BMJ Open

Integrative Medicine for Pain in Patients with Advanced Cancer Trial (IMPACT): A Protocol of a Randomized Controlled Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058281
Article Type:	Protocol
Date Submitted by the Author:	14-Oct-2021
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Keywords:	PAIN MANAGEMENT, COMPLEMENTARY MEDICINE, Cancer pain < ONCOLOGY

Title: **I**ntegrative **M**edicine for **P**ain in Patients with **A**dvanced **C**ancer **T**rial (**IMPACT**): A Protocol of a Randomized Controlled Trial

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Word Count: 3,999

Abstract

Introduction: Pain, comorbid fatigue, and sleep disturbances are common and distressing symptoms for patients with advanced cancer, negatively impacting their quality of life. Clinical guidelines recommend nonpharmacological interventions, including acupuncture and massage, for pain management in adult cancer patients in adjunct to conventional care. However, high-quality evidence about the comparative effectiveness and long-term durability of these therapies for symptom management is limited.

Methods and analysis: We describe the design of a two-arm, parallel group, multi-center randomized controlled trial that investigates the use of acupuncture versus massage for musculoskeletal pain among 300 patients with diverse types of advanced cancer. The primary aim is to evaluate the long-term effectiveness (26 weeks from randomization) of acupuncture versus massage for pain (primary outcome) and comorbid symptoms (fatigue, sleep disturbance, and quality of life). The secondary aim is to identify patient-level demographic characteristics (e.g., sex, race, age), clinical factors (e.g., insomnia, pain severity), and psychological attributes that are associated with a greater reduction in pain for either acupuncture or massage. Patients will receive weekly acupuncture or massage treatments for ten weeks, followed by monthly booster sessions up to 26 weeks. The primary endpoint will be the change in worst pain intensity score from baseline to 26 weeks. We will collect validated patient-reported outcomes at multiple timepoints over 26 weeks.

Ethics and dissemination: The Institutional Review Board at Memorial Sloan Kettering Cancer Center in New York approved this protocol. Results will be disseminated via peer-reviewed scientific journals and conference presentations. Our findings will help patients and healthcare providers make informed decisions about incorporating non-pharmacological treatments to manage pain for patients with advanced cancer.

Trial registration: Clinicaltrials.gov Identifier: NCT04095234

Keywords: cancer pain, complementary medicine, pain management

Strengths and limitations of this study:

- This study represents the largest randomized controlled trial to date comparing the effectiveness of acupuncture versus massage for pain management among patients with advanced cancer.
- By recruiting a diverse population in terms of race/ethnicity and cancer types, this study will offer insight into the sociodemographic, clinical factors, and physiological attributes that can inform and help predict factors to personalize treatment.
- All participants will be followed up to 26 weeks.
- The study design does not include a control group comparing the standard of care for pain management as prescribed by the clinical team.
- The study design does not allow crossover between the acupuncture and massage groups.

1. Introduction

Cancer is a leading cause of morbidity and mortality, second only to heart disease.[1] Because of recent innovations in cancer therapeutics, the definition for advanced cancer is challenging because some patients with metastatic cancer can now be "cured" or at least enter long-term remission leaving them to often live with symptomatic sequelae. Compared with the general population, patients with advanced cancer are at a greater risk for chronic physical and psychological symptoms.[2-5] Among patients with advanced cancer, symptoms of pain, fatigue, and insomnia are the most commonly reported, often clustered together, and are generally not well managed.[4-10] Previous studies have shown prevalence rates of pain as high as 66% among patients with advanced cancer.[11,12]

Historically, pain management in cancer has predominantly relied on drug therapies; however, increasing clinical evidence suggesting the potential harm over time of long-term opioid therapy for chronic cancer pain, not to mention the current opioid abuse epidemic sweeping the United States, underscore a need for additional treatments.[13,14] As more individuals with advanced cancer live longer, patient-centered pain management integrating non-pharmacological interventions based on research evidence has strong potential to improve the quality of pain management for this population. Hence, clinical guidelines and leading medical organizations recommend non-pharmacological interventions, including acupuncture and massage, in conjunction with drug therapies for pain management.[14-19]

Acupuncture, a therapy of traditional Chinese medicine (TCM), involves penetrating the skin with thin, solid, metallic needles that are manipulated by hand or electrical stimulation.[20] With respect to the efficacy of acupuncture for chronic pain in cancer populations, a systematic review and meta-analysis found that when acupuncture is incorporated into conventional cancer care, it is more effective than conventional drug management alone for cancer pain.[21] A recent comparative effectiveness randomized controlled trial (RCT) found that electro-acupuncture and auricular acupuncture were significantly more efficacious for pain reduction than usual care among diverse cancer survivors (N=360).[22] Further, there is some evidence suggesting that acupuncture may improve sleep disturbances, fatigue, and anxiety in cancer patients experiencing pain.[23,24]

Massage, which involves the manual manipulation of muscles and other soft tissue areas of the body, is one of the earliest known forms of pain relief. Since massage therapy techniques promote joint flexibility, relieve muscular tension, and improve range of motion, massage therapy has mechanistic plausibility for addressing musculoskeletal pain in patient populations.[13,25] In a recent meta-analysis conducted by the Evidence for Massage Therapy Working Group, massage therapy was effective at treating pain compared

to other controls (such as reading, usual care, or active attention) in cancer populations.[26] In addition to pain management, massage therapy may improve fatigue, sleep, and anxiety in cancer populations.[26-30]

Despite acupuncture and massage therapy both being widely available and commonly used as non-pharmacological treatments for pain,[13,31] there is currently a gap in the evidence regarding the comparative effectiveness of these options as well as the long-term durability of their treatment effects among patients living with advanced cancer. We planned a randomized controlled trial (RCT) to evaluate the long-term comparative effectiveness of acupuncture versus massage for pain in patients living with advanced cancer. Our primary aim is to compare the long-term effectiveness (26 weeks from randomization) of acupuncture versus massage for pain (primary outcome) and comorbid symptoms (fatigue, sleep disturbance, and quality of life) in patients living with advanced cancer. Our secondary aim is to identify patient-level demographic characteristics (e.g., sex, race, age), clinical factors (e.g., insomnia, pain severity), and psychological attributes (i.e., outcome expectation) that are associated with a greater reduction in pain for either acupuncture or massage.

2. Methods and Analysis

2.1 Study Design

The **I**ntegrative **M**edicine for **P**ain in Patients with **A**dvanced **C**ancer **T**rial (**IMPACT**) is a two-arm, parallel group RCT to compare the effectiveness of acupuncture and massage for pain and comorbid symptoms in a heterogeneous sample of 300 patients living with advanced cancer who have been experiencing moderate to severe pain (Figure 1). Eligible patients will be randomly assigned in a 1:1 ratio to acupuncture or massage. Patients will receive weekly acupuncture or massage treatments for ten weeks followed by monthly booster sessions up to week 26. All patients will continue to receive their standard medical care and pain management as prescribed by their physicians. The primary endpoint will be the change in worst pain intensity score (as assessed by the Brief Pain Inventory (BPI)) from baseline to 26 weeks. We will also collect validated patient-reported outcome measures of pain and comorbid symptoms at seven timepoints over 26 weeks (Table 1).

Table 1: Schedule of data collection

Outcome	Active Intervention			Follow Up			
	Week 0	Week 4	Week 10	Week 14	Week 18	Week 22	Week 26
Primary Outcome - Pain							
Brief Pain Inventory	X	X	X	X	X	X	X
Secondary Outcomes - Fatigue, Sleep, Anxiety, and Quality of Life							
Brief Fatigue Inventory	X		X		X		X
Insomnia Severity Index	X		X		X		X
Hospital Anxiety and Depression Scale	X		X		X		X
PROMIS-10 Global Health	X		X		X		X
Patients' Global Impression of Change			X		X		X
Covariates							
Demographics (e.g., age, sex, race/ethnicity)	X						X
Clinical Characteristics (e.g., tumor type, stage, cancer therapy)	X						X
Pain Medication Diary	X	X	X	X			X
Predictive Variables							
Mao Expectancy of Treatment Effects	X		X				

2.2 Participants

We will recruit study participants in the United States through Memorial Sloan Kettering Cancer Center (MSK), a National Cancer Institute-designated comprehensive cancer center, with a main campus in Manhattan and numerous regional sites in New York (Westchester County and Long Island) and New Jersey (Bergen, Monmouth, and Basking Ridge). We will also recruit patients from the Baptist Health Miami Cancer Institute (MCI), which is an affiliate of MSK's strategic alliance. For MSK-affiliated patients, we will use a population-based method by mailing out letters to potentially eligible patients identified through a data query of MSK's electronic health records. We will also use stakeholders and partnering clinicians to publicize the study and provide referrals. The target accrual goal is 300 participants. Enrollment began in October 2019 and study participant assessments are scheduled to be completed by July 2022.

