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Official Study Title: Evaluation of Cryotherapy and TRPA1 Receptors in Chemotherapy Induced Neuropathy

NCT number: NCT03329131

IRB Approval Date: 07.05.2021

Unique Protocol ID: CTMS # 17-0033

Title: Evaluation of Cryotherapy and TRPA1 Receptors in Chemotherapy Induced Neuropathy

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CTMS# 17-0033

IND Exempt

PROTOCOL Version 13
DATE: 6/22/21

INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Protocol Title: Evaluation of Cryotherapy and TRPA1 Receptors in Chemotherapy Induced Neuropathy, CTMS# 17-0033 and will adhere to the study requirements as presented, including all statements regarding confidentially. In addition, I will conduct the study in accordance with current international conference on harmonization (ICH) guidance, Good Clinical Practice (GCP) guidance, the Declaration of Helsinki, US Food and Drug Administration (FDA) regulations and local IRB and legal requirements.

Name of Clinical Investigator: Virginia Kaklamani, MD

Institution: Mays Cancer Center

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Investigator Signature Date

ABBREVIATIONS (sample list – please only use those that are relevant to your protocol)

AE	Adverse Event
BPI	Brief Pain Inventory
CIPN	Chemotherapy-Induced Peripheral Neuropathy
DSM	Data Safety Monitoring
DSMB	Data Safety Monitoring Board
DSMC	Data Safety Monitoring Committee
DQA	Director of Quality Assurance
EORTC QLQ-CIPN20	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy Induced Peripheral Neuropathy 20
FDA	Food and Drug Administration
FEPS	Familial Episodic Pain Syndrome
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IIS	Investigator Initiated Protocol
IND	Investigational New Drug
IRB	Institutional Review Board
NCI	National Cancer Institute
NCS	Nerve Conductive Studies
NGS	Next Gen Sequencing
NIH	National Institutes of Health
NPSI	Neuropathic Pain Symptom Inventory
PALS	Priority of Audit Level Score
PI	Principal Investigator
PRMS	Protocol Review and Monitoring System
QAD	Quality Assurance Division
QST	Quantitative Sensory Testing
SAE	Serious Adverse Event
TRPA1	Transient Receptor Potential Cation Channel Subfamily A Member 1
TRPM8	Transient Receptor Potential Cation Channel Subfamily M Member 8 (TRPM8)
TRPV1	Transient Receptor Potential Cation Channel Subfamily V Member 1 (TRPV1)
UPIRSO	Unanticipated Problem Involving Risks to Subjects or Others

Table of Contents

Study Synopsis

This is a therapeutic study investigating the use of cryotherapy in the prevention of chemotherapy-induced peripheral neuropathy (CIPN) and associated nail toxicities. The therapeutic intervention will involve patients wearing an Elasto-Gel cold glove and wrap on one hand and one foot (both on the right side or both on the left side). The patients will wear the glove and wrap during each infusion of taxane chemotherapy. Infusion therapy, assessments and patient questionnaires will take place in the Mays Cancer Center and the Nerve Conduction Studies (NCS) will be performed at the Medical Arts and Research Center (MARC). The primary aim is to demonstrate if cryotherapy is a safe and effective intervention in preventing peripheral neuropathy and nail toxicity in patients receiving taxane chemotherapy. The secondary aim is evaluating the relation of CIPN with gene expression profiles of TRPA1, TRPV1 and TRPM8 in peripheral blood.

Background

Breast cancer is the second most common cause of death for women and is the most common cause of death for women ages 45 to 55 [1]. The incidence varies worldwide, being more prevalent in North America than in Africa, as a consequence of environmental factors such as diet and exercise [1]. Multiple prognostic factors such as receptor status have been identified, therefore, making the treatment more effective due to better targeting. Women with node-positive disease and a significant percentage of node-negative women benefit from chemotherapy[2]. Although there are some well-known algorithms of treatments, the choice of which chemotherapy to use is based on variables like age, comorbidities, axillary node involvement and status of hormone receptors. For those patients receiving chemotherapy, multiple combinations are available; one commonly used is doxorubicin/cyclophosphamide and paclitaxel [3]. Taxanes improve the disease-free and overall survival in patients with early breast cancer [4]. There are multiple taxane chemotherapies, but they all share the common mechanism of action of stabilizing microtubules assembly[5-6] and thus preventing cell division. Toxicities are also shared within the taxane class and include a higher rate of myelosuppresion, febrile neutropenia [5-6], polyneuropathy and cutaneous toxicities such as nail bed hyperpigmentation and oncholysis [7]. Side effect incidence is related to the overall cumulative dose of taxanes[8]. Thus far, no specific genomic biomarker has been identified that can predict individual susceptibility to these know toxicities [9].

Chemotherapy inducted peripheral Neuropathy is a common treatment-related adverse effect and affects long-term quality of life[16]. CIPN is a dose-limiting side effect of many anti-cancer drugs including platinum drugs, taxanes, vinca alkaloids, epothilones, bortezomib, and lenolidamide[17-19]. The overall incidence of CIPN is estimated to be approximately 38% in patients treated with multiple agents[16] although this percentage varies depending on the different chemotherapy regimens used and the duration of the exposure. These effects of chemotherapy drugs can resolve after treatment ceases but many patients are left with permanent sensory deficient or chronic pain syndromes[18]. Treatments for CIPN have been disappointing, with most agents demonstrating no significant analgesic effect. Therefore, interventions that can reduce the prevalence or severity of neuropathic symptoms in patients receiving chemotherapy will immediately have a significant impact on patient care.

Breast cancer is a common malignancy that responds well to taxane-containing chemotherapeutic regimens[1]. Women who develop peripheral neuropathy as a result of treatment with taxane chemotherapy can have lasting side effects and significant decrease in their quality of life. Peripheral neuropathy can result in loss of ability to complete activities of daily living such as walking, standing and self-care, and can also lead to difficult to treat chronic pain syndromes [10-11]. Unfortunately, studies exploring a variety of agents for the prevention of taxane-induced peripheral neuropathy have so far been unsuccessful [12]. For example, recent studies of Amifostine and recombinant human leukemia inhibitory factor (rhuLIF, AM424, emfilermin) were shown to have no neuro-protective effect against paclitaxel [13-15].

In trials where neurosensory evaluation included electrophysiology or other quantitative sensory testing, the large majority of subjects receiving taxane containing chemotherapy regimens demonstrated physiologic changes indicative of peripheral neuropathy [8]. In a small prospective trial in women receiving paclitaxel for breast cancer, neuropathy occurred after the first or second dose in 84% of patients and was progressive in 7% [20]. In total, 97% developed signs of peripheral neuropathy when evaluated with quantitative sensory testing. In another

study, all patients receiving paclitaxel in combination with cisplatin, developed significant changes on electrophysiology measures [21]. Furthermore, in another trial, 20 of 21 patients (95%) developed a sensory-motor neuropathy 1 to 21 weeks after the initiation of paclitaxel therapy and progressed with each additional course. The neuropathy was reported to be symmetrical, length dependent (neurons with longer axons were more likely to be affected) and was more evident in patients receiving higher doses of paclitaxel[22].

Recently, we have found that chemotherapy drugs directly activate peripheral sensory nociceptors in *Drosophila* and mice via the activation of Transient Receptor Potential Cation Channel Subfamily A Member 1 (TRPA1) resulting in a neuropathic pain syndrome similar to human patients. (Boiko, N., Medrano, G., Montano, E., Jiang, N., Williams, C. R., Madungwe, N. B., et al. (2017). TrpA1 activation in peripheral sensory neurons underlies the ionic basis of pain hypersensitivity in response to vinca alkaloids. *PLoS ONE*, *12*(10), e0186888. http://doi.org/10.1371/journal.pone.0186888.g007). Our working model based on our data and others is that the activation of TRPA1 during chemotherapy is a significant contributor to the neuropathic pain syndrome associated with CIPN. Further, prolonged hyperexcitation of the sensory neuron by activation of TRPA1 could lead to excitotoxicity and neuropathy during chemotherapy treatment programs.

TRPA1 is a well-studied and evolutionarily-conserved chemical nociceptor expressed throughout the body including sensory nociceptors[23] , Importantly, a gain-of-function mutation in hTRPA1 has been linked to Familial Episodic Pain Syndrome (FEPS), a human pain syndrome associated with enhanced sensitivity to punctate stimuli and mustard oil [25]. This mutation was shown to result in a 5-fold increase in the inward current in response to channel activation supporting that inappropriate activation of hTRPA1 channels in sensory neurons is sufficient to generate pain in humans [25]. Thus, the activation of hTRPA1 during chemotherapy may be responsible for the neuropathic pain experienced during chemotherapy treatment and represent an important pathogenic event during CIPN. In addition to TRPA1, related genes in the Transient Receptor Potential Cation Channel Subfamily V member 1 (TRPV1) and Transient Receptor Potential Cation Channel Subfamily M Member 8 (TRPM8) may also play a role in development of CIPN. Currently, multiple clinical trials are studying TRPA1 antagonists [24]. Showing the effect of activated TRPA1 in vivo and the subsequent development of CIPN, would provide support for targeting TRPA1 for the treatment and prevention of CIPN in patients receiving taxane based chemotherapy. In addition, it is predicted that baseline TRPA1 activity in patients could represent an important biomarker for the prognosis of CIPN,

Recently, a form of cryotherapy using an Elasto-Gel frozen (4ºC) glove or wrap has been shown to reduce nail toxicity and oncholysis [30]. Its role in preventing peripheral neuropathy has not been thoroughly studied but preliminary observations suggest a potential beneficial effect (31 - 32). Cryotherapy has been extensively studied and the proposed mechanism of action is that local vasoconstriction reduces blood flow to the extremity and consequently reduces the exposure to the taxane [30]. This therapy has been shown to be effective in reducing toxicities within the oral cavity [33] and the scalp [32]. In regards to the oncholysis, a study with patients treated with docetaxel served as their own controls with a glove placed on the right hand starting 15 minutes prior to treatment, and extending 15 minutes after the infusion ended. Nail changes where observed in 51% in the untreated hand versus 11% in the cold glove hand [35]. In the second trial, patients wore a frozen sock on their right foot using the same protocol. Grade 1 and 2 nail toxicity was 0% in the treated side and 21% in the untreated extremity [36]. The intervention was well tolerated with only one of fifty patients withdrawing due to cold intolerances. Therefore, extremity cooling therapy provides a potential opportunity to reduce both peripheral neuropathies and nail toxicities related to taxane based chemotherapy.

