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FRED HUTCHINSON CANCER RESEARCH CENTER
UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE
SEATTLE CHILDREN'S

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Pilot study of oral cryotherapy vs. oral cryotherapy plus acupuncture and acupressure to decrease chemotherapy-induced peripheral neuropathy from oxaliplatin-based chemotherapy for GI cancers

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1.0 ABBREVIATIONS

5-FU	5-fluorouracil
BPI	Brief pain inventory
CRF	Case report form
CIPN	Chemotherapy-induced peripheral neuropathy
CRS	Clinical Research Support
CTCAE	Common Terminology Criteria for Adverse Events
DSMP	Data and Safety Monitoring Plan
DSMC	Data and Safety Monitoring Committee
EOT	End-of-treatment
FOLFIRINOX FOLFOXIRI	5-FU, oxaliplatin, irinotecan
FOLFOX	5-FU, oxaliplatin
IRB	Institutional Review Board
GI	Gastrointestinal
SNRI	Selective serotonin-norepinephrine reuptake inhibitor
SRC	Scientific Review Committee
SSRI	Selective serotonin reuptake inhibitor
TCM	Traditional Chinese Medicine
UW	University of Washington

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2.0 PROTOCOL SYNOPSIS

Protocol Title	Pilot study of oral cryotherapy vs. oral cryotherapy plus acupuncture and acupressure to decrease chemotherapy-induced peripheral neuropathy from oxaliplatin-based chemotherapy for GI cancers
Protocol Number	*Pending*
Protocol Funding	Safeway Early Career/Cancer Center Support Grant Pilot Award
Trial Phase	Phase II
Trial Type	Randomized Control Feasibility Trial
Clinical Indication	GI cancer for which a new oxaliplatin-based regimen is recommended
Study Objectives	Primary: To evaluate the severity of CIPN in GI cancer patients receiving oxaliplatin-based chemotherapy following 3 months of acupuncture/acupressure treatment plus oral cryotherapy compared to oral cryotherapy alone. Secondary 1: To estimate the incidence of grade 2 or higher CIPN in GI cancer patients receiving oxaliplatin-based chemotherapy following 3 months of acupuncture/acupressure treatment plus oral cryotherapy compared to oral cryotherapy alone. Secondary 2: To evaluate the severity of CIPN in GI cancer patients receiving oxaliplatin-based chemotherapy following 3 months of acupuncture/acupressure treatment plus oral cryotherapy compared to oral cryotherapy alone using objective measurement tools. Secondary 3: To assess the feasibility of delivering acupuncture during biweekly chemotherapy infusion and the feasibility of patient self-administered acupressure between infusions. Secondary 4: To evaluate the effect of oral cryotherapy with acupuncture/acupressure vs. oral cryotherapy alone in reducing pain, fatigue, nausea, oral dysesthesia, and anxiety in GI cancer patients receiving oxaliplatin-based chemotherapy.
Study Design	Randomized Controlled Feasibility Trial
Population	56 patients with a GI cancer malignancy with planned ≥3 months of a 5-FU- and oxaliplatin-based chemotherapy regimen. Eligibility criteria includes: 1) GI cancer (primary esophagus, gastric, pancreas, biliary, small bowel, appendix, colon, or rectal) scheduled to receive a new start of 5-FU, oxaliplatin, ± irinotecan [FOLFOX, FOLFIRINOX, FOLFOXIRI regimens] with plan for ≥3 months of therapy with the regimen, 2) age ≥18 years, 3) absolute neutrophil count >500 and platelet count >20,000, 4) not currently pregnant, 5) ability to understand and the willingness to sign a written informed consent document, 6) no baseline neuropathy from any cause, 7) no prior neurotoxic chemotherapy of any kind in the prior 3 years, 8) no planned initial dose of oxaliplatin <100% of the standard regimen-specified dose, 9) no receipt of acupuncture treatment in the prior 3 months, 10) no use of concomitant duloxetine for minimization of neuropathy, 11) no psychiatric illness/social situations that would limit compliance with study requirements.
Primary Endpoint	Chemotherapy-induced peripheral neuropathy as measured by the EORTC-CIPN 20.
Secondary Endpoints	1. Incidence of grade 2 or higher CIPN as measured by CTCAE version 5. 2. Severity of chemotherapy-induced peripheral neuropathy as measured by a Neuropen and tuning fork. 3. Proportion of patients assigned to the intervention arm who complete 60% of acupuncture treatments. 4. Incidence of pain, fatigue, nausea, oral dysesthesia, and anxiety as measured by the NCI PRO-CTCAE, Brief Pain Inventory (BPI), and CTCAE version 5.

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Type of control	Usual care + waitlist arm – receives no acupuncture during the 3-month intervention period
Investigation Drug	N/A
Dose	Acupuncture: 12 treatments with 30-minute needle retention
Route of administration	Acupuncture: filiform needle insertion
Regimen	12 sessions of acupuncture. Acupressure training and self-treatment.
Trial Blinding	None
Treatment Groups	Arm A: Acupuncture + Acupressure Intervention with standard-of-care cryotherapy: acupuncture during chemotherapy infusion (day 1) and 5-FU pump disconnect (day 3) of each biweekly chemotherapy infusion x6 cycles (*i.e.* 12 acupuncture treatments over 12 weeks) + self-acupressure Arm B: Waitlist Control Arm with standard-of-care cryotherapy: 6 acupuncture sessions after the completion of the trial
Treatment Schedule	Days 1 and 3 of each chemotherapy treatment cycle
Efficacy Assessments	Baseline 6 weeks 12 weeks
Number of trial subjects	56
Estimated duration of trial	24 months
Duration of Participation	3 months

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4.0 GENERAL INFORMATION

1.1 Protocol Title

Pilot study of oral cryotherapy vs. oral cryotherapy plus acupuncture and acupressure to decrease chemotherapy-induced peripheral neuropathy from oxaliplatin-based chemotherapy for GI cancers

5.0 INTRODUCTION TO THE PROTOCOL

5.1 Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) negatively impacts treatment delivery, both acutely (by requiring dose reductions, delays, or requiring early cessation of treatment) and chronically (by impacting quality of life for survivors). CIPN is a common side effect of oxaliplatin, which is a component of the majority of standard adjuvant and/or first-line metastatic therapies for gastroesophageal, pancreas, and colorectal cancer patients. In the MOSAIC trial of adjuvant 5-fluorouracil (5-FU) and oxaliplatin [FOLFOX], >90% of colon cancer patients reported CIPN during treatment, with 15% reporting symptoms four years later.[1] Similarly, in pancreas cancer patients receiving six months of 5-FU, irinotecan, and oxaliplatin [FOLFIRINOX] in the adjuvant setting, 61% had any-grade CIPN and 9-10% had grade 3+ CIPN in the landmark adjuvant and metastatic trials.[2, 3] The high prevalence of acute and persistent CIPN in multiple gastrointestinal (GI) cancer patient populations highlights the need to more effectively mitigate acute and chronic CIPN.

In additional to peripheral neuropathy symptoms, as a result of oxaliplatin administration, patients can experience oral dysesthesia, which can negatively impact oral intake. Patients are typically educated to avoid cold foods and fluids, which can significantly impact food choices and eating/drinking overall during the acute symptoms of neurotoxicity.[4] This is especially problematic in GI cancers, where digestion and oral intake are often compromised by the cancer itself.

Complementary therapies have been tested in the prevention and treatment of CIPN, with few effective treatments identified.[5] Calcium and/or magnesium infusions with oxaliplatin were standard-of-care for prevention of CIPN, but were unsupported by a large randomized trial.[6] Newer efforts have included both cryotherapy and acupuncture.

5.2 Clinical Data with Cryotherapy

Oral ice chip cryotherapy has recently been introduced as a method to prevent oral thermal hyperalgesia, thought to be mediated by vasoconstriction.[7] In this single institution study, 62 patients were randomized and 50 were evaluable (having received at least 2 cycles) for either oral ice chip cryotherapy, delivered for 120 minutes during oxaliplatin infusion versus a control group, who was asked to avoid ingesting anything cooler than room temperature for the duration of the infusion. Using a scoring system, the ice chip cryotherapy intervention group had less oral and peripheral neuropathy symptoms prior to cycle 2 as compared to the control group. This was also demonstrated longitudinally. The benefit from oral ice chip cryotherapy was dose-dependent, meaning that longer ice duration was associated with less CIPN. Based on this data, ice chip cryotherapy (in the form of oral ice, hand/foot ice packs) was adopted into standard clinical practice.

5.3 Clinical Data with Acupuncture and Acupressure

Acupuncture has been explored as a safe nonpharmacological method of preventing and treating CIPN. The mechanisms of acupuncture are not fully understood. Acupuncture has been shown to work by adjusting neurophysiologic and neurohormonal activity.[8, 9] Prior trials have had inconsistent results, likely due to differences in acupuncture protocols, use of electroacupuncture, timing of intervention, choice of comparator, and sample size, but the recent data suggests promise for using acupuncture for CIPN prevention.[10-15]

Acupressure has also demonstrated efficacy in decreasing fatigue, nausea, pain and improving quality of life in cancer patients.[16-21] A 2019 Systematic Review and Meta-Analysis found a moderate level of evidence that acupuncture and/or acupressure compared to a sham control were significantly associated with lower intensity in cancer-related pain inpatients with cancer, which suggests a potential for a combination of acupuncture with acupressure to reduce the amount of cancer-related pain that may require opioid use as a treatment.[21] Acupuncture and acupressure have potential to be scalable treatments for CIPN because they are both reproducible and standardized. Acupressure is an inexpensive and easy-to-perform self-care intervention.

5.4 Risks/Benefits

Oral cryotherapy and acupuncture have yet to be systemically tested together to assess this combination for maximal prevention of the onset and progression of CIPN. However, it is well recognized that CIPN can have acutely and chronically negatively impact quality of life. As there are few effective treatments outside of withdrawing the offending agent, prevention and minimization of neuropathic toxicities is highly necessary.