2.3 Inclusion and Exclusion Criteria

Patients will be eligible for the study if they are English or Spanish-speaking, over 18 years old, and able to walk with only occasional assistance (Karnofsky functional score of ≥60). They must also have a diagnosis of the following: stage III or IV lung cancer; any stage pancreatic cancer; unresectable cholangiocarcinoma; unresectable liver cancer; unresectable ampullary or peri-ampullary cancer or other

stage IV gastrointestinal cancer; stage III or IV ovarian or fallopian tube cancers or other stage IV gynecologic cancer; stage IV breast cancer; stage IV genitourinary cancer; stage III or IV sarcoma; stage IV melanoma; stage III or IV head/neck cancer; stage IV endocrine cancer; or hematological malignancies (lymphoma, myeloma, and leukemia). Patients will need to have an expected prognosis of six months or greater from their treating physician or the study clinician.

To be eligible, patients must also report ongoing musculoskeletal pain, defined as regional (e.g., joints, extremities, back, neck) or more generalized (i.e., fibromyalgia) pain, as their primary source of pain. The pain must be present for at least one month and occur for at least 15 days of the preceding 30 days. In addition, patients must report that their pain is four or greater on a numerical rating scale of 0 to 10. Non-musculoskeletal pain syndromes (e.g., headache, facial pain, chest pain or visceral abdominal pain) may be present if musculoskeletal pain is the primary source of pain. Patients will be excluded from the study if they have a blood platelet count of less than 15,000 platelets per microliter.

2.4 Procedure

All potential participants will undergo an initial screening with a research coordinator in person or over the telephone. At this initial contact, the research coordinator will explain the study goals and procedures and screen participants for eligibility. Next, a study healthcare provider will meet with screened and interested patients to confirm eligibility. Once deemed eligible, patients will complete the informed consent and undergo randomization. Patients will complete assessments online using Research Electronic Data Capture (REDCap), a data management software system, at seven time points: weeks 0, 4, 10, 14, 18, 22, and 26. To encourage adherence to the study procedures, participants will receive reminders to complete study assessments. Additionally, all participants will be compensated with a $40 gift card for completion of the week 10 visit and a $60 gift card for the completion of the week 26 visit, for a total of $100.

2.5 Randomization

We will randomize 300 participants to acupuncture or massage using MSK's Clinical Research Database (CRDB), a secure computer system that ensures full allocation concealment. Randomization will be performed by the method of random permuted block stratified by any current opioid use (yes versus no) and by accrual site (MSK main campus, MSK regional sites versus MCI). Given the nature of the interventions, patients and providers will not be blinded to treatment assignments. The study statisticians will be blinded to treatment assignments.

2.6 Primary Outcome

The short-form BPI is one of the most widely used instruments to measure pain and has been demonstrated to be a reliable, valid, and responsive measure (Cronbach's alpha 0.77 to 0.91).[32] The BPI contains four pain severity items and seven 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 seven pain interference items. A pain severity subscale score can similarly be computed for the four 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. 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.

2.7 Secondary Outcomes

The Patients' Global Impression of Change (PGIC) is a one item survey used to define a clinically important change in pain from the patient's perspective.[33,34] The PGIC can be used as an anchor to derive anchor-based minimally important differences for pain measures like the BPI. Participants will be asked "How would you describe your pain since the first clinical visit? I am: very much worse, much worse, a little worse, the same, a little improved, much improved, very much improved." Subjects reporting "much improved" or "very much improved" will be considered responders.

The Brief Fatigue Inventory (BFI) is a nine-item instrument designed to assess fatigue severity and has been shown to be reliable and valid in multiple languages and diverse populations.[35,36] Three items ask patients to rate the severity of their fatigue at its "worst," "usual," and "now" during normal waking hours, with 0 being "no fatigue" and 10 being "fatigue as bad as you can imagine." Six items ask patients to rate the amount that fatigue has interfered with different aspects of their life during the past 24 hours, with 0 being "does not interfere" and 10 being "completely interferes."[35] A composite fatigue severity score can be found by averaging the nine item scores.

The Insomnia Severity Index (ISI) is a reliable and valid seven-item scale used to assess subjective insomnia severity.[37,38] The items are scored on a five-point Likert response scale (e.g., 0 = no problem; 4 = very severe problem), yielding a total score ranging from 0 to 28 with higher scores representing more severe insomnia symptoms. Established cutoffs are: <8, no clinically significant insomnia; 8-14, subthreshold insomnia; 15-21, clinical insomnia (moderate severity); >21, clinical insomnia (severe).[37] A

reduction of eight points is considered to be clinically meaningful improvement among those with insomnia.[39]

The Hospital Anxiety and Depression Scale (HADS) is a 14-item scale with seven items measuring depression and seven items measuring anxiety that has been shown to be both reliable and valid.[40,41] Each item is answered by the patient on a four-point (0-3) response category so possible scores range from 0-21 for anxiety and depression, with higher scores indicating higher symptomatology. Established cutoffs are: 0–7 not significant; 8–10 subclinical; and 11-21 clinically significant depression/anxiety.[42]

The Patient Reported Outcomes Measurement Information System (PROMIS®) Scale v1.2 - Global Health is a brief instrument composed of ten items that demonstrates adequate reliability and validity[43,44] as a measure of health related quality of life (QOL) in general and clinical populations.[45,46] The measure yields two scores for physical health and mental health with higher scores indicative of better QOL.

2.8 Assessment of Outcome Expectancy as a Predictive Variable for Treatment Response

Outcome expectancy has long been considered an important predictor of treatment outcomes and has gained increasing recognition in clinical trials.[47,48] The Mao Expectancy of Treatment Effects (METE) is a four-item instrument to measure outcome expectancy and has demonstrated reliability and validity.[49] The score ranges from 4 to 20, with a higher score indicating greater expectancy.

2.9 Covariates

We will collect specific demographic (e.g., age, sex, race/ethnicity) and other relevant historical medical data (e.g., cancer treatment). We will also track participants' self-reported use of analgesic medications (e.g., acetaminophen, non-steroidal anti-inflammatory drugs, opioids, and adjuvants for neuropathic pain) by having participants complete weekly pain medication diaries to calculate weekly average analgesic medication usage throughout the study time period.[50] As pain often results in increased health care utilization, we will track emergency department visits and hospitalizations via the patient's electronic health record. Additionally, we will collect participants' reasons for either stopping treatment or dropping out of the clinical trial, such as treatment adverse events, disease complications, or scheduling issues with work.

2.10 Interventions

Licensed and oncology-experienced acupuncturists and massage therapists will deliver all treatments. All acupuncturists and massage therapists will be given a manual with the specific treatment protocols for

acupuncture and massage and will be trained by the principal investigator and/or lead acupuncturist and massage therapist. For quality assurance, the lead therapists will audit at least two charts for each therapist per week for adherence to treatment protocol and documentation standards, and all therapists will be re-certified twice yearly. We have extensive experience in conducting integrative medicine symptom trials including ensuring the quality of interventions.[22,23,29,51-53]

For the acupuncture intervention, we will use a treatment protocol developed and tested by our group that has demonstrated improvements in pain, fatigue, and sleep among patients with cancer.[22,23,52-54] After sterilizing the skin, the acupuncturist will place between ten and 20 needles at a minimum of four local points around the body area with the most pain and at individual points depending on the participant's comorbid symptoms. The acupuncture needles will be inserted to appropriate depths depending on the location on the body and body type of the participant.[55] The acupuncturist will manipulate the needles to achieve the "De Qi" sensation for the participants. "De Qi" is a local sensation of soreness, numbness, or distension that accompanies the insertion and manipulation of needles during acupuncture.[56] The needles at the four local points for pain will be electrically stimulated at 2 Hz by connecting to a TENS unit. The acupuncturist will leave the needles in place for 20 minutes with brief manipulation at the beginning and end of the treatment.