The importance of the study relies on the high incidence of debilitating symptoms as a result of breast cancer treatment, which has a high clinical and public health significance [37-39]. Additionally, after completing treatment only approximately 50-60% of the patients have improvement of the neuropathy; therefore, an important percentage of people remain affected by the symptoms. Furthermore there are no established agents that can be recommended for the prevention of CIPN in patients with cancer undergoing treatment with neurotoxic agents, and establishing a link between CIPN and activation of TRPA1, TRPV1 and TRPM8 genes allows for the exploration of prevention with TRPA1 agonists.

Statement of Study Objectives

Specific Aims

1. Evaluate the safety profile and efficacy of cryotherapy in the prevention of peripheral neuropathy during treatment with taxane chemotherapy.
2. Evaluate the safety profile and efficacy of cryotherapy in the prevention of nail toxicity during treatment with taxane chemotherapy.
3. Evaluate the role of TRPA1 in CIPN in patients receiving taxane-based chemotherapy

Primary Endpoints:

1. To determine rate and severity of chemotherapy induced neuropathy in extremities treated with cold gloves and wraps versus control extremities as measured by
    a. Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03
    b. Brief Pain Inventory (BPI)
    c. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy Induced Peripheral Neuropathy 20 (EORTC QLQ-CIPN20)
    d. the Neuropathic Pain Symptom Inventory (NPSI)
    e. To determine rate and severity of chemotherapy related oncholysis in extremities treated with cold gloves and wraps versus control extremities as measured using Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03

Secondary Endpoints:

1. Differences in amplitude and peak latency of Nerve Conduction Studies (NCS) at baseline, 3 weeks after completion of chemotherapy and 6 months follow up in treated and untreated extremities.
2. Correlating rates and severity of CIPN and oncholysis with the gene expression profiles of TRPA1, TRPV1 and TRPM8 genes. Genetic material for sequencing will be isolated from peripheral blood.
3. Correlating quantitative sensory testing of TrpA1 activation with rates and severity of CIPN.

Inclusion and Exclusion Criteria

Inclusion Criteria:

- Histologically confirmed diagnosis of early stage breast cancer (stage I-III).
- Planned to receive treatment with either adjuvant or neo-adjuvant taxane-based chemotherapy.
- Age $\geq$ 18 years. There is no upper age limit for participation in this study.
- Patients may have received any of the following therapies: surgery, chemotherapy, hormones, biologics, or radiation.
- Prior chemotherapies are permitted, except with prior treatments with taxanes, vinca alcaloids, gemcitabine, eribulin, ixabepilone, platinum drugs
- All patients will have given signed, informed consent prior to registration
- Patients must have a performance status of ECOG 0 or 1.

Exclusion Criteria

- Patients must not have received any prior taxane or platinum based chemotherapy.
- Patients must not have a history of peripheral neuropathy (regardless of cause).
- Patient must not have a history of Raynaud's disease.
- Patients with partial or complete limb amputations.
- Known hypersensitivity to cold
- Patient cannot be on the following medications: GABA analogues (such as Neurontin, Lyrica), tricyclic antidepressants (such as amitriptyline or nortriptyline)
- As judged by the investigator, severe uncontrolled concurrent medical conditions, psychiatric illness or social condition that would limit compliance with study requirements.
- Evidence of any significant clinical disorder or laboratory finding that makes it undesirable for the subject to participate in the clinical trial

- Must not be pregnant or breast feeding

Study Schedule

	Screening	C1D1	D1 each cycle	End of Tx (+/- 7 days)	6 month FU (+/- 7 days)
Eligibility Criteria[9]	X	X			
History & Physical [8,9]	X	X	X	X	X
Vital Signs, Height and Weight[9]		X	X	X	X
ECOG[8,9]	X	X	X	X	X
Informed Consent	X				
CBC, CMP Serum [8,9]	X		X	X	X
TSH, Folate, B12, HbA1c, purple top for next gen sequencing	X				
Pregnancy Test[2]	X				
Adverse Events[1,8] Sensory neuropathy, nail toxicity, photo of hands and feet		X	X	X	X
Concurrent medication review[8,9]	X	X	X	X	X
NCS[4]	X			X	X
Patient questionnaires BPI, EORTC-CIPN20, NPSI (verbal)		X	X	X	X
Elasto-Gel treatment			X[7]		
TrpA1 QST with mustard oil		X[5]			

1 - NCI-CTCAE v4.03 will be used to document adverse events.
2 - For women who are not post-menopausal for 1 year or more
3- Within 28 days of C1D1
4 – NCS Screening/Baseline NCS is the same NCS. End of Treatment NCS to be done 3 weeks post last day of last chemo cycle (+1 week window allowed and 6 months post last day of chemo),
5 – Sensory Testing on C1D1 to be done 15 minutes prior to cryotherapy on arm to be treated with cryotherapy and 15 minutes post infusion on opposite non-treated arm.
6 – Also, to be done at C5D1 and C6D1 if applicable depending on SOC treatment schedule per treating oncologists discretion.
7 - Will be worn each treatment day. Assessments done on Day 1 of each cycle. Elasto-Gel treatment worn on every day patient receives taxane infusion.
8 - ± 3 days between PE, ECOG, labs and taxane infusion
9 – Can occur up to and including C1D1

Master Table of Study Assessments							
	Baseline	C1D1	C2D1	C3D1	C4D1[6]	End of Tx (+/- 7 days) (i.e.3 weeks post Last Day of Last Chemo Cycle)	6 month FU (+/- 7 days) (i.e.6 months post Last Day of Last Chemo Cycle)
Surveys/Observational Data							
Patient Information Questionnaire Appendix 1	X						
CTCAE V4.03: Neuropathy Appendix 3		X	X	X	X	X	X
CTCAE V4.03: Nail Toxicity Appendix 3		X	X	X	X	X	X
Brief Pain Inventory (BPI) Appendix 4		X	X	X	X	X	X
EORTC Quality of Life – CIPN 20 Appendix 5		X	X	X	X	X	X
Neuropathic Pain Symptom Inventory (NPSI) Appendix 6		X	X	X	X	X	X
Quantitative Testing							
Quantitative Sensory Test (QST) Pre-chemo. Appendix 7	X						
Quantitative Sensory Test (QST) Post-chemo. Appendix 8						X	X
Nerve Conduction Study (NCS)[4]	X					X	X
Additional Assessments							
Blood Draw for Gene Expression Profiles	X						
Sensory Testing for TrpA1 Activation. Appendix 9		X[5]					

Study Design

Overview:
This is a therapeutic study investigating the use of cryotherapy in the prevention of taxane-induced peripheral neuropathy and associated nail toxicities. Study subjects will be recruited primarily at the Mays Cancer Center Breast Oncology Clinic. Patients who are to receive taxane based chemotherapy regimens as part of their breast cancer treatment will be offered participation in the trial. Informed consent will take place at the Mays Cancer Center. A member of the patient's medical team will introduce the coordinator, who will present the study and answer any questions or concerns of the patient. Once consented, the patient will complete the Patient Information Questionnaire and schedule a time for baseline data collection (Appendix 1). The questionnaire will cover: history of diabetes, peripheral vascular disease, Raynaud's, smoking, alcohol use, recent weight changes, current medications, as well as history of surgery to the extremities, pre-existing neurological conditions, and current activity level. Several of these demographic characteristics are suspected to be risk factors in the development of CIPN (e.g., diabetes, and alcoholism). Other risk factors have been implicated in the development of peripheral neuropathy not related to CIPN (e.g., statins, weight loss, pre-existing neurologic conditions).

Administration of therapy and assessments will take place in the Breast Oncology Clinic and Infusion Clinics at the Mays Cancer Center. A member of the research team will administer the neurological exams and questionnaires at each specified time point. The therapeutic intervention will involve patients wearing an Elasto-Gel cold glove and wrap on either their right or left side of their body, acting as their own controls. The treatment side will be determined by right or left side dominance and will be randomized based on dominance. Patients

will be given a randomization number once all screening procedures are performed. Patients with even study numbers will wear the gloves and wraps on their dominant hand and foot while patients with odd study numbers will wear the gloves on their non-dominant side. The patients will wear the glove and wrap during each taxane treatment session. Patients who do not start treatment will be given a screen fail number and not included in the randomization sequence.

This is an ideal study for a paired design, as patients will be their own control as only the right or the left sided extremities will have the cold glove and wrap applied. The value of a paired design is that it reduces undesirable variability because data from the same subject are much less variable than data from different subjects. It also insures exact matching of the treatment and non-treatment sides with respect to race, gender, age, and other potentially confounding variable. The cold therapy treatment side will be assigned, according to the patients assigned study number at the time of eligibility. The purpose of stratifying by dominance is to make sure that we don't end up with, for example, the treatment being more likely to be assigned to the non-dominant hand. Since the non-dominant hand gets less use and wear and tear than the dominant hand, it's possible that neuropathy would tend to be less severe or less noticed in the non-dominant hand.

