Protocol #: LCI-SUPP-MYE-ACUP-001
TITLE: Acupuncture for Chemo-Induced Peripheral Neuropathy (CIPN) in Multiple Myeloma (MM) Patients- A Randomized Controlled Trial

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Carolinas Myeloma Research Fund

The study will be conducted in compliance with the protocol, ICH/GCP and any applicable regulatory requirements.

PROTOCOL SIGNATURE PAGE

PROTOCOL TITLE: LCI-SUPP-MYE-ACUP-001: Acupuncture for Chemo-Induced Peripheral Neuropathy (CIPN) in Multiple Myeloma (MM) Patients- A Randomized, Controlled Trial

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

_____ _____

Signature of Sponsor-Investigator Date

_____Shamille Hariharan, MD_____

Sponsor-Investigator Name (printed)

SYNOPSIS

TITLE	Acupuncture for Chemo-Induced Peripheral Neuropathy (CIPN) in Multiple Myeloma (MM) Patients- A Randomized, Controlled Trial
STUDY POPULATION	Adult Multiple Myeloma patients with CIPN
SUMMARY OF STUDY RATIONALE	Multiple Myeloma (MM) is a blood cancer of the plasma cells. Treatment for MM includes bortezomib and bortezomib combination chemotherapy which causes Chemotherapy-Induced Peripheral Neuropathy (CIPN) in approximately 30% of patients. CIPN is characterized by sensory symptoms including tingling, numbness, burning, weakness, pain, and aching in the hands and/or feet. Individuals with CIPN experience reduced quality of life (QOL) due to poor physical function, greater disability, falls, reduced functioning, and dose limiting or early discontinuation of anti-cancer treatment. Treatments for CIPN typically include concomitant medications, (e.g., gabapentin, duloxetine) yet these approaches have limited evidence to support clinical use, have side effects, and are not universally effective. Previous research suggests acupuncture is effective in treating CIPN in other populations with few side effects, yet the effect of acupuncture on CIPN among MM patients is poorly understood.
STUDY DESIGN	This study is a randomized, controlled trial in which subjects will be assigned 2:1- 2 to acupuncture intervention to 1 standard subject care. Those assigned to acupuncture will receive a total of 12 sessions over approximately 10 weeks. During the first two weeks, acupuncture will occur twice per week and during weeks 3-10 acupuncture will occur once per week. All subjects will be assessed for sociodemographic and medical characteristics, neuropathy on a scale from 0=*no neuropathy*– 10=*worst possible neuropathy,* the FACT-GOG-NTX scale on CIPN symptoms, physical, social/family, emotional, and functional well-being, other specific symptoms, quality of life, and opioid and concomitant medication intake. Assessments will occur at Baseline, Midpoint, and Endpoint over the approximately 10 weeks subjects will be on study. Comparisons will be made between the intervention and control groups.
OBJECTIVES	*Primary Objective:* To evaluate the effectiveness of acupuncture plus standard subject management versus standard subject management in terms of reduction of neuropathy in multiple myeloma subjects being actively treated with bortezomib diagnosed with CIPN or multiple myeloma subjects who have discontinued bortezomib within the past 12 months but continue to have CIPN (even if they have started new therapy that could cause neuropathy). Neuropathy will be subject reported using an 11-point scale from 0-*No Neuropathy* to 10-*Worst Possible Neuropathy*. *Secondary Objectives:* • To compare subjects with and without acupuncture for the following symptoms assessed by the FACT-GOG-NTX questionnaire:

	• Specific features of CIPN utilizing the NTX sub-scale (e.g. numbness, tingling) • Nausea • Sadness • Nervousness • Sleep quality • Lack of energy • Pain. • To compare subjects with and without acupuncture for the following symptoms assessed by an adaptation of the FACT-GOG-NTX questionnaire: • Constipation • Dizziness • Dry mouth. • To compare Quality of Life in subjects with and without acupuncture using the CDC HRQoL-4 questionnaire. *Safety Objective:* • To summarize adverse events of special interest for subjects receiving acupuncture intervention *Exploratory Objectives:* To compare subjects with and without acupuncture for: • Opioid use, defined by Morphine Equivalent Daily Dose (MEDD) [1] • Concomitant medication use, including gabapentin, duloxetine, pregabalin, etc. • To evaluate whether there is a dose response based on the amount of acupuncture delivered, defined by the number of attended acupuncture sessions from 0 to 12 for those randomized to the acupuncture arm. • To evaluate the effect of acupuncture expectancy for subjects receiving acupuncture intervention

KEY INCLUSION CRITERIA	• Age ≥ 18 years at the time of consent • Subject has diagnosis of multiple myeloma (any stage) • Currently being treated with bortezomib or bortezomib-combination chemotherapy; also allowed are those subjects who have discontinued bortezomib within the past 12 months but continue to have CIPN (even if they have started new therapy that could cause neuropathy) • ECOG Performance status of 0-3 • Life expectancy of ≥ 12 weeks • Subject reported Neuropathy score of ≥2 • No planned hospital admission within the expected time frame of study participation. For potential participants with a transplant in their current MM treatment plan: Post-transplant subjects may enroll when recovered sufficiently from the transplant, i.e. platelets >50 x 10^3/uL, ANC> 0.5 x 10^3/uL, and ECOG performance status is 0-3.
KEY EXCLUSION CRITERIA	• Subjects with neuropathy pain as a result of any other cause other than chemotherapy • Subjects with needle phobia • Previous diagnosis of amyloidosis or POEMS syndrome • Documented local infection at or near the planned acupuncture sites (see Appendix A) • Subjects with metastatic involvement of the nervous system/active central nervous system disease • Plan to receive Healing Touch or Oncology Massage during study participation • Have received acupuncture within 30 days prior to enrollment
STATISTICAL CONSIDERATIONS	This study is designed with a primary objective to evaluate the effectiveness of acupuncture versus standard subject management in terms of reduction of neuropathy in actively treated multiple myeloma subjects diagnosed with CIPN. A Fisher's Exact Test with a 20% two-sided significance level will have 80% power to detect the difference between a standard of care group proportion of 0.10 and a treatment group proportion of 0.35 when the sample sizes are 22 and 44, respectively.
NUMBER OF SUBJECTS	66 evaluable (It is estimated that a total of 75 subjects may be enrolled to achieve 66 evaluable subjects)

SCHEMA

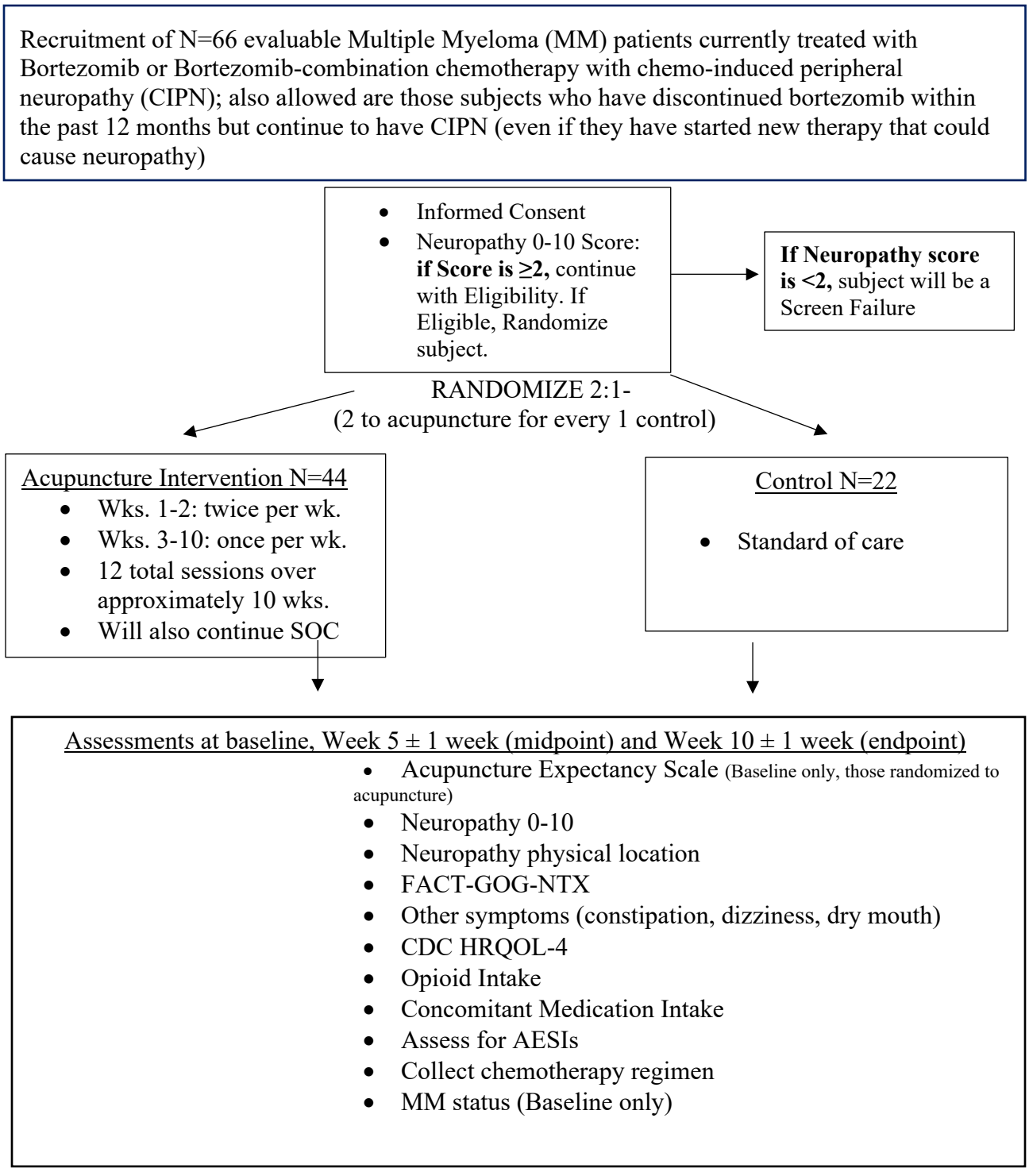
Recruitment of N=66 evaluable Multiple Myeloma (MM) patients currently treated with Bortezomib or Bortezomib-combination chemotherapy with chemo-induced peripheral neuropathy (CIPN); also allowed are those subjects who have discontinued bortezomib within the past 12 months but continue to have CIPN (even if they have started new therapy that could cause neuropathy)
Informed Consent
Neuropathy 0-10 Score: if Score is ≥2, continue with Eligibility. If Eligible, Randomize subject.
If Neuropathy score is <2, subject will be a Screen Failure
RANDOMIZE 2:1-
(2 to acupuncture for every 1 control)
Acupuncture Intervention N=44
Wks. 1-2: twice per wk.
Wks. 3-10: once per wk.
12 total sessions over approximately 10 wks.
Will also continue SOC
Control N=22
Standard of care
Assessments at baseline, Week 5 ± 1 week (midpoint) and Week 10 ± 1 week (endpoint)
Acupuncture Expectancy Scale (Baseline only, those randomized to acupuncture)
Neuropathy 0-10
Neuropathy physical location
FACT-GOG-NTX
Other symptoms (constipation, dizziness, dry mouth)
CDC HRQOL-4
Opioid Intake
Concomitant Medication Intake
Assess for AESIs
Collect chemotherapy regimen
MM status (Baseline only)