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6.0 OVERVIEW OF CLINICAL TRIAL

6.1 Study Objectives

6.1.1 Primary Objectives

To evaluate the severity of CIPN in GI cancer patients receiving oxaliplatin-based chemotherapy following 3 months of acupuncture/acupressure treatment plus oral cryotherapy compared to oral cryotherapy alone.

6.1.2 Secondary Objectives

1: To estimate the incidence of grade 2 or higher CIPN following 3 months of acupuncture/acupressure treatment plus oral cryotherapy compared to oral cryotherapy alone.

2: To evaluate the severity of CIPN in GI cancer patients receiving oxaliplatin-based chemotherapy following 3 months of acupuncture/acupressure treatment plus oral cryotherapy compared to oral cryotherapy alone using objective measurement tools.

3: To assess the feasibility of delivering acupuncture during biweekly chemotherapy infusion and the feasibility of patient self-administered acupressure between infusions.

4: To evaluate the effect of oral cryotherapy with acupuncture/acupressure vs. oral cryotherapy alone in reducing pain, fatigue, nausea, oral dysesthesia, and anxiety in GI cancer patients receiving oxaliplatin-based chemotherapy.

6.2 Study Population

Patients with a GI cancer malignancy with planned ≥3 months of a 5-FU- and oxaliplatin-based chemotherapy regimen.

6.3 Study Design

6.3.1 Primary Endpoint

Severity of CIPN as measured by the EORTC-CIPN 20.

6.3.2 Secondary Endpoints

Incidence of grade 2 or higher CIPN as measured by CTCAE version 5.

Severity of CIPN as measured by a Neuropen and tuning fork.

Proportion of patients assigned to the intervention arm who complete 60% of acupuncture treatments.

Incidence of pain, fatigue, nausea, oral dysesthesia, and anxiety as measured by the NCI PRO-CTCAE, BPI, and CTCAE version 5.

6.4 Estimated Accrual

Fifty-six patients will be enrolled, 28 randomized to each arm.

6.5 Name of Sponsor/Funding Source

This study is funded by a Safeway / Cancer Center Support Grant Pilot Award.

7.0 SUBJECT ELIGIBILITY

7.1 Inclusion Criteria

7.1.1 GI cancer (primary esophagus, gastric, pancreas, biliary, liver, small bowel, appendix, colon, rectal, anal, or gastrointestinal/pancreatic neuroendocrine tumor) scheduled to receive a new start of 5-FU, oxaliplatin, ± irinotecan [FOLFOX, FOLFIRINOX, FOLFOXIRI regimens] with plan for ≥3 months of therapy with the regimen

Chemotherapy can be given for neoadjuvant, adjuvant, or palliative intent.

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1 dose (cycle) of the intended regimen is permitted prior to study enrollment.
There is no limitation on the addition of a biologic agent to one of the above chemotherapy regimens, including, but not limited to: bevacizumab, cetuximab, panitumumab, trastuzumab, or the biosimilars of these agents.

7.1.2 Age ≥18 years

7.1.3 Absolute neutrophil count >0.5 thousand/microL and platelet count >20 thousand/microL

7.1.4 Not currently pregnant

7.1.5 Ability to understand and the willingness to sign a written informed consent document.

7.2 Exclusion Criteria

7.2.1 Baseline peripheral neuropathy from any cause

7.2.2 Planned oxaliplatin with capecitabine

7.2.3 Planned initial dose of oxaliplatin <100% of the standard regimen-specified dose
For most regimens, this would be 85mg/m^2 IV dosed every 14 days.

7.2.4 Receipt of acupuncture treatment in the prior 3 months

7.2.5 Use of concomitant duloxetine for minimization of neuropathy.

7.2.6 Psychiatric illness/social situations that would limit compliance with study requirements.

8.0 SUBJECT REGISTRATION

Subjects will be registered by the Fred Hutch/UW Study Coordinator and their data entered into OnCore CTMS. A complete, signed, study consent and HIPAA consent are required for registration.

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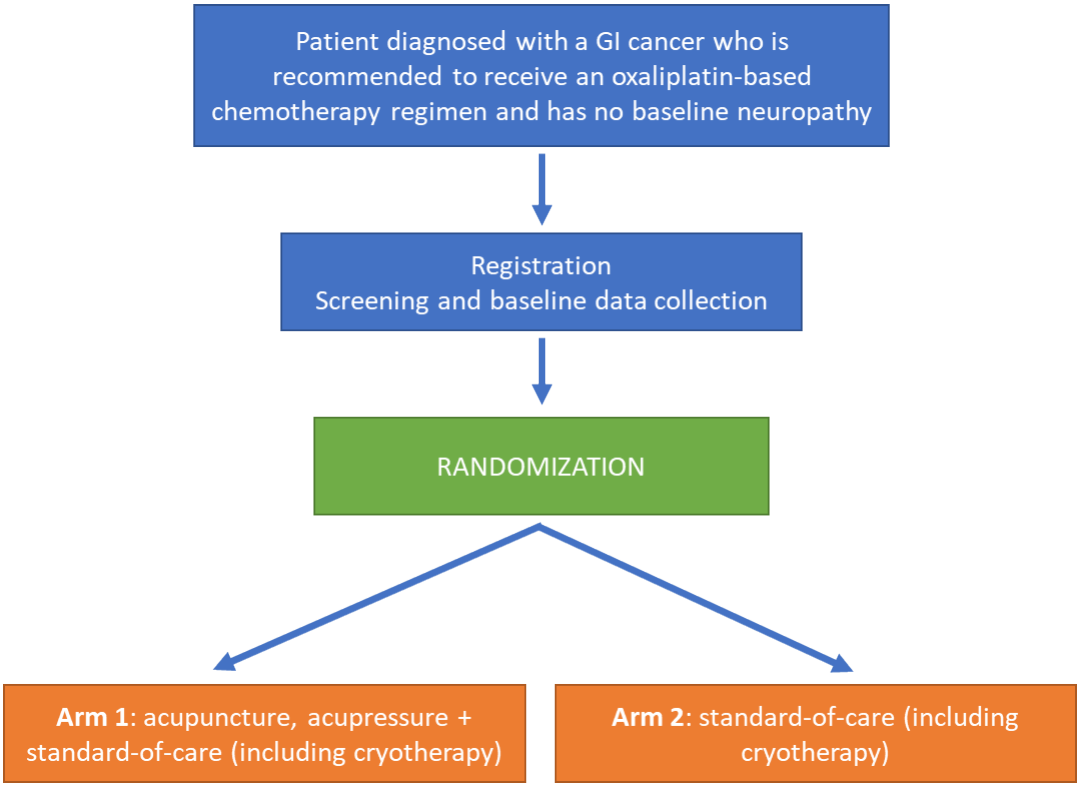
9.0 TREATMENT PLAN

56 patients will be randomized 1:1 to the intervention arm (n=28) of standard oral cryotherapy with acupuncture or the control arm (n=28) of oral cryotherapy alone. All patients will receive standard-of-care supportive care medications (analgesics, antiemetics, etc.) at the discretion of their treating physician.

9.1 Treatment Plan Overview



9.2 Acupuncture and Acupressure Intervention

The intervention group will receive acupuncture during chemotherapy infusion (day 1) and 5-FU pump disconnect (day 3) of each biweekly chemotherapy infusion x6 cycles (*i.e.* 12 acupuncture treatments over 12 weeks). Acupuncture treatments will be specifically targeted to prevent, treat, or mitigate neuropathy symptoms, pain, fatigue, nausea and anxiety. Patients will receive 30-minute acupuncture treatments in the seated or supine position. Standard acupoint techniques for point location[22] will be utilized and Clean Needle Technique[23] will be followed using 32-40-gauge x 30-40mm Seirin acupuncture needles.

On day 1 the acupuncture points will be needled bilaterally at: ST36, SP6, LI10, GB40, P6, auricular shen men, and on the midline at Yin Tang (EX-HN3) and GV20. On day 3 the acupuncture points will be needled bilaterally at: LI4, LR3, ST36, SP6, LI10, GB40, P6, auricular shen men, and on the midline at Yin Tang (EX-HN3) and GV20. For patients unable to tolerate peripheral cryotherapy, the day 3 acupuncture protocol will be administered on day 1.

After the initial acupuncture treatment, the study acupuncturist will instruct the patient on how to locate and self-administer acupressure for key acupoints: bilateral LI4 (for pain, oral dysesthesia), bilateral P6 (nausea), and midline GV20 (fatigue). These acupoints are based on previously published studies,[12-15] Traditional Chinese Medicine (TCM) theory,[22] and current understanding of innervation and neuromodulation of acupoints.[13] Auricular shen men points (anxiety) will be stimulated with vaccaria seeds applied by the acupuncturists on day 3 and removed after 4 days (day 7 of the cycle). Patients will be taught to self-administer an 11-minute acupressure regimen daily by stimulating each acupoint in a circular motion for 2 minutes on each bilateral points of LI4 and P6, 2 minutes on midline GV20, and to gently press the ear seeds on shen men for 30 seconds three times per day. The acupuncturists will provide additional teaching during the acupressure training on Cycle 1 Day 1 instructing the patients to utilize auricular Shen Men point during cryotherapy to help mitigate possible unpleasant effects of cryotherapy including: headache, toothache, and/or cold aversion/pain.

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If a patient misses an acupuncture session, it will not be made up. If a patient misses both sessions from study cycle 1 of chemotherapy, they will be removed from the study. Handouts describing acupuncture and acupressure will be provided to participants (Appendix L).

9.3 Cryotherapy

As per Seattle Cancer Care Alliance protocol, patients will hold ice chips in the mouth from up to 30 min prior through the end of the oxaliplatin infusion. The use and duration of ice chip exposure will be documented. Additionally, the use of ice packs on hands and/or feet (which is allowed, but not part of current standard-of-care cryotherapy) will also be documented. Duration of each will be recorded as 0, 1-30, 31-60, 61-90, 91-120, or >120 minutes. Patients will be given the Cryotherapy Questionnaire (Appendix O) on the day of infusion or contacted by study staff within 5 days of completion of their chemotherapy infusion and patient self-recall will be used to determine the method and duration of their cryotherapy (Appendices O and P). The Questionnaire may also be sent via email to be complete in the study portal.