For the massage intervention, we will use a treatment protocol developed and tested by our group that has shown improvements in pain and fatigue among patients with cancer undergoing chemotherapy.[29] Consistent with oncology massage practice, therapists will administer compressions with light to moderate pressure and will use any of the following oncology massage techniques: compression; muscle stripping; active/passive range of motion, post-isometric stretching; effleurage (gliding); myofascial release; positional release; and trigger/tender point release.[57,58] Therapists will start with a five-minute protocol including guided diaphragmatic breathing exercise, rib mobilizations, and occipital release to increase parasympathetic tone. Next, depending on the participant's primary area of pain, the therapist will focus 20 minutes of massage on that specific body area followed by effleurage toward the heart. The massage therapist will focus on the following identified areas of pain: head/jaw; cervical spine; thoracic spine; shoulder; upper extremity; lumbar; sacral; pelvic; hip; and lower extremity.

Before each massage or acupuncture treatment, the massage therapist or acupuncturist will review the participant's current health status and modify his/her techniques if needed. In the case of acupuncture, shallow needling with minimal stimulation will be used, and needles will only be placed in the extremities. For participants with electronically charged medical devices, no stimulation will be used. In

the case of massage, light touch will be used, and areas of bruising will be avoided. The massage therapist or acupuncturist will document any treatment modifications and the medical reason for the modification, which will allow us to systematically capture participants who received a modified treatment.

2.11 Analytic Approach

We will perform the analysis for each aim following the 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 drop-out or treatment adherence status). For all specific aims, our main analytic tool will be linear mixed-effects models (LMMs) because our primary outcome (worst pain severity) and secondary outcomes are repeated continuous outcomes over time.[59] The general template of each LMM will model the outcome as a function of treatment arm and assessment time, controlling for the randomization stratification variables (baseline opioid use and accrual site), and including a subject-specific random intercept and slope.

For Aim 1, we will plot the outcome measure trajectories by randomization arm over time and summarize each outcome measure at each assessment time by treatment arm using descriptive statistics. Tests of ITT differences between randomization arms with respect to changes in outcomes will be based on coefficients from specific time-by-arm interactions added to the general LMM template described above. Our primary effectiveness comparison will focus on changes in BPI Worst Pain from baseline to 26 weeks between acupuncture versus massage. Aim 1 secondary outcomes (e.g., fatigue, insomnia, QOL) will be analyzed using the same methods described above. We will also perform responder analyses by considering those who experienced 30% or greater reduction in BPI Worst Pain at end of treatment (week 10) as responders.[34,60,61] We will compare the proportion of responders in acupuncture and massage at the end of the intervention period using descriptive cross-tabulations and logistic regression adjusting for the randomization strata.

For Aim 2, we will conduct exploratory, hypothesis-generating heterogeneity of treatment effect (HTE) analyses to identify patient-level factors associated with treatment response to either acupuncture or massage by incorporating relevant variables (e.g., sex, expectation, opioid use) and variable-by-intervention interaction terms in linear regression models predicting week 26 worst pain controlling for baseline worst pain and stratification factors. Each variable of interest will be assessed for HTE in a separate model. Since our inclusion criteria allows for patients with various cancer types, we will also perform exploratory subgroup analysis to see if there is any difference in treatment effect (both primary and secondary outcomes) among patients with solid tumor cancers versus blood cancers.

To address missing data, we will perform sensitivity analyses (e.g. assess impact on results of adjusting for patient disease progression or death) and apply data analysis strategies that are as robust as possible to data losses. We will first explore whether missingness is associated with observed variables (e.g. randomization arm and the baseline outcome measures) by comparing participants with complete and incomplete data. Of note, the LMMs described above validly include participants 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; hence, we will perform sensitivity analyses to evaluate the robustness of our LMM results by refitting the models after imputing the missing week 26 outcomes using multiple imputation.

2.12 Power Analysis and Sample Size

For our sample size/power considerations, we calculated the smallest standardized effect size (i.e., Cohen's d) we will be able to detect with 80% power, given our sample size of 300 and other assumptions. Using the "power.mmrm" function from the R package "longpower," we applied the formulas in Lu et al,[62] to derive the smallest detectable effect size for the coefficient of the time-by-arm interaction term in our LMM, given our study design and assumptions, which we transformed to represent the standardized mean difference (i.e., Cohen's d) between the two arms at 26 weeks post- randomization. Assuming a 20% loss to follow-up, correlation between baseline and 26-week BPI Worst Pain of 0.5, and two-sided alpha of 0.05, and with 150 participants in each of the two active intervention arms, we will have 80% power to detect an effect size of 0.35 (standardized mean difference, Cohen's d) at 26 weeks post-randomization between acupuncture versus massage. Based on our own preliminary data in patients with stage IV cancer who experienced moderate to severe pain (N=284), the mean BPI Worst Pain score was 6.3 with standard deviation (SD) of 1.7. A difference of 1 on the BPI Worst Pain score (considered a clinically meaningful difference in pain) based on SD of 1.7 equals an effect size (Cohen's d) of 0.59. In this study, we have 99% power to detect this clinically meaningful mean difference of 1 point (Cohen's d of 0.59) on the BPI Worst Pain score. Our trial is more than sufficiently powered to detect a clinically meaningful difference between acupuncture and massage at 26 weeks.

2.13 Patient and Public Involvement

Recognizing the value of incorporating feedback from patients and their families, we organized a formal patient/stakeholder advisory board composed of ten members (i.e., patients, caregivers, and stakeholders from advocacy and cancer organizations) to contribute to the study design, optimal delivery of interventions, recruitment and retention strategies, and implementation and dissemination efforts. By

collaborating with patient/stakeholder partners, the patient perspective is included and helps to ensure that the research conducted is relevant and not unduly burdensome for patients. Our patient/stakeholder advisory board members helped generate the research questions, choose the comparison groups, develop patient-centered inclusion and exclusion criteria, determine the timing of the primary endpoint, refine the research protocol, choose the most appropriate outcomes, decide on specific measurement tools, and create patient-friendly recruitment materials. Throughout the project, our patient/stakeholder partners will have specific roles in recruitment activities and will help to ensure that our trial is accessible to participants from diverse communities. Additionally, patient/stakeholder partners' involvement will contribute to effectively translating and disseminating the study findings to patient, family, stakeholder, and research audiences to effect real-world change.

3. Discussion

Pain and comorbid fatigue and sleep disturbance are among the most common and distressing symptoms for patients living with advanced cancer.[4-9] These co-occurring symptoms also negatively impact patients' quality of life and functional performance.[10,63,64] Unlike drug therapies that mostly focus on treating one symptom, acupuncture and massage can address multiple symptoms during treatment, which makes them potentially beneficial not only for pain but also for its related comorbid symptoms (e.g., fatigue and sleep disturbance) among patients with advanced cancer. Acupuncture and massage are both widely available and commonly used nonpharmacological treatments for pain and other comorbid symptoms in cancer populations. Therefore, this RCT study will provide high quality evidence of the comparative effectiveness and durability of acupuncture versus massage that can be readily incorporated into clinical care to improve patient-centered decision-making for pain management.

4. Ethics and dissemination

The institutional review board at Memorial Sloan Kettering Cancer Center (MSK) approved the study protocol; most recent version of the protocol approved May 19, 2021. For this trial, we will adhere to the guidelines from the Consolidated Standards of Reporting Trials (CONSORT)[65] and Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA).[66] This trial is funded by the Patient-Centered Outcomes Research Institute (SMPAI-2018C2-12883) and is registered at Clinicaltrials.gov (Identifier: NCT04095234).