TABLE OF ABBREVIATIONS

Abbreviation	*Spelled out abbreviation*
AE	Adverse event
AESI	Adverse event of special interest
BIPN	Bortezomib-induced peripheral neuropathy
CIPN	Chemotherapy-induced peripheral neuropathy
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
ECOG	Eastern Cooperative Oncology Group
EMR	Electronic medical record
ESAS	Edmonton Symptom Assessment Scale
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
LCI	Levine Cancer Institute
MEDD	Morphine Equivalent Daily Dose
MM	Multiple myeloma
QOL	Quality of life
SOPS	Standard operating procedures
STRICTA	Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture
UAP	Unanticipated problems

TABLE OF CONTENTS

1. BACKGROUND AND RATIONALE

1.1 Background

1.1.1 Multiple Myeloma (MM)

MM is a blood cancer of the plasma cells classified as a blood disorder. Plasma cells are white blood cells that produce antibodies to protect against disease and infection. Myeloma hinders the production of antibodies within the bone marrow which leads to reduced immune response and kidney damage. Myeloma also damages bone which leads to bone pain and fractures. [2]

1.1.2 Chemo- Induced Peripheral Neuropathy (CIPN)

First-line treatment for MM is usually bortezomib (Velcade®) or bortezomib combination chemotherapy. [3-5] At Levine Cancer Institute, approximately 85% of MM patients receive bortezomib containing chemotherapy. Although chemotherapy is associated with improved survival, it is neurotoxic and causes CIPN in approximately 30% of patients.[6,7] CIPN is characterized by sensory symptoms including tingling, numbness, burning, weakness, pain, aching in the hands and/or feet, [8] and neuropathic pain in more severe cases. [9] The pathophysiological mechanisms of CIPN are complex and multi-factorial which include oxidative stress, apoptotic mechanisms, altered calcium homeostasis, axon degeneration, membrane remodeling, and neuroinflammation. [10] Bortezomib-induced peripheral neuropathy in MM patients usually presents within the first five cycles of treatment. [11]

Depending on the severity of CIPN, the dose of bortezomib may be reduced or discontinued to avoid debilitating side-effects. Dose reductions and discontinuation of treatment negatively impact the treatment's ability to prolong life. [11] Individuals with CIPN experience reduced quality of life (QOL) due to poor physical function, greater disability, falls, and reduced functioning. [12-15] CIPN may last for years past treatment and is sometimes permanent. [16]

1.1.3 Current Treatments for CIPN

There are no cures for CIPN; it can only be treated. [17] Treatments for CIPN include concomitant medications which target various pathophysiological mechanisms. Pharmacologic options include anticonvulsants (e.g., gabapentin, (Neurontin®, Gralise®), antidepressants (e.g., duloxetine (Cymbalta®)), over-the-counter (e.g. aspirin, ibuprofen),prescription (e.g., celecoxib (Celebrex®)), non-steroidal anti-inflammatory drugs (NSAIDs), and opioids in severe cases unresponsive to other treatments. Topical agents (e.g., amitriptyline, lidocaine) applied to the skin are also options. [18,19] These treatments, however, are not universally effective. Menthol and capsaicin can be used but [18] have side effects and there is limited evidence to support their clinical use.[6] Side effects of anticonvulsants include drowsiness and dizziness, and antidepressants are associated with dry mouth, nausea, drowsiness, dizziness, decreased appetite and constipation. [20] Nonpharmacologic options with varying levels of efficacy include neurostimulation, exercise, nonpharmacologic menthol and capsaicin topical agents, and

acupuncture. [18] For patients open to integrative modalities to lessen CIPN symptoms, acupuncture is a promising intervention.

1.1.4 Acupuncture for CIPN in Multiple Myeloma

Acupuncture is a nonpharmacologic practice within Traditional Chinese Medicine that involves the insertion of thin needles at specific sites on the body, known as acupoints, to affect the body's physical function and induce a therapeutic response. [21] Previous studies show promise for acupuncture's use for peripheral neuropathy in MM, [22-25] however, sample sizes have been small and additional studies are needed. [26]

In 2011, Bao and colleagues reported the first case study of a MM patient who experienced significantly reduced bortezomib-induced peripheral neuropathy (BIPN) after fourteen acupuncture treatments. The patient had significantly reduced neuropathic pain, less requirement for narcotics to treat pain, and improved physical function with minimal side effects. [27] Another case study by Mandıroğlu, Çevik, & Aylı (2014) found complete resolution from a BIPN pain score of eight to zero out of ten after six months of acupuncture without any side effects.

This was followed by a case series of five patients of the same population who all received immediate BIPN-related pain reduction after a single acupuncture treatment. Two of the three patients who had at least three acupuncture sessions experienced lasting pain relief and functional improvement after the last acupuncture session. There were no adverse effects. [23] The same author team then pursued a pilot study of twenty-seven MM patients with BIPN resistant to other medical interventions even after bortezomib had been discontinued. Neuropathic pain was significantly reduced and physical function was significantly improved after ten acupuncture sessions over ten weeks. [25] A feasibility study of nineteen MM patients with BIPN who were given twenty electroacupuncture sessions over nine weeks found significantly improved pain and physical functioning including walking, buttoning buttons and postural stability. [24] A systematic review and meta-analysis of the efficacy of acupuncture for CIPN found that acupuncture can relieve CIPN pain and functional limitations, which warrants larger scale studies.[28]

1.1.5 Acupuncture for Quality of Life and Other Symptoms

While primarily targeting CIPN, other QOL-related symptoms may also improve with acupuncture. Evidence suggests depression, [29,30] fatigue, [31-33] constipation, [34] nausea, vomiting, [35,36] sleep disturbance, [37,38] general pain, [39-42] and dry mouth [43,44] are reduced. Health-related quality of life (HRQOL) can be measured with the validated CDC HRQOL-4. [45,46] Studies indicate that those who expect that acupuncture will be beneficial tend to have better outcomes than those who do not believe acupuncture will have a positive effect. The expectancy effect can be controlled for using the validated Acupuncture Expectancy Scale. [47]

1.1.6 Acupuncture as Potentially Opioid and Concomitant Medication-Sparing

For some patients, the therapeutic benefits of acupuncture may lead to less need for pharmacologic management of symptoms. In a retrospective chart review of military patients,

those who experienced acupuncture had fewer opioid prescriptions and had better symptom control, ability to function and improved sense of well-being. Opioid prescriptions decreased 45%, muscle relaxants 34%, NSAIDs 43%, and benzodiazepines 14%. [48] In a small study of 35 chronic pain patients, electroacupuncture was associated with a more rapid reduction in opioid-like medications compared to sham electroacupuncture.[49]

1.1.7 Safety and Patient Acceptability of Acupuncture

Acupuncture is a low-cost treatment option [50,51] that is in-demand by patients. [52,53] It generally has very few adverse events (AEs) and is considered safe when provided by qualified acupuncturists. AEs can include minor bleeding, pain and/or bruising at the needling site, fatigue, sweating, and faintness (also called "needle shock"). [54] Serious AEs including infections, blood-borne diseases, and internal organ or tissue injury are rare. [55] In a study of 65,000 treatments over six years in Japan, only 94 minor AEs were reported. [56] In a study of over 760,000 treatments among 97,733 patients in Germany, there were 6 cases of potentially serious AEs including worsened depression, hypertensive crisis, asthma attack, vasovagal reaction, and pneumothorax. [57] Cancer patients are at higher risk for AEs than non-oncology patients. AE risk can be reduced by employing oncology-trained acupuncturists, following Clean Needling Technique (hand hygiene, using disposable needles, discarding used needles into sharps containers) and recommending against acupunture for those with conditions including neutropenia, thrombocytopenia, tumor involvement at the needling site, and other unstable medical conditions as determined by the acupuncturist and health care team, including oncologists. [55]

1.2 Study Rationale and Study Design

This randomized, controlled trial (see Schema) is designed to evaluate the effect of acupuncture on CIPN, other symptoms, and potential opioid and concomitant medication sparing effects in comparison to standard of care management in MM subjects. We hypothesize that acupuncture will be associated with: 1) a clinically significant and statistically significant reduction in CIPN; 2) statistically significant reduction of other symptoms such as nervousness and lack of energy; and 3) statistically significantly improved QOL at ten weeks. We also theorize that acupuncture will be opioid and concomitant medication sparing at ten weeks. We expect that the dose of acupuncture received will impact the outcomes, with higher doses of acupuncture being associated with better outcomes.