The efficacy of cryotherapy will be assessed with evaluation of patient reported adverse events using version 4.03 of the CTCAE for neuropathy and nail toxicities, validated patient symptom surveys, focused neurological evaluations and NCS's. Completion of these questionnaires will not require extra time outside of the patients scheduled appointments. Prior to beginning the cold therapy and taxane based chemotherapy, baseline data will be collected. If the patient is receiving anthracycline treatment, then this data can be collected during their last anthracycline infusion. If the patient is not receiving chemotherapy prior to starting on a taxane, then the baseline data with be collected at the clinic visit prior to starting taxane chemotherapy. The Post-Chemotherapy assessment will occur approximately 3 weeks (± 1 week) after the patient's last chemotherapy treatment cycle end date. It may require a separate trip to clinic at a time that is convenient for them. At all-time points, a member of the research staff will meet with the patient to complete the questionnaires and quantitative sensory tests. The Study Schedule outlines all of the assessments and the timing of those assessments during the study period. All assessment tools can be found in referenced section in the appendices section.

Patient questionnaires will be completed prior to starting taxane based chemotherapy, every cycle of treatment, three weeks after last dose of taxane and 6 months after completion of taxane therapy.

Assessments will be administered by a member of the research team who has personal qualifications to perform neurological exams.

Nerve Conduction Studies (NCS) will be completed at the neurology clinic at the MARC within 28 days of starting taxane chemotherapy for baseline, 3 weeks after completion of taxane chemotherapy, and again 6 months after completion of taxane chemotherapy. NCS will be completed and interpreted by a neurologist. One additional tube of blood (5ml) will be collected prior to starting on treatment for next-gen sequencing for TRPA1, TRPV1, and TRPM8 expression. These expression profiles will be analyzed and correlated to patient symptom severity, sensory testing and NCS findings. Sensory testing for TrpA1 activation will also be completed prior to the first infusion of taxane chemotherapy. This pre-treatment assessment will be completed in the chemotherapy infusion clinic during the first chemotherapy session and involves the topical application of mustard oil to the patient's forearm that is receiving the cold glove therapy. It will then be applied to the forearm not receiving cold glove therapy after taxane is completed. The first application is prior to taxane infusion to the treatment side receiving cold therapy, and the second is at the conclusion of the taxane infusion to the control side not receiving cold therapy. The degree of patient report punctate hyperalgesia. will be recorded by the researcher after each application of the mustard oil. The full protocol is listed in appendix 9 and is estimated to take appropriately 40 minutes of active time. Patient will not have any additional time requirement as this test will be done while the patient is in the chemotherapy infusion clinic for their scheduled chemotherapy.

Recruitment:

This study seeks to enroll patients diagnosed with breast cancer, who will be receiving taxane-based chemotherapy. Patient accrual will occur by clinician referral. The primary source of accrual will be dependent on clinician referrals to the study-coordinator. The study will be presented monthly at the Women's Cancer Site Team meeting and potential study candidates will be identified and screened for eligibility during regular encounters for their breast cancer treatment.

Informed consent will take place in clinic. A member of the patient's medical team will introduce the coordinator, who will present the study and answer any questions or concerns of the patient.

Once consented, the patient will complete the Patient Questionnaire and schedule a time for baseline data collection (Appendix 1). The questionnaire will cover: history of diabetes, peripheral vascular disease, Raynaud's, smoking, alcohol use, recent weight changes, current medications, as well as history of surgery to the extremities, pre-existing neurological conditions, and current activity level. Several of these demographic characteristics are suspected to be risk factors in the development of paclitaxel-induced peripheral neuropathy (e.g., diabetes, and alcoholism). Other risk factors have been implicated in the development of peripheral neuropathy not related to paclitaxel (e.g., statins, weight loss, pre-existing neurologic conditions).

Dosage:
Since we are not administering a drug, the study team will be required to make no dose modifications. All the patients enrolled in this study are being administered a taxane based regimen as part of their specific chemotherapy regimen. Therefore, any dose changes in the patient's chemotherapy regimen will be executed by the cancer care team based on standard practices. All dose changes or delays in the subject's chemotherapy regimen will be recorded in the study log as such fluctuations will likely impact the subject's neuropathy. This study recognizes the necessity of dose-adjustments in cases of severe and debilitating peripheral neuropathy secondary to taxane therapy. The signs and symptoms observed and reports should be examined for correlations with the dose administered on a particular date. The total dose of the patient's taxane therapy will be collected and recorded in the Patient Data file (Appendix 2).

If the patient is able to wear the glove and wrap for at least half of the infusion time, they can continue on study with intervention time noted. Patients will be allowed to continue with the cold therapy at subsequent chemotherapy treatments. The length of time in which they are able to maintain the cold therapy will be recorded in the Patient data file (appendix 2).

Cold Therapy Treatment
Duration of treatment: Patients will receive the cold therapy during the taxane portion of chemotherapy. The glove and wrap will be worn at every infusion. The glove and wrap will be worn for the duration of treatment including an additional 15 minutes before (± 20 minutes to accommodate for infusion nurse staffing and after the taxane infusion. However if the patient is able to maintain the cold therapy for at least 15 min prior to infusion and 50% of the infusion time, they will be considered as having received the full treatment. If the patient is unable to maintain the cold therapy for 50% of the infusion time for 2 consecutive treatments, then the patient will be withdrawn from the study for cold intolerance. The duration of the cold therapy will be recorded in the patient data file (appendix 2). In the event of trauma, not related to the study, to one or both extremities of the treatment side, treatment will be performed as tolerated applying the same rules as stated above.

Administration: The side being treated will be determined by dominance, alternating between the non-dominant and dominant side. Patients will be randomized based on the assigned study number. Patients with even study numbers will wear the gloves and wraps on their dominant hand and foot while patients with odd study numbers will wear the gloves and wraps on their non-dominant side. As a sanitary measure, patients will wear a disposable glove and sock liner each time they wear the glove and wrap. The glove and wrap will be secured by a Velcro strap at the wrist and ankle per manufacture instructions. The glove and wrap need to be kept at an approximate temperature of 4ºC (a range of 3 ºC - 6 ºC is acceptable). The gloves and wraps will be stored in a designated freezer check at approximately 4ºC. The study member will verify freezer temperature prior to starting the cold treatments and record this on provided study forms. In order to maintain cold therapy, gloves and wraps will be

replaced every 30-40 minutes during treatment. A member of the research team will be present during treatment to switch the gloves and wraps as needed within the time window. This research team member can be a chemotherapy infusion nurse, medical assistant, or the study coordinator depending on staffing needs on particular days. Length of treatment will vary between eight weeks and twelve weeks depending on if patient is prescribed bi-weekly or weekly paclitaxel treatments.

- Every patient will wear an Elasto-Gel glove and wraps for the duration of each neurotoxic chemotherapy agent infused that they have scheduled as part of their treatment plan at the infusion clinic at the Mays Cancer Center. The Elasto-Gel glove and wrap are made of a glycerin-based gel that maintains its flexibility at a temperature of 4ºC. The cover material is a water resistant four-way stretchable fabric with straps at the wrist and ankle to assure good position.
- Storage and stability: The gloves and wraps will be kept in a freezer located on the chemotherapy infusion room at the Mays Cancer Center. Each glove and wrap will be kept in individual plastic bags with the time placed in the fridge.
- Preparation: Gloves and wraps must be refrigerated for at least three hours prior to use. Each glove or wrap will be tagged on the plastic bag with the time and date recorded when it is placed in the refrigerator. The refrigerate temperature will be logged prior to removal of glove or wrap.
- Protocol: Patients will wear the glove and wrap on either the dominant hand or foot OR non-dominant hand and foot for the duration of each of their chemotherapy treatment (infusion). The gloves and wraps will be worn 15 minutes (± 20 minutes) prior to the start of the taxane infusion and 15 minutes after the completion this infusion. New cold gloves and wraps will be switched every 30-40 minutes until the end of each individual infusion in order to maintain the extremity cold with an ideal temperature of approximately 4ºC.
- Patients unable to wear the glove and/or wrap for 15 minutes prior to the start of taxane infusion and at least 50% of infusion time for 2 consecutive treatments will be considered “not tolerant of cold therapy” and cold therapy will not be continued with subsequent infusions on study. However, if able to wear the glove and wrap for 15 minutes prior to the start of taxane chemotherapy and at least 50% of the infusion time, patients will be allowed to continue the cold therapy at their next chemotherapy treatment.
- Use of the Elasto-Gel glove and wrap will be provided free of charge to patients.

Assessments [Neurological Exams and Questionnaires]

Patient Questionnaires

At each of the six time points the Brief Pain Inventory (BPI) (Appendix 4), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy Induced Peripheral Neuropathy 20 (EORTC QLQ-CIPN20) (Appendix 5), Neuropathic Pain Symptom Inventory (NPSI) (Appendix 6), will be administered. All questionnaires have been reproduced with permission from their authors.

To complement the patient-reported contributions to symptom evaluation, the researcher will complete the National Cancer Institute Common Toxicity Criteria version 4.03 (NCI-CTC v 4.03) neuropathy sub-scales (peripheral sensory neuropathy) and nail toxicities for both the treated and not treated hands and feet (Appendix 3). A picture will also be taken of both hands and feet pre-, and post-taxane treatments to access the changes that may occur as well as help evaluate the glove and wrap efficacy of preventing nail toxicities.

Quantitative Sensory Tests

The focused neurological examination will quantitatively measure the subject’s sensitivity to noxious semi-sharp pin-prick stimuli, fine motor skills/manual dexterity, as well as vibration detection threshold. These measures are currently used in a study looking into the prevalence of paclitaxel-induced peripheral neuropathy.

Although no gold standard for QST assessment has been developed and accepted, an examination of the current literature reveals that when CIPN patients complete anatomical pain diagrams to visually characterize the location and intensity of their symptoms, the result is frequently a “stocking and glove” distribution[5]. The symptoms of this neuropathy are usually symmetrically manifested with no significant right-to-left difference [6,13].

There are currently a few protocols available which can assess CIPN in a clinical setting [5,7,11,12]. Rolke et al, has written a Quantitative Sensory Tests protocol that details non-invasive tests to determine the presence of neuropathy. The protocol is well-accepted and has been validated in numerous CIPN studies. It also serves as a guide in a current study looking into the prevalence of PIPN.

To monitor the efficacy of the cold therapy, the following QST described below (with the exception of the fine motor tests) which will be administered on the right and left sides as well as both hands and feet.