The results of this study will be presented at national and international meetings, and a manuscript will be submitted for publication in a peer-reviewed journal. This research will inform which therapy (acupuncture or massage) is more effective for reducing pain and comorbid fatigue and insomnia in

patients living with advanced cancer. Such information will lead to evidence-based and patient-centered decision making to incorporate these approaches for optimal pain management for the growing population of individuals living with advanced cancer. By collaborating with patient/stakeholder partners, patient/stakeholder partners help to interpret both expected and unexpected study findings in a way that is culturally sensitive and relevant to patients' lived experiences. Patient/stakeholder partners' active involvement will contribute to effectively translating and disseminating the study findings to patient, family, stakeholder, and research audiences to effect real-world change by providing education and awareness of the benefits of integrative, non-pharmacological options for pain management in people with advanced cancer.

Data Availability: The datasets generated during and/or analyzed during the current study will be available from the principal investigator (Jun J. Mao) on reasonable request.

Acknowledgements: The authors would like to thank the patients, healthcare providers, clinical staff, research staff, and patient/stakeholder partners at all study sites for their contributions to this study.

Funding and Research Support: Research reported in this article was funded through a Patient-Centered Outcomes Research Institute (PCORI) award (SMPAI-2018C2-12883). The statements presented in this work are solely the responsibility of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute® (PCORI®), its Board of Governors or Methodology Committee. It was also supported in part by the Translational and Integrative Medicine Research Fund (award/grant number not applicable) at Memorial Sloan Kettering Cancer Center. The funders do not have any role in study design; collection, management, analysis, and interpretation of data; writing of the report; and decision to submit for publication.

Conflict of Interests: All authors declare no conflicts of interest.

Author Contributions:

Romero, Baser, Panageas, MacLeod, Walker, Barton-Burke, Mao, Epstein - Conceptualization

Baser, Panageas, Mao - Data curation

Baser, Panageas, Farrar- Formal analysis

Mao - Funding acquisition

Romero, Emard, Mao - Investigation

Romero, Emard, Mao - Project administration

Mao - Resources

Romero, Emard, Liou, Deng, Han, Mao - Supervision

Romero, Emard, Mao - Writing – original draft

All Authors - Writing – review & editing

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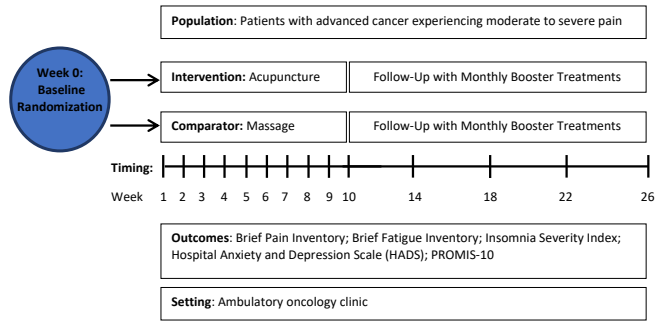
Figure Legend

Figure 1. Study Schema for the Integrative Medicine for Pain in Patients with Advanced Cancer Trial (IMPACT)


Population: Patients with advanced cancer experiencing moderate to severe pain
Week 0: Baseline Randomization
Intervention: Acupuncture
Follow-Up with Monthly Booster Treatments
Comparator: Massage
Follow-Up with Monthly Booster Treatments
Timing:
Week 1 2 3 4 5 6 7 8 9 10 14 18 22 26
Outcomes: Brief Pain Inventory; Brief Fatigue Inventory; Insomnia Severity Index; Hospital Anxiety and Depression Scale (HADS); PROMIS-10
Setting: Ambulatory oncology clinic

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	13
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 15
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5-6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9-11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9-11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig 1 and Table 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	5-7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6-7, 9-11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6-7, 11-12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11-12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11-12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11-12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9-11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9-11
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13-14
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	7
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Acupuncture Versus Massage for Pain in Patients Living with Advanced Cancer: A Protocol for the IMPACT Randomized Clinical Trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-058281.R1
Article Type:	Protocol
Date Submitted by the Author:	21-Apr-2022
Complete List of Authors:	Romero, Sally; University of California San Diego Emard, Nicholas; Memorial Sloan Kettering Cancer Center Baser , Raymond ; Memorial Sloan Kettering Cancer Center, Epidemiology-Biostatistics Panageas, Katherine ; Memorial Sloan Kettering Cancer Center MacLeod, Jodi; Memorial Sloan Kettering Cancer Center Walker, Desiree; Memorial Sloan Kettering Cancer Center Barton-Burke, Margaret; Memorial Sloan Kettering Cancer Center Liou, Kevin; Memorial Sloan Kettering Cancer Center Deng, G ; Memorial Sloan Kettering Cancer Center Farrar, John; University of Pennsylvania, Xiao, Han; Memorial Sloan Kettering Cancer Center Mao, Jun; Memorial Sloan Kettering Cancer Center, Epstein, Andrew; Memorial Sloan Kettering Cancer Center,
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Complementary medicine, Evidence based practice, Patient-centred medicine
Keywords:	PAIN MANAGEMENT, COMPLEMENTARY MEDICINE, Cancer pain < ONCOLOGY

Title: Acupuncture Versus Massage for Pain in Patients Living with Advanced Cancer: A Protocol for the IMPACT Randomized Clinical Trial

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Word Count: 4,454 (with Table 1) or 4,332 (without Table 1)

Abstract

Introduction: Pain, comorbid fatigue, and sleep disturbances are common and distressing symptoms for patients with advanced cancer, negatively impacting their quality of life. Clinical guidelines recommend nonpharmacological interventions, including acupuncture and massage, for pain management in adult cancer patients in adjunct to conventional care. However, high-quality evidence about the comparative effectiveness and long-term durability of these therapies for symptom management is limited.

Methods and analysis: We describe the design of a two-arm, parallel group, multi-center randomized controlled trial that investigates the use of acupuncture versus massage for musculoskeletal pain among 300 patients with diverse types of advanced cancer. The primary aim is to evaluate the long-term effectiveness (26 weeks from randomization) of acupuncture versus massage for pain (primary outcome) and comorbid symptoms (fatigue, sleep disturbance, and quality of life). The secondary aim is to identify patient-level demographic characteristics (e.g., sex, race, age), clinical factors (e.g., insomnia, pain severity), and psychological attributes that are associated with a greater reduction in pain for either acupuncture or massage. Patients will receive weekly acupuncture or massage treatments for ten weeks, followed by monthly booster sessions up to 26 weeks. The primary endpoint will be the change in worst pain intensity score from baseline to 26 weeks. We will collect validated patient-reported outcomes at multiple timepoints over 26 weeks.

Ethics and dissemination: The Institutional Review Board at Memorial Sloan Kettering Cancer Center in New York approved this protocol. Results will be disseminated via peer-reviewed scientific journals and conference presentations. Our findings will help patients and healthcare providers make informed decisions about incorporating non-pharmacological treatments to manage pain for patients with advanced cancer.

Trial registration: Clinicaltrials.gov Identifier: NCT04095234

Keywords: cancer pain, complementary medicine, pain management

Strengths and limitations of this study:

- This study represents the largest randomized controlled trial to date comparing the effectiveness of acupuncture versus massage for pain management among patients with advanced cancer.
- By recruiting a diverse population in terms of race/ethnicity and cancer types, this study will offer insight into the sociodemographic, clinical factors, and physiological attributes that can inform and help predict factors to personalize treatment.
- All participants will be followed up to 26 weeks.
- The study design does not include a control group comparing the standard of care for pain management as prescribed by the clinical team.
- The study design does not allow crossover between the acupuncture and massage groups.

