MSK PROTOCOL COVER SHEET

Opioid-Sparing Pain Treatment In Myeloma And Lymphoma Patients Undergoing High-Dose Chemotherapy (OPTIMAL-HiChemo)

Principal Investigator/Department:

Gary E Deng, MD, PhD/Medicine/Integrative Medicine Service

Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Study Title	Opioid-sparing Pain Treatment In Myeloma And Lymphoma Patients Undergoing High-Dose Chemotherapy (OPTIMAL-HiChemo)
Objective	To investigate how to optimize pain management during cancer treatment by combining nonpharmacologic and pharmacologic interventions: whether using acupuncture to prevent onset of severe pain, with opioids as backup, leads to lower risk of opioid use without compromising pain management and lower symptom burden, when compared to opioids as first line treatment.
Specific Aims	1: To determine the comparative effectiveness of ACU (acupuncture and opioids, further defined below) versus OPI (opioids only) in reducing opioid use during and after HiChemo among patients who do not use opioids at baseline before HiChemo and in reducing their symptom burden during HiChemo. 2: To determine the short-term (Day 7) and long-term (Day 90) effects of ACU compared to OPI on patient-reported pain, opioid side effects (e.g. drowsiness, constipation, nausea), and quality of life among the above study population. Exploratory: (1) Explore whether the effect of ACU treatment on Day 90 opioid use is mediated by its effect on Day 7 opioid use. (2) Explore potential heterogeneity of treatment effect (HTE) by various factors.
Study Design	A multicenter, 2-arm, parallel group, individual randomized (1:1 ratio) controlled trial comparing two pain management interventions.
Study Sites	Memorial Sloan Kettering Cancer Center, New York (MSK) Seattle Cancer Care Alliance (SCCA), Fred Hutchinson Cancer Research Center (Fred Hutch)
Interventions and Comparators	A) Acupuncture as a first-line pain preventive measure during HiChemo with opioids as back-up pain treatment (ACU), and B) opioids as first-line pain treatment (OPI). Every study patient will receive the same usual care for opioid administration, initiated and adjusted according to their pain levels as in standard of care.
Study Population	Opioid-naïve (defined as not using opioids in the week before enrollment) adult multiple myeloma, Hodgkin disease, and non-Hodgkin lymphoma patients undergoing HiChemo followed by hematopoietic stem cell transplantation (HSCT)
Total Enrollment	300
Time to Completion	36 months
Outcomes	The following will be assessed at baseline and days 7, 15, 30, and 90 after the first dose of HiChemo (Day 0):

	Primary outcomes: opioid use, and symptom burden measured by M. D. Anderson Symptom Inventory – Bone Marrow Transplantation (MDASI-BMT). Secondary outcomes: Brief Pain Inventory–Short Form, Patient-Reported Oral Mucositis Symptom Scale, Pain Medication Side Effects Questionnaire quality of life measured by Patient-Reported Outcomes Measurement Information System – 29 Items (PROMIS-29). Other outcomes: opioid dose, clinical features (diagnosis and disease status), Common Terminology Criteria for Adverse Events Version 5.0 (CTC-AE v5.0), Opioid Risk Tool, Acupuncture Expectancy, use of health care resources (length of hospital stays during HSCT, transfers to the intensive care unit (ICU) while hospitalized, urgent care/emergency room visits, and readmission rates during the first 30 days post-HSCT).
Analytic Methods	All analyses will be by intent-to-treat, with patients entered into analysis as randomized, irrespective of treatment actually received. For Aim 1 opioid use, we will utilize logistic regression to model the probability of opioid use at specific time points (i.e., day 7 and 90, separately), and generalized linear mixed models to model the probability of opioid use across all time points (i.e. days 7, 15, 30, and 90), as a function of study arm (ACU vs. OPI), time, and randomization stratification variables. For Aim 1 symptom burden and Aim 2 pain, side effects and QOL , we will use linear mixed models to similarly model those continuous endpoints over time. We will also explore potential causal mechanisms by testing mediation hypotheses (e.g. test whether the effect of treatment on Day 90 opioid use is mediated through the effect of treatment on Day 7 opioid use).
Funding Source	Peer-reviewed Patient-Centered Outcomes Research Institute (PCORI) contract

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Opioids are often used to treat acute pain during cancer treatment, yet this exposure to opioids is a risk factor for patients to become long-term opioid users. Cancer survivors have a higher risk for opioid use, with an odds ratio up to 2.55. Clinical practice guidelines all recommend a combination of pharmacologic and non-pharmacologic modalities for treatment of acute pain. But, currently there is no strong evidence guiding clinicians or patients on how best to combine the two. The proposed study in 300 patients undergoing high-dose chemotherapy (HiChemo) will generate high quality evidence to support clinicians and patients in making patient-centered decisions on the optimal management of acute pain during cancer treatment.

The overall objective is to investigate how to optimize pain management during cancer treatment by combining nonpharmacologic and pharmacologic interventions: does using acupuncture to prevent onset of severe pain, with opioids as backup, lead to lower risk of opioid use without compromising pain management and lower symptom burden, when compared to opioids as first line treatment.

Specific Aim 1: To determine the comparative effectiveness of ACU versus OPI in reducing opioid use during and after HiChemo among patients who do not use opioids at baseline before HiChemo and in reducing their symptom burden during HiChemo. Hypothesis 1 (a): ACU during HiChemo will significantly reduce the proportion of short-term opioid users (at Day 7 after HiChemo) when compared to OPI. Hypothesis 1 (b): ACU during HiChemo will significantly reduce the proportion of long-term opioid user (at Day 90 after HiChemo) when compared to OPI. Hypothesis 1 (c): ACU during HiChemo will significantly reduce the MDASI-BMT Total Symptom Severity score at Day 7 when compared to OPI.

Specific Aim 2: To determine the short-term (Day 7) and long-term (Day 90) effects of ACU compared to OPI on patient-reported pain, opioid side effects (e.g. drowsiness, constipation, nausea), and quality of life among the above study population. Hypothesis 2(a): ACU is not inferior to OPI in maintaining a low pain score at Day 7 and 90 after HiChemo. Hypothesis 2(b): ACU will reduce symptoms of drowsiness, constipation, nausea, and improve mental and physical quality of life at day 7 and 90 after HiChemo.

Exploratory Aim 1: Explore whether the effect of ACU treatment on Day 90 opioid use is mediated by its effect on Day 7 opioid use.

Exploratory Aim 2: Explore whether sex, race, ethnicity, gender, primary cancer diagnosis (MM versus HD versus NHL), Opioid Risk Tool (ORT), Acupuncture Expectancy Scale (AES) score, or concurrent use of other medications with analgesic effects influence response to interventions in this population (i.e., heterogeneity of treatment effect, HTE).

3.0 BACKGROUND AND RATIONALE

In 2018, an estimated 1.7 million new cases of cancer will be diagnosed in the U.S. and 0.6 million people will die from the disease. Among patients with cancer, pain is one of the most common, burdensome, and feared symptoms.[1] A meta-analysis of 122 studies (N=4,199) showed that about 55% of patients experience pain during cancer treatment; 40% experience pain after curative treatment.[1] Opioids are necessary and appropriate for patients with advanced cancer and intractable pain, but cancer survivors with no active cancer should not be using opioids unnecessarily. Cancer survivors have a higher risk for opiod use. A recent study using SEER and Medicare data of 46,789 older cancer survivors and 138,136 noncancer controls shows a significantly higher chronic opioid use in cancer survivors who had a higher pain burden during cancer treatment (colorectal cancer: odds ratio (OR) 1.34; 95% CI, 1.22 to 1.47; lung cancer: OR 2.55; 95% CI, 2.34 to 2.77). It takes six years for

opioid use to return to the level of controls.[2] Other studies showed the exposure to opioids during treatment for acute pain is a strong risk factor for patients to become long-term opioid users even when the acute pain has subsided and opioids are no longer appropriate.[3-6] The largest increments in probability of long-term opioid use were observed after the 5th and 31st days on short-term use.[7] Unnecessary use of opioids presents problems beyond the medical field, such as effects on mental health, impact on family members, financial costs, opioid misuse disorder, especially in light of the current opioid crisis.

Autologous hematopoietic stem cell transplantation (auto-HSCT) is a treatment for multiple myeloma (MM), Hodgkin disease (HD), and non-Hodgkin lymphoma (NHL). Patients receive high-dose chemotherapy (HiChemo) followed by infusion of hematopoietic stem cells days later. Pain is rated one of the top five symptoms during this treatment.[8] Oral mucositis from HiChemo is the main source of severe acute pain and the main reason patients are initiated on opioids. Between 30-43% of patients undergoing HiChemo and auto-HSCT experience severe (grade 3 or 4) mucositis which creates distress and interferes with eating and drinking. Mucositis pain follows a predictable course, usually starting shortly after HiChemo and peaking around day 7 after initiation of HiChemo. It begins to subside around days 15, and has usually resolved by Day 30. By Day 90, there should be no residual pain caused directly by HSCT. The pain can lead to periods of difficulty eating, malnutrition, dehydration, weight loss, depression, and impaired quality of life.[9-12] Opioids are usually used to manage the pain. Although effective, opioids are often associated with side effects like constipation, nausea, sedation, and delirium.[13-20] After mucositis has subsided, some patients may have become accustomed to opioids and use them chronically for other pain. The intensity of pain during HiChemo, the high incidence of opioid use in this population, and the predictable clinical course make HiChemo/HSCT an excellent model to study the effects of pain control interventions during cancer treatment on short- and long-term opioid use.