9.4 Waitlist Control

To increase participant willingness to be randomized and to increase trial retention, participants randomized to the control arm will receive coupons for six acupuncture treatments at SCCA South Lake Union clinic to be used any time after completion of the individual's duration (approximately 12 weeks) on the study (Appendices M and N). At the time of these visits, AEs and limited exam findings may be collection, which will be entered into the database as well. These visits will ideally be during or coordinated with standard-of-care visits. However, if patients have completed treatment, they may attend acupuncture-only visits.

9.5 Concomitant Medication and Supportive Care Guidelines

The use of duloxetine and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) are not permitted while on this study. Selective serotonin reuptake inhibitors (SSRIs) are permitted if prescribed for an indication other than the treatment of neuropathy (such as depression or anxiety).

Additional medications prescribed for the treatment of chemotherapy-induced peripheral neuropathy are not permitted. This includes gabapentin, alpha lipoic acid, B complex vitamin (or B1, B6, B12). These agents are permitted if prescribed for another indication.

Standard-of-care supportive care is recommended for the treatment of fatigue, pain, nausea, oral dysesthesia, and anxiety, and any other symptoms related to cancer or chemotherapy treatment.

9.6 Duration of Therapy

The intervention will be delivered over 3 months, concurrent with chemotherapy.

9.7 Duration of Follow-Up

Patients will not be followed after the intervention and end-of-treatment questionnaires are complete, with the exception of collection of data during waitlist control acupuncture visits if these are pursued.

9.8 Dosing Delays/Dose Modifications

Dose modifications, hold, and other alterations to planned chemotherapy will be at the discretion of the treating physician. Acupuncture treatments will be moved accordingly to co-occur with the chemotherapy treatments. If a patient discontinues use of oxaliplatin, he/she may continue to receive acupuncture either weekly or as protocolized (twice weekly every other week) until the completion of 3 months duration of acupuncture treatment.

9.9 End of Treatment (EOT) Visit Schedule and Procedures

The EOT visits for all subjects who discontinue from the study should ideally occur 14 days after day 1 of the prior cycle of chemotherapy (which would be 11 days from the last acupuncture treatment). The EOT visit is permitted in the range of 7-30 days after the last use of (Arm A) acupuncture treatment or (Arm B) cryotherapy use but must occur prior to beginning another treatment or receiving another dose of chemotherapy. Procedures to be performed during the EOT Visit include:

- Physical Exam
- Administration of the final QOL measures
- Vital Signs
- Performance Status
- AE Assessment
- Concomitant Medication

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As per 6.7. patients who are on the waitlist control arm and choose to use their acupuncture coupons will have the official EOT visit for uniform data collection, but will also have limited data collected at the time of each acupuncture session to note any toxicities or major symptoms at the time of those visit.

10.0 SUBJECT EVALUATION

10.1 On-Study Clinical Evaluations

Clinical evaluations take place according to the Study Calendar (Appendix B). The window between these visits should be as close to the scheduled time as possible, though delays in chemotherapy treatment as recommended by the treating physician are permitted and do not require cessation of protocol therapy.

- **Vitals**
  - Include blood pressure, pulse, temperature
- **Physical Exam**
- **Performance Status**
  - As per the ECOG performance scale (see Appendix A)
- **Labs (day 1 of each cycle, or up to 3 days prior):**
  - Hematology: CBC with absolute neutrophil count and platelets
- **Acupressure Diary (see Appendix J)**
  - Assessment of self-administered acupressure will be reviewed on day 1 of cycle 2 and each subsequent cycle. Patients who complete <50% of the prescribed acupressure regimen will be re-educated at cycle 2 on appropriate execution of the recommended acupressure regimen.
- **Clinical AE attribution**
  - CTCAE version 5.0

10.2 Quality of Life Assessments

These will be administered at baseline, 6 weeks, and 12 weeks. If a patient is receiving chemotherapy on the day of the assessments, the assessments must be completed before the chemotherapy treatment is administered.
At each time point the EORTC QLQ CIPN-20 (see Appendix D) will be used to assess neuropathy and targeted questions from the NCI-PRO CTCAE (Appendix E) for the assessment of fatigue, nausea, and anxiety. The Brief Pain Inventory (Appendix F) will be used to assess pain. An oral symptoms questionnaire (Appendix G) will be used to assess oral dysesthesia.

On cycle 4 day 8 (±2 days), a mid-cycle assessment will be done for the EORTC-QLQ CIPN-20, NCI-PRO CTCAE, and BPI. This may be administered by phone, on paper and returned at next clinic appointment, or electronically.

10.3 Neuropathic Assessments

These will be administered at baseline, 6 weeks, and 12 weeks. If a patient is receiving chemotherapy on the day of the assessments, the assessments must be completed before the chemotherapy treatment is administered.

10.3.1 Neuropen

The Neuropen is used to assess sensation with a 10g monofilament on one end and 40g Neurotip on the other end. For each patient evaluation, a 10-point examination of the dominant foot will be performed. After 100 such examinations, the monofilament needs to be replaced. The Neurotip is single use and must be replaced after each patient examination. A study-specific Neuropen will be used for all patient assessments by a trained clinician or research staff member.

Neuropen training will consist first of reviewing the user manual and instructional video for the Neuropen, which will follow standard protocols as described for the prior neuropathy trial SWOG 1714 (https://www.swog.org/required-s1714-training). Secondly, the staff member will need to be observed by Dr. Greenlee, or another trained member of the study team.

Touch and Pressure Perception: Touch and pressure sensation is assessed using the 10-g monofilament in the Neuropen on the subject's dominant foot. The dominant foot can be identified by asking the subject with which foot they would kick a ball. The clinician will follow the subsequent steps using the subject's dominant foot:

1. Ask the subject to remove sock and/or shoe on the dominant foot and lay flat or sit up on an examination table.
2. Fully extend the monofilament by sliding the button to the end of the device until a click is heard.
3. Wipe the end of the monofilament with an alcohol wipe or antiseptic solution.

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4. The 10 sites in the below figure (Figure 7.1) are to be tested at random on the dominant foot. Press the monofilament at a 90-degree angle to the skin surface and increase the pressure until it bows. The subject should not be able to see which site is being tested.
5. Hold in position for 1-2 seconds.
6. For each of the 10 sites tested, ask the subject if he/she can detect pressure applied from monofilament and name the location of sensation. Subjects may use the unmarked picture of the feet (similar to what is shown in Appendix H) to point to the location of sensation if they are unable to adequately name the location. Record subject response for each site tested.

Protective Pain and Sharpness Sensation: This is a calibrated and sterile pain/sharpness test on the subject's dominant foot. The spring mechanism is calibrated to exert a force of 40 grams to help identify subjects with a loss of pain sensation. The dominant foot can be identified by asking the subject with which foot they would kick a ball. The clinician will follow the subsequent steps using the subject's dominant foot:

1. Ask the subject to remove sock and/or shoe on the dominant foot and lay flat or sit up on an examination table.
2. Take an unused Neurotip and hold by the cap. Do not use if Neurotip cap has previously been removed.
3. Press Neurotip firmly down into the Neurotip carrier of the Neuropen as far as it will go and clicks into position. The Neurotip is correctly positioned when only one chevron can be seen on the Neurotip.
4. To expose the sterile semi-sharp tip, place thumb gently over the Neurotip pressure gauge and remove Neurotip cap by twisting and pulling outwards.
5. The 10 sites in the below figure (Figure 7.1) are to be tested at random. Press the Neurotip against the skin surface at a 90-degree angle. The subject should not be able to see which site is being tested.
6. Hold in position for 1-2 seconds before removing, taking care to depress within the 40-gram marked white area.
7. For each of the sites tested, ask the subject if they detect a sharp sensation and name the location of sharp sensation. Subjects may use the unmarked picture of the feet (similar to what is shown in Appendix H) to point to the location of sensation if they are unable to adequately name the location. Record subject response for each site tested.
8. Remove and discard the used Neurotip in an appropriate sharps container after completing the 10 site examinations.

10.3.2 Tuning fork

A study-specific 128-Hz tuning fork will be used to assess sensation by a trained clinician or research staff member. As above, this will consist first of reviewing the user manual and instructional video for the tuning fork, which will follow standard protocols as described for the prior neuropathy trial SWOG 1714 (https://www.swog.org/required-s1714-training). Secondly, the staff member will need to be observed by Dr. Greenlee, or another trained member of the study team.

Dominant Lower Extremity Vibration Sensation Testing

1. The tuning fork should be firmly tapped on the palm of the hand of the clinician to initiate vibration.
2. The vibrating tuning fork is first placed on the interphalangeal joint of the great toe of the dominant foot (Appendix I [A]). The dominant foot can be identified by asking the subject with which foot they would kick a ball. A timer is started once the vibrating tuning fork is placed on the interphalangeal joint of the great toe of the dominant foot.
3. The patient is instructed to report when vibration is no longer detected. The time at which the vibration is no longer detected should be noted.
4. If the patient feels the vibration for 15 seconds or longer, this is defined as normal and should be recorded as such. If vibration sensation is normal at the great toe, additional assessments of the lower extremity are not needed.
5. If vibration sensation in the great toe of the dominant foot is less than 15 seconds, this is defined as absent or decreased vibration sensation and should be recorded as such. If vibration sensation is absent or decreased in the interphalangeal joint of the great toe of the dominant foot, the clinician then conducts the testing at all additional sites listed below on the dominant side. For each site tested, the tuning fork should be firmly tapped on the palm of the hand of the clinician to initiate vibration and the vibrating tuning fork is placed on the site. Once the vibrating tuning fork is placed on the testing site, a timer is started to measure the time at which the vibration is no longer detected. This time should be noted for each site.
    a. The middorsal foot (Appendix I [B]): If the patient feels the vibration for 15 seconds or longer, this is defined as normal. If the patient feels the vibration less than 15 seconds, this is defined as absent or decreased vibration sensation.
    b. The medial malleolus (ankle) (Appendix I [C]): If the patient feels the vibration for 15 seconds or longer, this is defined as normal. If the patient feels the vibration less than 15 seconds, this is defined as abnormal.
    c. The midfibular region of the dominant lower extremity (Appendix I [D]): If the patient feels the vibration for 15 seconds or longer, this is defined as normal. If the patient feels the vibration less than 15 seconds, this is defined as absent or decreased vibration sensation.