1. Introduction

Cancer is a leading cause of morbidity and mortality, second only to heart disease.[1] Because of recent innovations in cancer therapeutics, the definition for advanced cancer is challenging because some patients with metastatic cancer can now be "cured" or at least enter long-term remission leaving them to often live with symptomatic sequelae. Compared with the general population, patients with advanced cancer are at a greater risk for chronic physical and psychological symptoms.[2-5] Among patients with advanced cancer, symptoms of pain, fatigue, and insomnia are the most commonly reported, often clustered together, and are generally not well managed.[4-10] Previous studies have shown prevalence rates of pain as high as 66% among patients with advanced cancer.[11,12]

Historically, pain management in cancer has predominantly relied on drug therapies; however, increasing clinical evidence suggesting the potential harm over time of long-term opioid therapy for chronic cancer pain, not to mention the current opioid abuse epidemic sweeping the United States, underscore a need for additional treatments.[13,14] As more individuals with advanced cancer live longer, patient-centered pain management integrating non-pharmacological interventions based on research evidence has strong potential to improve the quality of pain management for this population. Hence, clinical guidelines and leading medical organizations recommend non-pharmacological interventions, including acupuncture and massage, in conjunction with drug therapies for pain management.[14-19]

Acupuncture, a therapy of traditional Chinese medicine (TCM), involves penetrating the skin with thin, solid, metallic needles that are manipulated by hand or electrical stimulation.[20] With respect to the efficacy of acupuncture for chronic pain in cancer populations, a systematic review and meta-analysis found that when acupuncture is incorporated into conventional cancer care, it is more effective than conventional drug management alone for cancer pain.[21] A recent comparative effectiveness randomized controlled trial (RCT) found that electro-acupuncture and auricular acupuncture were significantly more efficacious for pain reduction than usual care among diverse cancer survivors (N=360).[22] Further, there is some evidence suggesting that acupuncture may improve sleep disturbances, fatigue, and anxiety in cancer patients experiencing pain.[23,24]

Massage, which involves the manual manipulation of muscles and other soft tissue areas of the body, is one of the earliest known forms of pain relief. Since massage therapy techniques promote joint flexibility, relieve muscular tension, and improve range of motion, massage therapy has mechanistic plausibility for addressing musculoskeletal pain in patient populations.[13,25] In a recent meta-analysis conducted by the Evidence for Massage Therapy Working Group, massage therapy was effective at treating pain compared

to other controls (such as reading, usual care, or active attention) in cancer populations.[26] In addition to pain management, massage therapy may improve fatigue, sleep, and anxiety in cancer populations.[26-30]

Despite acupuncture and massage therapy both being widely available and commonly used as non-pharmacological treatments for pain,[13,31] there is currently a gap in the evidence regarding the comparative effectiveness of these options as well as the long-term durability of their treatment effects among patients living with advanced cancer. We planned a randomized controlled trial (RCT) to evaluate the long-term comparative effectiveness of acupuncture versus massage for pain in patients living with advanced cancer. Our primary aim is to compare the long-term effectiveness (26 weeks from randomization) of acupuncture versus massage for pain (primary outcome) and comorbid symptoms (fatigue, sleep disturbance, and quality of life) in patients living with advanced cancer. Our secondary aim is to identify patient-level demographic characteristics (e.g., sex, race, age), clinical factors (e.g., insomnia, pain severity), and psychological attributes (i.e., outcome expectation) that are associated with a greater reduction in pain for either acupuncture or massage.

2. Methods and Analysis

2.1 Study Design

The **I**ntegrative **M**edicine for **P**ain in Patients with **A**dvanced **C**ancer **T**rial (**IMPACT**) is a two-arm, parallel group RCT to compare the effectiveness of acupuncture and massage for pain and comorbid symptoms in a heterogeneous sample of 300 patients living with advanced cancer who have been experiencing moderate to severe pain (Figure 1). Eligible patients will be randomly assigned in a 1:1 ratio to acupuncture or massage. Patients will receive weekly acupuncture or massage treatments for ten weeks followed by monthly booster sessions up to week 26. All patients will continue to receive their standard medical care and pain management as prescribed by their physicians. The primary endpoint will be the change in worst pain intensity score (as assessed by the Brief Pain Inventory (BPI)) from baseline to 26 weeks. We will also collect validated patient-reported outcome measures of pain and comorbid symptoms at seven timepoints over 26 weeks (Table 1).

Table 1: Schedule of data collection

Outcome	Active Intervention			Follow Up			
	Week 0	Week 4	Week 10	Week 14	Week 18	Week 22	Week 26
Primary Outcome - Pain							
Brief Pain Inventory	X	X	X	X	X	X	X
Secondary Outcomes - Fatigue, Sleep, Anxiety, and Quality of Life							
Brief Fatigue Inventory	X		X		X		X
Insomnia Severity Index	X		X		X		X
Hospital Anxiety and Depression Scale	X		X		X		X
PROMIS-10 Global Health	X		X		X		X
Patients' Global Impression of Change			X		X		X
Covariates							
Demographics (e.g., age, sex, race/ethnicity)	X						X
Clinical Characteristics (e.g., tumor type, stage, cancer therapy)	X						X
Pain Medication Diary	X	X	X	X			X
Predictive Variables							
Mao Expectancy of Treatment Effects	X		X				

2.2 Participants

We will recruit study participants in the United States through Memorial Sloan Kettering Cancer Center (MSK), a National Cancer Institute-designated comprehensive cancer center, with a main campus in Manhattan and numerous regional sites in New York (Westchester County and Long Island) and New Jersey (Bergen, Monmouth, and Basking Ridge). We will also recruit patients from the Baptist Health Miami Cancer Institute (MCI), which is an affiliate of MSK's strategic alliance. For MSK-affiliated patients, we will use a population-based method by mailing out letters to potentially eligible patients identified through a data query of MSK's electronic health records. We will also use stakeholders and partnering clinicians to publicize the study and provide referrals. The target accrual goal is 300 participants. Enrollment began in October 2019 and study participant assessments are scheduled to be completed by July 2022.

2.3 Inclusion and Exclusion Criteria

Patients will be eligible for the study if they are English or Spanish-speaking, over 18 years old, and able to walk with only occasional assistance (Karnofsky functional score of ≥60). They must also have a diagnosis of the following: stage III or IV lung cancer; any stage pancreatic cancer; unresectable cholangiocarcinoma; unresectable liver cancer; unresectable ampullary or peri-ampullary cancer or other

stage IV gastrointestinal cancer; stage III or IV ovarian or fallopian tube cancers or other stage IV gynecologic cancer; stage IV breast cancer; stage IV genitourinary cancer; stage III or IV sarcoma; stage IV melanoma; stage III or IV head/neck cancer; stage IV endocrine cancer; or hematological malignancies (lymphoma, myeloma, and leukemia). Patients will need to have an expected prognosis of six months or greater from their treating physician or the study clinician.

To be eligible, patients must also report ongoing musculoskeletal pain, defined as regional (e.g., joints, extremities, back, neck) or more generalized (i.e., fibromyalgia) pain, as their primary source of pain. The pain must be present for at least one month and occur for at least 15 days of the preceding 30 days. In addition, patients must report that their pain is four or greater on a numerical rating scale of 0 to 10. Non-musculoskeletal pain syndromes (e.g., headache, facial pain, chest pain or visceral abdominal pain) may be present if musculoskeletal pain is the primary source of pain. Patients will be excluded from the study if they have a blood platelet count of less than 15,000 platelets per microliter.

2.4 Procedure

All potential participants will undergo an initial screening with a research coordinator in person or over the telephone. At this initial contact, the research coordinator will explain the study goals and procedures and screen participants for eligibility. Next, a study healthcare provider will meet with screened and interested patients to confirm eligibility. Once deemed eligible, patients will complete the informed consent and undergo randomization. Patients will complete assessments online using Research Electronic Data Capture (REDCap), a data management software system, at seven time points: weeks 0, 4, 10, 14, 18, 22, and 26. To encourage adherence to the study procedures, participants will receive reminders to complete study assessments. Additionally, all participants will be compensated with a $40 gift card for completion of the week 10 visit and a $60 gift card for the completion of the week 26 visit, for a total of $100.

2.5 Randomization

We will randomize 300 participants to acupuncture or massage using MSK's Clinical Research Database (CRDB), a secure computer system that ensures full allocation concealment. Randomization will be performed by the method of random permuted block stratified by any current opioid use (yes versus no) and by accrual site (MSK main campus, MSK regional sites versus MCI). Given the nature of the interventions, patients and providers will not be blinded to treatment assignments. The PI, study statisticians, and outcome assessment clinical research coordinator will be blinded to treatment assignments.