Pain management during cancer treatment presents patients and clinicians with a decision dilemma. The Joint Commission,[21] American College of Physicians (ACP),[22,23] National Comprehensive Cancer Network (NCCN)[24,25] and American Society of Clinical Oncology (ASCO)[26] guidelines all recommend a combination of pharmacologic (mainly opioids during HiChemo) and non-pharmacologic modalities. However there is currently no strong evidence guiding clinicians or patients on how to combine non-pharmacologic and pharmacologic interventions to manage the pain patients experience during cancer treatment. In particular, there is a lack of evidence that considers what patients perceive as important, e.g. side effects and risk of long-term opioid use.[24-26]

Acupuncture is a non-pharmacologic modality that involves insertion of filiform needles into certain points on the body, followed by manual manipulation, heat, or electrical stimulation to elicit therapeutic effects. Numerous randomized controlled trials have shown its effectiveness in pain management.[27-29] A systematic review of 17 trials (N= 2,027) showed that acupuncture reduced the intensity of acute and chronic low back pain more than sham acupuncture, leading ACP's clinical practice guidelines to recommend acupuncture.[23] In a meta-analysis of 20,827 patients from 39 RCTs, the analgesic effect size of acupuncture was

0.5 SDs compared with no acupuncture control and close to 0.2 SDs compared with sham.[29] Neuroscience research has shown that acupuncture increases production of endogenous analgesic neurotransmitters, such as endorphins and adenosine.[30-35] In January 2020, Centers for Medicare & Medicaid Services (CMS) finalized a decision to cover acupuncture for Medicare patients with chronic low back pain. We conducted a pilot randomized study showing that acupuncture during HiChemo/HSCT has the potential to be an opioid-sparing non-pharmacologic therapy that significantly reduces opioid use and opioid side effects without compromising pain control.[36] We found that patients in the sham acupuncture group had greater than five times the odds of increasing pain medications from baseline compared with those in the true acupuncture group (OR 5.31, 95% Confidence Interval (CI) 1.35 to 20.93, P=0.017). The effect was most pronounced among patients who were not taking opioids at baseline ("opioid-naïve"). In those patients, any increase in opioid use was due to the pain induced by HiChemo/HSCT, rather than from pre-existing pain. Among opioid-naïve patients, 20% (4 of 20) of those who received sham acupuncture started to use opioids during HiChemo/HSCT (Day 5), 40% around Day 30, and 25% became long-term opioid users (Day 90). In contrast, among the 15 patients who received true acupuncture, none needed to use opioids on Day 5 (p=0.119) or Day 30 (p=0.006), and only one (7%) became a long-term opioid user (Day 90, p=0.365).[36] Acupuncture also reduces symptoms commonly associated with opioid use, such as nausea, poor appetite and drowsiness. The proposed study expands on that research and uses a patient-centered approach to address this gap in the evidence.

Patients and stakeholders took part in the formulation of the research question and the design of the study. We formed a Patient/Stakeholder Advisory Committee (PSAC) which consists of 3 patients who participated in the previous pilot study, a future HSCT patient, a patient caregiver, a representative from advocacy organization, 2 clinicians and 2 researchers. The PSAC helped with study design and development of patient-centered recruitment/retention strategies. One patient from the pilot study and one patient who is likely to receive HSCT in the near future will serve as consultants for the duration of the study.

The proposed study takes advantage of a highly efficient clinical pain model. Pain and other symptoms during HiChemo/HSCT follows a very predictable clinical course. This reduces variability and increases the statistical power of the study under a given sample size. It allows for a longitudinal evaluation of the transition from acute opioid use to chronic opioid use in each patient. The decision-making dilemma addressed by the study is commonly faced by patients and clinicians in clinical practice. The outcomes evaluated are all related to improving cancer care and patient-centered. The interventions are easy to implement. Patients, caregivers, clinicians and hospitals have a keen interest in incorporating non-drug-based pain management to reduced unnecessary opioid use. Such interest facilitates future dissemination of findings from this study. Thus, the proposed study will generate high quality evidence and potentially improve clinical practice.

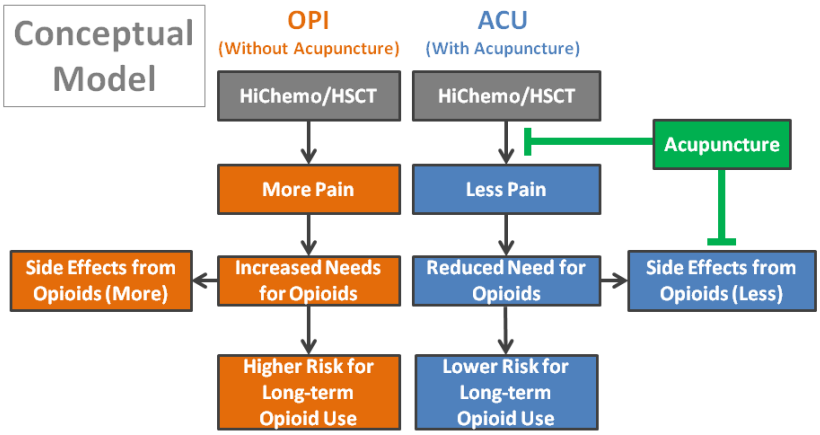
4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

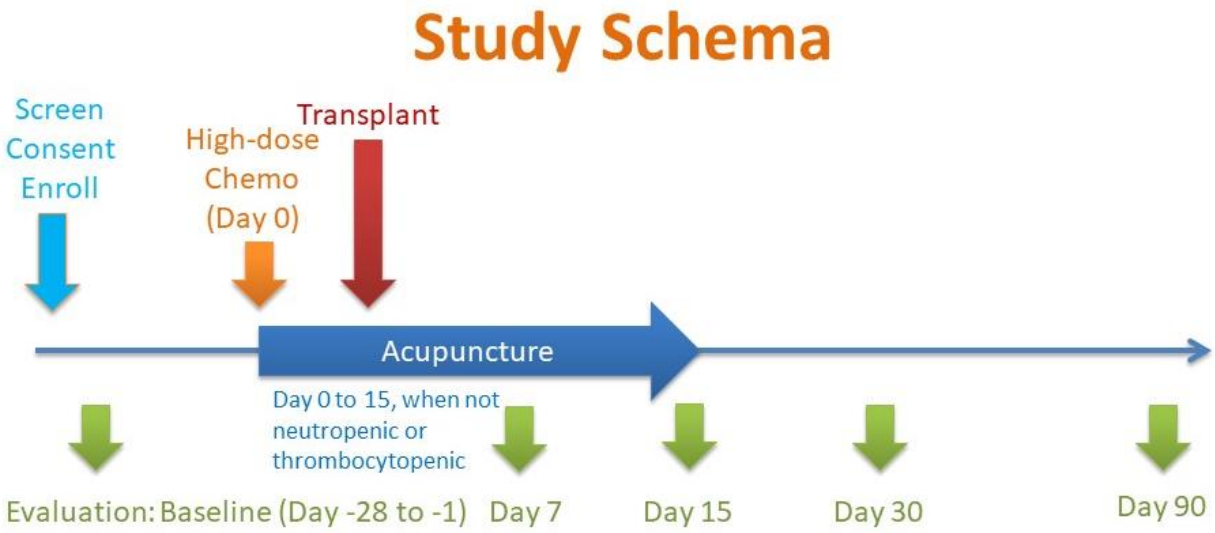
The study is a prospective, multicenter, two-arm parallel group, individual randomized (at 1:1 ratio) controlled trial with two pain management interventions as comparators. We chose this design because it helps balance the variables between treatment arms, therefore providing stronger causal inference than an observational or non-randomized design. It also reduces bias during analysis of heterogeneity of treatment effects. The multicenter design enhances diversity of the study population and the generalizability of study results. There have been many randomized controlled trials comparing acupuncture to sham acupuncture. Its efficacy in pain control is well established. In addition, PCORI is most interested in the pragmatic aspect of clincal interventions that improve patient-centered outcomes. Thus the control group in this study is usual care, not sham acupuncture.

4.2 Intervention

All patients in the study will receive usual HSCT care. Patients in both the ACU group and the OPI group will receive the same usual care for opioid administration, initiated and adjusted according to their pain levels as in standard of care in the study institutions. In addition, patients in the ACU group will receive acupuncture treatment as detailed in Section 10.0. The conceptual framework is shown in the diagram in this section.



The schema of interventions and outcome assessment is as follows.



5.0 THERAPEUTIC/DIAGNOSTIC AGENTS & NON-THERAPEUTIC ASSESSMENTS

Acupuncture is a non-pharmacologic modality that involves insertion of single-use disposable filiform needles into certain points on the body, followed by manual manipulation, heat, or electrical stimulation to elicit therapeutic effects. Acupuncture has been provided in both inpatient and outpatient settings at MSKCC for more than 15 years, as part of standard clinical services provided to MSKCC patients. Acupuncture the modality itself is not investigational. Its integration to symptom management in this clinical setting is the subject of investigation.

Seirin acupuncture needles at 30mm or 40mm and 0.16mm - 0.25 mm gauge will be used in this study. The needles are purchased and distributed from Seirin® in the United States (http://www.seirinamerica.com). Seirin acupuncture needles are approved by the FDA (http://www.accessdata.fda.gov/cdrh_docs/pdf/K962809.pdf).

Participants in the OPI group will receive pain management with opioids administered per institutional standards.