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d. The patellar region of the dominant lower extremity (Appendix I [E]): If the patient feels the vibration for 10 seconds or longer, this is defined as normal. If the patient feels the vibration less than 10 seconds, this is defined as absent or decreased vibration sensation.

Dominant upper extremity vibration sensation testing

1. The clinician will conduct the testing at all three sites below on the dominant upper extremity. The dominant upper extremity can be identified by asking the subject with which hand they write.
2. For each site tested, the tuning fork should be firmly tapped on the palm of the hand of the clinician to initiate vibration and the vibrating tuning fork is placed on the site. Once the vibrating tuning fork is placed on the testing site, a timer is started to measure the time at which the vibration is no longer detected. This time should be noted for each site. The three sites to be tested on the dominant upper extremity vibrating tuning fork are:
    a. The distal interphalangeal joint of the index finger (Appendix I [F]): If the patient feels the vibration for 25 seconds or longer, this is defined as normal. If the patient feels the vibration less than 25 seconds, this is defined as absent or decreased vibration sensation. Regardless of sensation at site (a), all three upper extremity sites will be tested.
    b. The ulnar styloid (wrist) (Appendix I [G]): If the patient feels the vibration for 15 seconds or longer, this is defined as normal. If the patient feels the vibration less than 15 seconds, this is defined as absent or decreased vibration sensation.
    c. The lateral epicondyle (elbow) (Appendix I [H]): If the patient feels the vibration for 15 seconds or longer, this is defined as normal. If the patient feels the vibration less than 15 seconds, this is defined as absent or decreased vibration sensation.

10.4 Acupuncture Expectancy Scale

During the screening period (and prior to randomization), participants will be queried regarding their expectations regarding the effects of acupuncture using the validated Acupuncture Expectancy Scale.[24] In order to not bias results due to knowledge of randomization assignment, this measure will be assessed prior to randomization in all study participants.

11.0 SUBJECT DISCONTINUATION OF ACTIVE TREATMENT

Subjects may be removed from this study at any time at their discretion. Subjects may also be removed from this protocol if they develop any untoward side effects from the study procedures (acupuncture).

If a subject withdraws consent to participate in the study or aspects of the study, attempts should be made to obtain permission to record survival data up to the protocol-described end of the subject follow-up period. Documentation in the medical record should state that the subject is withdrawing from the study and what, if any, selected data the subject will permit the investigator to obtain.

If a subject withdraws consent and has received less than 1 cycle of chemotherapy with associated study-specified treatment (including any planned acupuncture sessions for that cycle), an additional patient will be recruited. Patients who receive less than 1 cycle of chemotherapy will not be followed.

An explanation for discontinuing treatment is recorded for each subject discontinuing treatment on the appropriate CRF/eCRF. The PI must be notified immediately if a subject discontinues treatment. All subjects, irrespective of treatment status, will continue to be followed for survival. Treatment in this study must be discontinued for any of the following reasons:

- at Investigator's discretion;
- at the subject's request;
- if the subject enrolls in a trial of another investigational agent which does not permit concurrent treatment;
- if the patient misses both acupuncture sessions from cycle 1 of chemotherapy;
- Grade 4 or life-threatening toxicity (See Section 13, Adverse Events) attributable to the study intervention;
- change in chemotherapy regimen which no longer includes oxaliplatin;
- pregnancy.

If a patient discontinues use of oxaliplatin, he/she may continue to receive acupuncture either weekly or as protocolized (twice weekly every other week) until the completion of 3 months duration of acupuncture treatment.

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12.0 CONCOMITANT MEDICATIONS

Medications taken at baseline will be recorded in the source and in CRF.
Concomitant medication limitations are described in section 9.5

13.0 ADVERSE EVENTS

13.1 Adverse Event

According to ICH guidelines (Federal Register. 1997; 62(90):25691-25709) and 21 CFR 312.32, IND Safety Reports, and ICH E2A, Definitions and Standards for Expedited Reporting, an adverse event is defined as follows:

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Abnormal laboratory values for laboratory parameters specified in the study should not be recorded as an adverse event unless an intervention is required (repeat testing to confirm the abnormality is not considered intervention), the laboratory abnormality results in a serious adverse event or the adverse event results in study termination or interruption/discontinuation of study treatment.

Medical conditions present at screening (i.e., before the study treatment is administered) are not adverse events and should not be recorded on adverse event pages of the CRFs. These medical conditions should be adequately documented on the subject chart. However, medical conditions present at baseline that worsen in intensity or frequency during the treatment or post-treatment periods should be reported and recorded as adverse events.

13.2 Serious Adverse Event

An adverse event should be classified as an SAE if it meets one of the following criteria:

Fatal	Adverse event results in death.
Life threatening:	The adverse events placed the subject at immediate risk of death. This classification did not apply to an adverse event that hypothetically might cause death if it were more severe.
Hospitalization:	It required or prolonged inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before enrollment in the treatment plan or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization.
Disabling/incapacitating	Resulted in a substantial and permanent disruption of the subject's ability to carry out normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject exposed to the molecule or treatment plan regimen before conception or during pregnancy.
Medically significant:	The adverse event did not meet any of the above criteria but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above.

13.3 Unexpected Adverse Event

An unexpected adverse event is defined as an event that has a nature or severity, or frequency that is not consistent with the known risks of acupuncture of acupressure, or the prior medical condition of the subject or other treatment given to the subject. "Unexpected," as used in this definition, refers to an adverse experience that has not been previously observed and reported in preclinical or clinical studies of acupuncture and acupressure.

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13.4 Monitoring and Recording Adverse Events

All AEs will be assessed by the investigator or qualified designee and recorded in the CRFs. The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the adverse event and/or serious adverse event and not described as the individual signs or symptoms. The following information should be recorded:

- Description of the adverse event using concise medical terminology
- Description as to whether or not the adverse event is serious, noting all criteria that apply
- The start date (date of adverse event onset)
- The stop date (date of adverse event resolution)
- The severity (grade) of the adverse event
- A description of the potential relatedness of the adverse event to a study procedure or other causality
- The action taken due to the adverse event
- The outcome of the adverse event

13.5 Grading Adverse Event Severity

All AEs will be graded in severity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the adverse event.

13.6 Attribution of an Adverse Event

Association or relatedness to the study agent will be assessed by the investigator as follows:

- Definite: The event follows a reasonable temporal sequence from exposure to the investigational procedure, has been previously described in association with the investigational procedure, and cannot reasonably be attributed to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications; AND the event disappears or improves with withdrawal of the investigational procedure and/or re-appears on re-exposure.
- Probable: The event follows a reasonable temporal sequence from exposure to the investigational procedure and has been previously been described in association with the investigational procedure OR cannot reasonably be attributed to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.
- Possible: The event follows a reasonable temporal sequence from exposure to the investigational procedure, but could be attributable to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.
- Unlikely: Toxicity is doubtfully related to the investigational procedures(s). The event may be attributable to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.
- Unrelated: The event is clearly related to other factors such as the subject's clinical state, other therapeutic interventions or concomitant medications.

For general AE assessment, an AE is considered related if it is assessed as definitely, probably, or possibly related; unrelated if it is assessed as unlikely related or unrelated.

13.7 Adverse Event Recording Period

AEs will be monitored and recorded in study-specific case report forms (CRFs) from the time of first exposure to acupuncture. AEs with an onset date prior to the first exposure to an investigational procedure will not be recorded, except in the case of clinically significant worsening of the AE during the specified AE monitoring time frame.

13.8 Adverse Event Reporting Requirements

The investigator or designee must report events to the Fred Hutch IRB in accordance with the policies of the IRB.

14.0 DATA AND SAFETY MONITORING PLAN

Institutional support of trial monitoring will be in accordance with the Fred Hutch/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan (DSMP). Under the provisions of this plan, Fred Hutch Clinical Research Support (CRS) coordinates data and compliance monitoring conducted by consultants, contract research

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organizations, or Fred Hutch employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), Fred Hutch Scientific Review Committee (SRC) and the Fred Hutch/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating subjects. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state, and federal guidelines.

15.0 DATA MANAGEMENT/CONFIDENTIALITY

The investigator will ensure that data collected conform to all established guidelines. Each subject is assigned a unique subject number to protect subject confidentiality. Subjects will not be referred to by this number, by name, or by any other individual identifier in any publication or external presentation. The licensed medical records department, affiliated with the institution where the subject receives medical care, maintains all original inpatient and outpatient chart documents.

16.0 STATISTICAL CONSIDERATIONS

16.1 Study Design

This is a randomized, controlled feasibility trial of acupuncture treatment delivered during planned chemotherapy infusion and 5-FU pump disconnect appointments, and self-administered acupressure plus oral cryotherapy compared to oral cryotherapy alone for prevention of CIPN.

16.2 Primary/Secondary Endpoints and Analytical Methods

16.2.1 Primary Endpoint

The primary endpoint is CIPN as measured by the EORTC-CIPN-20.

16.2.2 Secondary Endpoints

- Incidence of grade 2 or higher CIPN as measured by CTCAE version 5
- Severity of CIPN as measured by a Neuropen and tuning fork.
- Proportion of patients assigned to the intervention arm who complete 60% of acupuncture treatments.
- Incidence of pain, fatigue, nausea, and anxiety as measured by patient-reported (NCI PRO-CTCAE, BPI, oral dysesthesia) and provider-assessed (CTCAE version 5) grading scales.