This study is novel in that it will be, to our knowledge, 1) the largest randomized, controlled trial to examine the effect of acupuncture on CIPN in MM patients 2) the first to explore the impact of acupuncture on opioid and concomitant medication intake.

This project aims to strengthen the care of persons with MM by improving quality of life (QOL) and ability to perform daily activities through reduced CIPN symptoms. CIPN debilitates and erodes QOL by preventing individuals from pursuing their normal activities of daily living. The features of CIPN, including physical, social/family, emotional, functional, and specific CIPN

symptoms, will be measured with the validated FACT-GOG-NTX. [58]This project brings necessary attention and scientific inquiry to supportive cancer care, which is sometimes de-prioritized behind disease treatment. [59,60] The potential for nonpharmacologic acupuncture to reduce CIPN and other symptoms with minimal side effects has beneficial implications for disease treatment. Patients with controlled symptoms are better able to tolerate life-prolonging treatment and avoid chemotherapy dose reductions which result from neurotoxic side effects of chemotherapy. [11,61,62].

African Americans are twice as likely to develop MM compared to Caucasians,[63,64] yet are less likely to receive supportive care to address side effects and QOL issues. [65,66] At Levine Cancer Institute, approximately one-third of MM patients are African American. Acupuncture can strengthen the care of persons with MM by supporting their treatment and improving QOL. This study may promote health equity by treating a marginalized population. While there is not an aim to examine disparities, it is important to highlight the vulnerability of the population.

Subjects will be referred from myeloma, palliative or supportive oncology clinics at Levine Cancer Institute. Subjects who consent and are determined to be eligible will be randomized to receive either acupuncture treatment or standard of care treatment for their CIPN. Subjects' sociodemographics, medical history, opioid and concomitant medication intake information will be collected. Subjects who are randomized to the acupuncture treatment arm will receive 12 sessions of acupuncture over approximately 10 weeks and their CIPN will continue to be treated by their physician. Subjects randomized to standard of care will continue only with standard of care therapy per their physician for treatment of their CIPN. All subjects will complete questionnaires at Baseline, midpoint, and endpoint. Responses to questionnaires will then be analyzed towards answering the study's objectives.

2. STUDY OBJECTIVES

2.1 Objectives

2.1.1 Primary Objective

- The primary objective of this study is to evaluate the effectiveness of acupuncture plus standard subject management versus standard subject management in terms of reduction of neuropathy in multiple myeloma subjects actively treated with bortezomib diagnosed with CIPN or multiple myeloma subjects who have discontinued bortezomib within the past 12 months but continue to have CIPN (even if they have started new therapy that could cause neuropathy). Neuropathy will be subject reported using an 11-point scale from 0-*no neuropathy* to 10-*worst possible neuropathy*.

2.1.2 Secondary Objectives

- To compare subjects with and without acupuncture for the following symptoms assessed by the FACT-GOG-NTX questionnaire:
    - Specific features of CIPN utilizing the NTX sub-scale (e.g. numbness, tingling)
    - Nausea

  - Sadness
  - Nervousness
  - Sleep quality
  - Lack of energy
  - Pain

- To compare subjects with and without acupuncture for the following symptoms assessed by an adaptation of the FACT-GOG-NTX questionnaire:
  - Constipation
  - Dizziness
  - Dry mouth.

- To compare Quality of Life in subjects with and without acupuncture using the CDC HRQoL-4 questionnaire.

2.1.3 Safety Objective

- To summarize adverse events of special interest for subjects receiving acupuncture intervention

2.1.4 Exploratory Objectives

- Exploratory objectives are to compare subject with and without acupuncture for:
  - Opioid use, defined by Morphine Equivalent Daily Dose (MEDD) [1]
  - Concomitant medication use, including gabapentin, duloxetine, pregabalin, etc.
- To evaluate whether there is a dose response based on the amount of acupuncture delivered, defined by the number of attended acupuncture sessions from 0 to 12, for subjects randomized to the acupuncture arm.
- To evaluate the effect of acupuncture expectancy for subjects receiving acupuncture intervention

3. SUBJECT SELECTION

3.1 Subject Identification and Recruitment

Adult subjects will be recruited at Levine Cancer Institute (LCI). Subjects will be recruited regardless of their sex, race, and ethnicity.

3.2 Inclusion Criteria

Subject must meet all the following applicable inclusion criteria to participate in this study:

1. Written informed consent and HIPAA authorization for release of personal health information. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.

2. Age ≥ 18 years at the time of consent

3. Subject has diagnosis of Multiple Myeloma (any stage)

4. Currently being treated with bortezomib or bortezomib-combination chemotherapy OR subjects who have discontinued bortezomib within the past 12 months but continue to have CIPN (even if they have started new therapy that could cause neuropathy)

5. ECOG Performance status of 0-3

6. Life expectancy of ≥ 12 weeks

7. Subject-reported Neuropathy score of ≥2

8. No planned hospital admission within the expected time frame of study participation. For potential participants with a transplant in their current MM treatment plan: Post-transplant subjects may enroll when recovered sufficiently from the transplant, i.e. platelets >50 x 10^3/uL, ANC> 0.5 x 10^3/uL, and ECOG performance status is 0-3.

9. As determined by the enrolling physician, ability of the subject to understand and comply with study procedures for the entire length of the study

3.3 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Uncontrolled intercurrent illness/medical condition or psychiatric illness/social situations that would limit compliance with study requirements as determined by the investigator

2. Subjects with neuropathy pain as a result of any other cause other than chemotherapy

3. Subjects with needle phobia

4. Previous diagnosis of amyloidosis or POEMS syndrome

5. Documented local infection at or near the planned acupuncture sites (see Appendix A) as determined by the enrolling investigator

6. Subjects with metastatic involvement of the nervous system/active central nervous system disease

7. Plan to receive Healing Touch or Oncology Massage during study

8. Have received acupuncture within 30 days prior to enrollment

3.4 Screen Failures

A subject who, for any reason (e.g., failure to satisfy the eligibility criteria or withdraws consent), terminates his/her study participation before randomization is regarded as a "screen failure." All screen failures will be tracked. Reasons (e.g. specific inclusion/exclusion criteria) for screen failure will be recorded in the dataset.

4. SUBJECT ALLOCATION

4.1 Randomization

Subjects will be randomized in a 2:1 fashion to either acupuncture plus standard subject management or standard of care alone and assigned a Sequence Number. This will be accomplished utilizing the CTMS, whereby a list of Sequence Numbers and associated treatment arm assignments randomly generated prior to study activation will be uploaded by a member of the Levine Cancer Institute Biostatistics Core. The Sequence Number will be a four digit, randomly generated ID number, ranging from 0001 to 9999. A stratified block randomization will be utilized including the following stratification factors to reduce confounding of comparisons between the treatment arms:

- Baseline neuropathy score (neuropathy score 2 – 6 vs 7 – 10)

Blinding will not be possible within this trial because the subjects and study personnel will be able to decipher intervention from control based on the study activities. Those exposed to acupuncture will understand that they are in the intervention group and those given standard of care only will understand that they are in the control group. If a subject in the control group has an acupuncture session while enrolled, they will be discontinued from the study and all further assessments at that point.

5. STUDY PLAN

See Schema

This randomized, controlled trial is designed to evaluate the effect of acupuncture on CIPN, other symptoms, and potential opioid and concomitant medication sparing effects in comparison to standard of care management in MM subjects. Enrollment in this study should not affect subject care in any way. Subjects will not be reimbursed for study participation; however, the acupuncture treatments will be covered by the study and will be at no cost to the subject. This study will open as a single center study at LCI Morehead.

Potential participants with a transplant in their current MM treatment plan: Subjects may be enrolled in this study either prior to stem cell transplant or after they have completed their transplant. Subjects will be enrolled prior to transplant if they are able to complete the study prior to hospitalization for transplant. Subjects will be enrolled post-transplant if scheduling will not allow them to complete the study prior to hospitalization or transplant. Post-transplant

subjects may enroll when recovered sufficiently from the transplant, i.e. platelets >50 x 10^3/uL, ANC> 0.5 x 10^3/uL, and ECOG performance status is 0-3.