6.0 CRITERIA FOR PARTICIPANT ELIGIBILITY

We will conduct the study in “opioid-naïve” multiple myeloma (MM), Hodgkin disease (HD), and non-Hodgkin lymphoma (NHL) patients who are undergoing HiChemo and autologous HSCT. In this study, “opioid-naïve” patients are defined as those who have not been taking opioids regularly in the week preceding registration to the study, not literally as those who never have taken opioids. We are targeting pain caused by chemotherapy, not severe preexisting pain caused by cancer that requires pain medication prior to HiChemo. Our preliminary data showed that those who are not taking opioids for preexisting pain before HiChemo benefitted the most from acupuncture. One-time dosing of opioids in that period for

a painful procedure (e.g. placement of a venous port) is allowed. Patients undergoing allogeneic HSCT (allo-HSCT) are not included. They tend to have more variable clinical courses and higher incidence of post-HSCT complications (infection, engraftment failure, disease relapse, or graft versus host disease).

6.1 Participant Inclusion Criteria

- age 18 or older
- pathological diagnosis of MM, HD or NHL
- scheduled for high dose chemotherapy for auto-HSCT in the following month (30 days)
- not taking opioids regularly in the week prior to consent (one-time dosing of opioids for a painful procedure is allowed)

6.2 Participant Exclusion Criteria

- absolute neutrophil count (ANC) of <500/µl, platelet count of <20,000/ µl or INR >2.0
- acupuncture within two weeks prior to HiChemo (to avoid residual effects of acupuncture)
- unable to provide informed consent

7.0 RECRUITMENT PLAN

All MM, HD, and NHL patients who are scheduled to receive auto-HSCT at the Adult Bone Marrow Transplantation (BMT) Service at a participating study site will be screened for eligibility by the clinical and/or research staff in the study. All such patients will be screened and enrolled, if eligible, regardless of their gender or ethnicity/race.

Potential research subjects will be identified by a member of the patient's treatment team, a protocol investigator, or research staff. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study. The principal investigator and research staff may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is

eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, MSK and participating sites seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

The research staff in conjunction with the clinical staff will explain to an eligible patient the study, potential risks and benefits of participating in the study, that participation in the research study is completely voluntary, and that they have the right to refuse participation or withdraw at any point in the study without influencing any aspect of their medical treatment. Once a patient is deemed eligible, they may be enrolled through an in-person consent appointment, econsent or by a verbal consent conducted over the phone. For patients interested in consenting remotely, they may be enrolled through MSK eConsent modules to conduct electronic consent as in Section 8.0. Patients who do not have a desktop or laptop computer capable of a remote econsent and who cannot travel to study sites may be consented using a verbal consent.

Similarily, at participating sites, each week, study staff will review new incoming BMT patients for eligibility. Staff will receive a list of new patients every week and will screen for eligibility using available electronic health records. If a patient is eligible based upon medical record review, a consent coordinator on the patient's medical team and/or the research coordinator will provide the patient with initial study information either virtually (via Zoom) or in person at the SCCA clinic. If the patient is interested and eligible, study staff will consent the participant and enroll them into the study prior to initiation of BMT treatment.

7.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. Written documentation of consent form and authorization will be waived for verbal consent. See Section 8.0 for Informed Consent procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional

requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

7.2 Randomization

After registration, research staff will randomize patients via MSK's secure Clinical Research Database (CRDB) using permuted blocks of random length. The allocation ratio will be 1:1 for ACU:OPI. Using the institutional randomization standard procedure with random blocks for RCTs will ensure full allocation concealment. Randomization will be stratified by study site, primary cancer diagnosis (MM versus HD versus NHL) and transplantation setting (inpatient versus outpatient) to ensure these characteristics are comparably distributed between the two study arms.

8.0 INFORMED CONSENT PROCEDURES

Scenario 1: Standard written consent scenario

The consent form/research authorization meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature, objectives, potential risks, and benefits of the intended study.

2. The length of study, what it entails, and the likely follow-up required.

3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)

4. The name of the investigator(s) responsible for the protocol.

5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

6. How the participants' data will be protected, who will have access to their PHI, and what data will be disclosed for research purposes

Prior to inclusion in the study and before protocol-specified procedures are carried out, the consenting professionals will explain the details of the protocol as outlined in the consent and research authorization to the participants/LARs. The participant/LAR will also be informed that they are free to withdraw from the study at any time. The consent discussion may occur in person or remotely via teleconference, telephone, or videoconference.

All participants/LARs must sign an IRB/PB-approved consent form/research authorization indicating their consent to participate. Each participant/LAR and consenting professional will sign and date the consent form. The participant/LAR must receive a copy of the signed informed consent form.

Scenario 2: Documentation of consent waived (e.g.,, verbal consent, only consenting professional signs)

The verbal informed consent/research authorization meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent/research authorization script will include the following:

1. The nature, objectives, potential risks, and benefits of the intended study.

2. The length of study, what it entails, and the likely follow-up required.

3. Alternatives to the proposed study.

4. The name of the investigator(s) responsible for the protocol.

5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

6. How the participants' data will be protected, who will have access to their PHI, and what data will be disclosed for research purposes.

Prior to inclusion in the study and before protocol-specified procedures are carried out, consenting professionals will explain the details of the protocol to participants/LARs. Participants/LARs will also be informed that they are free to withdraw from the study at any time. The consent discussion may occur in person or remotely via teleconference, telephone, or videoconference.

The consenting professional must sign an IRB/PB-approved consent /research authorization script to document the consent discussion and the participant's agreement.

In following the Code of Federal Regulations Title 45, Part 46, Subpart A, the IRB is waiving the requirement for an investigator to obtain a signed consent form from the participant as the research:

· presents no more than minimal risk of harm to participants, and

· involves no procedures for which written consent is normally required outside of the research context.

In following the Code of Federal Regulations Title 45, Part 164, Subpart E, IRB/PB is waiving the requirement for the investigator to obtain signed research authorization from the participant as:

· the use or disclosure of the PHI involves no more than minimal risk to the privacy of the individuals, based on the following elements:

o An adequate plan to protect identifiers from improper use and disclosure;

o An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research (unless there is a health or research justification for retaining the identifiers, or such retention is otherwise required by law); and

o Adequate written assurances that the PHI will not be reused or re-disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use of disclosure of PHI would be permitted by HIPAA.

· The research could not be practicably conducted without access to and use of the PHI.

· The research could not practicably be conducted without the waiver.

If a verbal consent is being conducted, the consenting professional will use the IRB/PB-approved verbal informed consent script when calling patients. If the patient agrees to participate, the consenting professional will sign and date the verbal consent, and a copy will be sent to the patient. A verbal consent would be used in cases where individuals do not have access to a computer and those who are unable to travel to study sites for an in-person consent appointment. This research involves no more than minimal risk to participants and use of a verbal consent would not adversely affect the rights and welfare of the research participants.

Informed consent can be obtained remotely with a telehealth platform and through an electronic-consenting process, using the MSK eConsent module. Electronic consent will be made available to potential patients who wish to enroll using the MSK eConsent modules. At participating sites, electronic consent will be made available to potential patients who wish to enroll using MSK's REDCap eConsent platform. FH/SCCA may use MSK's REDCap eConsent platform to electronically consent potential patients, and the MSK study team will maintain the REDCap eConsents. All participants/LARs must sign an IRB/PB-approved consent form via REDCap indicating their consent to participate. A consenting professional signature is not required as noted in IRB SOP IC-706. The participant/LAR must receive a copy of the signed informed consent form. Consenting professionals will perform the informed consent procedures using a telehealth audio/video platform. A copy of the written informed consent with standard research authorization document will be available as a file download for the patient's reference. Contact information for the study team will also be available should participants need to reach out with any questions. Patients interested in study participation will be able to sign the electronic consent once they have reviewed the consent form in its entirety and discussed the study with the consenting professional. Those who decline participation will not be contacted further. Reasons for refusal to take part in the study will be tracked if provided. Once consented, a PDF copy of the electronic consent form will be stored in the project's file repository survey archive. This document will record the date stamp, participant identifier information, IP address and the consent version number. A copy of the consent will be sent to the participant via email or standard mail based on his/her preference.

MSK may verbally consent patients, whereas FH/SCCA will always obtain written consent.The participant must receive a copy of the signed or verbal informed consent form, and a copy of the signed or verbal consent form will be sent to the patient's EMR.

9.0 PRE-TREATMENT/INTERVENTION

Enrolled patients will receive the following baseline assessments within 4 weeks before the first dose of HiChemo. Detailed descriptions of each assessment are in Section 11.0 and 13.1.

- Demographic and Clinical Features
- Symptom Burden (MDASI-BMT), paper or electronic
- Brief Pain Inventory – Short Form (BPI), paper or electronic
- Patient-Reported Oral Mucositis Symptom Scale (PROMS) ,paper or electronic
- Pain Medication Side Effects Questionnaire,paper or electronic
- Quality of Life (PROMIS-29), paper or electronic
- Adverse Events (CTCAE v5)
- Opioid Risk Tool (ORT), paper or electronic
- Acupuncture Expectancy Scale (AES), paper or electronic

10.0 TREATMENT/INTERVENTION PLAN

All study patients will receive the usual HSCT care and pain management regimens as per standard practice at the study institution. For patients randomized to the ACU group, they will receive acupuncture as follows.