16.3 Sample Size and Power

This is a pilot study in which preliminary estimates of CIPN severity will be obtained under two treatment conditions. Complete data from 50 patients will provide 80% power to detect a difference in EORTC-CIPN-20 of 0.7 standard deviation units, based on a t-test with 1-sided alpha=0.05. To account for 10% potential loss to follow-up, we will enroll 56 patients, 28 on the intervention arm of acupuncture/acupressure and 28 on the standard-of-care arm. Patients who enroll, but are not treated, or received less than one cycle of chemotherapy with associated study-specific treatment (including any planned acupuncture sessions for that cycle), may be replaced as detailed in section 11.0.

16.4 Randomization

Patients will be randomized 1:1 between the intervention arm and control arm.

16.5 Statistical Analysis

Severity of CIPN (EORTC-CIPN-20 score) at 3 months will be summarized for each treatment arm, and treatment comparisons made via linear regression model with adjustment for baseline severity level. Adherence to acupuncture treatment among patients in the intervention arm will be described as a proportion with 95% confidence interval. Reasons for treatment non-adherence and delivered dose intensity of chemotherapy will be noted. Incidences of CIPN (grade 2 or higher), pain, fatigue,

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nausea, and anxiety will be compared between treatment arms using Chi-squared or Fisher's exact tests as appropriate. As this is a pilot study, we will not have adequate power to adjust for covariates such as age, gender, and existing comorbidities.

16.6 Ethnic and Gender Distribution Chart

Projected Target Accrual
ETHNIC AND GENDER DISTRIBUTION CHART

TARGETED / PLANNED ENROLLMENT: 60			
Ethnic Category	Sex / Gender		
	Females	Males	Total
Hispanic or Latino	2	3	5
Not Hispanic or Latino	21	30	51
Ethnic Category Total of All Subjects*	23	33	56
Racial Categories			
American Indian / Alaska Native	0	1	1
Asian	2	4	6
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	2	3
White	18	23	41
More Than One Race	2	3	5
Racial Categories: Total of All Subjects*	23	33	56

17.0 INVESTIGATOR OBLIGATIONS

The PI is responsible for the conduct of the clinical trial at the site and is responsible for personally overseeing the treatment of all study subjects. The PI must assure that all study site personnel, including sub-Investigators and other study staff members, adhere to the study protocol and to all applicable regulations and guidelines regarding clinical trials both during and after studycompletion.

All subjects are informed of the nature of the program, its possible hazards, and their right to withdraw at any time, and each subject signs a form indicating their consent to participate prior to receiving any study-related procedures (see Appendix B).

18.0 ADMINISTRATIVE AND REGULATORY CONSIDERATIONS

18.1 Pre-Study Documentation

The following documentation will be filed prior to initiation of the trial: curricula vitae of the PI and all Sub-Investigators; copy of the correspondence from the IRB/EC indicating approval of the protocol and Informed Consent Forms, signed by the IRB/EC chairperson or designee; an IRB/EC membership list containing the names and occupations of the IRB/EC members; copy of the Informed Consent Forms that were reviewed and approved by the IRB/EC.

18.2 Study Site Training

Before initiation of the study, the PI or her designated representatives will review and discuss the following items with the Investigator and clinic staff: the protocol, study procedures, record keeping and administrative requirements, drug accountability, AE reporting, Good Clinical Practice guidelines, CRF/eCRF completion guidelines, monitoring requirements, and the ability of the site to satisfactorily complete the protocol. Additional documents with instructions for study compliance and CRF/eCRF completion will be provided.

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18.3 Documentation

The PI and study staff will maintain a comprehensive and centralized filing system containing all study-related documentation. These files must be suitable for inspection by any applicable regulatory agencies/competent authorities at any time, and should consist of the following elements: subject files (complete medical records, laboratory data, supporting source documentation, and the Informed Consent); study files (the protocol with all amendments, copies of all pre-study documentation, and all correspondence between the Competent Authorities, IRB/EC, etc.).

18.4 Access to Source Data

The PI will permit applicable regulatory authorities to monitor the study as needed. The CRF/eCRF and related source documents will be reviewed in detail by applicable regulatory authorities as needed. Only original source documents are acceptable for review. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm information contained in the CRF/eCRF, such as past history, secondary diagnoses, and concomitant medications. Other study records, such as correspondence with Competent Authorities, and IRB/EC and screening logs will also be inspected. All source data and study records must also be available for inspection by representatives of regulatory agencies.

18.5 Data Collection

Data will be collected and stored in an electronic database. Any changes or corrections made to the CRF/eCRF must be subsequently reviewed and signed by the PI. All data fields in the CRF/eCRF must be completed.

18.6 Protocol Interpretation and Compliance

The procedures defined in the protocol are carefully reviewed by the PI and his/her staff prior to the time of study initiation to ensure accurate representation and implementation. Protocol amendments, if any, are reviewed and implemented promptly following IRB/EC and relevant Competent Authorities approval.

18.7 Disclosure of Data/Publication

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Such medical information may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by regulatory agencies, the Sponsor or its designee and by the IRB/EC. It is anticipated that the final results of this study will be submitted to a peer-reviewed scientific journal. Authorship on such a paper will be acknowledged with customary scientific practice.

18.8 Ethical Considerations

The Investigator agrees to conduct this study in accordance with applicable United States FDA clinical trial regulations and guidelines, applicable United States FDA clinical trial regulations and guidelines, the ICH (E6) GCP guidelines, the IRB/EC and local legal requirements and with the Declaration of Helsinki (1989). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the applicable regulatory agencies.

18.9 Informed Consent

The PI assumes the responsibility of obtaining written Informed Consent for each subject or the subject's legally authorized representative before any study-specific procedures are performed. Subjects meeting the criteria set forth in the protocol will be offered the opportunity to participate in the study. To avoid introduction of bias, the Investigator must exercise no selectivity with regard to offering eligible subjects the opportunity to participate in the study. Subjects or parents/legal guardians of all candidate subjects will receive a comprehensive explanation of the proposed treatment, including the nature of the therapy, alternative therapies available, any known previously experienced adverse reactions, the investigational status of the study treatment, and other factors that are part of obtaining a proper Informed Consent. Subjects will be given the opportunity to ask questions concerning the study, and adequate time to consider their decision to or not to participate.

Informed Consent will be documented by the use of a written Consent Form that includes all the elements required by FDA regulations and ICH guidelines. The form is to be signed and dated by the subject or subject's legally authorized representative and by the person who administers the consent process. A copy of the signed form will be given to the person who signed it, the original signed Consent Form will be filed with the subject's medical records, and copy maintained with the subject's study records. The date and time of time of the Informed Consent must be recorded in the source documents.

If an amendment to the protocol changes the subject participation schedule in scope or activity, or increases the potential risk to the subject, the Informed Consent Form must be amended. Any amended Informed Consent must be

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approved by the IRB/EC prior to use. The revised Informed Consent Form must be used to obtain re-consent from any subjects currently enrolled in the study if the subject is affected by the amendment, and must be used to document consent from any new subjects enrolled after the approval date of the amendment.

18.10 Institutional Review Board/Ethics Committee

The PI will assure that an appropriately constituted IRB/EC that complies with the requirements of 21 CFR Section 56 or written assurance of compliance with ICH (E6) guidelines will be responsible for the initial and continuing review and approval of the clinical study. Before initiation of the study, the PI or designee will forward copies of the protocol and Consent Form to be used for the study to the IRB/EC for its review and approval.

The PI or designee will also assure that all changes in the research activity and all unanticipated problems involving risks to human subjects or others will be reported promptly to the IRB/EC, and that no changes will be made to the protocol without prior Sponsor and IRB/EC approval, except where necessary to eliminate apparent immediate hazards to human subjects.

The Investigator or designee will be responsible for submitting periodic progress reports to the IRB/EC at intervals appropriate to the degree of subject risk involved in the study, but not less than once per year and at the completion or termination of the study.

18.11 Subject Privacy

The Investigators affirm and uphold the principle of the subject's right to privacy. The Investigators shall comply with applicable national and local privacy laws.

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20.0 APPENDICES

Appendix A: ECOG Performance Status Scale
Appendix B: Study Calendar
Appendix C: Location of Acupuncture and Acupressure Points
Appendix D: EORTC QLQ CIPN-20
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20.1 APPENDIX A: ECOG Performance Status Scale

ECOG Performance Status Scale

GRADE	SCALE
0	Fully active, able to carry out all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

20.2 APPENDIX B: Study Calendar

Study Calendar

Procedure	Screening within 14 days	Cycle 1		Cycles 2-3[6]		Cycle 4[6]			Cycles 5-6[6]		End of Tx[7]		Waitlist control visit[8]
		Day 1	Day 3	Day 1	Day 3	Day 1	Day 3	Day 8 ± 2 days	Day 1	Day 3			
Physical Exam[1]	X	X		X		X			X		X		X
Medical History	X	X		X		X			X		X		
Pregnancy Test	X												
CBC[2]	X	X		X		X			X				
Oxaliplatin-based chemotherapy		X		X		X			X				
Acupuncture treatment		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]		X[3]	X[3]			X
Acupressure training[3,4]		X		X	X								
Acupressure diary review				X		X			X		X		
Cryotherapy		X		X		X			X				
AE Assessment		X		X		X			X		X		X[9]
PROs[5]		X				X		X[5]			X		
Neuropen, tuning fork		X				X					X		
Acupuncture Expectancy Scale	X												

[1] On day 3, only vital signs are needed (a complete physical exam is not required). For waitlist control visits, this will include notation of pulse, tongue color, and any other findings considered notable to the acupuncturist

[2] Labs may be obtained up to 3 days prior. If lab values are below the accepted treatment thresholds, they must be repeated and above treatment parameters before treatment delivery.

[3] Patients in Arm A (intervention arm) only

[4] Acupressure retraining will be completed at the cycle 2, day 1 visit if a patient has completed <50% of the prescribed regimen

[5] PROs for all time points: EORTC QLQ CIPN-20, NCI-PRO CTCAE, BPI, oral symptoms. At C4D8, a sub-set of the PROs will be re-administered: EORTC QLQ CIPN-20, NCI-PRO CTCAE, BPI

[6] Study procedures will be timed with patient chemotherapy. If chemotherapy is delayed, then the acupuncture, acupressure, and standard-of-care treatments will be delayed accordingly.