Monofilaments for Touch Stimulus

To determine the subject's sensitivity innocuous mechanical touch stimulation, we will use a set of Semmes-Weinstein Monofilaments called The Touch-Test™ Sensory Evaluators (.008 g - 300 g) produced by North Coast Medical, Inc. The monofilaments will be used to apply the stimulus via the "method of limits" on the patient's right and left upper and lower extremity: the glabrous tip of the right and left index finger and at the tip of the hallux of the foot on both sides.

To begin, we will ask the patient to place her right or left forearm on a stable surface with her palm up and face away with her eyes closed. The patient will be told to vocally say "Yes" to when she feels the stimulus. Nonverbal patients may tap the table lightly with the opposite hand (not being tested) when the stimulus is felt. The lightest monofilament in the set (.008 g) will be touched to the skin of the fingertip and depressed until it bows. Using a stopwatch for accuracy, the researcher holds the filament in this position for 2 seconds and then smoothly raises it. If the subject does not indicate that she felt a stimulus, then the researcher uses the next-lightest monofilament in the set (.02 g) and applies the stimulus in the same manner (gently depress until it bows), for the same amount of time (2 seconds) to a slightly different site on the fingertip. If the patient indicates that she felt the stimulus, then the researcher returns to the previous monofilament (.008 g). If the patient does not indicate that the stimulus was felt, then the researcher again moves to the next monofilament in the set (.04 g). This pattern is repeated until a total of five (5) stimuli have been applied. These data are recorded on the Monofilament Data Sheet, part of the Quantitative Sensory Test Data (Appendix 7) and then entered into a spreadsheet, which will determine the patient's final threshold (the geometric mean of the five-recorded weights) and generate a graphical representation of this datum to be used later in analysis. If paclitaxel-induced peripheral neuropathy causes an increase in sensitivity, then a significant disparity will appear between the "before paclitaxel" threshold and the "after paclitaxel" threshold.

25 –hole Pegboard test for Manual Dexterity

To assess the subject's manual dexterity, we will administer a 25-hole pegboard test manufactured by Lafayette Instrument Company. At each time point, the researcher will give the patient a practice test. The patient will be asked to use her dominant hand to pick up the pegs one at a time from the container and place them in the holes until all 25 holes are filled. This time will be recorded in 25-Hole Peg Test Data Sheet.

Rydel-Seiffer tuning fork for Vibratory Detection Threshold

The final sensory test will assess the patient's ability to detect vibration. We will use the Rydel-Seiffer tuning fork produced by US Neurologicals. The tuning fork will be used on the following four regions of the patient's right and left upper extremity and the right and left lower extremity: dorsum of index finger DIP joint, dorsum of IP of hallux (great toe) on both sides.

The researcher will place the base of the tuning fork, with the dampers facing the researcher, on the bony prominences listed above. To create a vibration, the tynes are pressed together between the thumb and index finger then rapidly released. As the prongs start to oscillate, the illusion of two triangles is visible on each damper. These are black and white triangles on the dampers that are each marked with a scale from 0 to 8. As the intensity of the vibration starts to diminish the two triangles move closer together again and their point of intersection moves slowly upward. The intensity at which the patient no longer detects the vibration is read as the number adjacent the intersection of the vibrating triangles. This number can be read off the white or black triangle depending on the amount of light available or which scale is more easily readable. According to

manufacturer instructions, the black triangle intersection from the base up and the white triangle intersection from the apex down seem to produce the most accurate readings between triangles for any particular moment in time.

The patient will be told to vocally say “Yes” immediately once the vibration is no longer detected. (Reading the tuning fork assessment)This procedure will then be repeated four more times per region (fingertip and toe), with the first reading being discarded and the last three being recorded on the Vibration Test data section of the Quantitative Sensory Tests Data sheet.

RESPONSE ASSESSMENT

The primary objective of this study is to reduce or prevent paclitaxel-induced peripheral neuropathy. The primary focuses of concerns being the pain and oncholysis that often occur during the paclitaxel portion of the patient’s chemotherapy regimen. Therefore, the response assessment will involve a comparison of the patient’s treated hand and foot with the non-treated hand and foot. Allowing the patients to act as their own controls will reduce variability, ensuring the matching of the treated and non-treated sides with respect to demographic differences and potentially confounding variables.

Data Management/Interpretation of Results

Redcap and Velos will be used for data management and statistical analysis. All data will be coded and entered into a database by a research assistant and checked for errors by the principal investigator. Manipulation, analysis, and reporting of the data will be performed in an aggregate fashion and in no way will identify individual subjects. Data will be maintained by study personnel in a secure location, within a locked office and a password protected computer. Both databases are supported by UT Health Cancer Center and are password secured.

Because the data will have statistically non-normal distributions, nonparametric statistical methods will be used to analyze the data. The analyses will be done separately for each time point. A 0.05 significance level will be used for all statistical two-sided tests

Null and Alternative Hypotheses

The test for the primary efficacy will be performed with respect to cryotherapy versus control. The untreated hand or feet will act as control for each patient. The difference between cryotherapy and control in NCI-CTC at 8 or 12 weeks will be used for analysis for the primary endpoint.

The null hypothesis tested for the primary efficacy analysis is that the difference between cryotherapy and control in NCI-CTC score at 8 or 12 weeks equals zero. The alternative hypothesis is that the difference in NCI-CTC score does not equal zero. To test the null hypothesis, one-sample paired t-tests will be used for continuously distributed outcomes and McNemar tests will be used for binary outcomes.

Randomization for the Cold Gloves

Determining right or left side dominance is important prior to the study in order to establish randomization. The purpose of stratifying by dominance is to avoid biasing the intervention to the dominant hand. Since the non-dominant hand utilized less for activity, it’s possible that neuropathy could be perceived as less severe in the non-dominant hand. Patients with even study numbers will wear the gloves and wraps on their dominant hand and foot while patients with odd study numbers will wear the gloves and wraps on their non-dominant side.

Sample Size Calculation

With regard to the occurrence of adverse events as assessed by the NCI-CTC method and dichotomizing this outcome to none or at least one, a sample size of 63 pairs achieves 80% power to detect an odds ratio of 2.9 using a two-sided McNemar test with a significance level of 0.05. The odds ratio is equivalent to a difference between two paired proportions of 0.27 which occurs when the proportion in one off diagonal cell is 0.41 and the proportion in the other off diagonal is 0.14 and the proportion of discordant pairs is 0.55. Due to possibility of drop out, the target accrual is 65 patients.

Statistical Methods
The significance of within-subject changes in the BPI and EORTC and NPSI scores will be assessed with paired-tests. Other continuously distributed secondary outcomes will be assessed similarly. The significance of within-subject changes in binary outcomes will be assessed with McNemar tests. All statistical testing will be two-sided with a significance level of 5%. SAS Version 9.4 or R will be used throughout.

8.3 Infection Control Intervention:
The same set of gloves and wraps will be used for multiple patients. Thus, preventive measures will be made in order to decrease the chances of infection spread between patients. After each use, the gloves and wraps will be wiped down with an antibacterial and antiseptic wipe, and patients will wear a disposable standard medical glove and a disposable shoe liner during each infusion.

8.4 Dosage of Anti-Cancer Therapy
Since we are not administering a drug, the study team will be required to make no dose modifications. All the patients enrolled in this study are being administered anti-drug therapy that is well known to cause CIPN like taxanes. Therefore, any dose changes in the patient's chemotherapy regimen will be made by the adult medical oncology team and not by the clinical trial team. All dose changes or delays in the subject's chemotherapy regimen will be recorded in the study log as these fluctuations will likely impact the subject's risk of developing neuropathy. The total dose of the anti-cancer drug will be recorded in the Patient Data File (Appendix 2).

This study recognizes the necessity of dose-adjustments in cases of severe and debilitating peripheral neuropathy secondary to anti-cancer therapy. The signs and symptoms observed should be examined for correlations with the dose administered on a particular date. Any dose reductions due to the occurrence of any toxicity from anti-cancer therapy will also be recorded in the same data file.

8.5 Discontinuation of Cold Gloves Therapy
- Patients will discontinue the cold glove and wrap therapy if they are not able to complete at least 50% of the infusion time for 2 consecutive treatments.
- Development of grade 2 nail toxicities or neuropathy on the treated extremity that is not also present on the non-treatment extremity.
- Discontinuation of taxane based chemotherapy regimen
- Patients may withdraw consent at any time.

8.6 Next-gen sequencing for Correlative Studies: Correlative studies will be conducted as secondary outcome measure to provide information on toxicity prediction. One purple top tube of peripheral blood (approximately 5 cc) will be collected at baseline and sent for next-gen sequencing assays for TRPA1, TRPV1 and TRPM8 which will take place at the lab of Dr Benjamin Eaton at UT Health San Antonio. This single tube will be placed on ice, marked with study ID number and delivered to Dr. Eaton's lab for processing.

Data and Safety Monitoring
A Data and Safety Monitoring Plan (DSMP) is required for all an individual protocols conducted at The Mays Cancer Center. All protocols conducted at the Mays Cancer Center are covered under the auspices of the Mays Cancer Center Institutional Data Safety Monitoring Plan.

The Mays Cancer Center Institutional DSMP global policies provide individual trials with:
- institutional policies and procedures for institutional data safety and monitoring,
- an institutional guide to follow,
- monitoring of protocol accrual by the Mays Cancer Center Protocol Review Committee,
- review of study forms and orders by the Forms Committee,
- tools for monitoring safety events,
- monitoring of UPIRSO's by the Director of Quality Assurance and DSMC,
- determining level of risk (Priority of Audit Level Score – PALS),
- oversight by the Data Safety Monitoring Committee (DSMC), and

- verification of protocol adherence via annual audit for all Investigator Initiated Studies by the Mays Cancer Center Quality Assurance Division.