In addition to usual care, patients in the ACU group will receive acupuncture treatments. Acupuncture treatments will be scheduled to cover the period of high symptom burden. Acupuncture will start on Day 0 and continue once daily to Day 15, as long as the patient is inpatient or comes to the clinic for post-transplantation follow-up. For myeloma patients getting melphalan, the day of melphalan infusion is counted as Day 0 in the study. For lymphoma patients getting BEAM (carmustine, etoposide, cytarabine, melphalan), the day of melphalan infusion is counted as Day 0. For lymphoma patients getting TBC (thiotepa, busulfan and cyclophosphamide), the day of thiotepa infusion is counted as Day 0. For the occasional patients on investigational conditioning chemotherapy regimen, Day 0 will be determined by the BMT physician and the PI.

Acupuncture will not be done on days patients are neutropenic (absolute neutrophil counts <500/microliter) or thrombocytopenic (platelet counts <20,000/microliter). Acupuncture does not have to be done on days when acupuncturists are not available, for example during weekend days or on days there is a staff shortage, or when a patient declines an

acupuncture treatment. The total number of acupuncture treatment a patient has received will be recorded. Patients will be instructed to do self-acupressure at LI-4 and PC-6 acupuncture points when they experience pain or nausea.

Patients in the OPI group will receive usual care and will not receive acupuncture.

In this study, acupuncture needles will be inserted at bilateral PC6, LI4, ST36, SP6, KI3, LR3, and ear shenmen acupuncture points and unilateral GV20 and Ex-HN3 points. The needles will be manualy manipulated for deqi and left in place for 20 minutes before removal. Electrical stimulation (e-acupuncture) may be applied to the ST36 and SP6 points when appropriate as per standard acupuncture practice.

Prior to acupuncture, the acupuncturist will check the patient's Complete Blood Counts (CBC) from the same day (HSCT patients have daily CBCs and will not provide the treatment if the patient's absolute neutrophil counts are less than 500/microliter or platelet counts less than 20,000/microliter. If an acupuncture point falls on an area of skin that is not safe to do acupuncture (e.g. wound or skin infection), the point will not be used and the deviation from point prescription will be recorded. A needle counting will be performed at the end of the treatment to ensure all needles are removed. Any adverse event noted during or immediately after acupuncture will be address according to standards in the profession of acupuncture and documented in the research record. Any serious adverse event will be reported to the study PI or a co-I immediately.

Participants will be asked to complete patient reported outcomes assessments online using REDCap or, If they prefer, via pencil and paper or over the phone with a Clinical Research Coordinator to reduce participant burden and ensure timely completion.

11.0 EVALUATION DURING TREATMENT/INTERVENTION

We will assess all study participants for the study outcomes at baseline (within 4 weeks before HiChemo) and on or about days 7, 15, 30, and 90 after the first dose of HiChemo (See Schema in Section 4.0). The total burden in time to patients is about 30-45 minutes at each time point.

The following outcome measurements will be carried out on and about Day 7, 15, 30 and 90 (Day 0 being the day of first dose of HiChemo), either in the Integrative Medicine or BMT clinic in order to minimize unnecessary visits. The instruments are attached in appendices, and may be administered electronically (on a tablet if in clinic, via secure link if at home) or on paper.

- Opioid Use (drug administration record while inpatient and pill count while outpatient)
- Symptom Burden (MDASI-BMT)
- Brief Pain Inventory – Short Form (BPI)

- Patient-Reported Oral Mucositis Symptom Scale (PROMS)
- Pain Medication Side Effects Questionnaire
- Quality of Life (PROMIS-29)
- Adverse Events (CTCAE v5)

Collection of demographic and clinical features (diagnosis, disease status, chemotherapy regimen and mortality) data and assessement of use of healthcare resources will also be carried out on and about Day 90. Use of healthcare resources includes the length of hospital stays and transfers to the intensive care unit during HSCT, and total inpatient days, emergency room visits and readmissions during the first 30 days post-HSCT.

Schema of Data Collection	By Patient vs. By Study Team (ST)	Baseline	Day 7 (± 2 day)	Day 15 (± 3 days)	Day 30 (± 7 days)	Day 90 (± 14 days)
Demographic and Clinical Features	ST	X				X
Opioid Use (Primary Outcome)	Patient and ST	X	X	X	X	X
Symptom Burden (MDASI-BMT)	Patient	X	X	X	X	X
Brief Pain Inventory – Short Form (BPI)	Patient	X	X	X	X	X
Patient-Reported Oral Mucositis Symptom Scale (PROMS)	Patient	X	X	X	X	X
Pain Medication Side Effects Questionnaire	Patient	X	X	X	X	X
Quality of Life (PROMIS-29)	Patient	X	X	X	X	X
Adverse Events (CTCAE v5)	ST	X	X	X	X	X
Opioid Risk Tool (ORT)	Patient	X				
Acupuncture Expectancy Scale (AES)	Patient (ACU)	X				
Use of Health Care Resources	ST					X
*Day 0 = Day of the first dose of high dose chemotherapy						

12.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will be considered off-study upon completion of Day 90 assessments. Study intervention will be discontinued if severe, unexpected adverse events attributable to acupuncture has occurred or discontinuation is deemed by the principal investigator to be in the best interest of the patient. Those patients will remain in the study for outcome assessments. Patients will be removed from the study if the patient wishes to withdraw from the study. Removed patients will continue to be evaluated for outcomes if they give permission for us to do so.

13.0 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY

13.1 Criteria for Therapeutic Response/Outcome Assessment

Demographic data (age, gender, race, ethnicity, height and weight) and clinical features (cancer diagnosis, disease status, and regimen of the high-dose chemotherapy) will be collected.

Our first primary outcome is the proportion of patients who are opioid users (the number of patients using opioids at a given time divided by the total number of patients randomized to that group at Day 7 and Day 90). In this study, we define opioid user as a patient who uses any opioids during the seven days preceding the day of assessment. At baseline, patients will be asked whether they have a prescription for any opioids, any access to non-prescription opioids and whether they used any opioids in the preceding seven days. During an inpatient period, all administrations of pain medications are recorded on hospital drug administration records, which will serve as our primary data source. For outpatient, we will use pill-counting to collect this data and data on opioid dose actually consumed by the patient in the week prior to the time point (Appendix 2).[37-39] Pill-counting can be done remotely with a telehealth platform.

Our second primary outcome is the symptom burden at Day 7, measured by the MDASI-BMT Total Symptom Severity score. MDASI-BMT (M.D.Anderson Symptom Inventory – Blood and Marrow Transplantation) is a 24-item multi-symptom patient-reported outcome (PRO) measure for clinical and research use.[40] The MDASI-BMT consists of the core MDASI plus 5 items specific to BMT patients. It assesses 13 core symptoms common across cancer types and treatments (pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, difficulty remembering, lack of appetite, drowsiness, dry mouth, sadness, vomiting, and numbness/tingling). In addition to the 13 core symptom items, it has 6 items that assess symptom-related interference. The MDASI has several advantages over other symptom-assessment scales in that it applies broadly across cancer types and treatments, is easy for patients to complete, includes items related to symptom interference with daily life, and it is easily translated into other languages. It takes five minutes to complete and has a Cronbach alpha reliability range from 0.82 to 0.94. For MDASI-BMT, five additional symptoms important to this population were added. The BMT symptoms rated are feeling physically sick, weak, diarrhea, mouth sores, and bleeding. All symptoms are rated with reference to “the last 24 hours” on 0–10 numeric scales from “not present” to “as bad as you can imagine.” Patients also rate the amount of interference with daily activities caused by symptoms on 0–10 numeric scales from “did not interfere” to “interfered completely.” The MDASI-BMT has demonstrated good internal reliability in prior studies.[41,42] Three symptom and one interference subscale scores can be calculated from the MDASI-BMT items by taking the means of particular item subsets: Core Symptom Severity (13 core MDASI items), BMT Symptom Severity (5 BMT-specific items), Total Symptom Severity (13 core plus 5 BMT-specific items), and Interference (6 interference items). The subscale scores may be calculated when more than half of the items on a subscale have valid, non-missing responses, and should otherwise be considered missing. In the current study, the MDASI-BMT Total Symptom Severity score will serve as the symptom burden primary endpoint.

The Brief Pain Inventory–Short Form (BPI, internal consistency Cronbach's α of 0.77–0.91) is a well-validated and widely used instrument to assess pain in cancer patients.[43] It uses numerical rating scales (NRS) to quantify pain intensity and patient interference. The BPI

contains 4 pain severity items and 7 pain interference items, all rated on a scale from 0 to 10 (higher ratings indicate worse pain intensity/interference). A pain interference subscale can be computed by taking the average rating of the 7 pain interference items. A pain severity subscale score can similarly be computed for the 4 pain severity items; however, the Worst Pain severity item and the Average Pain severity item are often examined separately from the pain intensity subscale in clinical research because they tend to be more sensitive indicators of changes in patients' perceived pain. As such, the primary outcome of this study will be the patient's rating of their Worst Pain in the past week with response choices of 0 "no pain" to 10 "pain as bad as you can imagine." The Average Pain rating in the past week and the pain interference subscale will be used as secondary pain outcomes. This takes 5 minutes to complete.

Because the main source of pain in the study population is mucositis caused by high-dose chemotherapy, we will complement the BPI with an instrument that specifically assesses mucositis pain. We will use the PROMS (Patient-Reported Oral Mucositis Symptom) scale,[11] which was developed using HSCT patients from baseline to 60 days post-HSCT (similar to our study population), has excellent psychometric properties, and is easy to administer. The PROMS scale has ten items, each quantified through a 100-mm Visual Analog Scale (VAS), and a Cronbach's α of 0.86–0.98. This takes 3 minutes to complete.