[7] See section 9.9 for a description of the permitted time range for the EOT visit.

[8] Patients in Arm B (control arm) only

[9] Limited AE assessment of acupuncture-associated toxicities (bruising, bleeding, pain, other) will be assessed, as well as chief complaint, and any other major considerations for the acupuncturist.

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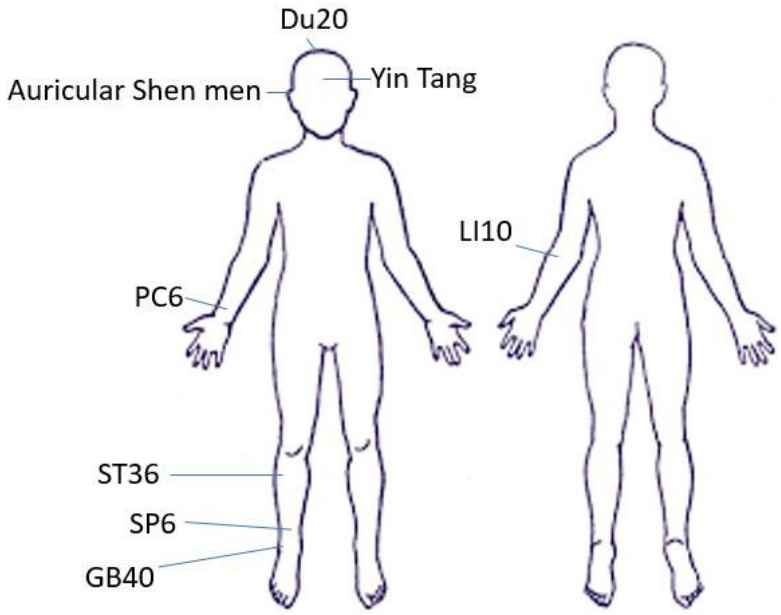
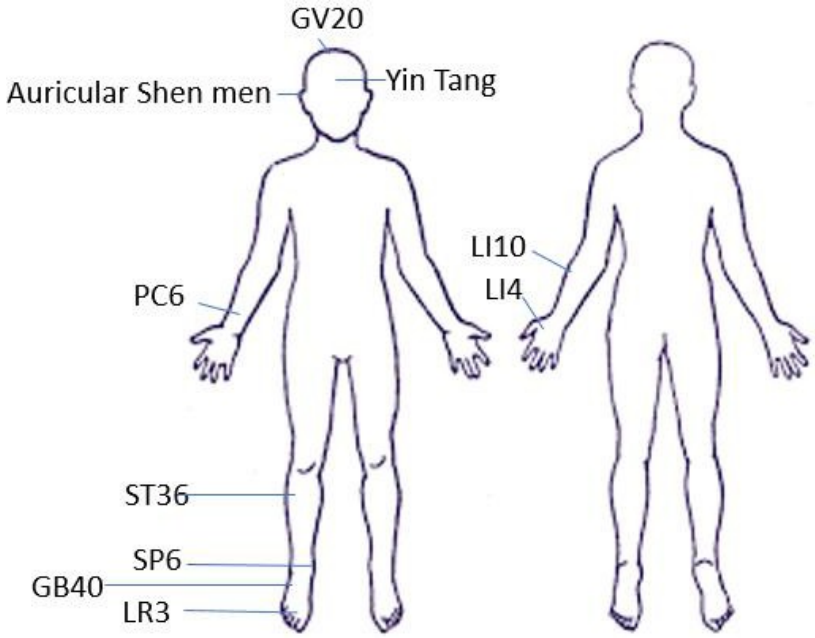
20.3 APPENDIX C: Location of Acupuncture and Acupressure Points

Location of acupuncture points. All points needled bilaterally (except midline points)
Day 1 Acupuncture Protocol



Day 3 Acupuncture Protocol



Location of acupressure points. All points pressured bilaterally (except midline GV20)

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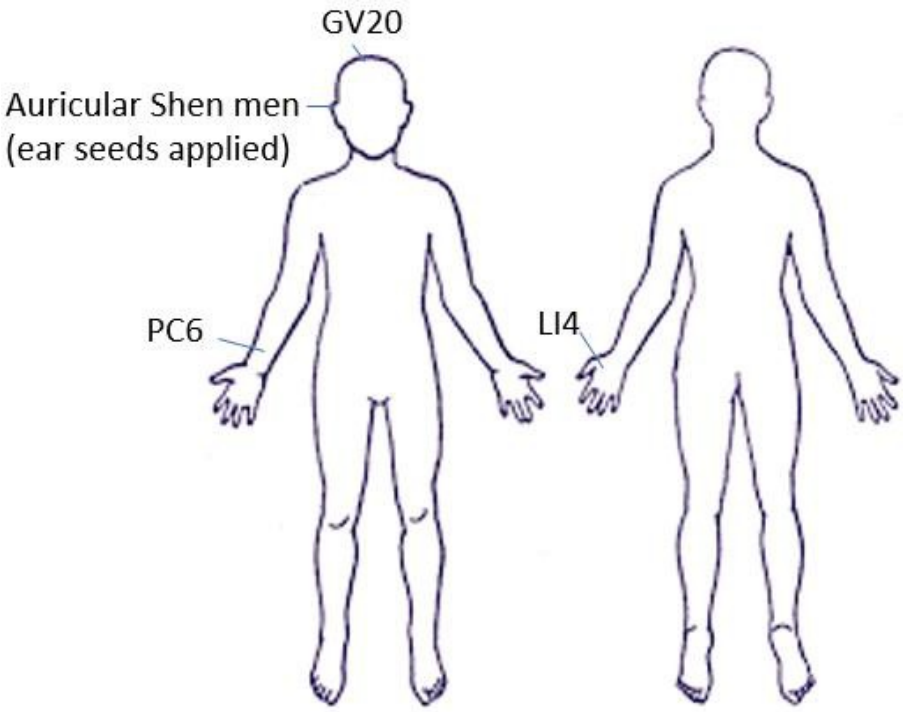

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20.4 APPENDIX D: EORTC QLQ CIPN-20

EORTC QLQ – CIPN20				
Patients sometimes report that they have the 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.				
	Not at all	**A little**	**Quite a bit**	**Very much**
During the past week				
1. Did you have tingling fingers or hands?	1	2	3	4
2. Did you have tingling toes or feet?	1	2	3	4
3. Did you have numbness in your fingers or hands?	1	2	3	4
4. Did you have numbness in your toes or feet?	1	2	3	4
5. Did you have shooting or burning pain in your fingers or hands?	1	2	3	4
6. Did you have shooting or burning pain in your toes or feet?	1	2	3	4
7. Did you have cramps in your hands?	1	2	3	4
8. Did you have cramps in your feet?	1	2	3	4
9. Did you have problems standing or walking because of difficulty feeling the ground under your feet?	1	2	3	4
10. Did you have difficulty 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 manipulating small objects with your fingers (for example, fastening small buttons)?	1	2	3	4

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13. Did you have difficulty opening a jar or bottle because of weakness in your hands?	1	2	3	4
During the past week				
14. Did you have difficulty walking because your feet dropped downwards?	1	2	3	4
15. Did you have difficulty 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
18. Did you have difficulty hearing?	1	2	3	4
Please answer the following question only if you drive a car				
19. Did you have difficulty using the pedals?	1	2	3	4
Please answer the following question only if you are a man				
20. Did you have difficulty getting or maintaining an erection?	1	2	3	4

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20.5 APPENDIX E: NCI PRO-CTCAE

NCI PRO-CTCAE

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

1.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

2.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

3.	In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

4.	In the last 7 days, how OFTEN did you have PAIN?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your PAIN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PAIN INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

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5.	In the last 7 days, what was the SEVERITY of your INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

6.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

7.	In the last 7 days, how OFTEN did you feel ANXIETY?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost con-stantly
	In the last 7 days, what was the SEVERITY of your ANXIETY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ANXIETY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

8.	In the last 7 days, how OFTEN did you FEEL THAT NOTHING COULD CHEER YOU UP?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost con-stantly
	In the last 7 days, what was the SEVERITY of your FEELINGS THAT NOTHING COULD CHEER YOU UP at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FEELING THAT NOTHING COULD CHEER YOU UP INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

9.	In the last 7 days, how OFTEN did you have SAD OR UNHAPPY FEELINGS?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost con-stantly
	In the last 7 days, what was the SEVERITY of your SAD OR UNHAPPY FEELINGS at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did SAD OR UNHAPPY FEELINGS INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

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20.6 APPENDIX F: Brief Pain Inventory

Brief Pain Inventory

Please rate your pain by circling the one number the 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

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20.7 APPENDIX G: Oral symptoms questionnaire

ORAL SYMPTOMS QUESTIONNAIRE: Think about any cold sensitivity you may have experienced in your mouth in the past 2 weeks.