2.6 Primary Outcome

The short-form BPI is one of the most widely used instruments to measure pain and has been demonstrated to be a reliable, valid, and responsive measure (Cronbach's alpha 0.77 to 0.91).[32] The BPI contains four pain severity items and seven 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 seven pain interference items. A pain severity subscale score can similarly be computed for the four 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. 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.

2.7 Secondary Outcomes

The Patients' Global Impression of Change (PGIC) is a one item survey used to define a clinically important change in pain from the patient's perspective.[33,34] The PGIC can be used as an anchor to derive anchor-based minimally important differences for pain measures like the BPI. Participants will be asked "How would you describe your pain since the first clinical visit? I am: very much worse, much worse, a little worse, the same, a little improved, much improved, very much improved." Subjects reporting "much improved" or "very much improved" will be considered responders.

The Brief Fatigue Inventory (BFI) is a nine-item instrument designed to assess fatigue severity and has been shown to be reliable and valid in multiple languages and diverse populations.[35,36] Three items ask patients to rate the severity of their fatigue at its "worst," "usual," and "now" during normal waking hours, with 0 being "no fatigue" and 10 being "fatigue as bad as you can imagine." Six items ask patients to rate the amount that fatigue has interfered with different aspects of their life during the past 24 hours, with 0 being "does not interfere" and 10 being "completely interferes."[35] A composite fatigue severity score can be found by averaging the nine item scores.

The Insomnia Severity Index (ISI) is a reliable and valid seven-item scale used to assess subjective insomnia severity.[37,38] The items are scored on a five-point Likert response scale (e.g., 0 = no problem; 4 = very severe problem), yielding a total score ranging from 0 to 28 with higher scores representing more severe insomnia symptoms. Established cutoffs are: <8, no clinically significant insomnia; 8-14,

subthreshold insomnia; 15-21, clinical insomnia (moderate severity); >21, clinical insomnia (severe).[37] A reduction of eight points is considered to be clinically meaningful improvement among those with insomnia.[39]

The Hospital Anxiety and Depression Scale (HADS) is a 14-item scale with seven items measuring depression and seven items measuring anxiety that has been shown to be both reliable and valid.[40,41] Each item is answered by the patient on a four-point (0-3) response category so possible scores range from 0-21 for anxiety and depression, with higher scores indicating higher symptomatology. Established cutoffs are: 0–7 not significant; 8–10 subclinical; and 11-21 clinically significant depression/anxiety.[42]

The Patient Reported Outcomes Measurement Information System (PROMIS®) Scale v1.2 - Global Health is a brief instrument composed of ten items that demonstrates adequate reliability and validity[43,44] as a measure of health related quality of life (QOL) in general and clinical populations.[45,46] The measure yields two scores for physical health and mental health with higher scores indicative of better QOL.

2.8 Assessment of Outcome Expectancy as a Predictive Variable for Treatment Response

Outcome expectancy has long been considered an important predictor of treatment outcomes and has gained increasing recognition in massage and acupuncture clinical trials.[47,48] The Mao Expectancy of Treatment Effects (METE)[49], originally developed as the Acupuncture Expectancy Scale,[50] is a four-item instrument to measure outcome expectancy for various interventions (e.g. acupuncture, herbs, cognitive behavioral therapies[49,51]) and has demonstrated reliability and validity.[50] The score ranges from 4 to 20, with a higher score indicating greater expectancy. We will use this measure to explore whether expectancy predicts treatment outcomes and may impact the observed differences between groups.

2.9 Covariates

We will collect specific demographic (e.g., age, sex, race/ethnicity) and other relevant historical medical data (e.g., cancer treatment). We will also track participants' self-reported use of analgesic medications (e.g., acetaminophen, non-steroidal anti-inflammatory drugs, opioids, and adjuvants for neuropathic pain) by having participants complete weekly pain medication diaries to calculate weekly average analgesic medication usage throughout the study time period.[52] As pain often results in increased health care utilization, we will track emergency department visits and hospitalizations via the patient's electronic health record. Additionally, we will collect participants' reasons for either stopping treatment or dropping out of the clinical trial, such as treatment adverse events, disease complications, or scheduling issues with work.

2.10 Interventions

Licensed and oncology-experienced acupuncturists and massage therapists will deliver all treatments. All acupuncturists and massage therapists will be given a manual with the specific treatment protocols for acupuncture and massage (see Appendix 1 and 2) and will be trained by the principal investigator and/or lead acupuncturist and massage therapist. For quality assurance, the lead therapists will audit at least two charts for each therapist per week for adherence to treatment protocol and documentation standards, and all therapists will be re-certified twice yearly. We have extensive experience in conducting integrative medicine symptom trials including ensuring the quality of interventions.[22,23,29,53-55]

For the acupuncture intervention, we will use a treatment protocol developed and tested by our group that has demonstrated improvements in pain, fatigue, and sleep among patients with cancer.[22,23,54-56] After sterilizing the skin, the acupuncturist will place between ten and 20 needles at a minimum of four local points around the body area with the most pain and at individual points depending on the participant's comorbid symptoms. The acupuncture needles will be inserted to appropriate depths depending on the location on the body and body type of the participant.[57] The acupuncturist will manipulate the needles to achieve the "De Qi" sensation for the participants. "De Qi" is a local sensation of soreness, numbness, or distension that accompanies the insertion and manipulation of needles during acupuncture.[58] The needles at the four local points for pain will be electrically stimulated at 2 Hz by connecting to a TENS unit. The acupuncturist will leave the needles in place for 20 minutes with brief manipulation at the beginning and end of the treatment.

For the massage intervention, we will use a treatment protocol developed and tested by our group that has shown improvements in pain and fatigue among patients with cancer undergoing chemotherapy.[29] Consistent with oncology massage practice, therapists will administer compressions with light to moderate pressure and will use any of the following oncology massage techniques: compression; muscle stripping; active/passive range of motion, post-isometric stretching; effleurage (gliding); myofascial release; positional release; and trigger/tender point release.[59,60] Therapists will start with a five-minute protocol including guided diaphragmatic breathing exercise, rib mobilizations, and occipital release to increase parasympathetic tone. Next, depending on the participant's primary area of pain, the therapist will focus 20 minutes of massage on that specific body area followed by effleurage toward the heart. The massage therapist will focus on the following identified areas of pain: head/jaw; cervical spine; thoracic spine; shoulder; upper extremity; lumbar; sacral; pelvic; hip; and lower extremity.

Before each massage or acupuncture treatment, the massage therapist or acupuncturist will review the participant's current health status and modify his/her techniques if needed. In the case of acupuncture, shallow needling with minimal stimulation will be used, and needles will only be placed in the extremities. For participants with electronically charged medical devices, no stimulation will be used. In the case of massage, light touch will be used, and areas of bruising will be avoided. The massage therapist or acupuncturist will document any treatment modifications and the medical reason for the modification, which will allow us to systematically capture participants who received a modified treatment. Patients will be monitored for side effects at each visit. Adverse events related to the administration of either acupuncture or massage will be collected each week before and after each treatment by the acupuncturist/massage therapist or clinical research coordinator. The Common Terminology Criteria for Adverse Events (CTCAE) Version 5 will be utilized for toxicity evaluation.

2.11 Analytic Approach

We will perform the analysis for each aim following the 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 drop-out or treatment adherence status). For all specific aims, our main analytic tool will be linear mixed-effects models (LMMs) because our primary outcome (worst pain severity) and secondary outcomes are repeated continuous outcomes over time.[61] The general template of each LMM will model the outcome as a function of treatment arm and assessment time, controlling for the randomization stratification variables (baseline opioid use and accrual site), and including a subject-specific random intercept and slope.