Side effects are a major concern for patients using opioids.[18,44] There is currently no gold standard instrument for specifically evaluating opioid side effects.[45-47] We will use the method from Martel et al., which is specific for opioids side effects.[48] Patients will be asked to complete a questionnaire in which they rate the intensity of each of the following symptoms in the last 24 hours on a visual analog scale (VAS) that ranges from 0 (minimum) to 10 (maximum): 1) nausea, 2) constipation, 3) headaches, 4) dry mouth, 5) itching, 6) sneezing, 7) sweating, 8) weakness, 9) dizziness, 10) confusion, 11) memory problems, and 12) visual problems. This takes 2 minutes to complete.

We will assess patients' overall quality of life (QOL) using the Patient-Reported Outcomes Measurement Information System 29 Items (PROMIS-29), which resulted from a National Institutes of Health initiative to develop state-of-the-science self-report measures to assess functioning and well-being in physical, mental and social domains of health. The PROMIS-29 v2.0 profile measure is analogous to the most widely used profile measure to date, the SF-36. But the PROMIS-29 v2.0 profile items were selected from PROMIS item banks calibrated using item response theory (IRT) analyses and all items in a domain are scored on the same underlying metric.[49] This takes 10 minutes to complete.

We will monitor and record adverse events (AEs) as per the Common Terminology Criteria for Adverse Events Version 5.0 (CTC-AE v5.0). The adverse events will be collected by the study team, and assessed (grade/attribution) by the clinician. The Opioid Risk Tool (ORT) is a brief, self-report screening tool designed for use with adult patients to assess risk for opioid abuse.[50] It is recommended by the National Institute on Drug Abuse (NIDA) as an instrument

to screen for opioid misuse risk, and takes 2 minutes to complete. This data will be collected at baseline and used in Heterogeneity of Treatment Effect (HTE) analysis to assess whether it influences the effects of acupuncture. Expectancy for acupuncture may influence its clinical effects.[51-54] We will assess patients at baseline using the Acupuncture Expectancy Scale (AES). This is a validated instrument (takes about 3 minutes to complete) with an internal consistency (Cronbach's α) of 0.95 and test-retest reliability of 0.62 over four weeks without acupuncture treatment.[55,56] This data will be used as a variable in HTE analyses for predictor to response and sensitivity analyses. We will also track use of healthcare resources, such as the length of hospital stays and transfers to the intensive care unit during HSCT, and emergency room visits and readmission during the first 30 days post-HSCT. These are exploratory endpoints to generate preliminary data about impact on the health care system, e.g. iatrogenic adverse events from opioids and delayed discharge from opioid side effects.

All patient-reported measures will be administered either electronically (on a tablet if in clinic, via secure link if at home) or on paper.

13.2 Criteria for Study Endpoint Evaluability

All patients who are randomized and who have their opioid use evaluated at Day 7 will be considered evaluable for the Day 7 opioid primary endpoint. Similarly, patients who have their opioid use evaluated at Day 90 will be evaluable for the Day 90 opioid primary endpoint. For the Day 7 symptom burden primary endpoint, all patients who are randomized and who have at least a baseline MDASI-BMT Total Symptom Severity score will be considered evaluable. In general, patients will be considered evaluable for continuous study endpoints as long as they have at least the baseline measurement. No patient will be replaced after randomization. All randomized patients meeting these additional evaluability criteria will be included in the analyses using the modified intention-to-treat (ITT) principle (i.e. participants will be analyzed according to the treatment group to which they will be randomly allocated regardless of treatment adherence status).

14.0 BIOSTATISTICS

This is a multicenter, two-arm randomized controlled trial to compare the effects of two pain management strategies on opioid use, symptom burden, and other patient-reported outcomes among patients receiving high-dose chemotherapy (HiChemo) followed by HSCT. Opioid-naïve adult multiple myeloma, Hodgkin disease, and non-Hodgkin lymphoma patients undergoing HiChemo followed by HSCT will be randomized (at 1:1 ratio, see Section 7.2) to receive either acupuncture as a first-line pain preventive measure during HiChemo with opioids as back-up pain treatment (ACU), or opioids as first-line pain treatment (OPI). Study outcomes will be measured at pre-HiChemo baseline and at Days 7, 15, 30, and 90 after the first dose of HiChemo, with the Day 7 (short-term) and Day 90 (long-term) outcomes of particular interest. We expect to accrue approximately 12 patients per month, and we anticipate the study will be open to enrollment for approximately 30 months. We expect the

total study duration to be 3 years.

14.1. Sample Size Considerations. This study has 3 primary endpoints: opioid use at Day 7, opioid use at Day 90, and symptom burden at Day 7. The statistical plan takes that into consideration. Our overall Type I error rate for testing these 3 primary endpoints is set to alpha = 0.05. To maintain this Type I error rate, we will allocate alpha = 0.02 to each of the tests of opioid use at Day 7 and at Day 90, and we will allocate alpha = 0.01 to the test of symptom burden at Day 7.

In our pilot study, among "opioid-naïve" patients, 25% of sham acupuncture (SA) patients and 7% of true acupuncture (TA) patients were opioid users at Day 90. For our sample size/power estimates for Aim 1, we conservatively assume that patients in the OPI arm will have similar Day 90 opioid usage (25%) as the SA patients in our prior study, and that 10% of patients in the ACU arm will be using opioids at Day 90 (slightly higher than the TA arm in our pilot study). This translates to a relative reduction of 60% fewer opioid users in the ACU arm, and an odds ratio of 0.33, which would be considered clinically meaningful. The attrition rate was only 5% in our pilot study. However, we will conservatively plan for a high 10% attrition rate by randomizing 300 patients (150 per arm) in order to obtain 270 patients (135 per arm) with evaluable Day 90 endpoints. With an initial sample size of 300 patients and a 10% attrition rate, we will have 81% statistical power to detect this Day 90 difference between the two arms (i.e. 10% vs 25%) at a significance threshold of $p<0.02$ using logistic regression analysis and a two-sided significance test. It is possible that the OPI group will have higher opioid use than the SA patients in our pilot study, as sham acupuncture is known to have some placebo effect.[23,28] We therefore expect a larger effect size than we observed in the pilot study where true acupuncture was compared to sham acupuncture. In that scenario, assuming 30% in the OPI group use opioids versus 10% in ACU group, our power will increase to 96%.

We based our sample size exclusively on having adequate power for the Day 90 comparison of opioid use. This was due to the high public health priority to find pain interventions that can reduce long-term opioid use. That said, we expect the Day 7 comparison to have similar power as the Day 90 comparison. We believe this is a conservative assumption, and that we most likely have higher power at Day 7 due to lower attrition and potentially a larger effect size at Day 7 relative to Day 90. For example, in our pilot study, 20% of sham acupuncture (SA) patients were using opioids at Day 5 (opioid usage not collected at Day 7) compared to none of the true acupuncture (TA) patients.

For our sample size/power considerations for comparing symptom burden between ACU vs. OPI at Day 7, we calculated the smallest standardized effect size (aka, Cohen's d) we will be able to detect with 80% power, given our sample sizes of 150 in each of the two arms. To estimate this smallest detectable effect size, we used the methods of Lu, Luo, & Chen (2008),[57] which describes sample size calculations for a class of analyses called the "mixed model for repeated measures" (MMRM) in randomized clinical trials with participant attrition. Our LMM analyses fall under this MMRM class of analyses. Using the "power.mmrm"

function from the R package "longpower", we applied the formulas in Lu et al. (2008) to our study design and assumptions to derive the smallest detectable effect size for the coefficient of the time-by-arm interaction term in our LMM (with time including only the Day 0 and Day 7 assessments, see Section 14.2), which we transformed to represent the standardized mean difference (aka, Cohen's d) of the changes in symptom burden from baseline between the two arms at Day 7 post-HSCT. With 150 participants in each of the two arms, we will have power of 0.80 to detect an effect size for symptom burden as small as 0.41 (standardized difference, Cohen's d) at Day 7 between acupuncture vs. usual care, assuming 10% attrition, correlation between baseline and Day 7 symptom burden scores of 0.50, and two-sided alpha of 0.01. The MDASI-BMT Total Symptom Severity score does not have an empirically-established minimum clinically important difference (MCID). A research-based rule-of-thumb for PRO instruments lacking empirical MCIDs is to adopt a standardized difference of 0.50 as the MCID.[58] Given our detectable effect size of 0.41, we will be able to detect a MCID in symptom burden between the two arms.

For Aim 2, we will test whether mean ACU pain scores are non-inferior to mean OPI pain scores at two timepoints, Day 7 and Day 90. To limit the type I error rate for this family of two tests to 0.05, we will use a significance threshold for each test of 0.025. The Aim 2 key endpoint is Day 7 pain scores, since pain due to HiChemo is expected to peak around Day 7 and resolve well before Day 90 for both study arms. We present power considerations below for the Day 7 non-inferiority test. The same assumptions apply to the Day 90 test; however, we expect ACU pain scores to be well within our non-inferiority margin by Day 90. WeWe will have 80% power to find mean ACU pain scores non-inferior to mean OPI pain scores within a non-inferiority margin of 0.34 standard deviations (SD), assuming 300 patients, 10% attrition, and one-sided significance threshold of 0.025. Our non-inferiority margin (0.34 SD) is smaller than the typical minimum clinically important difference (MCID) for self-report measures (i.e., MCID = 0.50 SD for BPI[59]). Therefore, this margin represents an acceptable pain control benchmark for ACU in comparison to OPI.

