[20] 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).[21] However, NCS are invasive; can be mildly painful for the patient; require expertise and time to administer; and can only detect TIPN once it has progressed to the point that there is functional impairment of large peripheral nerves; these problems make it less preferable for the routine clinical evaluation for TIPN-like symptoms.[22] Other functional assays besides NCS have been investigated. Sudomotor testing is a novel technique that uses the topical administration of acetylcholine to measure the sweat response that is mediated by the small fibers of 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 neuropathy;[23] but has not yet been studied for TIPN.

Skin biopsies are able to detect TIPN with good diagnostic sensitivity that may be superior to NCS in chronic TIPN.[24] Measurement of the intraepidermal nerve fiber (IENF) density is a standard clinical assessment used in the evaluation of 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.[25,26] Typical IENF density findings in TIPN 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).[27] 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.[28] However, IENF density has not been shown to be predictive of chemotherapy-induced peripheral neuropathy and, similar to NCS, skin biopsies are invasive and may be mildly painful.

The inflammatory mechanism by which TIPN causes neurotoxicity is poorly understood. Mast cells may have a role in the pathophysiology of some other types of chemotherapy-induced peripheral neuropathy. A mouse study found that prevention of mast cell degranulation by a congenital mast cell deficiency or administration of a mast cell stabilizer could prevent oxaliplatin neuropathy.[29] Mast cell markers can be detected in serum and increased number or atypia of mast cells can be detected on skin biopsy.

Given the lack of a consensus approach to the diagnosis of TIPN, further research is needed to better characterize TIPN that ideally uses non-invasive methods to facilitate serial measurements if they are needed. The accurate assessment of TIPN allows for appropriate adjustment of taxane chemotherapy dosing and potential improvement of clinical outcomes in breast cancer patients. This pilot study will assess the utility of ultrasound as a novel technique to assess TIPN.

2.0 Objectives

2.1 Primary Objectives

2.1.1 To compare tibial motor nerve ultrasound CSA between TIPN patients and historical data among healthy adults.

2.2 Secondary Objective

2.2.1 To compare sural sensory nerve ultrasound CSA between TIPN patients and historical data among healthy adults.

2.2.2 To determine if the above changes in nerve CSA correlate with NCS changes in the same TIPN patients.

2.2.3 To determine if the above changes in nerve CSA correlate with changes on a self-reported neuropathy scale (QLQ-CIPN20) in the same TIPN patients.

2.2.4 To determine if the above changes in nerve CSA correlate with IENF density changes on skin biopsy in the same TIPN patients.

2.3 Exploratory Objectives

2.3.1 To assess activated mast cells in skin biopsies in TIPN patients in relation to severity of symptoms and above findings.

2.3.2 To assess serum inflammatory markers in TIPN patients in relation to severity of symptoms and above findings.

3.0 Study Population

This study is designed to enroll breast cancer patients with clinically documented symptoms consistent with TIPN.

3.1 Inclusion Criteria

- Breast cancer (any stage).
- Previously or currently receiving taxane-based chemotherapy.
- Clinical symptoms of peripheral neuropathy noted in medical record and suspected to be secondary to taxane-based therapy.
- Ability and willingness to understand and sign an informed consent.

3.2 Exclusion Criteria

- Self-reported or documented history of pre-existing peripheral neuropathy prior to initiation of taxane chemotherapy.
- Male patients.
- Unable to provide history.

3.3 Inclusion of women and minorities

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

3.3.2 The study consent form will also be provided in Spanish for Spanish-speaking participants. Male patients will be excluded as the frequency of breast cancer among males is low and the frequencies needed to treat men for male breast cancer are currently unknown; therefore, 100% of participants to be women. We plan to enroll at least 20% Black or African American (N=4). Because of the low incidence among American Indian/Alaska Native, Asian, and Hispanic/Latino women 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 these 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.

   Contact Information:
   Protocol Registrar PHONE (336) 713-6767
   Protocol Registrar FAX (336) 713-6772
   Protocol Registrar E-MAIL (registra@wakehealth.edu)

   *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.