For Aim 1, we will plot the outcome measure trajectories by randomization arm over time and summarize each outcome measure at each assessment time by treatment arm using descriptive statistics. Tests of ITT differences between randomization arms with respect to changes in outcomes will be based on coefficients from specific time-by-arm interactions added to the general LMM template described above. Our primary effectiveness comparison will focus on changes in BPI Worst Pain from baseline to 26 weeks between acupuncture versus massage. Aim 1 secondary outcomes (e.g., fatigue, insomnia, QOL) will be analyzed using the same methods described above. We will also perform responder analyses by considering those who experienced 30% or greater reduction in BPI Worst Pain at end of treatment (week 10) as responders.[34,62,63] We will compare the proportion of responders in acupuncture and massage at the end of the intervention period using descriptive cross-tabulations and logistic regression adjusting for the randomization strata.

For Aim 2, we will conduct exploratory, hypothesis-generating heterogeneity of treatment effect (HTE) analyses to identify patient-level factors associated with treatment response to either acupuncture or massage by incorporating relevant variables (e.g., sex, race/ethnicity, expectation, opioid use) and variable-by-intervention interaction terms in linear regression models predicting week 26 worst pain controlling for baseline worst pain and stratification factors. Each variable of interest will be assessed for HTE in a separate model. For these exploratory regression analyses, we will guard against inflated type I error due to multiple testing by adjusting the variable-by-intervention interaction p-values for the false discovery rate.[64,65] Our current focus on evaluating and reporting HTE will be based on the approach proposed by Kent et al.[66] However, we will also apply promising emerging Bayesian[67,68] and machine learning[69,70] methods, which can identify HTE and subgroups based on multiple variables simultaneously and are potentially more powerful than traditional univariate methods. Since our inclusion criteria allows for patients with various cancer types, we will also perform exploratory subgroup analysis to see if there is any difference in treatment effect (both primary and secondary outcomes) among patients with solid tumor cancers versus blood cancers. Because our trial will enroll patients with advanced cancer, interventions may need to be modified for patient safety issues such as for those with low platelets or bruising in the area where there is pain. We will conduct exploratory analyses to examine if there are any differences in outcomes for those patients who received non-modified treatments versus those who had modified treatments. We will also conduct exploratory analyses to see whether individuals with low platelet counts experienced more adverse events compared to patients with normal platelet counts.

To address missing data, we will perform sensitivity analyses (e.g. assess impact on results of adjusting for patient disease progression or death) and apply data analysis strategies that are as robust as possible to data losses. We will first explore whether missingness is associated with observed variables (e.g. randomization arm and the baseline outcome measures) by comparing participants with complete and incomplete data. Of note, the LMMs described above validly include participants 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; hence, we will perform sensitivity analyses to evaluate the robustness of our LMM results by refitting the models after imputing the missing week 26 outcomes using multiple imputation.

2.12 Power Analysis and Sample Size

For our sample size/power considerations, we calculated the smallest standardized effect size (i.e., Cohen's d) we will be able to detect with 80% power, given our sample size of 300 and other assumptions. Using the "power.mmrm" function from the R package "longpower," we applied the

formulas in Lu et al,[71] to derive the smallest detectable effect size for the coefficient of the time-by-arm interaction term in our LMM, given our study design and assumptions, which we transformed to represent the standardized mean difference (i.e., Cohen's d) between the two arms at 26 weeks post- randomization. Based on our prior experience[72,73] and given that patients living with advanced cancer may have unanticipated health issues (e.g., hospitalizations, death), we conservatively anticipate loss to follow up to be 20% by 26 weeks. Assuming this 20% loss to follow-up, correlation between baseline and 26-week BPI Worst Pain of 0.5, and two-sided alpha of 0.05, and with 150 participants in each of the two active intervention arms, we will have 80% power to detect an effect size of 0.35 (standardized mean difference, Cohen's d) at 26 weeks post-randomization between acupuncture versus massage. Based on our own preliminary data in patients with stage IV cancer who experienced moderate to severe pain (N=284), the mean BPI Worst Pain score was 6.3 with standard deviation (SD) of 1.7. A difference of 1 on the BPI Worst Pain score (considered a clinically meaningful difference in pain) based on SD of 1.7 equals an effect size (Cohen's d) of 0.59. In this study, we have 99% power to detect this clinically meaningful mean difference of 1 point (Cohen's d of 0.59) on the BPI Worst Pain score. Our trial is more than sufficiently powered to detect a clinically meaningful difference between acupuncture and massage at 26 weeks.

2.13 Patient and Public Involvement

Recognizing the value of incorporating feedback from patients and their families, we organized a formal patient/stakeholder advisory board composed of ten members (i.e., patients, caregivers, and stakeholders from advocacy and cancer organizations) to contribute to the study design, optimal delivery of interventions, recruitment and retention strategies, and implementation and dissemination efforts. By collaborating with patient/stakeholder partners, the patient perspective is included and helps to ensure that the research conducted is relevant and not unduly burdensome for patients. Our patient/stakeholder advisory board members helped generate the research questions, choose the comparison groups, develop patient-centered inclusion and exclusion criteria, determine the timing of the primary endpoint, refine the research protocol, choose the most appropriate outcomes, decide on specific measurement tools, and create patient-friendly recruitment materials. Throughout the project, our patient/stakeholder partners will have specific roles in recruitment activities and will help to ensure that our trial is accessible to participants from diverse communities. Additionally, patient/stakeholder partners' involvement will contribute to effectively translating and disseminating the study findings to patient, family, stakeholder, and research audiences to effect real-world change.

3. Discussion

Pain and comorbid fatigue and sleep disturbance are among the most common and distressing symptoms for patients living with advanced cancer.[4-9] These co-occurring symptoms also negatively impact patients' quality of life and functional performance.[10,74,75] Unlike drug therapies that mostly focus on treating one symptom, acupuncture and massage can address multiple symptoms during treatment, which makes them potentially beneficial not only for pain but also for its related comorbid symptoms (e.g., fatigue and sleep disturbance) among patients with advanced cancer. Acupuncture and massage are both widely available and commonly used nonpharmacological treatments for pain and other comorbid symptoms in cancer populations. Therefore, this RCT study will provide high quality evidence of the comparative effectiveness and durability of acupuncture versus massage that can be readily incorporated into clinical care to improve patient-centered decision-making for pain management.

4. Ethics and dissemination

The institutional review board at Memorial Sloan Kettering Cancer Center (MSK) approved the study protocol; most recent version of the protocol approved May 19, 2021. For this trial, we will adhere to the guidelines from the Consolidated Standards of Reporting Trials (CONSORT)[76] and Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA).[77] This trial is funded by the Patient-Centered Outcomes Research Institute (SMPAI-2018C2-12883) and is registered at Clinicaltrials.gov (Identifier: NCT04095234).

The results of this study will be presented at national and international meetings, and a manuscript will be submitted for publication in a peer-reviewed journal. This research will inform which therapy (acupuncture or massage) is more effective for reducing pain and comorbid fatigue and insomnia in patients living with advanced cancer. Such information will lead to evidence-based and patient-centered decision making to incorporate these approaches for optimal pain management for the growing population of individuals living with advanced cancer. By collaborating with patient/stakeholder partners, patient/stakeholder partners help to interpret both expected and unexpected study findings in a way that is culturally sensitive and relevant to patients' lived experiences. Patient/stakeholder partners' active involvement will contribute to effectively translating and disseminating the study findings to patient, family, stakeholder, and research audiences to effect real-world change by providing education and awareness of the benefits of integrative, non-pharmacological options for pain management in people with advanced cancer.

Data Availability: The datasets generated during and/or analyzed during the current study will be available from the principal investigator (Jun J. Mao) on reasonable request.

Acknowledgements: The authors would like to thank the patients, healthcare providers, clinical staff, research staff, and patient/stakeholder partners at all study sites for their contributions to this study.

Funding and Research Support: Research reported in this article was funded through a Patient-Centered Outcomes Research Institute (PCORI) award (SMPAI-2018C2-12883). The statements presented in this work are solely the responsibility of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute® (PCORI®), its Board of Governors or Methodology Committee. It was also supported in part by the Translational and Integrative Medicine Research Fund (award/grant number not applicable) at Memorial Sloan Kettering Cancer Center. The funders do not have any role in study design; collection, management, analysis, and interpretation of data; writing of the report; and decision to submit for publication.