14.2. Statistical Methods.

14.2.1. General Approaches. All analyses will be by intent-to-treat, with patients analyzed as randomized, irrespective of treatment actually received. Demographics and other relevant variables (e.g., number of acupuncture sessions received in the ACU arm) will be summarized by treatment arm using standard descriptive statistics. All data at all assessment time points will be summarized by treatment arm using standard descriptive statistics and plotted to visually assess trajectories over time. In the following subsections, we present specific analysis plans that are tailored to address our specific aim hypotheses, focus on single assessment time points, have relatively straightforward interpretations, and will be used to draw our primary conclusions regarding the Aims of this trial. However, our more general analysis approach will use more complex models to capitalize on the longitudinal nature of the study design and allow us to examine plots of the model-based trajectories of our outcome measures over time by study arm, giving us a visual overview of each outcome measure that incorporates all of the available data. For Aim 1, we will utilize generalized

linear mixed models (GLMM) to model the probability of opioid use across all time points (i.e. Day 7, 15, 30, and 90) as a function of study arm (ACU vs. OPI), time, the arm-by-time interaction, and randomization stratification variables.. For Aim 1 symptom burden, and for the continuous Aim 2 outcome measures, we will use linear mixed models (LMM) to similarly model those continuous endpoints over time. For both the GLMM and LMM analyses, we will use interaction terms between time and study arm to allow us to plot the arm-specific outcome trajectories over time. These statistical procedures (GLMM and LMM) account for within-subject correlations from repeated measurements in the same subjects and allow estimation of between-group differences without necessitating exclusion of participants with missing data.

14.2.2. Specific Aim 1 Analysis Methods. To test Aim 1 hypotheses, we will test whether ACU has fewer opioid users compared to OPI at Day 7 (Hypothesis 1a) and at Day 90 (Hypothesis 1b) using separate but similar logistic regression models. Each model will predict opioid use at the given time point as a function of treatment arm (ACU vs. OPI), controlling for the randomization stratification variables (study site and cancer diagnosis). To test whether ACU reduces symptom burden at Day 7 compared to OPI (Hypothesis 1c), we will use a LMM to model the baseline and Day 7 MDASI-BMT Total Symptom Severity scores as a function of study arm (ACU vs. OPI), time (Day 0 and Day 7), and the arm-by-time interaction (coefficient of interest), controlling for the randomization stratification variables.

14.2.3. Specific Aim 2 Analysis Methods. For the Aim 2 hypotheses we will first test (Hypothesis 2a) whether mean pain scores among ACU patients were non-inferior to those among OPI patients (within a non-inferiority margin of 0.34 standard deviations) at Day 7 (key Aim 2 endpoint) using a LMM containing arm, time (Days 0 and 7), and the arm-by-time interaction as predictors, controlling for the randomization stratification factors. That is, if the mean Day 7 pain score in the ACU arm is not significantly ($p < 0.025$) more than 0.34 standard deviations higher than the mean OPI pain score, then we will consider ACU to be non-inferior to OPI with respect to Day 7 pain control. A similar analysis will be performed for the Day 90 pain scores. For Hypothesis 2b, we will estimate mean differences (and 95% confidence intervals) between ACU vs. OPI side effect ratings, PROMIS-29 scores, and PROMS scores using separate linear mixed models for the Day 7 and Day 90 outcomes, controlling for the randomization stratification variables and baseline score (when relevant). We will have 80% power to detect unadjusted differences between study arms on these outcomes as small as 0.34 SD (i.e., Cohen's $d = 0.34$) using two-sided tests and $p<0.05$. By convention, this effect size is between a small (i.e., $d=0.20$) and moderate ($d= 0.50$) effect size. We will have power to detect smaller effect sizes in the covariate-adjusted regression analyses described above, but we have insufficient preliminary data on which to base estimates of these adjusted effect sizes.

We will adjust all comparisons between the two treatment arms for the randomization stratification factors - study site and primary cancer diagnosis (MM versus HD versus NHL) - by including them as fixed effects in our statistical models.

14.2.4. Exploratory Aim 1, Mediation. We will explore potential causal mechanisms by testing mediation hypotheses[60] (e.g. test whether the effect of treatment on Day 90 opioid use is mediated through the effect of treatment on Day 7 opioid use). We will use the approach to testing mediation hypotheses outlined in Imai, Keele, & Tingley (2010)[60] in which a series of models are fit that allow estimation of the total, direct, and indirect (i.e., through the mediator) effects of treatment arm on Day 90 opioid use.

14.2.5. Exploratory Aim 2, Heterogeneity of Treatment Effect (HTE). We expect patients will respond differently to study interventions but we do not have enough preliminary to data to generate hypotheses. Our HTE analyses will be exploratory and hypothesis-generating. We will explore whether sex, race, ethnicity, gender, primary cancer diagnosis (MM versus HD versus NHL), Opioid Risk Tool (ORT), Acupuncture Expectancy Scale (AES) score, or concurrent use of other medications with analgesic effects influence response to interventions in this population. We will add these variables and variable-by-arm interaction terms to our Day 7 and Day 90 logistic and linear regression models to identify potential patient-level factors associated with differential responses to treatment with respect to our primary and secondary outcomes. Each variable of interest will be assessed for HTE in a separate model. We will guard against inflated type I errors due to multiple testing by adjusting the variable-by-intervention interaction p-values for the false discovery rate.[61,62] We intend to approach the evaluation of HTE based on existing literature and patient/clinician input. Our current focus on evaluating and reporting HTE will be based on the approach proposed by Kent et al.[63] However we will also apply promising emerging Bayesian[64,65] and machine learning[66,67] methods, which can identify HTE and subgroups based on multiple variables simultaneously and are potentially more powerful than traditional univariate methods. We recognize that these types of sub-group analyses, although patient-centered, may need to be interpreted with caution and cannot replace the primary analyses.

14.3. Missing Data. We will first explore whether missingness is associated with observed variables (particularly randomization arm and the baseline outcome measures) by comparing patients with complete and incomplete data. Of note, our general longitudinal data analysis approaches described above (GLMM and LMM) validly include patients with incomplete data under the missing at random assumption. However, our exploration of the data may deem the missing at random assumption to be inappropriate, and not all our hypotheses will be tested using these longitudinal modeling approaches. In these cases, we will use well-established methods such as multiple imputation and pattern mixture models to help us deal with these issues.[68,69] We will perform sensitivity analyses to evaluate the robustness of our main findings by using multiple imputation to impute the missing outcomes (particularly for Day 7 and Day 90) and duplicating the analyses using the multiply imputed data sets.

14.4 Populations for Analyses

- Modified Intention-to-Treat Analysis Dataset, Opioid Use: For the Day 7 analysis, this will include all randomized patients who have Day 7 opioid use assessed. For the Day 90 analysis, this will include all randomized patients who have Day 90 opioid use assessed.

- Modified Intention-to-Treat Analysis Dataset, Symptom Burden: This will include all randomized patients who have, at least, a valid baseline MDASI-BMT Total Symptom Severity score.
- Modified Intention-to-Treat Analysis Dataset, Other Continuous Endpoints: For a given continuous endpoint, this will include all randomized patients who have, at least, a valid baseline endpoint measurement.

15.0 TOXICITIES/RISKS/SIDE EFFECTS

Potential Risks. All potential risks that might occur as a result of participation will be detailed in an informed consent form, and will also be fully discussed with each subject prior to enrollment. We will also explain to each subject that in the unlikely event of an injury directly resulting from the research procedures, every effort will be made to make the facilities and professional skills of our institutions available to them. While some risks are unpredictable, we will take every precaution consistent with the best medical practices to protect the health and safety of subjects. We will document all adverse event (AEs) attributed to acupuncture and report them to the IRB in regular continuing review forms.

Physical Risks: Acupuncture has a known safety record.[70] According to data from 97,733 patients and more than 760,000 treatments, the most common AEs (in around 7% treatments) were pain experienced during needling and loss of blood when the acupuncture needle was removed, all grade 1 and self-limiting. In clinical trial settings, SAEs are rare and found to be at a rate of around 0.005% of patients and 0.0008% of treatments.[71] In our pilot study, no SAEs from acupuncture were encountered.[72] Adverse effects of opioids include dry mouth (42%), constipation (20–41%), sweating (34%), weight gain (29%), somnolence (14–29%), problems with sleep (25%), memory deficits (24%), loss of appetite (23%), nausea (17–33%), concentration deficits (19%), fatigue (19%), sexual dysfunction (18%), dizziness (12–22%), vomiting (11–15%), pruritus/dry skin (10%) and urinary retention,[14-20] with as many as 80% patients experience at least one adverse event.[73] Serious adverse effects are uncommon (around 0.60% of admission) and include altered mentation, cardiovascular depression, respiratory depression and even death.[74] *Psychological Risks:* It is possible that a patient may experience psychological distress when completing the Patient Reported Outcome (PRO) measurements.

Financial and Legal Risks: There are no financial or legal risks to the study patients. All research interventions and evaluations are provided free of charge to study participants.

Privacy and/or Confidentiality Risks: Information about study subjects may be inadvertently disclosed to a person not authorized to access such information.