Please circle the most accurate response to each item:

I have had sensations of prickling, burning, tingling, or pins and needles in my mouth	Not at all	I've had this rarely	I've had this occasionally	I've had this frequently	I've have this constantly
Drinking or eating cold things causes strange sensations in my mouth, such as prickling, burning, or pins and needles	Not at all	I've had this rarely	I've had this occasionally	I've had this frequently	I've have this constantly
These symptoms have made it difficult for me to eat or drink cold foods and/or beverages	Not at all	My symptoms rarely limit me	My symptoms occasionally limit me	My symptoms frequently limit me	My symptoms constantly limit me
The sensations in my mouth have made it difficult for me to eat or drink *anything*	Not at all	My symptoms rarely limit me	My symptoms occasionally limit me	My symptoms frequently limit me	My symptoms constantly limit me
My quality of life is lower because of the sensations in my mouth	Not at all	My quality of life is mildly lower	My quality of life is moderately lower	My quality of life is severely lower	My quality of life is ruined
I would characterize my symptoms as:	Nonexistent	Mild	Moderate	Severe	Intolerable

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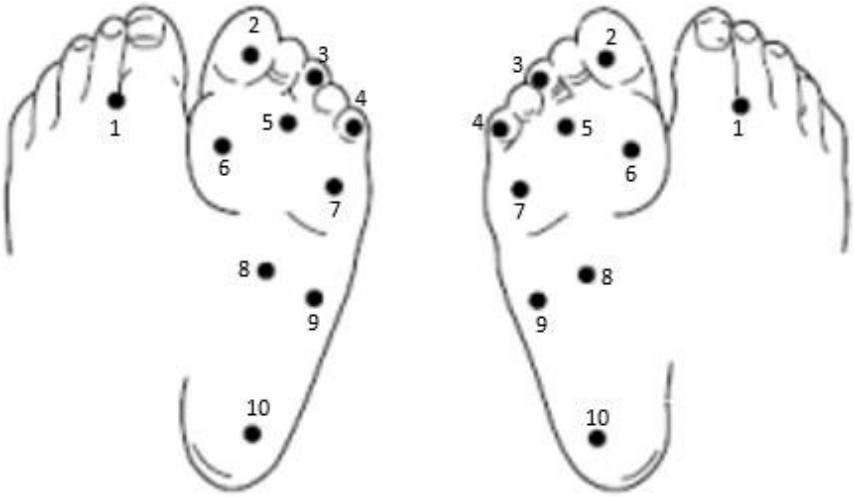
20.8 APPENDIX H: Neuropen Assessment Points

Sites on the feet to be evaluated with Neuropen monofilament and Neurotip



Left foot

Right foot

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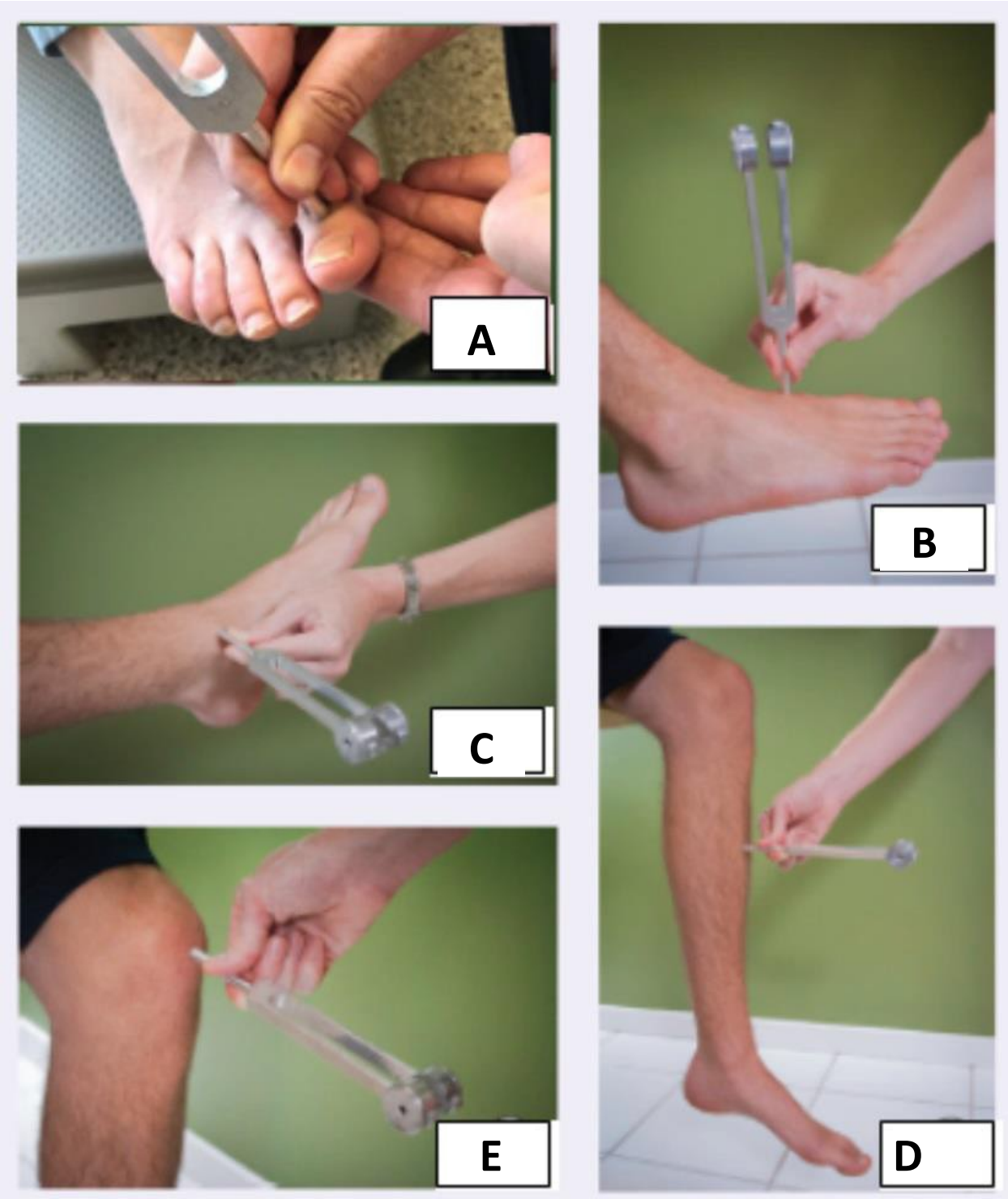
20.9 APPENDIX I: Tuning Fork Assessment Points

Sites on the feet to be evaluated with the tuning fork



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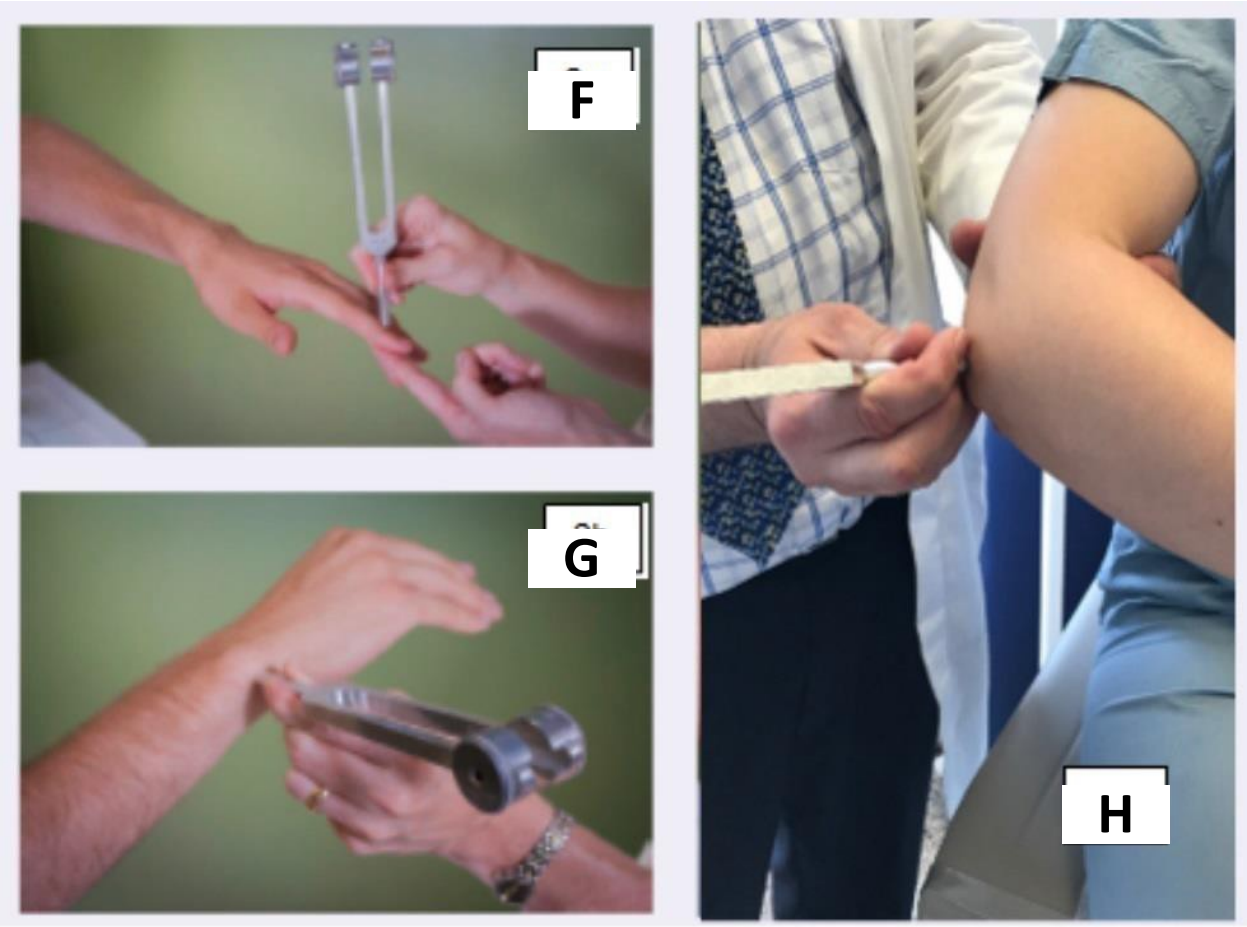
Note: The tuning fork is firmly tapped on the palm and then placed on the interphalangeal joint of the great toe (A). If vibration sensation is diminished or absent in the great toe, testing should be performed at the middorsal foot (B) and the medial malleolus (C), followed by the mid-fibular (D) and patellar (E) regions.



Note: The tuning fork is firmly tapped on the palm and then placed at the distal interphalangeal joint of the index finger (F), the ulnar styloid (G), and the lateral epicondyle (H).