Note: If labs were performed at an outside institution, provide a printout of the results. Ensure that the most recent lab values are sent.

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*				
	Encounter 1	**Encounter 2**	**Encounter 3**	**Follow-up: 30 days to confirm adequate healing of biopsy**
Informed Consent	X			
Medical history (Appendix C)		X		
Physical exam		X		
QLQ-CIPN20[f]		X		
Blood draw[c,f]		X		
Abbreviated Neurologic Exam[a]			X	
Nerve Conduction Study[b]			X	
Ultrasound[d]			X	
Skin Biopsies[e]			X	
Follow-up skin assessment				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, and the blood draw and the QLQ-CPIN20 should be performed on the same day. 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: exam to include strength assessment of the tibialis anterior and gastrocnemius and deep tendon reflex exam of the Achilles on the limb to be examined with NCV and US.
b: Sural and Tibial nerve assessments
c: Green top heparin tube: 12 ml blood sample
d: Sural and Tibial nerve assessments
e: Two skin biopsies will be obtained as 4mm punch biopsies at distal end of leg in sural nerve territory (10cm above lateral malleolus) and from the thigh
f: The blood draw and the QLQ-CIPN20 should be performed on the same day.

4.3 Study setting

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

4.4 Enrollment (Encounter 1)

Recruitment information will be posted in the CCC outpatient clinics in the rooms where breast cancer patients are treated. Study investigators will also review medical records and work with WFBMC clinicians to identify patients who would potentially meet inclusion criteria. If a breast cancer patient expresses interest in enrollment on the study, a study investigator or research employee will meet the patient in clinic to ensure that they are eligible and to obtain consent for enrollment on the study. We anticipate an accrual rate of 1-2 participants per month. This is feasible because 242 breast cancer patients received taxanes (52% paclitaxel, 45% docetaxel) in 2016 at the WFBCCC alone and with additional breast cancer patients treated at the Clemmons satellite office.

4.5 Clinical assessment (Encounter 2)

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), breast 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 to document strength and reflexes. The QLQ-CIPN20 questionnaire will also be administered at this encounter.

In most cases, blood testing will be added on to regularly scheduled phlebotomy for clinical labs which are drawn as part of routine oncology care. Some participants may require an additional blood draw if insufficient blood samples were collected. For the purposes of our study, 12mL of venous blood will be collected in a sodium heparin (green-top) collection tube and then transferred directly to Dr. Shiozawa's lab for processing.

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 two green-top vacutainer tubes containing heparin (60 USP Units of Lithium Heparin/6ml tube), and immediately inverted 8-10 times to prevent coagulation. **Attention: Protocol #: CCCWFU # (97217) and the ORIS 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 Diagnostic testing (Encounter 3)

Participants will be referred to Diagnostic Neurology clinic for and abbreviate neurological exam to assess strength of the tibialis anterior and gastrocnemius and deep tendon reflex exam of the Achilles tendon on the limb to be examined in nerve conduction studies and ultrasound evaluation during this encounter. Further, a skin biopsy will be obtained. These tests will be completed at a single visit and no further follow-up with neurology is required as part of the study protocol. All of these studies are considered standard clinical tests for the evaluation of peripheral neuropathy and sensory neuropathy. Patients will receive a Visa gift card upon completion of the neuropathy assessment.

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.(2008) [8] 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.

NCS technique and reference values for the sural and tibial nerves among healthy adults are based on data from Chen et al. (2016) and standard institutional practice [30]. 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.

Two skin biopsies will be obtained as 4-5mm punch biopsies at distal end of leg in sural nerve territory (10cm above lateral malleolus) and in the upper thigh. As described in a review by Lauria and Devigili (2007),[31] 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-terminal hydrolase expressed throughout the peripheral nervous system. Slides will be reviewed by Dermatopathology (Dr. Ahn and/or 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.(1998))[25] 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 and transferred to Dr. Shiozawa's lab for staining and testing of mast cell concentration, tryptase, chymase and histamine. The results will be recorded on Appendix E for transfer into REDCap.