Alternative Treatments: The alternative to participating in the study is receiving standard HSCT care without participating in the study. Patients may receive opioid-based pain management and/or acupuncture depending on their treating clinician's clinical judgment. During the informed consent process, study candidates will be informed of this alternative,

that their participation in the study is entirely voluntary, and that their care will not be affected in any way if they decide not to participate in the study.

CTCAE Version 5 will be utilized for toxicity evaluation.

15.1 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE. Hospital admission as part of standard hematopoietic stem cell transplantation care and attributable as unrelated to acupuncture is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected

- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

16.0 PROTECTION OF HUMAN PARTICIPANTS

Protection Against Physical Risks. To reduce risks associated with acupuncture, we will exclude patients in whom acupuncture may not be safe - those with neutropenia (absolute neutrophil counts less than 500/microliter) or thrombocytopenia (platelet counts less than 20,000/microliter). We will also not perform acupuncture on patients who become neutropenic or thrombocytopenic during the study. HSCT patients have daily complete blood counts (CBC) during the transplantation period. The acupuncturists will check a patient's CBC before giving them acupuncture. Our acupuncturists have been trained to recognize AEs that occur during or immediately after acupuncture treatment. They will exercise safety precautions as is standard in their professional discipline and inform the primary oncology team when an AE is deemed unusual or beyond what is expected for acupuncture.

Protection Against Psychological Risks. If a Research Assistant (RA) observes a patient displaying elevated psychological distress during an assessment, the RA will inform the site PI so that s/he can assess the situation and potentially refer the patient to psychiatric care, if clinically warranted. In the unlikely event of significant acute distress, patients will be referred for urgent evaluation by psychiatry at the study institution.

Protection Against Privacy and/or Confidentiality Risks. Information about study subjects will be kept confidential and managed according to the HIPAA requirements. The paper data files will be kept in locked cabinets and electronic files will be kept in password-protected computers that only personnel with a need-to-know can access. The data will be disclosed to the IRB upon request for data safety monitoring. We will not attempt secondary use of the data after the study ends without subsequent IRB approval.

Vulnerable Subjects. No specific class, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations, will be included in the study.

Potential Benefits of the Proposed Research to Research Participants and Others. Our preliminary research suggests that acupuncture may reduce pain medication use and some side effects commonly associated with pain medication use without compromising pain management in HiChemo/HSCT patients. Patients in the proposed study may experience the

same benefits. If confirmed by the proposed research, future HiChemo patients may have an additional tool for pain management available to them and may experience fewer symptoms and better quality of life during their cancer treatment. The risks to subjects are small in comparison to the scientific information and potential benefit to cancer patients that may result from the conduct of this study. Patients will receive the following payments for their time and effort while participating this study: $40 upon completion of Day 30 assessments, and $60 upon completion of Day 90 assessments.

Alternative to Participation. The alternative to participating in the study is to receive standard HSCT care without acupuncture or receive these therapies outside of this study. During the informed consent process, potential study participants will be informed of this alternative, that their participation in the study is entirely voluntary, and that their care will not be affected in any way if they decide not to participate in the study.

16.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals/entities described in the Research Authorization form. A Research Authorization form must be approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de-identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other at the time of study publication.

16.2 Data Management

The Clinical Research Coordinator(s) (CRC(s)) assigned to this study will be responsible for project compliance, data collection, abstraction and entry, data reporting, regulatory and quality control monitoring, problem identification, and prioritization. Coordination of the study team activities will be the responsibility of our Clinical Research Supervisor (CRS) and/or Clinical Research Manager (CRM). The CRS and CRM will work with the CRC on problem resolution, organization, and quality control. We hold regular meetings attended by the research staff and the Principal Investigator to review study progress and to manage any difficulties encountered. For any communication with participants, all security precautions will be taken, including making sure to activate MSKSecure in e-mail correspondences.

Registration and patient study status will be entered into CTMS per institution requirement. CRDB will be utilized for randomization. Subject recruitment will be tracked in Excel. Other study-related data will be in REDCap. Participants will be asked to complete patient reported

outcomes assessments online using REDCap, as described below. If they prefer, patients will have the option to complete the measures via pencil and paper or over the phone with a CRC to reduce participant burden and ensure timely completion.

REDCap (Research Electronic Data Capture) is a data management software system supported by the Clinical Research Administration (CRA) at MSK. Members of the CRA supporting the REDCap software will have access to REDCap projects hosted by MSK's servers for the purpose of ensuring the proper functioning of the database and the overall software system. REDCap is a tool for the creation of customized, secure data management systems including web-based data entry forms, reporting tools, and a full array of security features including user- and group-based privileges with a full audit trail of data manipulation and export procedures. REDCap is maintained on MSK-owned servers that are kept in a locked server room with appropriate environmental modifications (e.g. proper ventilation, power redundancy and fault tolerance arrangement) and backed up nightly with some back-up tapes stored off-site. The MSK Information Systems group is responsible for applying all operating system patches and security updates to the REDCap servers. All connections to REDCap utilize encrypted (SSL-based) connections. Nationally, the REDCap software is developed, enhanced, and supported through a multi-institutional consortium led by Vanderbilt University.

Source documentation will be available to support the computerized patient data. The confidentiality of patient information will be carefully protected. Following data entry by Integrative Medicine Service research staff, data will be maintained in a secure location in the Integrative Medicine offices. All data will be stored in a fashion consistent with FDA guidelines (21CFR11 compliant) and HIPAA security rules.

Final data sets for publication will be locked and stored centrally for potential future access requests from outside entities.

16.3 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.4 Data and Safety Monitoring

The Data and Safety Monitoring Plan utilized for this study must align with the MSK DSM Plan, where applicable.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-in-Chief, Clinical Research.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

17.0 REFERENCES

1. Sheinfeld Gorin S, Krebs P, Badr H, et al. Meta-analysis of psychosocial interventions to reduce pain in patients with cancer. *J Clin Oncol.* 2012;30(5):539-547.
2. Salz T, Lavery JA, Lipitz-Snyderman AN, et al. Trends in Opioid Use Among Older Survivors of Colorectal, Lung, and Breast Cancers. *J Clin Oncol.* 2019;37(12):1001-1011.
3. Barnett ML, Olenski AR, Jena AB. Opioid-Prescribing Patterns of Emergency Physicians and Risk of Long-Term Use. *N Engl J Med.* 2017;376(7):663-673.
4. Edlund MJ, Martin BC, Russo JE, DeVries A, Braden JB, Sullivan MD. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain: the role of opioid prescription. *Clin J Pain.* 2014;30(7):557-564.
5. Harbaugh CM, Lee JS, Hu HM, et al. Persistent Opioid Use Among Pediatric Patients After Surgery. *Pediatrics.* 2018;141(1).
6. Gil JA, Gunaseelan V, DeFroda SF, Brummett CM, Bedi A, Waljee JF. Risk of Prolonged Opioid Use Among Opioid-Naive Patients After Common Shoulder Arthroscopy Procedures. *Am J Sports Med.* 2019;47(5):1043-1050.

7. Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use - United States, 2006-2015. *MMWR Morb Mortal Wkly Rep.* 2017;66(10):265-269.
8. Wang XS, Shi Q, Shah ND, et al. Inflammatory markers and development of symptom burden in patients with multiple myeloma during autologous stem cell transplantation. *Clin Cancer Res.* 2014;20(5):1366-1374.
9. Cheng KK, Leung SF, Liang RH, Tai JW, Yeung RM, Thompson DR. Severe oral mucositis associated with cancer therapy: impact on oral functional status and quality of life. *Support Care Cancer.* 2010;18(11):1477-1485.
10. Raber-Durlacher JE, Barasch A, Peterson DE, Lalla RV, Schubert MM, Fibbe WE. Oral complications and management considerations in patients treated with high-dose chemotherapy. *Support Cancer Ther.* 2004;1(4):219-229.
11. Kushner JA, Lawrence HP, Shoval I, et al. Development and validation of a Patient-Reported Oral Mucositis Symptom (PROMS) scale. *J Can Dent Assoc.* 2008;74(1):59.
12. Cheng KK. Oral mucositis and quality of life of Hong Kong Chinese patients with cancer therapy. *Eur J Oncol Nurs.* 2007;11(1):36-42.
13. Fann JR, Hubbard RA, Alfano CM, Roth-Roemer S, Katon WJ, Syrjala KL. Pre- and post-transplantation risk factors for delirium onset and severity in patients undergoing hematopoietic stem-cell transplantation. *J Clin Oncol.* 2011;29(7):895-901.
14. Papaleontiou M, Henderson CR, Jr., Turner BJ, et al. Outcomes associated with opioid use in the treatment of chronic noncancer pain in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc.* 2010;58(7):1353-1369.
15. Candiotti KA, Gitlin MC. Review of the effect of opioid-related side effects on the undertreatment of moderate to severe chronic non-cancer pain: tapentadol, a step toward a solution? *Curr Med Res Opin.* 2010;26(7):1677-1684.
16. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician.* 2008;11(2 Suppl):S105-120.
17. Brown RT, Zuelsdorff M, Fleming M. Adverse effects and cognitive function among primary care patients taking opioids for chronic nonmalignant pain. *J Opioid Manag.* 2006;2(3):137-146.
18. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *CMAJ.* 2006;174(11):1589-1594.
19. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. *Arthritis Res Ther.* 2005;7(5):R1046-1051.
20. Eisenberg E, McNicol ED, Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials. *JAMA.* 2005;293(24):3043-3052.
21. Commission TJ. R3 Report Issue 11: Pain assessment and management standards for hospitals 2018; https://www.jointcommission.org/r3_issue_11/. Accessed June 25, 2018.
22. Qaseem A, Wilt TJ, McLean RM, Forciea MA, Clinical Guidelines Committee of the American College of P. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. *Ann Intern Med.* 2017;166(7):514-530.
23. Chou R, Deyo R, Friedly J, et al. Nonpharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med.* 2017;166(7):493-505.
24. Swarm RA, Abernethy AP, Anghelescu DL, et al. Adult cancer pain. *Journal of the National Comprehensive Cancer Network : JNCCN.* 2013;11(8):992-1022.