Subjects will be enrolled over approximately twelve months. Each enrolled subject will be on study for approximately 3 to 4 months.

5.1 Study Intervention

Study subjects in the intervention arm will experience acupuncture in a group setting when possible to resemble the conditions of regular clinical practice at Levine Cancer Institute, therefore enhancing external validity and the ability to apply the conclusions of the study to "real-world" contexts outside of the study setting. For as long as COVID-19 is a concern, the acupuncture team will follow these additional safety measures: subjects will be seated at an appropriate distance apart and wear masks, and additional time will be allotted between sessions to allow for additional, thorough cleaning/sanitizing of equipment.

The acupuncture sessions will begin with a more intensive, twice weekly treatment for the first two weeks and taper to once per week for the remaining eight weeks. This amounts to 12 total sessions over approximately 10 weeks.
The acupuncture procedure and specific acupoints will be performed in accordance with the Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) guidelines [67] in **Appendix A**.

Consenting and all conversations with subjects regarding their medical history and medications will be held privately. Questionnaires will also be administered privately. All subjects will be able to answer the questionnaires via two options: 1) on paper (in person or via certified mail) or 2) via RedCap electronic survey. Phone contact for questionnaires is acceptable if unable to be completed by other stated routes. The form of questionnaire administration will be based on the appointment situation, needs and/ or preference of the subject, and subject access to technology (e.g., computer, tablet, smartphone). Subject will need to be willing to provide an active email to which the questionnaires can be sent to utilize the electronic survey option.

Subjects randomized to the control arm will have their CIPN treated by their physician per standard of care. Subjects randomized to the intervention arm will begin acupuncture sessions within two weeks of enrollment and will continue their SOC treatment for CIPN as per their physician.

Subjects in both the treatment arm and the control arm will complete the study questionnaires at protocol defined timepoints, even if bortezomib/bortezomib-combination therapy is removed from their treatment regimen during the study (for those on active treatment). Questionnaires should be completed at protocol defined timepoints even if those on the acupuncture arm have not received the acupuncture session on schedule or if sessions are missed.

5.2 Missed Study Assessments

If data from questionnaires are missing, when possible, the reason for the missing data will be categorized and documented as follows:

- subject felt too ill;
- clinician or nurse felt the subject was too ill;
- subject felt it was inconvenient or took too much time;
- subject felt it was a violation of privacy;
- subject didn't understand the actual language or was illiterate;
- administrative failure to distribute the questionnaire;
- not required at this time point;
- other, specify;
- unknown

5.3 Sociodemographics, Medical History, Opioid and Concomitant Medication Intake

The electronic medical record (EMR) will be consulted to abstract demographic, medical history, opioid and concomitant medication data. Subjects will be asked to verify and add any information about their demographics, medical history, opioid and concomitant medications.

5.3.1 Sociodemographics

The sociodemographic information to be collected at baseline only includes:

- Age
- Sex
- Race/ethnicity
- Health insurance type
- Home environment (e.g., lives alone/independent, lives with spouse/partner, lives with children)
- Marital status
- Employment status
- Zip code

5.3.2 Medical History

The medical history information to be collected at baseline only, includes:

- Peripheral (sensory) neuropathy Grade by CTCAE 5.0 criteria[68] (only if recorded in medical record)
- MM diagnosis date and staging
- ECOG performance status[69]
- Body mass index (BMI) calculated by height and weight
- History of diabetes (excluding gestational diabetes)
- Cardiovascular disease
- Chronic kidney disease
- Vertebral fractures

- Current chemotherapy regimen and all bortezomib/bortezomib-combination treatment given prior to enrollment

5.3.3 Opioid Intake

The electronic medical record will be consulted for opioids in the opioid medication list and verified with the subject. Subjects will be asked if there are any other opioids they are taking which might not be documented in the EMR. This information will be collected at the baseline, midpoint and endpoint visit. Subjects will be asked to provide the information based on a past 7-day recall. The self-reported quantities will be converted to Morphine Equivalent Daily Dose (MEDD), using an opioid conversion calculator (See Appendix B).

These opioids include but are not limited to:

- fentanyl (such as Fentora®)
- hydromorphone (such as Dilaudid®)
- long-acting hydromorphone (Exalgo®)
- oxycodone (such as Oxycontin®)
- oxycodone with acetaminophen (such as Percocet®)
- oxymorphone (such as Opana®)
- hydrocodone with acetaminophen (such as Vicodin®, Hycet®)
- tramadol (such as Ultram®, Conzip®)
- morphine (such as MS-Contin®)
- methadone (such as Methadose, Dolophine®)

5.3.4 Concomitant Medication Intake

The electronic medical record will be consulted for concomitant medications as listed below and verified with the subject. Subjects will be asked if there are any other concomitant medications (including over-the-counter medications) which might not be documented in the EMR. This will be asked and collected at the baseline, midpoint, and endpoint visit. Subjects will be asked to provide the information based on a past 7-day recall.

These concomitant medications include but are not limited to:

Prescription non-steroidal anti-inflammatory drugs

- ketoprofen (such as Actron®, Orudis®)
- celecoxib (such as Celebrex®)
- meloxicam (such as Vivlodex®, Mobic®)

Other prescription medications

- gabapentin (such as Neurontin®, Gralise®,Horizant®)
- duloxetine (such as Cymbalta®)

- pregabalin (such as Lyrica®)
- venlafaxine (such as Effexor XR®)
- amitriptyline, (such as Elavil ®, Venatrip ®)
- doxepin (such as Silenor®, Zonalon®)
- nortriptyline (such as Pamelor®)

Over the counter non-steroidal anti-inflammatory drugs (no prescription needed)

- aspirin (such as Bayer®, Excedrin®, Bufferin®)
- acetaminophen (such as Tylenol®)
- ibuprofen (such as Motrin®, Advil®, Motrin IB®, Nuprin®)
- naproxen (such as Aleve®)

Topical treatments applied to the skin

- Capsaicin creams
- Lidocaine patches or gel

Note: Collect any other medications the subject identifies for management of CIPN symptoms

5.4 Questionnaires

Questionnaires will be administered privately, preferably **prior** to the acupuncture session for those on intervention arm. All subjects will be able to answer the questionnaires via two options: 1) on paper (in person or via certified mail) or 2) via RedCap electronic survey. Phone contact for questionnaires is acceptable if unable to be completed by other stated routes. The form of questionnaire administration will be based on the appointment situation, needs and/ or preference of the subject, and subject access to technology (e.g., computer, tablet, smartphone).

Questionnaires to be completed at Baseline, midpoint and endpoint visits, even if those on the acupuncture arm have not received the acupuncture session on schedule or if sessions are missed.

5.4.1 Acupuncture Expectancy Scale

The validated [47] Acupuncture Expectancy Scale consists of 4 items about subjects' expectations (e.g., my illness will improve a lot, my energy levels will increase) of the effects of acupuncture on a 5-point Likert-type scale from 1=*not at all agree* to 5=*completely agree*. Higher scores indicate greater expectations for the impact of acupuncture. Previous research suggests those who expect that acupuncture will be beneficial have better outcomes than those who are skeptical about the effect of acupuncture. This scale is appropriate only for those subjects randomized to the intervention acupuncture arm and will be performed only once- after Randomization but prior to the first acupuncture session.

5.4.2 Neuropathy 0-10

The primary outcome measure is subject-reported global 'neuropathy' right now, measured on an 11-point scale modeled after the Edmonton Symptom Assessment (ESAS) [70] from 0=*no neuropathy* -10= *worst possible neuropathy.* This measure is of unknown validity, although it has been used in previously published studies on CIPN. [23,71] For clarity, subjects are provided with a definition of neuropathy with symptom descriptors.

5.4.3 Neuropathy Physical Location

Subjects will be asked about the physical location of their neuropathy, with options *hands/arms only, feet/legs only, both hands/arms and feet/legs, throughout the body, and other* with a write-in line. (This question is included on the Neuropathy 0-10 questionnaire)

5.4.4 FACT-GOG-NTX

The validated [58] FACT-GOG-NTX questionnaire consists of 39 total items with a 7-day recall period on a 5-point Likert-type scale from 0=*not at all* to 5=*very much*. The questions address CIPN-specific symptoms (e.g., I have numbness or tingling in my hands, I have trouble buttoning buttons), physical well-being (e.g., I have a lack of energy), social/family well-being (e.g., I feel close to my friends), emotional well-being (e.g., I feel sad, I am satisfied with how I am coping with my illness), and functional well-being (e.g., I am able to work including work at home). This questionnaire has been previously used with myeloma patients. [62]

5.4.5 Other Symptoms

The FACT-GOG-NTX covers multiple symptoms of interest (i.e. nausea, sadness, nervousness, sleep quality, lack of energy, and general pain), however there are additional symptoms that will be examined in the current study. To avoid duplication and reduce respondent burden, only those symptoms not covered in the FACT-GOG NTX will be asked about separately. These are constipation, dizziness, and dry mouth. [72] These will be assessed with the same 7-day recall period on a 5-point Likert-type scale from 0=*not at all* to 5=*very much* as the FACT-GOG-NTX to make the symptoms comparable. This is a self-created measure of unknown validity.