Monitoring Safety:
Due to the low risk associated with participation in this protocol, the Principal Investigator will perform primary assessment of adverse events, adverse event trends and treatment effects on this study. The PI will conduct independent semi-annual review and report findings to the Mays Cancer Center Data Safety Monitoring Board (DSMB) and the UT Health San Antonio IRB.

Baseline events and adverse events will be captured using the Mays Cancer Center Master Adverse Events Document for each patient using CTCAE V 4.03 for the grading and attribution of adverse events. Usage of the Mays Cancer Center Master Adverse Events Document centrally documents:

- the event and grades the seriousness of it,
- if the event was a change from baseline,
- determines the relationship between the event and study intervention,
- if the event was part of the normal disease process, and
- what actions were taken as a result of the event.

Safety Definitions:
For this study, the following safety definitions will be applicable:

Adverse Event Definition: An adverse event (AE) is defined as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research For this study, all adverse events will be documented starting with the first use of the cold therapy device and ending 30 days after the last dose use of the cold therapy device, regardless of the length of time the device was used.

Serious Adverse Event Definition: is any adverse event that:

1. results in death;
2. is life-threatening (places the subject at immediate risk of death from the event as it occurred);
3. results in inpatient hospitalization or prolongation of existing hospitalization;
4. results in a persistent or significant disability/incapacity;
5. results in a congenital anomaly/birth defect; or
6. based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition

Unanticipated Problems Involving Risks to Subjects or Others Definition: Unanticipated problem involving risk to subjects or others includes any incident, experience or outcome that meets all of the following criteria:

A. unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied (note: the unfounded classification of a serious adverse event as "anticipated" constitutes serious non-compliance);
B. definitely related or probably related to participation in the research; and
C. suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

Reporting Requirements
For this study, all Master Adverse Events Documents collected on patients for this protocol will be reviewed by the Principal Investigator on a monthly basis to determine if a serious safety problem has emerged that result in a change or early termination of a protocol such as:

- suspending enrollment due to safety or efficacy, or

- termination of the study due to a significant change in risks or benefits.

Endpoints for termination of the study are: frostbites. If there are more than 5% of patients with frostbites then the study will be terminated

As per the Mays Cancer Center DSMP, any protocol modifications, problematic safety reports, unanticipated problems, and suspension or early termination of a trial must be reported to all members of the research team. Suspension and early termination of a trial must also be reported immediately to the Director of Quality Assurance (DQA) who will promptly notify the sponsor and the UT Health San Antonio IRB.

The PI will review the Master Adverse Events document to determine the significance of the reported events and will file the Investigator Initiated Study Quarterly DSM Report Form on a semi-annual basis with the Mays Cancer Center DSMC. The Investigator Initiated Study Quarterly DSMB Report Form includes information on adverse events, current dose levels, number of patients enrolled, significant toxicities per the protocol, patient status (morbidity and mortality), dose adjustments with observed response, and any interim findings. Any trend consisting of three or more of the same event will be reported to the Mays Cancer Center DSMB for independent review outside of the quarterly reporting cycle, which begins three months following protocol start up. Conflict of interest is avoided by the independent review of the Mays Cancer Center DSMC and by ongoing independent review of adverse events trends by the Director of Quality Assurance.

All SAE and UPRISO's will be reported following the Mays Cancer Center and UT Health San Antonio institutional guidelines.

UTHSCSA SAE/UPRISO REPORTING REQUIREMENTS		
Type Event	Report to	Timeframe
All AE, SAE and UPIRSO	Regulatory Affairs and DQA	Same as other notification timeframes except for SAE/AE which should be reported on Monday for the prior week
SAE	Clinical Trial Sponsor	within 24 hours
AE/SAE	UT Health San Antonio IRB	Annually
UPIRSO - all	Clinical Trial Sponsor	within 24 hours of the PI determining a UPIRSO exists
UPIRSO - life threatening	UT Health San Antonio IRB	within 48 hours of the PI determining a UPIRSO exists
UPIRSO - non-life threatening	UT Health San Antonio IRB	within 7 days of the PI determining a UPIRSO exists

Sponsor-Investigators are responsible for investigating all safety concerns and reporting to both the FDA and the IRB as needed.

An unanticipated adverse device effect is "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3(s)).

Any unanticipated adverse device events must be reported to FDA and the reviewing IRB as well as all participating investigators within 10 working days after the Sponsor-Investigator is aware of the occurrence. The FDA and IRB may request additional reports. Such reports should be clearly labeled "IDE Safety Report

AE's and SAE events that occur in subjects enrolled in this clinical trial should be reported under the IDE program (21 CFR 812.150) using FDA's MedWatch Form 3500.

Assuring Compliance with Protocol and Data Accuracy

As with all studies conducted at the Mays Cancer Center, the PI has ultimate responsibility for ensuring protocol compliance, data accuracy/integrity and responding to recommendations that emanate from monitoring activities. Source verification of data will be performed every 12 weeks Protocol compliance, data accuracy and reporting of events is further ensured by an annual audit conducted by the Data Safety Officer, whose audit report is shared with the PI, the research team, and will be reviewed by the Mays Cancer Center DSMC.

10.0 References/Bibliography

1. "Early-Stage and Locally Advanced Breast Cancer | The MD Anderson Manual of Medical Oncology, 3e | AccessMedicine | McGraw-Hill Medical". Retrieved on July 31, 2016.
2. "Breast Cancer | Harrison's Principles of Internal Medicine, 19e | AccessMedicine | McGraw-Hill Medical". Retrieved on July 31, 2016.
3. "NCCN Guidelines Version 2.2016 Invasive Breast Cancer". Retrieved on July 31, 2016. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
4. Henderson, I. C. "Improved Outcomes From Adding Sequential Paclitaxel but Not From Escalating Doxorubicin Dose in an Adjuvant Chemotherapy Regimen for Patients With Node-Positive Primary Breast Cancer". *Journal of Clinical Oncology* 21, num. 6 (15 of March 2003): 976–83. doi:10.1200/JCO.2003.02.063.
5. "Taxol (Paclitaxel) injection label- FDA: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020262s049lbl.pdf. Accessed 3/15/17
6. "Docetaxel: Highlights of Prescribing Information". http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020449s059lbl.pdf Accessed 3/15/17
7. Goodman, Louis S., Alfred Gilman, Laurence L. Brunton, John S. Lazo, y Keith L. Parker, eds. *Goodman & Gilman's the pharmacological basis of therapeutics*. 11th ed. New York: McGraw-Hill, 2006.
8. Grisold, Wolfgang, Guido Cavaletti, y Anthony J Windebank. "Peripheral neuropathies from chemotherapeutics and targeted agents: diagnosis, treatment, and prevention". *Neuro-Oncology* 14 Suppl 4 (September 2012): iv45-iv54. doi:10.1093/neuonc/nos203.
9. Iuliis, Francesca De, Gerardo Salerno, Ludovica Taglieri, y Susanna Scarpa. "Are Pharmacogenomic Biomarkers an Effective Tool to Predict Taxane Toxicity and Outcome in Breast Cancer Patients? Literature Review". *Cancer Chemotherapy and Pharmacology* 76, num. 4 (22 of July 2015): 679–90. doi:10.1007/s00280-015-2818-4.
10. "Rehabilitation in Women with Breast Cancer". Retrieved on August 1, 2016. https://www-clinicalkey-com.bdigital.ces.edu.co:2443/service/content/pdf/watermarked/1-s2.0-S1047965107000460.pdf?locale=en_US.
11. Kolb NA, Smith A, Singleton J, y et al. "The association of chemotherapy-induced peripheral neuropathy symptoms and the risk of falling". *JAMA Neurology* 73, núm. 7 (1 of July 2016): 860–66. doi:10.1001/jamaneurol.2016.0383.
12. Greenlee, Heather, Katherine D. Crew, Jillian Capodice, Danielle Awad, Donna Buono, Zaixing Shi, Anne Jeffres, et al. "Randomized Sham-Controlled Pilot Trial of Weekly Electro-Acupuncture for the Prevention of Taxane-Induced Peripheral Neuropathy in Women with Early Stage Breast Cancer". *Breast Cancer Research and Treatment* 156, num. 3 (25 of March 2016): 453–64. doi:10.1007/s10549-016-3759-2.
13. Stillman, Mark, y Juan P. Cata. "Management of Chemotherapy-Induced Peripheral Neuropathy". *Current Pain and Headache Reports* 10, num. 4 (August 2006): 279–87. doi:10.1007/s11916-006-0033-z.
14. Malik, Bushra, y Mark Stillman. "Chemotherapy-Induced Peripheral Neuropathy". *Current Neurology and Neuroscience Reports* 8, núm. 1 (enero de 2008): 56–65. doi:10.1007/s11910-008-0010-5.
15. Brewer, Jamie R., Gladys Morrison, M. Eileen Dolan, y Gini F. Fleming. "Chemotherapy-Induced Peripheral Neuropathy: Current Status and Progress". *Gynecologic Oncology* 140, núm. 1 (enero de 2016): 176–83. doi:10.1016/j.ygyno.2015.11.011.
16. Hershman, D. L., C. Lacchetti, R. H. Dworkin, E. M. Lavoie Smith, J. Bleeker, G. Cavaletti, C. Chauhan, et al. "Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy in Survivors of

Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline". *Journal of Clinical Oncology* 32, num. 18 (20 of June 2014): 1941–67. doi:10.1200/JCO.2013.54.0914.
17. Argyriou, A.A. et al., 2012. Chemotherapy-induced peripheral neurotoxicity (CIPN): An update. *Critical Reviews in Oncology / Hematology*, 82(1), pp.51–77.
18. Miltenburg, N.C. & Boogerd, W., 2014. Cancer Treatment Reviews. *Cancer Treatment Reviews*, 40(7), pp.872–882.
19. Seretny, M. et al., 2014. Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: A systematic review and meta-analysis. *Pain*, 155(12), pp.2461–2470.
20. Forsyth, P. A., C. Balmaceda, K. Peterson, A. D. Seidman, P. Brasher, y L. M. DeAngelis. "Prospective Study of Paclitaxel-Induced Peripheral Neuropathy with Quantitative Sensory Testing". *Journal of Neuro-Oncology* 35, num. 1 (October 1997): 47–53.
21. Boehmerle, Wolfgang, Petra Huehnchen, Sarah Peruzzaro, Mustafa Balkaya, and Matthias Endres. "Electrophysiological, behavioral and histological characterization of paclitaxel, cisplatin, vincristine and bortezomib-induced neuropathy in C57Bl/6 mice". *Scientific Reports* 4 (18 September 2014): 6370. doi:10.1038/srep06370.
22. Chaudhry, Vinay, Eric K. Rowinsky, Susan E. Sartorius, Ross C. Donehower, and David R. Cornblath. "Peripheral Neuropathy from Taxol and Cisplatin Combination Chemotherapy: Clinical and Electrophysiological Studies". *Annals of Neurology* 35, núm. 3 (March 1994): 304–11. doi:10.1002/ana.410350310.
23. Kang, K. et al., 2010. Analysis of Drosophila TRPA1 reveals an ancient origin for human chemical nociception. *Nature*, 464(7288), pp.597–600.
24. Kaneko, Y. & Szallasi, A., 2014. Transient receptor potential (TRP) channels: a clinical perspective. *British Journal of Pharmacology*, 171(10), pp.2474–2507.
25. Kremeyer, B. et al., 2016. Clinical Study. pp.1–10.
26. Nassini, R. et al., 2011. Oxaliplatin elicits mechanical and cold allodynia in rodents via TRPA1 receptor stimulation. *Pain*, 152(7), pp.1621–1631.
27. Julius, D., 2013. TRP Channels and Pain. *Annual review of cell and developmental biology*, 29(1), pp.355–384.
28. Li, Y. et al., 2015. The Cancer Chemotherapeutic Paclitaxel Increases Human and Rodent Sensory Neuron Responses to TRPV1 by Activation of TLR4. *Journal of Neuroscience*, 35(39), pp.13487–13500.
29. re, D.A.B. et al., 2012. Paclitaxel therapy potentiates cold hyperalgesia in streptozotocin-induced diabetic rats through enhanced mitochondrial reactive oxygen species production and TRPA1 sensitization. *Pain*, 153(3), pp.553–561.
30. McCarthy, Alexandra L., Ramon Z. Shaban, Kerri Gillespie, y Joanne Vick. "Cryotherapy for Docetaxel-Induced Hand and Nail Toxicity: Randomised Control Trial". *Supportive Care in Cancer* 22, num. 5 (May 2014): 1375–83. doi:10.1007/s00520-013-2095-x.
31. Scotte F, Tourani JM, Banu E, Peyromaure M, Levy E, Marsan S et al. (2005) Multicenter study of a frozen glove to prevent docetaxel-induced onycholysis and cutaneous toxicity of the hand. J Clin Oncol 23:4424–4429
32. Can G, Aydiner A, Cavdar I (2012) Taxane-induced nail changes: predictors and efficacy of the use of frozen gloves and socks in the prevention of nail toxicity. Euro J Oncol Nurs 16:270–275
33. Mahood DJ, Dose AM, Loprinzi CL, Veeder MH, Athmann LM, Therneau TM, Sorensen JM, Gainey DK, Mailliard JA, Gusa NL et al (1991) Inhibition of fluorouracil-induced stomatitis by oral cryotherapy. J Clin Oncol 9(3):449–452
34. Katsimbri P, Bamias A, Pavlidis N (2000) Prevention of chemotherapy-induced alopecia using an effective scalp cooling system. Eur J Cancer 36(6):766–771
35. Scotte, F. "Multicenter Study of a Frozen Glove to Prevent Docetaxel-Induced Onycholysis and Cutaneous Toxicity of the Hand". *Journal of Clinical Oncology* 23, num. 19 (1 of July 2005): 4424–29. doi:10.1200/JCO.2005.15.651.
36. Scotté, Florian, Eugeniu Banu, Jacques Medioni, Eric Levy, Christelle Ebenezer, Sandrine Marsan, Adela Banu, Jean Marc Tourani, Jean-Marie Andrieu, y Stéphane Oudard. "Matched Case-Control Phase 2 Study to Evaluate the Use of a Frozen Sock to Prevent Docetaxel-Induced Onycholysis and

Cutaneous Toxicity of the Foot". *Cancer* 112, num. 7 (1 of April 2008): 1625–31. doi:10.1002/cncr.23333.

37. Reyes-Gibby, Cielito, Phuong Khanh Morrow, Michael I. Bennett, Mark P. Jensen, y Sanjay Shete. "Neuropathic Pain in Breast Cancer Survivors: Using the ID Pain as a Screening Tool". *Journal of Pain and Symptom Management* 39, núm. 5 (mayo de 2010): 882–89. doi:10.1016/j.jpainsymman.2009.09.020.
38. Loprinzi, C. L., B. N. Reeves, S. R. Dakhil, J. A. Sloan, S. L. Wolf, K. N. Burger, A. Kamal, et al. "Natural History of Paclitaxel-Associated Acute Pain Syndrome: Prospective Cohort Study NCCTG N08C1". *Journal of Clinical Oncology* 29, núm. 11 (10 of April 2011): 1472–78. doi:10.1200/JCO.2010.33.0308.
39. Wood, Alastair J.J., Charles L. Shapiro, y Abram Recht. "Side Effects of Adjuvant Treatment of Breast Cancer". *New England Journal of Medicine* 344, núm. 26 (28 of Junio 2001): 1997–2008. doi:10.1056/NEJM200106283442607.

Appendices

1. Patient Information Questionnaire
2. Patient Data File
3. NCI-CTCAE Assessment for peripheral neuropathy and nail changes
4. Brief Pain Index
5. EORTC-CIPN 20
6. NPSI Hand survey
7. Quantitative Sensory Tests BASELINE
8. Quantitative Sensory Tests POST CHEMO
9. Quantitative Sensory Testing for TrpA1 Activation Protocol
10. Cold Glove and Cold Wrap Patient Dosing Record

Appendix 1:
Patient ID: _____
Date: _____
Date of consent: _____

Patient Information Questionnaire

Thank you for participating in this study. This brief questionnaire will ask about your past health history. If any of the questions are unclear of you feel uncomfortable answering, please let me know. All answers will remain confidential and only be seen by those involved in this study.

1.) **Date of Birth** (mm/dd/yyyy) ____/_____/_____

2.) **Race:**

- ❑ American Indian or Alaska Native
- ❑ Asian
- ❑ Black or African American
- ❑ Native Hawaiian or Other Pacific Islander
- ❑ White (non-Hispanic)
- ❑ White (Hispanic)
- ❑ Other (please specify:) _____

3.) **Do you have a history of any of the following?** (Please check all that apply)

- Diabetes ❑Year of diagnosis: _____
- Peripheral Vascular Disease (numbness and tingling in your feet or hands) ❑Year of diagnosis: _____
- Raynaud's (Pain and color changes in hands and toes when exposed to cold) ❑Year of diagnosis: _____

4.) **Your particular chemotherapy regimen is often given to patients before or after surgery (i.e: lumpectomy, mastectomy or axial node dissection). Which applies to you?**

- ❑ I am receiving chemotherapy **after** surgery.
- ❑ I am receiving chemotherapy **before** surgery.

5.) **How many alcoholic beverages do you consume per week (average): _____**
For how many years have you been drinking? _____

6.) **Do you smoke?** ❑Yes ❑ No, I use to smoke ❑No, never smoked

If Yes, how many ***packs*** of cigarettes do you smoke each day: _____
If you smoked in the past, Year Quit: _____

For how many years have/did you smoked? _____ (Pack years:_____)

7.) **In the last six (6) months, approximately how much weight have you gained/lost:**
(Please check one)

- ❑Gained: _____lbs
- ❑Lost: _____lbs
- ❑Virtually no change

8.) **Are you on a cholesterol-lowering statin drug**?

- ❑ I am not taking any statins

If Yes, please select which one(s) below:
(If you have been on more than one, check each statin that applies and please write down how long you were taking that particular statin)

- ❑ Zocor (simvastatin) _____ year(s)
- ❑ Lipitor (atorvastatin) _____ year(s)
- ❑ Lescol (fluvastatin) _____ year(s)
- ❑ Mevacor (lovastatin) _____ year(s)
- ❑ Pravachol (pravastatin) _____ year(s)
- ❑ Crestor (rosuvastatin) _____ year(s)

9.) **Past Surgical History**

❑ I have not had any surgeries

Surgery:	*Date of Surgery:*
Carpal tunnel surgery	
Trauma surgery on **arms**	
Trauma surgery on **legs**	
Hip or **knee** replacement surgery	
Arthroscopic surgery on **legs**	

Surgery:	*Date of Surgery:*	*Description:*

Other surgery on **Arm(s) or Hand(s)**		
Other surgery on **Leg(s) or Feet**		

10.) **What is your current physical activity level?**

❑Sedentary ❑Low ❑Moderate ❑Heavy

What is your level of activity?

❑Able to walk / run a mile in 15 minutes
❑Able to walk 2 blocks without stopping
❑Able to walk up a flight of stairs
❑Able to complete normal activities of daily living
❑ Unable to do any of the above activities

11.) **Do you have any skin problems?**
❑No
❑Active Shingles
❑Eczema
❑Open Wound
❑Ulcers
❑New Rash
❑Other_____

Appendix 2:

PATIENT DATA FILE

ID: _____

Date of consent: _____

CONTROL HAND/FEET: RIGHT or LEFT
TREATED HAND/FEET: RIGHT or LEFT

Lab Values:

Chem Panel	
Date:	
Sodium	
Potassium	
Chloride	
Glucose	
BUN	
Creatinine	
Calcium	

CBC	
Date:	
White Cell	
Red Cell	
Hgb	
HCT	
MCV	
MCH	
MCHC	
RDW	
Plt	

Misc. Lab Values:

TSH: _____ Date drawn: _____
Folate: _____ Date drawn: _____
HgA1c: _____ Date drawn: _____
B12: _____ Date drawn: _____

Current Weight: _____ lbs Date: _____

Total Taxol Dose: _____mg/m^2

Paclitaxel dose:

	Paclitaxel 1	Paclitaxel 2	Paclitaxel 3	Paclitaxel 4
Date:				
Dose:				

	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Date:												
Dose:												

Appendix 3

NCI –CTCAE v 4.03

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Peripheral (Sensory Neuropathy)	Asymtomatic; loss of deep tendon reflexes of paresthesia	moderate symptoms; limiting instrumental ADL	severe symptoms limiting self-care ADL	Life-threatening consequences; urgent intervention indicated

Activities of daily living: These are activities that are essential to self care: maintaining your own health and hygiene, such as showering, eating, brushing teeth and dressing.