Storage of Serum and Skin Biopsy Material
Venous blood will be stored in lab refrigerator prior to transfer (in oncology lab) and after transfer (in Dr. Shiozawa's lab). Serum and left over skin biopsy material from patients will be stored in Dr. Shiozawa's laboratory in the Department of Cancer Biology until use.

Tests Using Serum
Serum testing for inflammatory markers will be performed using commercially available kit that may include but not be limited to ELISA and will be performed according to the

manufacturers' instructions and modified accordingly if needed given the type of sample and/or target of interest to be detected. Data resulting from these experiments may be kept in laboratory notebooks or in on the data sheets provided in Appendix C.

4.7 Follow-up

Results of diagnostic testing will be made available in the participant's medical record. If unexpected abnormalities are detected, the primary oncologist will be contacted and a Neurology referral can be placed as part of the patient's routine clinical care. The patient will also be followed for 30 days to ensure the biopsy site is healing adequately. This follow up may be by telephone or in person.

4.8 Data entry/storage

Paperwork with identifying patient information will be stored at the investigator's workspace in the locked workroom of the Hem/Onc 1st floor Watlington office or in the lab notebook of Dr. Shiozawa in his locked lab; both are located on the WFBMC campus. Electronic data will be stored on the secure personal computers of the investigators on the medical center campus prior to transfer into the secure RedCap online database.

5.0 Outcome Measures

Listed below are the primary, secondary and exploratory outcomes. However, given 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, and other qualitative descriptions of nerve changes.

5.1 Primary Outcome

5.1.1 Tibial nerve CSA as determined by ultrasound in the tibial nerve in TIPN patients and derived from historical controls.

5.2 Secondary Outcomes

5.2.1 Sural nerve CSA as determined by ultrasound of the sural nerve in TIPN patients and derived from historical controls.

5.2.2 Amplitude, distal latency, and conduction velocity of nerve response derived from NCS in TIPN patients.

5.2.3 Self-reported neuropathy score as assessed by the EORTC QLQ-CIPN20.

5.2.4 Nerve fiber density in the skin (IENF/mm) in TIPN patients.

5.3 Exploratory Outcome

5.3.1 The number of activated mast cells (per mm) in TIPN patients

5.3.2 Serum levels of inflammatory molecules in TIPN patients chosen at the investigators discretion

5.4 Covariates

5.4.1 BMI

5.4.2 Age

5.4.3 Breast cancer staging

5.4.4 Types/dosages of chemotherapy and corticosteroids received

5.4.5 Presence of previously documented comorbidities (diabetes, B12 deficiency, thyroid disorders, alcoholism, depression, carpal tunnel syndrome, sciatica)

5.4.6 Use of analgesics or treatments for neuropathy

5.4.7 History of clinically documented compressive neuropathy (carpal tunnel syndrome)

6.0 Analytic Plan

6.1 Sample Size and Power

6.1.1 Primary outcome:

This current study will enroll a sample size of 22 in TIPN patients to compare to historical data that was previously collected from 60 healthy patients. Using a two-sided test and significance level of 0.05, we will have an 80% power to detect an effect size of 0.73 (unit: standard deviation [SD]) when comparing TIPN patients to that historical data. We have permission to utilize historical data (primary data) collected from healthy patients which found that the mean and SD of the tibial nerve CSA were 14.2 and 4.4 mm^2, respectively (published by Cartwright et al., 2008). Assuming the same SD in TIPN patients, we will have more than 80% power to detect a difference of 3.2 mm^2 for the tibial nerve. Based on Riazi et al. (2012),[32] the mean increase in size of tibial nerve was 5.3 when comparing subjects with diabetic sensorimotor polyneuropathy and control subjects. Even though the study sample is not exactly the same, with the minimal detectable difference equal to 3.2, we should have sufficient power for this analysis.

6.1.2 Secondary outcome:

In historical data collected from healthy patients (Cartwright et al., 2008),[8] the mean and standard deviation (SD) of the sural nerve CSA were 5.3 and 1.8 mm^2, respectively. Assuming the same SDs in TIPN patients, we will have more than

80% power to detect a detectable difference of 1.3 mm^2 for the sural nerve between TIPN patients and healthy patients.