5.4.6 CDC HRQOL-4

The CDC HRQOL-4 is a validated [45,46] four-item questionnaire used to measure health related quality of life (HRQOL). The first question asks about general health with response options *excellent, very good, good, fair,* and *poor.* The remaining three questions ask about the *number of days* in the past 30 days that the respondent was in poor physical health, poor mental health, and was unable to do their usual activities. This questionnaire has been used in the Behavioral Risk Factor Surveillance System (BRFSS) since 1993, the National Health and Nutrition Examination Survey (NHANES) from 2000-2012, and the Medicare Health Outcome Survey (HOS) since 2003. [73]

6. STUDY CALENDAR

Procedures/Assessments	Screening Visit	Baseline (complete within 2 weeks from consent, can be done at screening AFTER Randomization)	Weeks 1-2[2]: Twice per week	Weeks 3-10[2]: Once per week	Week 5 ± 1 week [3,5] Midpoint	Week 10 ± 1 week[3,5] Endpoint	Early Termination (if applicable)[7]	Follow Up (30 days [+7] from last Acup tx)
Informed Consent Form	X							
Randomization via CTMS (within 2 weeks from consent)		X[12]						
Sociodemographics & Medical History (see 5.3.1 and 5.3.2)		X						
Multiple Myeloma status[6]		X						
ECOG	X							
Height / Weight/ BMI		X						
Acupuncture Expectancy Scale[4]		X[4]						
Acupuncture Treatment[1,2]			X[2]	X[2]				
Collect Chemotherapy regimen information[10]	X					X	X	
Adverse Events of Special Interest[8]			Continuously, starting at First Acupuncture session				X	X[13]
CIPN: Neuropathy 0-10 & neuropathy physical location	**X[11]**				X	X	X	
CIPN: FACT-GOG-NTX		X[14]			X	X	X	
Other Symptoms: Constipation, dizziness, dry mouth		X[14]			X	X	X	
Quality of Life: CDC HRQOL-4		X[14]			X	X	X	
Opioid Intake/ Morphine Equivalent Daily Dose (see Appendix B)		X[9]			X	X	X	
Concomitant Medication: (See Section 5.3.4 for which medications to collect)		X[9]			X	X	X	

Key to Footnotes

[1] First acupuncture session to occur within 2 weeks of enrollment (date randomized). Acupuncture treatment schedule to start on a Monday or Thursday only.

[2] Week 1 for subjects on the acupuncture/intervention arm is the week when the first acupuncture session occurs. Window for acupuncture sessions during Week 1 and Week 2 is at least 1 day (minimum) and no more than 8 days (maximum) between visits. Window for sessions during Weeks 3-10 is at least 2 days (minimum) and no more than 9 days (maximum) between visits. During Week 1 and Week 2, if an acupuncture session is missed, it may be made up the following week (there will be 3 sessions that following week). During Weeks 3-10, no sessions will be made up if missed.

[3] Questionnaires at Midpoint and Endpoint should still be collected even if subject decides to discontinue the acupuncture sessions but is willing to stay on study. Week 1 for the control group begins at Randomization.

[4] Acupuncture Expectancy Scale questionnaire to be collected only from subjects on Intervention (Acupuncture) arm at any time AFTER Randomization has occurred, but PRIOR to first acupuncture session.

[5] For acupuncture arm, Midpoint occurs at Week 5 ± 1 week from first acupuncture session, with Endpoint occurring at Week 10 ± 1 week from first acupuncture session. For control arm, Midpoint occurs at Week 5 ± 1 week from Randomization with Endpoint occurring at Week 10 ± 1 week from Randomization.

[6] Collect MM date of diagnosis and staging at Baseline

[7] If a subject decides or needs to be withdrawn from the study early (all visits and acupuncture assessments, if applicable), but is willing to complete an Early Termination visit, subject will complete assessments a final time, and will be considered Off Study (See section 8.2). Subjects do not need to complete questionnaires if they have done so within the last 2 weeks.

[8] AESIs should only be collected on subjects randomized to acupuncture arm, beginning with first acupuncture session until 30 days after final acupuncture session.

[9] For collection of opioid medication intake and concomitant medications, collect what has been taken over the past 7 days.

[10] Collect chemotherapy regimen information throughout the study (if applicable).

[11] CIPN Neuropathy 0-10 & neuropathy physical location questionnaire is to be completed the first time **after consenting and prior to any other baseline procedures or assessments** to determine if the subject qualifies for enrollment into the study (see section 7.1.1).

[12] Notify subject of their randomization result.

[13]Follow Up on AESIs: Can be done over the phone- this follow up for AESIs is only for subjects randomized to Acupuncture treatment arm.

[14] Questionnaire may be completed after consent and prior to or after Randomization

7. ADDITIONAL INFORMATION ON STUDY PROCEDURES

7.1.1 Screening/Baseline

Subjects will be consented to the trial, and the CIPN Neuropathy 0-10 (and physical location) questionnaire will be administered. Subjects who score <2 on the CIPN Neuropathy 0-10 questionnaire will be a screen failure and will not be randomized or enrolled into the study. If CIPN Neuropathy 0-10 is answered sufficiently for inclusion (score ≥2), the rest of the baseline assessments are to be completed within two weeks from consent. Once eligibility is confirmed, subject will be randomized via CTMS to either Acupuncture (intervention arm) or Standard of Care. Subjects will be notified of their randomization result. Those randomized to Intervention Arm will begin acupuncture sessions within two weeks of enrollment.

7.1.2 Midpoint and Endpoint visits

The following assessments and questionnaires will be repeated at the Midpoint visit (Week 5 ± 1 week) and at the Endpoint visit (Week 10 ± 1 week) from randomization for the control arm. The assessments and questionnaires will be completed for the acupuncture arm at Midpoint visit (Week 5 ± 1 week) and Endpoint (Week 10 ± 1 week) from first acupuncture session. The questionnaires (see section 5.4) will be administered either in the clinic or via electronic survey or certified mail. The questionnaires should be completed with subjects in both arms, and regardless of whether the intervention (acupuncture) was received. Subjects in both arms will complete the study questionnaires at protocol defined timepoints, even if bortezomib/bortezomib-combination therapy is removed from their treatment regimen during the study (for those on active bortezomib treatment).

Note: These same assessments and questionnaires will be performed if the subject has an Early Termination visit (see study calendar).

See section 5.4 for more detailed information on the study questionnaires.

- Collect AESI information, if applicable (for those on acupuncture arm)
- Collect chemotherapy regimen information.
- CIPN: Neuropathy 0-10
- CIPN: Neuropathy physical location
- CIPN: FACT-GOG-NTX
- Other symptoms (constipation, dizziness, dry mouth)
- CDC HRQOL-4
- Morphine Equivalent Daily Dose (Past 7-day recall)
- Concomitant medication intake (Past 7-day recall)

7.1.3 Collection of AESIs

Subjects on the Intervention arm will be asked specifically at the Midpoint and Endpoint timepoints if they have had any of the designated AESIs. If subject happens to report an AESI or

if there is documentation in the EMR of an AESI at any other time during the study, starting at first acupuncture session, the study team will collect this information. See Section 10.1 for further details including timeframe for collection of AESIs.

7.1.4 Acupuncture

The acupuncture procedure and specific acupoints will be performed in accordance with the Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) guidelines [67] in **Appendix A.** Acupuncture in this study will occur twice during weeks 1-2, then once weekly during weeks 3-10. During Week 1 and Week 2, if an acupuncture session is missed, it may be made up the following week (there will be 3 sessions that following week). During Weeks 3-10, no sessions will be made up if missed. The date of acupuncture sessions completed and acupoints received will be documented. Subjects may continue to receive acupuncture sessions per protocol even if bortezomib or bortezomib-combination treatment is discontinued. Subjects should continue per protocol acupuncture sessions even if their neuropathy resolves.

8. REMOVAL OF SUBJECTS FROM STUDY

8.1 Off Treatment

If subjects on the acupuncture arm decide to discontinue the acupuncture sessions but continue the questionnaires and other assessments, they will be considered Off Treatment. Reasons for coming off treatment would include, but not be limited to:

- Completed protocol therapy
- Adverse event (toxicity)
- Non-compliance
- Investigator decision
- Consent withdrawal for acupuncture sessions
- Subject death
- Study closure

8.2 Off Study

Once all on-study assessments and procedures are completed, subject will be considered Off Study. Subjects on the acupuncture arm will be followed for AESIs for 30 days post the last acupuncture session, then they will be Off Study.

Subjects may stop their participation in this study at any time if they no longer wish to participate, or if the investigator believes this to be in the best interest of the subject.
When subjects are removed from the study, the reason for study removal and date the subject was removed should be documented. Reasons a subject may be removed from study include, but are not limited to:

- Subject non-compliance with study participation, in the opinion of the investigator
- The subject withdraws study consent
- The subject is lost to follow-up
- Investigator's decision to withdraw the subject

- Subject death

Subjects that are Off Study will not participate in any study related procedures, including data collection.

9. DATA AND SAFETY MONITORING PLANS

9.1 Safety Monitoring

This protocol will be monitored according to the processes in effect for all LCI investigator-initiated studies and the protocol-specific monitoring plan and will abide by standard operating procedures (SOPs) set forth by both Atrium Health Office of Clinical and Translational Research and the LCI Clinical Trials Office. It is the responsibility of the Sponsor-Investigator to monitor any safety data (i.e., unanticipated problems/potential risks as per Section 9) for this study. The Sponsor-Investigator, Statistician, and other team members as needed will meet regularly to monitor subject consents, enrollment and retention, safety data, and validity/integrity of the data. Documentation of these meetings will be kept with the study records. The Sponsor-Investigator will submit data to the LCI Data and Safety Monitoring Committee as required.