Function: These are activities that connect you to the outside world, such as professional work, housework and running errands.

Grade 0: Denies any pain.
Grade 1: States pain 1 – 3, pain doesn't interfere with function.
Grade 2: States pain 4 – 6, pain interferes in function but not in activities of daily living (ADL).
Grade 3: States pain 7 – 10, pain interferes with ADL.
Grade 4: Disabling.

NCI-CTC Data Collection Sheet-Overall

	Date:	*Grade:*	*Description (if applicable)*
Baseline			
Tx1			
Tx2			
Tx3			
Tx4			
Tx5			
Tx6			
Tx7			
Tx8			
Tx9			
Tx10			
Tx11			
Tx12			
3 weeks post chemo			
6 months post chemo			

ID: _____

NCI-CTCAE V.4.03 **Nail Toxicity Criteria**

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Nail discoloration	Asymptomatic; clinical or diagnostic oberservations only; intervention no indicated	-	-	-

Definition: A disorder characterized by loss of all or a portion of the nail

Feet:

	Date:	*RIGHT Grade:*	*LEFT Grade:*	*Description (if applicable)*
pre				
Tx1				
Tx2				
Tx3				
Tx4				
Tx5				
Tx6				
Tx7				
Tx8				
Tx9				
Tx10				
Tx11				
Tx12				
3 weeks post				
6 months post				

ID: _____

NCI-CTCAE V.4.03 **Nail Toxicity Criteria**

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Nail discoloration	Asymptomatic; clinical or diagnostic oberservations only; intervention no indicated	-	-	-

Definition: A disorder characterized by loss of all or a portion of the nail

Hands:

	Date:	*RIGHT Grade:*	*LEFT Grade:*	*Description (if applicable)*
pre				
Tx1				
Tx2				
Tx3				
Tx4				
Tx5				
Tx6				
Tx7				
Tx8				
Tx9				
Tx10				
Tx11				
Tx12				
3 weeks post				
6 months post				

Appendix 4: Brief Pain Index

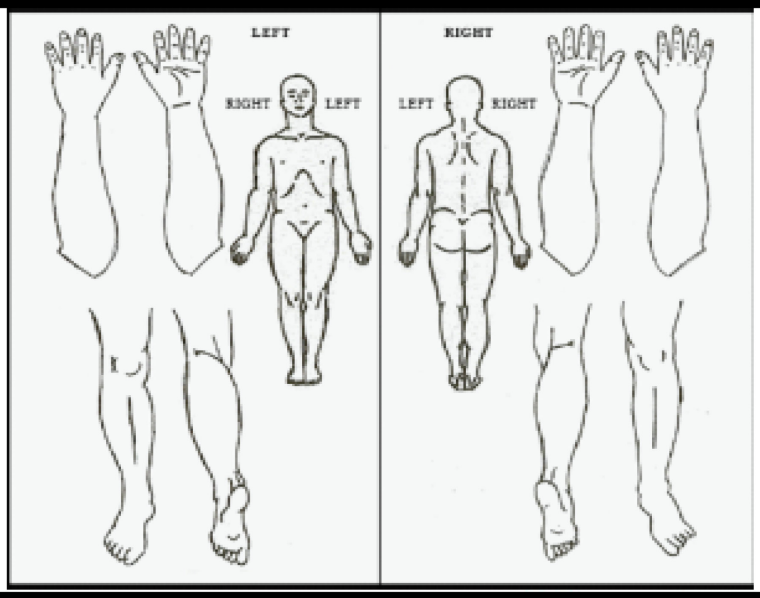
Patient ID:_____
Date:_____
Time point:_____

BRIEF PAIN INVENTORY

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
No Pain — Pain As Bad As You Can Imagine

Patient ID:_____
Date:_____
Time point:_____

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐ No Relief	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

Appendix 5

EORTC-CIPN 20
Patient ID:_____
Date:_____ Time point:_____
Control:_____ Treated:_____

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

	Not at All	A Little	Quite a Bit	Very Much
During the Past Week:				
RIGHT: Did you have ***tingling fingers or hands***?	1	2	3	4
LEFT: you have ***tingling fingers or hands***?	1	2	3	4
RIGHT: Did you have ***tingling toes or feet***?	1	2	3	4
LEFT: Did you have ***tingling toes or feet***?	1	2	3	4
RIGHT: Did you have ***numbness in your fingers or hands***?	1	2	3	4
LEFT: Did you have ***numbness in your fingers or hands***?	1	2	3	4
RIGHT: Did you have ***numbness in your toes or feet***?	1	2	3	4
LEFT: Did you have ***numbness in your toes or feet***?	1	2	3	4
RIGHT: Did you have ***shooting or burning pain in your fingers or hands***?	1	2	3	4
LEFT: Did you have ***shooting or burning pain in your fingers or hands***?	1	2	3	4
RIGHT: Did you have ***shooting or burning pain in your toes or feet***?	1	2	3	4
LEFT: Did you have ***shooting or burning pain in your toes or feet***?	1	2	3	4
RIGHT: Did you have ***cramps in your hands***?	1	2	3	4
LEFT: Did you have ***cramps in your hands***?	1	2	3	4
RIGHT: Did you have ***cramps in your feet***?	1	2	3	4
LEFT: Did you have ***cramps in your feet***?	1	2	3	4
R HAND: Did you have ***difficulty distinguishing between hot and cold water***?	1	2	3	4
L HAND: Did you have ***difficulty distinguishing between hot and cold water***?	1	2	3	4
R Foot: Did you have ***difficulty distinguishing between hot and cold water***?	1	2	3	4
L Foot: Did you have ***difficulty distinguishing between hot and cold water***?	1	2	3	4

Appendix 6

HANDS (NPSI)

Patient ID:_____

Date:_____

Time point:_____

We wish to know if you feel spontaneous pain that is pain without any stimulation. For each of the following questions, please circle the number that best describes you **average spontaneous pain severity during the past 24 hours.** Circle **0** if you have not felt such pain. *(Circle one number only)*

Does your pain feel like burning?

On a scale from 0 to 10; 0 being no burning to 10 being the worst burning imaginable

Control Hand	0	1	2	3	4	5	6	7	8	9	10
Treated Hand	0	1	2	3	4	5	6	7	8	9	10

Does your pain feel like squeezing?

On a scale from 0 to 10; 0 being no squeezing to 10 being the worst squeezing imaginable

Control Hand	0	1	2	3	4	5	6	7	8	9	10
Treated Hand	0	1	2	3	4	5	6	7	8	9	10

Does your pain feel like pressure?

On a scale from 0 to 10; 0 being no pressure to 10 being the worst pressure imaginable

Control Hand	0	1	2	3	4	5	6	7	8	9	10
Treated Hand	0	1	2	3	4	5	6	7	8	9	10

During the past 24 hours, your **spontaneous pain has been present** in your _____:

Control hand

- ☐ Permanently
- ☐ Between 8-12 hours
- ☐ Between 4-7 hours
- ☐ Between 1-3 hours
- ☐ Less than 1 hour

Treated hand

- ☐ Permanently
- ☐ Between 8-12 hours
- ☐ Between 4-7 hours
- ☐ Between 1-3 hours
- ☐ Less than 1 hour

We wish to know if you have brief attacks of pain. For each of the following question, please circle the number that best describes the **average severity of your painful attacks during the past 24 hours.** Circle **0** if you have not felt such pain. *(Circle one number only).*

Does your pain feel like electric shocks?

On a scale from 0 to 10; 0 being no electric shock to 10 being the worst electric shock imaginable

Control Hand	0	1	2	3	4	5	6	7	8	9	10
Treated Hand	0	1	2	3	4	5	6	7	8	9	10

Does your pain feel like stabbing?

On a scale from 0 to 10; 0 being no stabbing to 10 being the worst stabbing imaginable

Control Hand	0	1	2	3	4	5	6	7	8	9	10
Treated Hand	0	1	2	3	4	5	6	7	8	9	10

HANDS (NPSI)

Patient ID:_____

Date:_____

Time point:_____

During the past 24 hours, how many of these pain attacks have you had in your _____?

Control hand

- ☐ More than 20
- ☐ Between 11 and 20
- ☐ Between 6 and 10
- ☐ Between 1 and 5
- ☐ No pain attack

Treated hand

- ☐ More than 20
- ☐ Between 11 and 20
- ☐ Between 6 and 10
- ☐ Between 1 and 5
- ☐ No pain attack

We wish to know if you feel pains provoked or increased by brushing, pressure, contact with something cold on the painful area. For each of the following questions, please circle the number that best describes the **average severity of your provoked pains during the past 24 hours**. Circle **0** if you have not felt such pain. (*Circle one number only).*

Is your pain provoked or increased by brushing on the painful area?

On a scale of 0-10; 0 being no pain to 10 being the worst pain imaginable

Control Hand	0	1	2	3	4	5	6	7	8	9	10
Treated Hand	0	1	2	3	4	5	6	7	8	9	10

Is your pain provoked or increased by pressure on the painful area?