6.2 Analysis of Primary Outcome

The distribution of the primary outcome, nerve CSA, will be transformed to satisfy conditional normality assumption if necessary. It will be compared to the historical data from healthy patients using two-sample t-test (two-sample t-test selected as primary data from the historical control patients is available and will be used for analysis). We will also compare the nerve CSA in our study sample to that in the historical diabetic neuropathy patients and historical oxaliplatin neuropathy patients using one-sample t-test. The general linear model will be used to evaluate any factors (e.g., age) that may be associated with the nerve CSA. Due to the limited sample size, no more than two covariates will be included in the model.

6.3 Analysis of Secondary Outcome

The analysis of sural sensory nerve CSA will be the same as that specified for primary outcome. To examine the associations between nerve CSA and NCS measures, the self-reported neuropathy scale, and intraepidermal nerve fiber density, Spearman's rank correlation coefficient will be used. The general linear model will be also used to evaluate the association after adjusting for one or two risk factors (e.g., age). Nerve CSA will be treated as the dependent variable. NCS measures, the self-reported neuropathy scale, and intraepidermal nerve fiber density are the covariates of interest. They will be fitted in the model one at a time.

6.4 Analyses of Exploratory Outcomes

Spearman's rank correlation coefficient will be used to assess the associations between activated mast cells in skin biopsies, serum inflammatory markers, severity of symptoms, and primary outcome and secondary outcomes in TIPN patients.

6.5 Accrual Rate

1-2 participants per month

6.6 Length of Study

16-20 months

7.0 Data Management

Informed consent document	EPIC
Protocol Eligibility Form	
Protocol Registration Form (Appendix B)	ORIS
Race and Ethnicity Verification Form	
Clinical Evaluation from History/Exam (Appendix D)	REDCap
Exploratory Outcome Data Collection Form (Appendix E)	REDCap
EORTC QLQ-CIPN20 (neuropathy scale) (Appendix F)	REDCap
Nerve Fiber Density Data Collection Form (Appendix G)	REDCap
Ultrasound Nerve Diameter Data Form (Appendix H)	REDCap

Nerve Conduction Study Data Collection Form (Appendix I)	REDCap
Adverse Events Log (Appendix J)	ORIS

8.0 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 (state the anticipated time the data will be destroyed, e.g. three years after closure of the study, and the method of destruction), 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.

9.0 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.

10.0 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.

Adverse events will be tracked for 30 days following skin biopsy. This time is adequate to evaluate for potential adverse events from this and all study procedures. Adverse events will not be tracked beyond 30 days following the neurodiagnostic and skin biopsy procedures unless a delayed event is felt to be related to the study intervention.

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Appendix A: Subject Eligibility Checklist

IRB Protocol No. 00043631	**CCCWFU Protocol No. 97217**
Study Title: A Pilot Study Using Ultrasound for the Detection of Taxane-Induced Peripheral Neuropathy	
Principal Investigators: Roy Strowd, M.D., Glenn Lesser, M.D	

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 cancer (any stage).	☐	☐	
Previously or currently receiving taxane-based chemotherapy	☐	☐	
Clinical symptoms of peripheral neuropathy noted in medical record	☐	☐	
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 pre-existing peripheral neuropathy prior to initiation of taxane chemotherapy	☐	☐	
Unable to provide history	☐	☐	
Male patients	☐	☐	

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

ORIS Assigned PID: __ __ __ __ __ __ __ __

Signature of research professional confirming eligibility:_____
Date: __ __/__ __/__ __

Signature of Treating Physician: _____Date: __ __/__ __/__ __

Signature of Principal Investigator**: _____ Date: __ __/__ __/__ __

* 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: ___ ___ /___ ___/___ ___

Performance Status: ___ ___ ___ ☐ ECOG ☐ Karnofsky

PROTOCOL INFORMATION

Date of Registration: ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started: ___ ___ / ___ ___ / ___ ___

Informed written consent: ☐ YES ☐ NO

(consent must be signed prior to registration)

Date Consent Signed: ___ ___ / ___ ___ / ___ ___

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

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 Latino/a
   - ☐ Not Hispanic or Latino/a

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

ORIS PID: __ __ __ __ __ __ __ __ **Date Completed:** __ __ / __ __ / __ __

PI: Roy Strowd, M.D., Glenn Lesser, M.D. **Study Number:** CCCWFU 97217

Instructions: To be filled out by medical staff.