9.2 Data Monitoring

This study will be organized, performed, and reported in compliance with the study protocol, SOPs of the LCI and Atrium Health Office of Clinical and Translational Research (and/or other participating institutional SOPs), and other applicable regulations and guidelines (e.g. GCP).

Subjects will be monitored by LCI Quality Assurance Monitors per the study-specific monitoring plan and LCI/Atrium Health SOPs for data quality. Data from this study will be collected on electronic case report forms (eCRFs) and stored in the study database. Monitoring will be done by comparing source documentation to the eCRFs. Any variation between the two data sets will be discussed with the investigator, Sponsor-Investigator and/or other study team members as appropriate.

The study database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be generated and addressed by the appropriate study team member. Only authorized personnel will make corrections to the study database and all corrections will be documented in an electronic audit trail.

It is important for the investigators and their relevant personnel to be available during the monitoring visits and for sufficient time to be devoted to the process.

10. POTENTIAL RISKS/UNANTICIPATED PROBLEMS

10.1 Adverse Events of Special Interest

Adverse Events of Special Interest will be collected only for those subjects on the intervention arm, beginning with start of first acupuncture session. AESIs will be collected through 30 days post last acupuncture session. Subjects who experience an AESI will be medically managed by their physician or acupuncturist through standard of care, as appropriate. These events should only be captured if deemed **related** to the acupuncture intervention per the Investigator.

All AESIs will be graded per CTCAE 5.0.

10.1.1 Acupuncture Site AESI

Potential adverse events that may occur at the acupuncture site to be documented and followed in this study are:

- Bleeding, Grade ≥2; (Use "General disorders and administration site conditions, other, specify: "bleeding")
- Bruising, Grade ≥1
- Skin Infection, Grade ≥1
- Edema, localized, Grade ≥2
- Dry Skin, Grade ≥2
- Urticaria (hives), Grade ≥1
- Pruritus (itching), Grade ≥1
- Rash, maculopapular, Grade ≥1
- Pain, Grade ≥2
- Flushing, Grade ≥2

10.1.2 Other AESI

Other potential adverse events to be documented and followed in this study are noted below. However, these should only be captured if they are deemed **related** to the acupuncture intervention per the Investigator.

- Dizziness, Grade ≥2
- Syncope, Grade ≥3
- Fatigue, Grade ≥2
- Hyperhidrosis, (Sweating) Grade ≥2

10.2 Subject Confidentiality

We do not anticipate any breach of confidentiality as no records will be shared with any personnel outside the research team. All medical information including assessments and other medical records will be recorded and stored in a database. The database will exist on a password protected secured server. Medical records data will be abstracted by the Research Designee. All records will be kept confidential.

10.3 Emotional Distress

Some questions in the questionnaires could create emotional distress or confusion. If a subject experiences distress or confusion, the questionnaire process will be interrupted or discontinued, and the Research Designee will follow-up with the Sponsor-Investigator.

10.4 Unanticipated Problems (UAP)

10.4.1 Definition

A UAP is any incidence, experience or outcome that is unexpected (e.g., a lost or stolen laptop computer that contains sensitive study information) given the information provided in research-related documentation (e.g., informed consent) and the study population characteristics, that is related or possibly related to participation in the research study and places the participant at an increased risk.

10.4.2 Reporting

All UAPs occurring during the conduct of a protocol and meeting the definition of a UAP will be reported to the Sponsor-Investigator and IRB per IRB reporting requirements.

11. STATISTICAL CONSIDERATIONS

11.1 Milestones

11.1.1 Registration Date

The date the subject signs the informed consent.

11.1.2 Enrollment Date/On Study Date

The date the subject is randomized.

11.1.3 On Treatment Date

For subjects randomized to the acupuncture arm, the on-treatment date will be the date of the first acupuncture session.

11.1.4 Treatment Discontinuation Date

For subjects randomized to the acupuncture arm, the treatment discontinuation date will be the date the investigator decides to discontinue the subject from receiving acupuncture treatment. See Section 8.1.

11.2 Sample Size

This study is designed with a primary objective to evaluate the effectiveness of acupuncture versus standard subject management in terms of reduction of neuropathy in actively treated multiple myeloma subjects diagnosed with CIPN. A Fisher's Exact Test with a two-sided alpha = 0.20 significance level will have at least 80% power to detect the difference between a standard of care group proportion of 0.10 and a treatment group proportion of 0.35 when the sample sizes are at least 22 and 44 evaluable subjects, respectively. In order to identify at least 66 evaluable subjects, we anticipate enrolling 75 subjects.

11.3 Endpoints

11.3.1 Definition of Primary Endpoint

The primary endpoint for this study is a binary variable that will be determined for each subject indicating whether or not they experienced at least a 2-point improvement in neuropathy between the baseline score and the score obtained at Week 10 (+/- 1 week).

11.3.2 Definition of Secondary Endpoints

- Specific features of CIPN
    - Specific features of CIPN assessed through the NTX subscale from FACT-GOG-NTX will be determined for each subject as a composite measure, which is calculated as the sum of the responses to the NTX subscale questions. For subjects who complete all 12 NTX subscale questions, the composite score will range from 0 to 48.
- Nausea
    - Nausea assessed through question GP2 on the FACT-GOG-NTX subject-reported assessment will be determined for each subject as 5 level ordinal variable from 0 = not at all to 4 = very much.
- Sadness
    - Sadness assessed through question GE1 on the FACT-GOG-NTX subject-reported assessment will be determined for each subject as 5 level ordinal variable from 0 = not at all to 4 = very much.
- Nervousness
    - Nervousness assessed through question GE4 on the FACT-GOG-NTX subject-reported assessment will be determined for each subject as 5 level ordinal variable from 0 = not at all to 4 = very much.
- Sleep quality
    - Sleep quality assessed through question GF5 on the FACT-GOG-NTX subject-reported assessment will be determined for each subject as 5 level ordinal variable from 0 = not at all to 4 = very much.
- Lack of energy
    - Lack of energy assessed through question GP1 on the FACT-GOG-NTX subject-reported assessment will be determined for each subject as 5 level ordinal variable from 0 = not at all to 4 = very much.
- Pain
    - Pain assessed through question GP4 on the FACT-GOG-NTX subject-reported assessment will be determined for each subject as 5 level ordinal variable from 0 = not at all to 4 = very much.
- Constipation
    - Constipation assessed through additional question amended to FACT-GOG-NTX subject-reported assessment will be determined for each subject as a 5-level ordinal variable from 0 = not at all to 4 = very much.
- Dizziness

    - Dizziness assessed through additional question amended to FACT-GOG-NTX subject-reported assessment will be determined for each subject as a 5- level ordinal variable from 0 = not at all to 4 = very much.
- Dry Mouth
    - Dry mouth assessed through additional question amended to FACT-GOG-NTX subject-reported assessment will be determined for each subject as a 5- level ordinal variable from 0 = not at all to 4 = very much.
- Quality of Life
    - General Health assessed through CDC-HRQOL Question 1 will be calculated for each subject as a 5- level ordinal variable from Poor to Excellent
    - The number of unhealthy days will be calculated as the average of the number of physically unhealthy days (CDC-HRQOL Question 2) and the number of mentally unhealthy days (CDC-HRQOL Question 3), with a maximum of 30 days. [74] This will be calculated for each subject as a quantitative value between 0 and 30, representing the number of days out of the past 30 that the subject's health was not good.
    - The number of activity limitation days assessed through CDC-HRQOL Question 4 will be calculated for each subject as a quantitative value between 0 and 30, representing the number of days out of the past 30 that the subject's health kept them from doing their usual activities.

11.3.3 Definition of Safety Endpoints

- Adverse Events of Special Interest will be determined for each subject as binary variables indicating whether or not they experienced an AESI. These will be determined by preferred term, system organ class, and overall.

11.3.4 Definition of Exploratory Endpoints

- Opioid use
    - Opioid use assessed through Morphine Equivalent Daily Dose (MEDD) will be calculated for each subject as a quantitative value.
- Concomitant medication use
    - Concomitant medication use assessed through medication name and dose will be determined for each subject.
- Acupuncture administration
    - Acupuncture administration will be defined for each subject on the acupuncture arm as the number of attended acupuncture sessions from 0 to 12.
- Acupuncture expectancy
    - The acupuncture expectancy score will be captured quantitatively for each subject as a composite score ranging from 4 to 20.

11.4 Analysis Populations

The intent to treat (ITT) population will consist of all randomized subjects. The ITT population will be used to summarize the CONSORT diagram, subject disposition, and baseline subject disease characteristics. The evaluable population will consist of enrolled subjects who have complete baseline and Week 10 (± 1 weeks) neuropathy scores. The evaluable population will be

used for the analyses of all primary and secondary endpoints. Additionally, an intervention-compliant population will be defined as all subjects in the evaluable population who meet all of the following criteria:

- Subjects randomized to the acupuncture arm who have received at least 75%, or 9 of the 12 sessions in up to 13 weeks from randomization.
- Subjects randomized to the control arm who have not received any acupuncture at any time while they are on study.