On a scale from 0-10; 0 being no pain to 10 being the worst pain imaginable

Control Hand	0	1	2	3	4	5	6	7	8	9	10
Treated Hand	0	1	2	3	4	5	6	7	8	9	10

Is your pain provoked or increased by contact with something cold on the painful area?

On a scale from 0 to 10; 0 being no pain to 10 being the worst pain imaginable

Control Hand	0	1	2	3	4	5	6	7	8	9	10
Treated Hand	0	1	2	3	4	5	6	7	8	9	10

Do you feel pins and needles?

On a scale from 0 to 10; 0 being no pins and needles to 10 being the worst pins and needles imaginable

Control Hand	0	1	2	3	4	5	6	7	8	9	10
Treated Hand	0	1	2	3	4	5	6	7	8	9	10

Do you feel tingling?

On a scale from 0 to 10; 0 being no tingling to 10 being the worst tingling imaginable

Control Hand	0	1	2	3	4	5	6	7	8	9	10
Treated Hand	0	1	2	3	4	5	6	7	8	9	10

Appendix 7

Quantitative Sensory Tests BASELINE
Patient ID:_____
DATE:_____
CONTROL SIDE: _____
TREATED SIDE: _____

Monofilaments

CONTROL HAND: ☐ Right ☐ Left

		First	PFR	Pattern	Last	Low	High
Baseline	Fingertip 1						
	Fingertip 2						
	Fingertip 3						
	Average						

TREATED HAND: ☐ Right ☐ Left

		First	PFR	Pattern	Last	Low	High
Baseline	Fingertip 1						
	Fingertip 2						
	Fingertip 3						
	Average						

CONTROL FEET: ☐ Right ☐ Left

		First	PFR	Pattern	Last	Low	High
Baseline	Toe Tip 1						
	Toe Tip 2						
	Toe Tip 3						
	Average						

TREATED FEET: ☐ Right ☐ Left

		First	PFR	Pattern	Last	Low	High
Baseline	Toe Tip 1						
	Toe Tip 2						
	Toe Tip 3						
	Average						

Performed by:_____ Date:_____ Time:_____

Patient ID:_____
DATE:_____

Twenty-Five hole Pegboard

Dominant hand: ☐ Right ☐ Left

	Control
Baseline Time:	

Performed by:_____ Date:_____ Time:_____

Patient ID:_____
DATE:_____

Vibration Test using a Rydel-Seiffer tuning fork

CONTROL: ☐ Right ☐ Left

Baseline	Hands	Feet
1		
2		
3		
average		

TREATED: ☐ Right ☐ Left

Baseline	Hands	Feet
1		
2		
3		
average		

Performed by:_____ Date:_____ Time:_____

Appendix 8

Quantitative Sensory Tests POST CHEMO

Patient ID:_____

DATE:_____

CONTROL SIDE: _____

TREATED SIDE: _____

Von Frey Monofilaments

CONTROL HAND: ☐ Right ☐ Left

		First	PFR	Pattern	Last	Low	High
POST-CHEMO	Fingertip 1						
	Fingertip 2						
	Fingertip 3						
	Average						

TREATED HAND: ☐ Right ☐ Left

		First	PFR	Pattern	Last	Low	High
POST-CHEMO	Fingertip 1						
	Fingertip 2						
	Fingertip 3						
	Average						

CONTROL FEET: ☐ Right ☐ Left

		First	PFR	Pattern	Last	Low	High
POST-CHEMO	Toe Tip 1						
	Toe Tip 2						
	Toe Tip 3						
	Average						

TREATED FEET: ☐ Right ☐ Left

		First	PFR	Pattern	Last	Low	High
POST-CHEMO	Toe Tip 1						
	Toe Tip 2						
	Toe Tip 3						
	Average						

Performed by:_____ Date:_____ Time:_____

Patient ID:_____
DATE:_____

Twenty-Five hole Peg

Dominant hand: ☐ Right ☐ Left

	Control
Post-Chemo Time:	

Patient ID: _____
Date:_____

Performed by:_____ Date:_____ Time:_____

Vibration Test using a Rydel-Seiffer tuning fork

CONTROL: ☐ Right ☐ Left

Post-Chemo	Hands	Feet
1		
2		
3		
average		

TREATED: ☐ Right ☐ Left

Post-Chemo	Hands	Feet
1		
2		
3		
average		

Performed by:_____ Date:_____ Time:_____

Patient Satisfaction:
On a scale from 0-4, how satisfied are you with the frozen glove and wrap treatment?
0 being not at all satisfied to 4 being the most satisfied

0 1 2 3 4

Appendix 9

Quantitative Sensory Testing for TrpA1 activity

Materials:

500 ul Mustard Oil solution (400 ul mustard oil plus 100 ul olive oil) in 1.5 ml Eppendorf tube
5-1.5 empty Eppendorf tubes
5- square spot bandages (Band-Aid Tru-Stay Clear Spots)
~5 inch strip of paper tape~5 inch strip of paper tape
Von Frey fiber (4.0 g force)
1 pencil or pen for patient

Instructions:

1) Prior to receiving chemotherapy, patient reports baseline arm pain on a scale of 1-10, 1=no pain and 10= worst pain ever to the treatment arm. Score is recorded on the MO data score sheet.

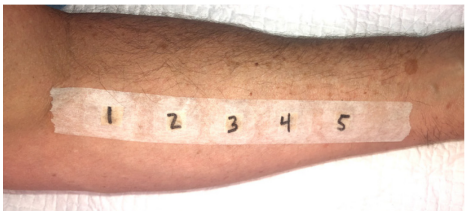
2) The CIPN strip is prepared as follows:

A. using a black Sharpie, write each number (1-5) on the back of the bandage. DO NOT write on the cotton pad. Number should be visible through paper tape. These can be made in advance.
B. Attach numbered bandages side by side to the sticky side of a strip of paper tape. Remove bandage backing to expose cotton pads.
C. Add 40 ul of appropriate test solution to the specific pad. A serial dilution is made as described below.
D. Place a strip with wetted pads down on the ulnar region of the "treated: arm with spot #5 towards the wrist. Write numbers next to the appropriate bandage if needed for visualization.

Serial dilution of Tube (#5 made first) for CIPN Strip:

Tube #	**1**	**2**	**3**	**4**	**5**
Condition	Veh only	1:250 dil	1:50 dil	1:10 dil	1:2 dil
Recipe	100ul veh	120ul veh + 30ul #3	120ul veh + 30ul #4	120ul veh + 30ul #5	100ul + 100ul MO soln

VEH=Olive Oil



3) After 10 minutes post-application, patients are asked to record responses on the data sheet

4) The strip is removed and the technician records all spots with a visible flare by photograph.

5) Patients are asked to look away and **punctate hyperalgesia** assayed using a single poke of Von Frey fiber (4g) beginning at spot #1 and moving towards spot #5. Patients are asked to indicate when poke changes from a slight prick to something more painful. Patients should also indicate which spots are numb to the poke. It is helpful for the patient if a couple of test pokes are administrated on the arm away from the test zone so they can get a sense of the baseline sensation. Scores are recorded on data sheet provided.

6) After chemotherapy treatment, Steps 1-5 are repeated on opposite arm (the control arm).

MO Strip Data Sheet **Patient:** _____

A. To be completed prior to first chemotherapy drug infusion: Indicate the level of arm-specific pain today (1-10; 1=no pain and 10= worst pain ever): _____

Instructions: The MO strip is attached to the ulnar area of the patient's treatment arm. After 10 minutes the patient should answer the questions below (numbers refers to application spots on the strip):

1) Indicate all numbers where you feel pain: 1 2 3 4 5 NONE

2) Indicate all numbers where you feel burning/stinging: 1 2 3 4 5 NONE

3) Indicate all numbers where you feel tingling/prickly: 1 2 3 4 5 NONE

For the technician:

4) Remove the MO strip and circle all numbers with a visible flare: 1 2 3 4 5 NONE

Punctate hyperalgesia (4g Von Frey fiber)

5) Indicate all numbers that feel painful to the touch of the fiber: 1 2 3 4 5 NONE

6) Indicate all numbers that feel numb to the touch fiber: 1 2 3 4 5 NONE

Comments:

B. To be completed immediately after the first chemotherapy drug infusion:

Indicate the level of arm-specific pain today (1-10; 1=no pain and 10=worst pain ever): _____

Instructions: The MO strip is attached to the ulnar area of the control arm. Incubate at room temp for 10 minutes and then answer the questions below (numbers refer to application spots on strip):

1) Indicate all numbers where you feel pain: 1 2 3 4 5 NONE

2) Indicate all numbers where you feel burning/stinging: 1 2 3 4 5 NONE

3) Indicate all numbers where you feel tingling/prickly: 1 2 3 4 5 NONE

For the technician:

4) Remove the MO strip and circle all numbers with a visible flare: 1 2 3 4 5 NONE

Punctate hyperalgesia (4g Von Frey fiber)

5) Indicate all numbers that feel painful to the touch of the fiber: 1 2 3 4 5 NONE

6) Indicate all numbers that feel numb to the touch fiber: 1 2 3 4 5 NONE

Comments:

Appendix 10

Cold Glove and Cold Wrap Patient Dosing Record

Patient ID: _____

Treatment Date:			Drug and Course #:		
Pre-med start time:			Chemo Start time:		
□ Temp confirmed at approx. 4° C			Actual Temp:		
Randomized to Dominant or Non-dominant side			Corresponds to Left or Right side		
Glove			Wrap		
Temp confirmed	Time Applied	Time Removed	Temp confirmed	Time applied	Time removed
#1 □			#1 □		
#2 □			#2 □		
#3 □			#3 □		
#4 □ or □ N/A			#4 □ or □ N/A		
#5 □ or □ N/A			#5 □ or □ N/A		
#6 □ or □ N/A			#6 □ or □ N/A		
#7 □ or □ N/A			#7 □ or □ N/A		

Comments_____
_____
_____
_____
_____

Name and Initials of Person(s) applying cryotherapy Treatment to Patient:

_____

_____

Date/Time of completion of cryotherapy: _____/_____