1. Oncologic history
   Diagnosis and stage: _____

   a. Most immediate prior cancer therapy (select one):
   ☐ chemotherapy ☐ radiation ☐ surgery ☐ hormone ☐ other:
   _____

   b. Specify most immediate prior taxane chemotherapy:
   _____

   Dates of administration: Started: __ __ / __ __ / __ __ Stopped: __ __ / __ __ / __ __

   Dose _____ & total # of treatments _____

   c. Other prior cancer therapies (excluding 1b.) for most recent cancer. Mark all that apply:
   ☐ None ☐ Chemotherapy ☐ Radiation ☐ Surgery ☐ Hormone therapy ☐ Other:
   _____

Regimen Name	Total # of Treatments	Date of Last Treatment, or 'ongoing' for certain HT
1.		__ __ / __ __ / __ __
2.		__ __ / __ __ / __ __
3.		__ __ / __ __ / __ __
4.		__ __ / __ __ / __ __
5.		__ __ / __ __ / __ __
6.		__ __ / __ __ / __ __
7.		__ __ / __ __ / __ __
8.		__ __ / __ __ / __ __
9.		__ __ / __ __ / __ __
10.		__ __ / __ __ / __ __

Site of RT	Total Dose in Gy	Date of Last Treatment
1.		__ __ / __ __ / __ __
2.		__ __ / __ __ / __ __
3.		__ __ / __ __ / __ __
4.		__ __ / __ __ / __ __
5.		__ __ / __ __ / __ __

Type of surgery	Date of surgery
1.	__ __ / __ __ / __ __
2.	__ __ / __ __ / __ __

Hormone Therapy Name	Dose	Date of Last Treatment
1.		__ __ / __ __ / __ __
2.		__ __ / __ __ / __ __

Other	Dose	Date of Last Treatment
1.		__ __ / __ __ / __ __
2.		__ __ / __ __ / __ __

2. Medical history (check all that apply):
   - ☐ Thyroid Disorder
   - ☐ Hyperthyroidism ☐ Hypothyroidism
   - ☐ 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
     end organ damage? Yes ☐ No ☐
   - ☐ AIDS
   - ☐ Depression
   - ☐ Other major medical condition; specify

     _____
     _____
     _____

4. Concurrent medications and supplements
   a. 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

b. List all supplements (excludes prescription supplements)

Supplement Name	Is it PRN?	Supplement 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. Physical exam:
   - Derm – ☐ WNL ☐ Abnormal, specify _____
   - HEENT – ☐ WNL ☐ Abnormal, specify _____
   - CV – ☐ WNL ☐ Abnormal, specify _____
   - Pulm – ☐ WNL ☐ Abnormal, specify _____
   - GI – ☐ WNL ☐ Abnormal, specify _____
   - Other – ☐ Abnormal, specify _____

Appendix E: Exploratory Outcomes Data Collection Form

ORIS PID: __ __ __ __ __ __ __ __ **Date Completed:** __ __ / __ __ / __ __

PI: Roy Strowd, M.D., Glenn Lesser, M.D. **Study Number:** CCCWFU 97217

Instructions

- Use the ORIS PID to Identify the Sample
- Date is the date of experimentation
- Target Name (Serum Outcomes): Name of the target of the assay
- Record amounts to 3 decimal places (serum outcomes)
- 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.