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20.10 APPENDIX J: Acupressure Diary

Acupressure Weekly Diary

Complete the diary on the back each day and bring it to your Day 1 acupuncture sessions

Mark each time you complete your self-acupressure sessions

A session consists of stimulating all four acupoints for a total of seven areas

Use the Comments area for questions or were not able to complete the full session

Brief Summary of Acupoint Locations and Instructions

Use your thumb or fingertips to apply gentle, firm pressure to each point

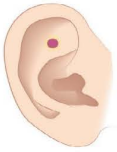
Press and hold or make circular motions on the acupoint, do not press so hard that it hurts

These acupressure points help prevent or decrease pain, nausea, fatigue and anxiety

Apply acupressure to each of these points on your left and right hands for two minutes

Apply acupressure to this point on the center of your head

Apply acupressure to the point on each ear for 30 seconds



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Study ID:				Date *Cycle Day 1*		
Cycle # *circle one*	1	2	3	4	5	6
	Session #1	Session #2	Session #3	Comments		
Day 1				*Acupuncture in clinic*		
Day 2						
Day 3				*Acupuncture in clinic*		
Day 4						
Day 5						
Day 6						
Day 7						
Day 8				*Remove Vaccaria Ear Seeds*		
Day 9						
Day 10						
Day 11						
Day 12						
Day 13						
Day 14						

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20.11 APPENDIX K: Acupuncture Expectancy Scale

For each statement, please choose the closest answer

Every individual may have different expectation of the effects of acupuncture. If we use the following statements to describe your expectation of acupuncture's effect on your treatment side effects after the entire course of acupuncture therapy, how much do you agree?

		Not at all agree	Agree a little	Moderately agree	Mostly agree	Completely agree
1	My treatment side effects will improve a lot.					
2	I will be able to cope with my treatment side effects better.					
3	The symptoms of my treatment side effects will disappear.					
4	My energy level will increase.					

		Acupuncture and acupressure during treatment?	Waitlist, with the option of receiving acupuncture after your treatment is complete?
5	Which of the two treatment assignments do you prefer?		

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20.12 APPENDIX L: Acupressure Ear Seed Care Instructions

Seattle Cancer Care Alliance

Acupressure Ear Seed Care Instructions

RG1121095 (PI: Cohen)

Home care for your acupressure seed treatment

Acupressure seed treatments include the placement of small seeds on specific points of the body or ear that serve to help relieve symptoms. The seed is applied to the skin with stick-on-adhesive similar to medical tape. These acupressure seeds are applied topically only. The skin is not punctured and there is no needle inserted. Acupressure seeds may be used as an adjunct to regular acupuncture treatments, to enhance and prolong its effects, or as the primary form of treatment.

Instructions:

- Gently stimulate the points by pressing on the seeds with light to moderate pressure during your acupressure sessions
- It is common to feel some pressure or tenderness when stimulating the seeds

The acupressure seeds do not require any special care, but there are some guidelines and precautions:

- **All acupressure seeds should be removed after 4 days (day 7 of the cycle)**
- **If the acupressure seeds become painful or the surrounding skin becomes red, itchy or sore gently remove the tape and seed**
- Do not replace a used acupressure seed if it comes off accidentally
- Acupressure seeds can be disposed of in the trash

You will have a nonmetallic vaccaria seed placed on one acupoint in the upper part of each ear.

These acupressure seeds are safe if left in during imaging (such as CT, MRI, X-Ray, or PET scans).

Acupressure Seed Care 10/8/21 Page 1 of 1

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20.13 APPENDIX M: Waitlist Acupuncture Voucher

Seattle Cancer Care Alliance

Acupuncture Voucher
RG1121095 (PI: Cohen)

Thank you for participating in the "Pilot study of oral cryotherapy vs. oral cryotherapy plus acupuncture and acupressure to decrease chemotherapy-induced peripheral neuropathy from oxaliplatin-based chemotherapy for GI cancers" study.

You are eligible to receive six (6) acupuncture sessions at no charge.

- All six acupuncture sessions are scheduled as a series of weekly treatments to optimize the potential benefits of acupuncture.
- We recommend that you wear comfortable, loose-fitting clothes to your acupuncture visit.
- Acupuncture will be scheduled in the GI Care Neighborhood or the SCCA Wellness Center, depending on your ongoing treatment plan.
- If you need to cancel your appointment, please notify the GI scheduling team 24 hours in advance of your appointment by calling (206) 606-2282 . Your appointment will be rescheduled at the end of your series of acupuncture appointments. If you are hospitalized or ill and will not make your visit, please let us know that as soon as you are able.
- Missed acupuncture appointments, not cancelled 24 hours in advance, will not be rescheduled.

When you are ready to schedule your series of 6 acupuncture appointments, please:

1. Contact study research coordinator, Taylor Vlaming, to begin the scheduling process at: (206) 606-7350 or tvlaming@seattlecca.org.
2. Next, the GI scheduling team will contact you to schedule your acupuncture treatments.
3. The acupuncture appointments will take place in either the GI Care Neighborhood or the SCCA Wellness Center, depending on your current treatment plan.
4. If you are scheduled in the SCCA Wellness Center, you will receive directions and parking information for acupuncture appointments.
5. All of your acupuncture appointments need to be completed 6 months after you complete study participation.
6. **Your voucher will expire on:** _____

If you have any questions, please call Taylor Vlaming at (206) 606-7350 or email tvlaming@seattlecca.org.

Thank you for your study participation!

RG1121095 (PI: Cohen) – Waitlist Control Acupuncture Voucher 10/08/21 Page 1 of 1

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20.14 APPENDIX N: Research Acupuncture Appointments in the Wellness Clinic

Seattle Cancer Care Alliance

Acupuncture Voucher
RG1121095 (PI: Cohen)

Thank you for participating in the "Pilot study of oral cryotherapy vs. oral cryotherapy plus acupuncture and acupressure to decrease chemotherapy-induced peripheral neuropathy from oxaliplatin-based chemotherapy for GI cancers" study.

You are eligible to receive six (6) acupuncture sessions at no charge.

- All six acupuncture sessions are scheduled as a series of weekly treatments to optimize the potential benefits of acupuncture.
- We recommend that you wear comfortable, loose-fitting clothes to your acupuncture visit.
- Acupuncture will be scheduled in the GI Care Neighborhood or the SCCA Wellness Center, depending on your ongoing treatment plan.
- If you need to cancel your appointment, please notify the GI scheduling team 24 hours in advance of your appointment by calling (206) 606-2282 . Your appointment will be rescheduled at the end of your series of acupuncture appointments. If you are hospitalized or ill and will not make your visit, please let us know that as soon as you are able.
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3. The acupuncture appointments will take place in either the GI Care Neighborhood or the SCCA Wellness Center, depending on your current treatment plan.

4. If you are scheduled in the SCCA Wellness Center, you will receive directions and parking information for acupuncture appointments.

5. All of your acupuncture appointments need to be completed 6 months after you complete study participation.

6. **Your voucher will expire on:** _____

If you have any questions, please call Taylor Vlaming at (206) 606-7350 or email tvlaming@seattlecca.org.

Thank you for your study participation!

RG1121095 (PI: Cohen) – Waitlist Control Acupuncture Voucher 10/08/21 Page 1 of 1

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20.15 APPENDIX O: Cryotherapy Phone Script

Seattle Cancer Care Alliance
Fred Hutch · Seattle Children's · UW Medicine

Cryotherapy Phone Script
RG1121095 (PI: Cohen)

Cryotherapy Phone Script

To be completed within 3 days of the patient visit

- The research team member (treating investigator and/or study coordinator) will introduce himself/herself.
- The research team member will verify patient's identity by asking the patient to state their name and date of birth.
- The research team member will collect the required data:

1. These questions are regarding your treatment given on ___ (date)
2. Did you hold ice chips in your mouth during the oxaliplatin infusion? (yes/no; if yes, ask follow up question 2a)
    a. Approximately how many minutes did you keep ice chips in your mouth? (record as: 0, 1-30, 31-60, 61-90, 91-120, or >120 minutes)
3. Did you put ice packs on your hands? (yes/no; if yes, ask follow up question 3a)
    a. Approximately how many minutes did you keep the ice packs on your hands? (record as: 0, 1-30, 31-60, 61-90, 91-120, or >120 minutes)
4. Did you put ice packs on your feet? (yes/no; if yes, ask follow up question 4a)
    a. Approximately how many minutes did you keep the ice packs on your feet? (record as: 0, 1-30, 31-60, 61-90, 91-120, or >120 minutes)

- The research team member will then ask the participant if they have any additional questions or additional information to share

Cryotherapy Phone Script 11/17/21 Page 1 of 1

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20.16 APPENDIX P: Cryotherapy Questionnaire

Pilot study of oral cryotherapy vs. oral cryotherapy plus acupuncture and acupressure to decrease chemotherapy-induced peripheral neuropathy from oxaliplatin-based chemotherapy for GI cancers

NAME:_____

Treatment Date:_____

*Please circle the approximate time you kept the ice chips in your **mouth** during the oxaliplatin infusion*

0 (not used)	61-90 min
1-30 min	91-120 min
31-60 min	>120 minutes

*Please circle the approximate time you used ice packs on your **hands** during the oxaliplatin infusion*

0 (not used)	61-90 min
1-30 min	91-120 min
31-60 min	>120 minutes

*Please circle the approximate time you used ice packs on your **feet** during the oxaliplatin infusion*

0 (not used)	61-90 min
1-30 min	91-120 min
31-60 min	>120 minutes

Questions? Email: giresearch.SCCA@fredhutch.org
Nurses: Return to GI Research folder or send a scan to the email above.

Pilot study of oral cryotherapy vs. oral cryotherapy plus acupuncture and acupressure to decrease chemotherapy-induced peripheral neuropathy from oxaliplatin-based chemotherapy for GI cancers

NAME:_____

Treatment Date:_____

*Please circle the approximate time you kept the ice chips in your **mouth** during the oxaliplatin infusion*

0 (not used)	61-90 min
1-30 min	91-120 min
31-60 min	>120 minutes

*Please circle the approximate time you used ice packs on your **hands** during the oxaliplatin infusion*

0 (not used)	61-90 min
1-30 min	91-120 min
31-60 min	>120 minutes

*Please circle the approximate time you used ice packs on your **feet** during the oxaliplatin infusion*

0 (not used)	61-90 min
1-30 min	91-120 min
31-60 min	>120 minutes

Questions? Email: giresearch.SCCA@fredhutch.org
Nurses: Return to GI Research folder or send a scan to the email above