The intervention-compliant population will be utilized for sensitivity analyses.

11.5 Analysis Methods

11.5.1 Timing of Analysis

A single and final analysis will occur after 66 enrolled subjects have been identified in the evaluable population.

11.5.2 Subject Disposition

A summary of all consented subjects will be provided. This will include a summary of subjects who consented, were enrolled, treated, discontinued treatment (including reasons), died, were lost to follow-up or withdrew consent.

11.5.3 Baseline Subject Characteristics

A summary of subject demographics will be completed and selected subject medical history will be assessed.

11.5.4 Primary Analysis

The frequency and proportion of subjects who experienced at least a 2-point improvement in neuropathy between the baseline score and the score obtained at Week 10 (+/- 1 week) will be calculated for each study arm. A two-sided Fisher Exact test will be executed, testing the null hypothesis that there is no difference in neuropathy improvement rate between the arms. Additionally, logistic regression will be used to evaluate the impact of acupuncture while adjusting for potential baseline confounding factors, including the stratification variable, baseline neuropathy severity grade. Univariate models will be used to identify baseline factors that are individually prognostic. Statistically significant factors identified from the univariate models will then be included in a multivariable model. Backward elimination will be used to identify baseline factors that are independently prognostic. A treatment indicator variable will be added to obtain an adjusted odds ratio.

11.5.5 Secondary Analysis

An analysis similar to that described in the primary analysis will be performed for scores obtained at 5 weeks. Additionally, a repeated measures model including a random effect for subject will be estimated for the binary neuropathy improvement score measured at baseline,

week 5 and week 10. Additional baseline factors as previously described above may be added to this model as well.

The secondary endpoint composite measure of specific CIPN symptoms will be treated as a continuous measure and analyzed using analysis of variance techniques. The secondary endpoints measured on a 5-level ordinal scale will be summarized with frequencies and proportions and analysis of variance techniques on the ranks test will be used to test for differences by arm. The number of unhealthy days and activity limitation days will be analyzed using analysis of variance techniques.

11.5.6 Safety Analysis

Adverse events of special interest will be summarized by frequencies and proportions for subjects on the acupuncture intervention arm. Clopper-Pearson 95% confidence intervals will be estimated.

11.5.7 Exploratory Analysis

The exploratory endpoint of Morphine Equivalent Daily Dose (MEDD) will be treated as a continuous measure and analyzed using analysis of variance techniques. Total counts and descriptive statistics of class and dose of concomitant medication use will be summarized by study arm.

In order to evaluate the dose response, dose will be treated as a categorical variable with levels of no acupuncture (0 sessions), low dose (1 – 3 sessions), medium dose (4 – 7 sessions), high dose (8 – 11 sessions) and complete dose (12 sessions). Logistic regression will be performed to investigate the association between dose of acupuncture and CIPN improvement. Acupuncture expectancy will be determined for each subject as a composite measure, which is calculated as the sum of the responses to the four questions on the acupuncture expectancy scale. Logistic regression will be used to evaluate the effect of acupuncture expectancy on the primary endpoint, 2-point improvement in neuropathy.

12. STUDY COMPLETION OR TERMINATION

12.1 Completion

The study will be considered complete when one or more of the following conditions is met:

- All subjects have withdrawn from the study
- All subjects have discontinued from the study
- The IRB, LCI DSMC, or Sponsor-Investigator discontinues the study because of safety considerations
- The Sponsor-Investigator defines an administrative or clinical cut-off date

12.2 Termination

The study will be terminated early when one or more of the following conditions occur:

- If risk-benefit ratio becomes unacceptable owing to, for example,
    - Safety findings from this study (e.g., UAPs)
    - Results of parallel clinical studies
    - If the study conduct (e.g., recruitment rate, drop-out rate, data quality, protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame
- The Sponsor-Investigator has decided to close the trial at any site and at any time

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions must be informed as applicable according to local law.
- In case of a partial study closure, ongoing subjects, including those in follow- up, must be taken care of in an ethical manner.

13. STUDY MANAGEMENT

13.1 IRB Approval

The study protocol, the informed consent(s) and any other necessary documents must be approved by the Sponsor IRB and site(s) IRB of record in accordance with federal regulations and obtained prior to implementation.

The Sponsor IRB and site(s) IRB of record will be informed of any amendment to the protocol, informed consent(s), and any other necessary documents in accordance with IRB reporting requirements. The study protocol will undergo continuing IRB review based on the level of risk as assessed by the IRB no less than annually, or as applicable, in accordance with IRB requirements.

13.2 Informed Consent

Before recruitment and screening/enrollment onto this study, the subject will be given a full explanation of the study, the opportunity to review the consent form, and the opportunity to have all their questions answered. Prior to a subject's participation in the trial, the informed consent(s) will be reviewed, signed and personally dated by the subject and by the person who conducted the informed consent discussion. A copy of each informed consent will be given to the subject and each original will be placed in the subject's research record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

13.3 Protocol Adherence

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

13.3.1 Amendments to the Protocol and Informed Consent

If it is necessary for the study protocol to be amended and/or the informed consent revised, the amendment or a new version of the study protocol and/or revised informed consent must be approved by the Sponsor-Investigator and the Sponsor IRB.

13.4 Other Protocol Deviations

If a deviation occurs, the event should be reported to the Sponsor-Investigator via entry in the CTMS within 10 business days of awareness. Any IRB reportable event that occurs must be reported to the IRB and to the Sponsor-Investigator as soon as possible but no later than 10 business days of awareness.

Protocol deviations that, in the Investigator's judgment, potentially caused harm to participants or others or indicates that the participants or others are at an increased risk of harm, or has adversely impacted data integrity will be reported promptly to the IRB per IRB reporting requirements.

Planned protocol deviations should be submitted to the Sponsor for approval prior to the anticipated deviation occurring. After Sponsor approval has been obtained, planned deviations should be submitted to the IRB prior to the anticipated deviation occurring. IRB approval must be obtained prior to deviation occurrence. No exceptions for eligibility criteria are not allowed.

13.5 Retention of Records

Essential documentation (e.g., source documents, Sponsor-Investigator correspondence, monitoring reports, and regulatory documents), including all IRB correspondence, will be retained for at least 2 years after the investigation is completed. Documentation will be readily available upon request.

13.6 Ethical and Legal Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigator abide by GCP guidelines. The study will also be carried out in full conformity with Regulations for the Protection of Human Subjects of Research codified in the ICH E6 and in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate agencies will be obtained for all participating centers before the start of the study, according to GCP, local laws, regulations and organizations.

Strict adherence to this protocol is required for all aspects of study conduct; the investigators may not modify or alter the procedures described in this protocol.
The Sponsor-Investigator is responsible for the conduct of the trial at the sites in accordance with the Declaration of Helsinki. The Sponsor-Investigator is responsible for overseeing all study subjects. The Sponsor-Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all applicable regulations and guidelines regarding clinical trials both during and after study completion.

The Sponsor-Investigator will be responsible for assuring that all the required data will be collected and properly documented.

13.7 Confidentiality of Records

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

13.8 Compliance with ClinicalTrials.gov

The Sponsor-Investigator is solely responsible for determining whether the trial and its results are subject to the requirements for submission to ClinicalTrials.gov (http://www.clinicaltrials.gov).

14. REFERENCES

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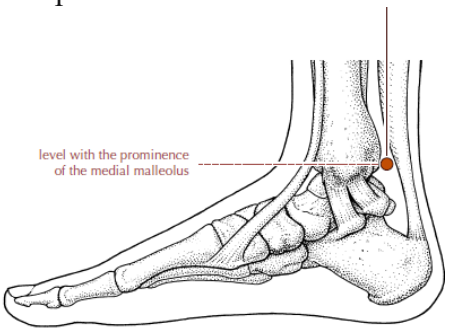
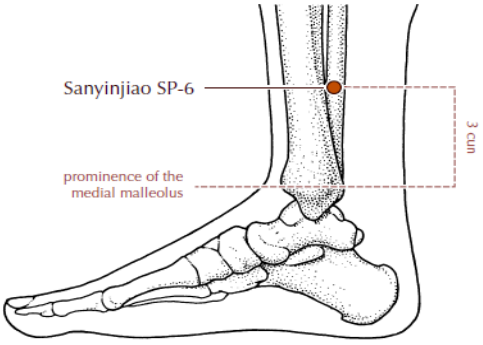
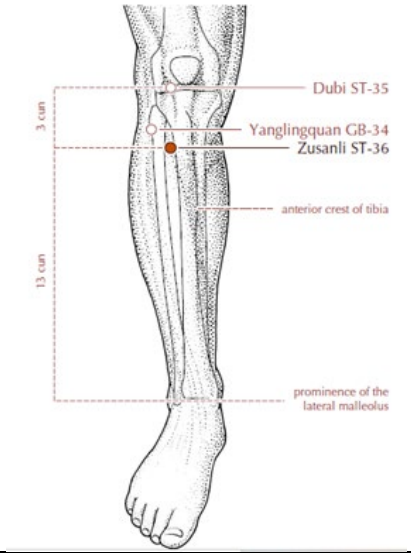
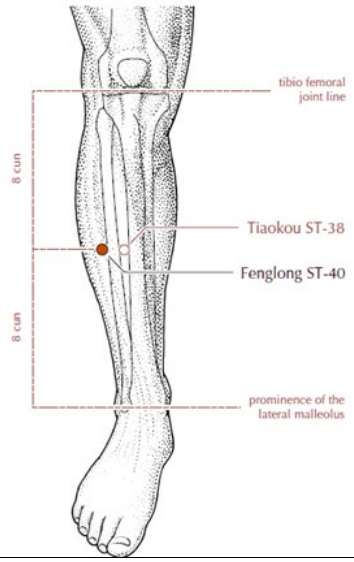
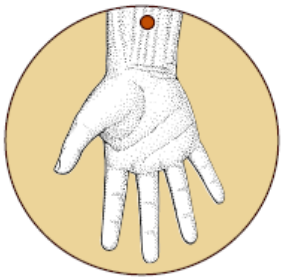
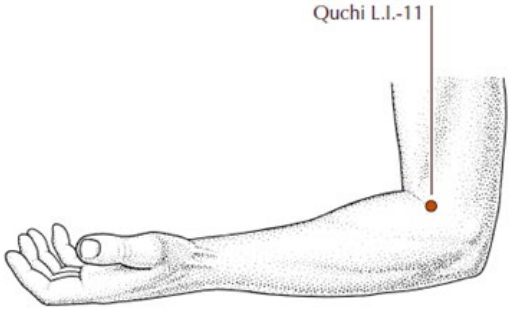
15. APPENDICES