Exploratory Outcomes Data Form							
	Serum Outcomes			IHC and Positive Cell Count			
Date of blood sample collection	Target Name	Amount (ng/ml)	Initials	Mast Cell Number	Tryptase	Chymase	Histamine
__ __/__ __/__ __							

Appendix F QLQ-CIPN20

ORIS PID: __ __ __ __ __ __ __ __ Date Completed: __ __ / __ __ / __ __
PI: Roy Strowd, M.D., Glenn Lesser, M.D. **Study Number:** CCCWFU 97217

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 cramp in your hands?	1	2	3	4
8) Did you have cramp in your feet?	1	2	3	4
9) Did you have problems standing or walking because of a difficulty in 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 hand?	1	2	3	4
14) Did you have difficulty 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
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
Please, answer the following question, only if you drive a car				
18) Did you have difficulty using pedals?	1	2	3	4
Please, answer the following question, only if you are a man				
19) Did you have difficulty in having or maintaining an erection?	1	2	3	4

Adapted from Postma et al. 2005 and Cavaletti et al. 2009

Excludes the question: "Did you have difficulty in hearing?"

Appendix G: Nerve Fiber Density Data Collection Form

ORIS PID: __ __ __ __ __ __ __ __ **Date Completed:** __ __ / __ __ / __ __

PI: Roy Strowd, M.D., Glenn Lesser, M.D. **Study Number:** CCCWFU 97217

Instructions

- Use the ORIS PID to Identify the Sample
- Date is the date of experimentation and listed before the technique. Use the following format: __ __/__ __/__ __
- 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: __ __/__ __/__ __

Nerve Fiber Density Form		
Location of Biopsy (Distal/Leg or Proximal/Thigh)	Nerve Fiber Density (IENF/mm)	Initials of Dermatologist/ Pathologist

Appendix H: Ultrasound Nerve Diameter Data Form

ORIS PID: __ __ __ __ __ __ __ __ **Date Completed:** __ __ / __ __ / __ __

PI: Roy Strowd, M.D., Glenn Lesser, M.D. **Study Number:** CCCWFU 97217

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

Date of Procedure: __ __/__ __/__ __

SAGITTAL VIEW

Nerve and Side	Probe Location and Landmark	Max/Min #1	Max/Min #2	Max/Min #3	Mobility	Echo	Vasc	Other

SEGMENTS SCREENED

Nerve and Side	Axial segments imaged	Sagittal segments imaged

LEGEND

Echogenicity = scores include **N** (normal), **INC** (increased), DEC (decreased), or **A** (absent)
Axial/Sagittal Motion = describes nerve motion with passive or active flexion of relevant joint: scores include **N**, **INC**,
Vascularity = describes presence of vascular activity *within* nerve
Other = Includes *Persistent Median Artery* (PMA), *Bifid Nerve*, *Trifid Nerve*, *FDS in CTS*, etc.

Person recording information: _____

Appendix I: Nerve Conduction Study Data Collection Form

ORIS PID: __ __ __ __ __ __ __ __ **Date Completed:** __ __ / __ __ / __ __

PI: Roy Strowd, M.D., Glenn Lesser, M.D. **Study Number:** CCCWFU 97217

Instructions

- Use the ORIS PID to Identify the Sample
- Date is the date of experimentation and listed before the technique. Use the following format: __ __/__ __/__ __
- Initials of person collecting the data.

*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							
	Conduction studies						
	Tibial			Sural			
Date of Nerve Conduction Study	Amplitude	Latency	Conduction Velocity	Amplitude	Latency	Conduction Velocity	Initials of Neurologist
__ __/__ __/__ __							

Appendix J: Adverse Events Log

CCCWFU 97217 Adverse Event (AE) Log

PI: Roy Strowd, M.D., Glenn Lesser, M.D **PID: __ __ __ __ __ __ __ __** **MRN: __ __ __ __ __ __ __ __**

Adverse Event CTC Term	**Value** (-5 if non-numeric)	**Grade** (0-5) per CTC	**Start Date**	**Attribution** 1=Related 2=Probably 3=Possible 4=Unlikely 5=Unrelated	**Treating MD Initials/Date**	**End Date**	**Expected** 1=Yes 0=No	***Serious Adverse Event (SAE)** 1=Yes 0=No	**Dose Limiting Toxicity (DLT)** 1=Yes 0=No	**Action Taken** 1=None 2=Tx withheld 3=Tx D/C 4=Tx adjusted 5=Other	**Reportable?** 1=IRB 2=STRC 3=FDA 4=Sponsor
Injection site reaction											
Skin infection											
Infections and infestations - other											
Bruising											
Dizziness											
Syncope											