25. Network NCC. NCCN Clinical Practice Guidelines in Oncology: Adult Cancer Pain Version I.2018. 2018; https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf. Accessed June 22, 2018.
26. Paice JA, Portenoy R, Lacchetti C, et al. Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol.* 2016;34(27):3325-3345.
27. Vickers AJ, Cronin AM, Maschino AC, et al. Acupuncture for chronic pain: individual patient data meta-analysis. *Arch Intern Med.* 2012;172(19):1444-1453.
28. Vickers AJ, Linde K. Acupuncture for chronic pain. *JAMA.* 2014;311(9):955-956.
29. Vickers AJ, Vertosick EA, Lewith G, et al. Acupuncture for Chronic Pain: Update of an Individual Patient Data Meta-Analysis. *J Pain.* 2018;19(5):455-474.
30. Liao HY, Hsieh CL, Huang CP, Lin YW. Electroacupuncture Attenuates Induction of Inflammatory Pain by Regulating Opioid and Adenosine Pathways in Mice. *Sci Rep.* 2017;7(1):15679.
31. Sawynok J. Adenosine receptor targets for pain. *Neuroscience.* 2016;338:1-18.
32. Otti A, Noll-Hussong M. Acupuncture-induced pain relief and the human brain's default mode network - an extended view of central effects of acupuncture analgesia. *Forsch Komplementmed.* 2012;19(4):197-201.
33. Wang SM, Kain ZN, White P. Acupuncture analgesia: I. The scientific basis. *Anesth Analg.* 2008;106(2):602-610.
34. Kaptchuk TJ. Acupuncture: theory, efficacy, and practice. *Ann Intern Med.* 2002;136(5):374-383.
35. Clement-Jones V, McLoughlin L, Tomlin S, Besser GM, Rees LH, Wen HL. Increased beta-endorphin but not met-enkephalin levels in human cerebrospinal fluid after acupuncture for recurrent pain. *Lancet.* 1980;2(8201):946-949.
36. Deng G, Giralt S, Chung DJ, et al. Acupuncture for reduction of symptom burden in multiple myeloma patients undergoing autologous hematopoietic stem cell transplantation: a randomized sham-controlled trial. *Support Care Cancer.* 2017.
37. Lee JK, Grace KA, Foster TG, et al. How should we measure medication adherence in clinical trials and practice? *Ther Clin Risk Manag.* 2007;3(4):685-690.
38. Choo PW, Rand CS, Inui TS, et al. Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. *Med Care.* 1999;37(9):846-857.
39. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clin Ther.* 1999;21(6):1074-1090; discussion 1073.
40. Cohen MZ, Rozmus CL, Mendoza TR, et al. Symptoms and quality of life in diverse patients undergoing hematopoietic stem cell transplantation. *J Pain Symptom Manage.* 2012;44(2):168-180.
41. Anderson KO, Giralt SA, Mendoza TR, et al. Symptom burden in patients undergoing autologous stem-cell transplantation. *Bone Marrow Transplant.* 2007;39(12):759-766.
42. Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. *Cancer.* 2000;89(7):1634-1646.
43. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore.* 1994;23(2):129-138.
44. Gregorian RS, Jr., Gasik A, Kwong WJ, Voeller S, Kavanagh S. Importance of side effects in opioid treatment: a trade-off analysis with patients and physicians. *J Pain.* 2010;11(11):1095-1108.

45. Becker WC, Fraenkel L, Edelman EJ, et al. Instruments to assess patient-reported safety, efficacy, or misuse of current opioid therapy for chronic pain: a systematic review. *Pain.* 2013;154(6):905-916.
46. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev.* 2010(1):CD006605.
47. Noble M, Tregear SJ, Treadwell JR, Schoelles K. Long-term opioid therapy for chronic noncancer pain: a systematic review and meta-analysis of efficacy and safety. *J Pain Symptom Manage.* 2008;35(2):214-228.
48. Martel MO, Finan PH, Dolman AJ, et al. Self-reports of medication side effects and pain-related activity interference in patients with chronic pain: a longitudinal cohort study. *Pain.* 2015;156(6):1092-1100.
49. Hays RD, Spritzer KL, Schalet BD, Cella D. PROMIS((R))-29 v2.0 profile physical and mental health summary scores. *Qual Life Res.* 2018;27(7):1885-1891.
50. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: preliminary validation of the Opioid Risk Tool. *Pain Med.* 2005;6(6):432-442.
51. Bauml J, Xie SX, Farrar JT, et al. Expectancy in real and sham electroacupuncture: does believing make it so? *J Natl Cancer Inst Monogr.* 2014;2014(50):302-307.
52. Wasan AD, Kong J, Pham LD, Kaptchuk TJ, Edwards R, Gollub RL. The impact of placebo, psychopathology, and expectations on the response to acupuncture needling in patients with chronic low back pain. *J Pain.* 2010;11(6):555-563.
53. Kong J, Kaptchuk TJ, Polich G, et al. An fMRI study on the interaction and dissociation between expectation of pain relief and acupuncture treatment. *Neuroimage.* 2009;47(3):1066-1076.
54. Pariente J, White P, Frackowiak RS, Lewith G. Expectancy and belief modulate the neuronal substrates of pain treated by acupuncture. *Neuroimage.* 2005;25(4):1161-1167.
55. Mao JJ, Xie SX, Bowman MA. Uncovering the expectancy effect: the validation of the acupuncture expectancy scale. *Altern Ther Health Med.* 2010;16(6):22-27.
56. Mao JJ, Armstrong K, Farrar JT, Bowman MA. Acupuncture expectancy scale: development and preliminary validation in China. *Explore (NY).* 2007;3(4):372-377.
57. Lu K, Luo X, Chen PY. Sample size estimation for repeated measures analysis in randomized clinical trials with missing data. *Int J Biostat.* 2008;4(1):Article 9.
58. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care.* 2003;41(5):582-592.
59. Wong K, Zeng L, Zhang L, et al. Minimal clinically important differences in the brief pain inventory in patients with bone metastases. *Support Care Cancer.* 2013;21(7):1893-1899.
60. Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. *Psychol Methods.* 2010;15(4):309-334.
61. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society Series B (Methodological).* 1995;57(1):289-300.
62. Benjamini Y, Yekutieli D. The control of the false discovery rate in multiple testing under dependency. *Ann Statist.* 2001;29(4):1165-1188.
63. Kent DM, Rothwell PM, Ioannidis JP, Altman DG, Hayward RA. Assessing and reporting heterogeneity in treatment effects in clinical trials: a proposal. *Trials.* 2010;11:85.
64. Henderson NC, Louis TA, Wang C, Varadhan R. Bayesian analysis of heterogeneous treatment effects for patient-centered outcomes research. *Health Services and Outcomes Research Methodology.* 2016;16(4):213-233.

65. Wang C, Louis TA, Henderson NC, Weiss CO, Varadhan R. beanz: An R Package for Bayesian Analysis of Heterogeneous Treatment Effects with a Graphical User Interface. *2018.* 2018;85(7):31.
66. Imai K, Ratkovic M. Estimating treatment effect heterogeneity in randomized program evaluation. *Ann Appl Stat.* 2013;7(1):443-470.
67. Wager S, Athey S. Estimation and Inference of Heterogeneous Treatment Effects using Random Forests. *Journal of the American Statistical Association.* 2017:1-15.
68. Siddique J, Harel O, Crespi CM. Addressing Missing Data Mechanism Uncertainty using Multiple-Model Multiple Imputation: Application to a Longitudinal Clinical Trial. *Ann Appl Stat.* 2012;6(4):1814-1837.
69. Ibrahim JG, Molenberghs G. Missing data methods in longitudinal studies: a review. *Test (Madr).* 2009;18(1):1-43.
70. Jindal V, Ge A, Mansky PJ. Safety and efficacy of acupuncture in children: a review of the evidence. *J Pediatr Hematol Oncol.* 2008;30(6):431-442.
71. Melchart D, Weidenhammer W, Streng A, et al. Prospective investigation of adverse effects of acupuncture in 97 733 patients. *Arch Intern Med.* 2004;164(1):104-105.
72. Deng G, Chan Y, Sjoberg D, et al. Acupuncture for the treatment of post-chemotherapy chronic fatigue: a randomized, blinded, sham-controlled trial. *Support Care Cancer.* 2013;21(6):1735-1741.
73. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain.* 2004;112(3):372-380.
74. Herzig SJ, Rothberg MB, Cheung M, Ngo LH, Marcantonio ER. Opioid utilization and opioid-related adverse events in nonsurgical patients in US hospitals. *J Hosp Med.* 2014;9(2):73-81.

18.0 APPENDICES

Appendix 1. Acupuncture Intervention Protocol

Appendix 2. Procedures to Determine Outpatient Opioid Use and Dose Consumed

Appendix 3. MCT External Site SAE Report Form Template