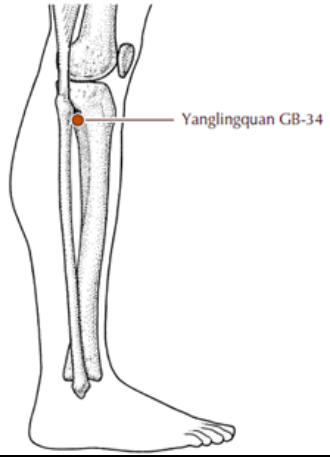
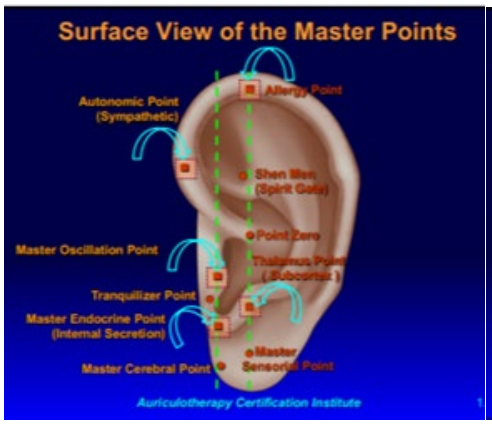
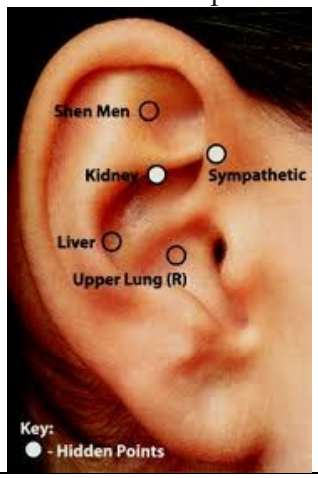
15.1 APPENDIX A: Acupuncture Procedure- STRICTA Guidelines and Acupuncture Site Locations

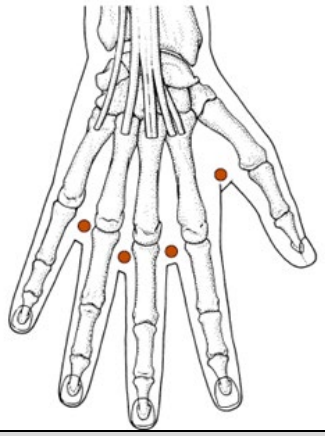
Item	Detail	Specifics
1. Acupuncture rationale (Explanations and examples)	1a) Style of acupuncture (e.g. Traditional Chinese Medicine, Japanese, Korean, Western medical, Five Element, ear acupuncture, etc)	Traditional Chinese Medicine Ear Acupuncture points
	1b) Reasoning for treatment provided, based on historical context, literature sources, and/or consensus methods, with references where appropriate	Symptom mitigation, for CIPN. Additional questions to field for positive systemic effect on common opioid symptomology
	1c) Extent to which treatment was varied	Protocol + hand and/or foot points dependent on predominant physical CIPN location
2. Details of needling (Explanations and examples)	2a) Number of needle insertions per subject per session (mean and range where relevant)	As needed
	2b) Names (or location if no standard name) of points used (uni/bilateral)	see text in section 7
	2c) Depth of insertion, based on a specified unit of measurement, or on a particular tissue level	Typically ½" insertion, with exception of ear points
	2d) Response sought (e.g. *de qi* or muscle twitch response)	Elicit mild *de qi* response in most acupoints
	2e) Needle stimulation (e.g. manual, electrical)	Manual only
	2f) Needle retention time	Min. 30 max 50 minutes, average 40-45 minutes

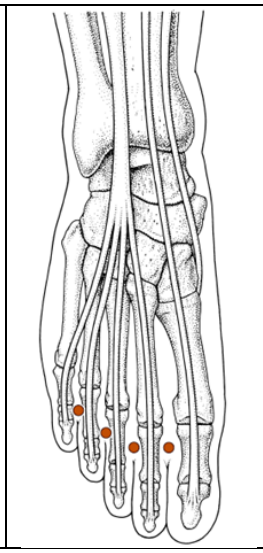
	2g) Needle type (diameter, length, and manufacturer or material)	diameter 0.20mm, length 15mm & 30mm
3. Treatment regimen (Explanations and examples)	3a) Number of treatment sessions	12 total sessions
	3b) Frequency and duration of treatment sessions	Twice per week for weeks 1-2; once per week for weeks 3-10
4. Other components of treatment (Explanations and examples)	4a) Details of other interventions administered to the acupuncture group (e.g. moxibustion, cupping, herbs, exercises, lifestyle advice)	none
	4b) Setting and context of treatment, including instructions to practitioners, and information and explanations to patients	Group acupuncture following COVID-19 protocols
5. Practitioner background (Explanations and examples)	5) Description of participating acupuncturists (qualification or professional affiliation, years in acupuncture practice, other relevant experience)	Master's level accredited acupuncturists with at least 8 years of experience.
6. Control or comparator interventions (Explanations and examples)	6a) Rationale for the control or comparator in the context of the research question, with sources that justify this choice	The control condition will be standard of care for CIPN. No sham acupuncture will be used.
	6b) Precise description of the control or comparator. If sham acupuncture or any other type of acupuncture-like control is used, provide details as for Items 1 to 3 above.	Standard of care control
7. Specific Acupoints	All subjects will receive the protocol's full body acupoints at each session. Depending on the physical location of CIPN, à-la-carte acupoints can be added. BĀXIÉ can be added for neuropathy in the hands and BĀFĒNG can be added for neuropathy in the feet. If Neuropathy is present in both the hands and feet, BĀXIÉ and BĀFĒNG can be used.	See following

POINTS	LOCATION
Full body acupuncture points given to all subjects at each session	
Ki3 – Taixi	In the depression between the medial malleolus and the Achilles tendon, level with the prominence of the medial malleolus. 
Sp6 – Sanyinjiao	On the medial side of the lower leg, 3 cun superior to the prominence of the medial malleolus, in a depression close to the medial crest of the tibia. 
St36 – Zusanli	Below the knee, 3 cun inferior to Dubi ST-35, one fingerbreadth lateral to the anterior crest of the tibia. 

St40 – Fenglong	On the lower leg, midway between the tibiofemoral joint line (level with the popliteal crease) and the lateral malleolus, two finger-breadths lateral to the anterior crest of the tibia (i.e. one finger-breadth lateral to Tiaokou ST-38). 
PC 6 – Nèiguān	On the flexor aspect of the forearm, 2 cun proximal to Dàlíng P-7, between the tendons of palmaris longus and flexor carpi radialis. 
LI11 – Quchi	At the elbow, midway between Chize LU-5 and the lateral epicondyle of the humerus, at the lateral end of the transverse cubital crease. 
GB 34 – Yánglíngquán	Below the lateral aspect of the knee, in the tender depression approximately 1 cun anterior and inferior to the head of the fibula.

	
Ear SNS (Autonomic)	The Sympathetic ear point is on the inside of the helix following the path of the lower part of the antihelix crus  
Ear Shenmen	Situated at the apex of the triangular fossa 
Ear Kidney	On the lower border of the inferior antihelix crus, equidistant and directly beneath Ear Shenmen (situated at the apex of the triangular fossa).

	
à-la-carte acupuncture points dependent on physical CIPN location	
Hands	
BĀXIÉ	When the hand is made into a fist, six of these points lie in the depressions between the metacarpal heads, proximal to the web margins. The remaining two points lie equidistant between the thumb and index metacarpals, proximal to the web margins. 
Feet	
BĀFĒNG	On the dorsum of the foot, between the toes, 0.5 cun proximal to the margin of the web.

15.3 APPENDIX B: Advanced Opioid Conversion Calculator -Morphine equivalents

https://globalrph.com/medcalcs/advanced-opioid-conversions-equianalgesic-morphine-equivalents/