*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

Appendix K: Follow-up Form for Skin Biopsy

ORIS PID: __ __ __ __ __ __ __ __ **Date Completed:** __ __ / __ __ / __ __

PI: Roy Strowd, M.D., Glenn Lesser, M.D. **Study Number:** CCCWFU 97217

Date of Skin Biopsy	Phone / In-person assessment completed within 30 days (circle one)	Any skin biopsy problems reported by participant?
__ __/__ __/__ __	Yes / No	
__ __/__ __/__ __		Yes / No

Appendix L: Mandatory STRC SAE Reporting Requirements

Safety and Toxicity Review Committee (STRC; previously known as CROC) Serious Adverse Event (SAE) Notification SOP	**Date: 11/17/2016**

Mandatory STRC SAE Reporting Requirements

This document describes STRC reporting and use of the electronic submission form that is submitted **for unexpected grade 4 and any grade 5 (death during protocol intervention) SAEs on CCCWFU Institutional interventional trial patients**. There are multiple entities that require reporting of SAEs. Each entity has different rules for what is reported, and how it is reported.

Rules used by other entities (Institutional Review Board (IRB), AdEERS, MedWatch, etc.) should NOT be used to evaluate whether an event should be reported to STRC. Only the rules for reporting described in this document should be considered.

As defined in the NCI Data Table 4 reporting guidelines, **CCCWFU Institutional Interventional studies covered by these reporting requirements are defined as: In-house, internally reviewed trials, including those collaborative studies conducted with industry sponsorship in which the center is a primary contributor to the design, implementation, and monitoring of the trial, or participation in a multi-site trial initiated by an institutional investigator at another center.** Institutional trials are almost always authored by a researcher here at CCCWFU. Institutional protocols are labeled NCI Code="I" for Institutional on the protocol screen in ORIS. Cooperative group protocols are **not** considered Institutional, but Research Base trials **are** classified as Institutional.

The STRC is responsible for reviewing SAEs for CCCWFU Institutional Interventional studies, as defined above. STRC currently requires that unexpected grade 4 and all grade 5 SAEs on these trials be reported to the STRC for review. All Clinical Protocol and Data Management (CPDM) staff members assisting a PI in documenting and reporting an SAE that qualifies for STRC reporting are responsible for informing a clinical member of the STRC by phone (or in-person), followed by informing the entire committee via the required email notification.

THESE REPORTING REQUIREMENTS APPLY TO any faculty or staff member on the study team for a CCCWFU Institutional Interventional trial. Once an event is observed, it is the responsibility of the person who observed the event to be sure that it is reported.

What is considered an SAE under this mandatory procedure?
Any **unexpected grade 4** event and **all grade 5 events** (death during protocol intervention) should be reported. These events should be reported if they occur while a patient is on study treatment or if they occur within 30 days of last study treatment (even if patient begins a new 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. In addition, if it is not clear whether the Grade 4 is unexpected it should be reported.

Table 1: Summary of STRC Reporting Requirements for Institutional Pilot, Phase 1, Phase 2 and Phase 3 Interventional Trials
STRC reporting may not be appropriate for specific expected adverse events for protocols. In those situations the adverse events that will not require STRC reporting **must be specified in the text of the approved protocol.**

	ADVERSE EVENT					
	Grade 1, Grade 2, Grade 3		**Grade 4**		**Grade 5**	
	Unexpected	**Expected**	**Unexpected**	**Expected**	**Unexpected**	**Expected**
Unrelated	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Unlikely	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Possible	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Probable	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**
Definite	Not Required	Not Required	**REPORT TO STRC**	Not Required	**REPORT TO STRC**	**REPORT TO STRC**

STRC notification responsibilities of the person handling the reporting/documenting of the SAE:
1. Make a phone call (or speak in person) to the appropriate clinical member of the STRC as listed below (page if necessary)—see note 2 below
2. Submit the STRC Notification Form WITHIN 24 HOURS of first knowledge of the event. This form is found at either the ORIS main menu page or by going to http://ccc.wfubmc.edu/oris/strc.aspx.
   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 your

confirmation. (Form instructions will walk you through the required fields, consult the help page for further instructions.)

3. Ensure that you document that the appropriate person(s) on the STRC has been contacted. This documentation is placed on the STRC Notification form described above.
4. Follow up with/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 to complete the electronic STRC form:
Please use 'reply to All' when responding with one of these terms: Definite, Probable, Possible, Unlikely, or Unrelated

1. Patient ID (ORIS PID)
2. Patient Name
3. Patient MR#
4. CCCWFU(ORIS) Study Number
5. Title
6. PI Name
7. PI Contact Number
8. PI Comments
9. STRC Clinician notified by Phone
10. Notified Date
11. Notified Time
12. STRC Clinician Comments
13. Category [This is the Grade – Either Unexpected Grade 4 or Grade 5 should be entered]
14. Additional Information (IRB Reporting)(after discussion with PI or STRC Clinician
    i. Is This Event Related to Protocol Treatment?
    ii. Is Suspension of the Protocol Needed?
    iii. Any Changes to Consent or Protocol Needed?
    iv. Was Nature or Severity of Event Unexpected?
15. Date of the event.
16. Brief description (include brief clinical history relevant to this event, including therapies believed related to event).
17. Date of Last Dose before event
18. Relevant tests/labs.
19. Other Relevant Treatment Information
20. Other Comments/Notes (include regimen of chemo and dates the patient received them if known).
21. Cc (email) (include treating Physician; separate email list with comma",")
22. Your Name
23. Your Email
24. Confirm Your Email

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

Bayard Powell, MD – Director-at-Large, CCCWFU; Section Head, Hematology/Oncology
Glenn Lesser, MD – Hematology Oncology
Stefan Grant, MD, JD-Hematology Oncology
Jimmy Ruiz, MD-Hematology Oncology
Kathryn Greven, MD – Vice Chair – Radiation Oncology
Marissa Howard-McNatt, MD – General Surgery
Mercedes Porosnicu, MD- Hematology Oncology

Definition of Unavailable:

As a general guideline if the first clinician that is contacted does not respond to the phone call or page within a reasonable amount of time, then initiate contact with their backup. Give the back-up a reasonable amount of time to respond to a phone call or page before contacting another member. This is a general guideline. You must use your best judgment as a clinical research professional given 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 your STRC notification form. The important criteria is that you have taken reasonable steps to notify and document that you have initiated some type of contact 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 agree with the investigator's assessment if STRC does not agree with the investigator. STRC reserves the right to suspend the trial pending further investigation.
Is there any immediate danger or harm that could be present for a future patient based on the information provided in the STRC report – and if so an immediate suspension of enrollment should take place.

AMENDMENTS TO PREVIOUS REPORTS

If you are not able to supply all pertinent information with the initial submission, once the additional information is available **do not submit a new report**. Go to the original email that was received by STRC and others "reply to all" and entitle your email "**Amendment** for (list date of event and patient ID) this will avoid duplications of the same event. List the additional information which you are reporting.

Acronyms and Definitions

STRC-Safety and Toxicity Review Committee
SAE-Serious Adverse Event
IRB-Institutional Review Board
CCCWFU-Comprehensive Cancer Center Wake Forest University
ORIS-Oncology Research Information System
NCI-National Cancer Institute
CPDM-Clinical Protocol and Data Management
Interventional Trials-Therapeutic Level 1 and Level 2 trials
Therapeutic Level 1-A cancer treatment protocol aimed at directly treating/curing the patient's cancer.
Therapeutic Level 2-A therapeutic protocol not cancer treatment involves clinical activity to treat symptoms, improve the patient's quality of life, or prevent cancer.