Conflict of Interests: All authors declare no conflicts of interest.

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Baser, Panageas, Mao - Data curation

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Mao - Funding acquisition

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Romero, Emard, Mao - Project administration

Mao - Resources

Romero, Emard, Liou, Deng, Han, Mao - Supervision

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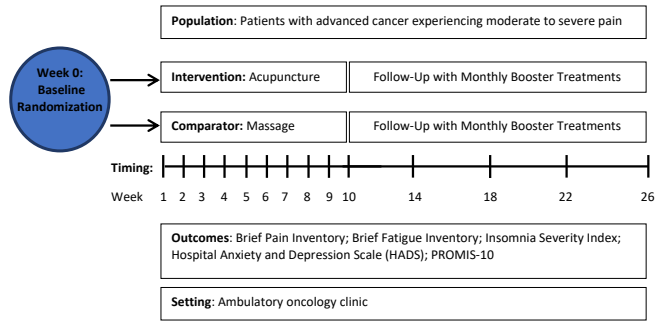
Figure Legend

Figure 1. Study Schema for the Integrative Medicine for Pain in Patients with Advanced Cancer Trial (IMPACT)


Population: Patients with advanced cancer experiencing moderate to severe pain
Week 0: Baseline Randomization
Intervention: Acupuncture
Follow-Up with Monthly Booster Treatments
Comparator: Massage
Follow-Up with Monthly Booster Treatments
Timing:
Week 1 2 3 4 5 6 7 8 9 10 14 18 22 26
Outcomes: Brief Pain Inventory; Brief Fatigue Inventory; Insomnia Severity Index; Hospital Anxiety and Depression Scale (HADS); PROMIS-10
Setting: Ambulatory oncology clinic

Appendix 1: Acupuncture Intervention

Background of the Intervention: The following acupuncture procedures and protocol were developed by Dr. Mao in consultation with experienced acupuncturists in China and U.S. The acupuncture points and techniques were selected to treat musculoskeletal pain and are based on classical and modern foundational acupuncture textbooks written in Chinese and/or English. We have piloted versions of this protocol in our prior research to demonstrate efficacy in pain reduction and adequate safety in the cancer population.

Operating Procedure:

Prior to the treatment session, the acupuncturist will:

- Review relevant medical history, laboratory results, and imaging studies to rule out absolute contraindications and to ensure appropriate precautions are taken.
- Greet patient/support members and escort them into private room.
- Take a focused history on pain and co-morbid symptoms (e.g. general aching, psychological distress, fatigue, or poor sleep).
- Conduct a focused physical examination with close attention to medical equipment (e.g. intravenous lines, chemotherapy ports) and areas of swelling/infection/deformities that may affect treatment protocol. If applicable, incorporate tongue/pulse diagnosis to guide acupuncture point selection.
- Assist patient onto table. Establish comfortable body positioning that is appropriate for treatment approach. Offer pillow, and/or bolster to maximize comfort.
- Instruct patient to adjust their clothing per his/her preferences and as indicated for treatment.

During the treatment session, the acupuncturist will:

- Insert needles by following the acupuncture treatment protocol as described below and in Tables 1 and 2.
- Offer blanket to maximize comfort.
- Dim lights and offer quiet music.

After the treatment session, the acupuncturist will:

- Assist patient to get off table.
- Ask patient to re-assess pain and other symptoms, evaluate for adverse events, and invite feedback to be incorporated into future treatment sessions.
- Complete clinical/research documentation.

Acupuncture Treatment Protocol (Total Duration: 30 Minutes)

- Identify one focal body area that the patient considers to be the most painful (e.g. neck, shoulder, back). This will be the primary area of focus for the entire treatment course.
- Choose at least four acupuncture points from Table 1 to address the primary area of pain. The acupuncturist may use clinical judgment to select additional acupuncture points or local trigger points (“ashi” or tender points) not listed in Table 1. The rationale for choosing unlisted points should be clearly documented. All selected points should be specified in clinical/research documentation.
- Choose at least four acupuncture points from Table 2 to address the patient’s co-morbid symptoms. The acupuncturist may use clinical judgment to select additional acupuncture points not listed in Table 2. The rationale for choosing unlisted points should be clearly documented. All selected points should be specified in clinical/research documentation.
- Limit the total number of points to 10-20.
- Sanitize hands and clean the skin at needle insertion sites with alcohol pads using aseptic technique.
- Insert needle to appropriate depth with brief manual stimulation to achieve “De Qi” sensation.
- Connect TENS unit to four points near the primary area of pain by attaching positive/negative leads to the needles. Set electrical frequency at 2 Hz. Turn on TENS unit and gradually increase electrical intensity to appropriate level, i.e. the patient should feel the stimulation, but it should not be painful.
- Set timer for 20 minutes, then leave room.
- Document acupuncture procedure, including points used and total needle count.

- After 20 minutes, enter room, turn off TENs unit and detach leads from needles.
- Sanitize hands and remove needles and wipe any blood with a sterile cotton-tipped applicator.
- Perform a final needle count to ensure all needles were removed.
- Sanitize hands.

Table 1: Acupuncture Point Selection Guide for Musculoskeletal Pain

Primary Pain Location	Acupuncture Points					
Head / Neck	Jianjing (G.B.21)	Huatuo (Extra)	Luozhen (Extra)	Dazhui (G.V.14)	Fengchi (G.B.20)	
Scapula	Tianzong (S.I.11)	Bingfeng (S.I.12)	Jianwaishu (S.I.14)	Gaohuangshu (U.B.43)		
Shoulder	Jianyu (L.I.15)	Jianliao (S.J.14)	Jianzhen (S.I.9)	Naoshu (S.I.10)	Houxi (S.I.3)	
Elbow	Quchi (L.I.11)	Chize (Lu. 5)	Tianjing (S.J.10)	Waiguan (S.J.5)	Hegu (L.I.4)	
Wrist	Yangchi (S.J.4)	Neiguan (P.C.6)	Daling (P.C.7)	Hegu (L.I.4)	Daling (L.I.5)	Yanglao (S.I.6)
Hand / Finger	Houxi (S.I.3)	Sanjian (L.I.3)	Baxie (Extra)	Hegu (L.I.4)		
Back	Shenshu (U.B.23)	Dachangshu (U.B.25)	Weizhong (U.B.40)	Chengshan (U.B.57)	Huatuo (Extra)	Kunlun (U.B.60)
Hip	Huantiao (G.B.30)	Yinmen (U.B.37)	Juliao (G.B.29)	Quixu (G.B.40)	Fengshi (G.B.31)	
Leg	Chengshan (U.B.57)	Feiyang (U.B.58)	Fengshi (G.B.31)			
Knee	Lianqiu (St.34)	Dubi (St.35)	Xiyan (Extra)	Yanlingquan (G.B.34)	Xiyangguan (G.B.33)	Yinlingquan (Sp.9)
Ankle	Jiexi (St.41)	Shangqui (Sp.5)	Quixu (G.B.40)	Kunlun (U.B.60)	Taixi (K.3)	
Foot / Toe	Gongsun (Sp.4)	Shugu (U.B.65)	Bafeng (Extra)	Taixi (Liv. 3)		

Table 2: Acupuncture Point Selection Guide for Addressing Co-Morbid Symptoms Associated with Pain

Co-Morbid Symptoms	Acupuncture Points					
General Aching	Houxi (S.I.3)	Shenmai (U.B.62)	Dabao (Sp.21)	Geshu (U.B.17)	Yinlingquan (Sp.9)	Hegu/Taixi (L.I.4/Liv.3)
Psychological Distress	Neiguan (P.C.6)	Taixi (Liv.3)	Yin Tang (Extra)	ShenMen (Auricular)	Baihui (Du.20)	
Fatigue	Sanxinjiao (Sp.6)	Zusanli (St.36)	Qihai (CV6)			
Sleep	Shenmen (Ht.7)	Anmian (Extra)				

Appendix 2: Massage Intervention

Background of the Intervention: The following massage procedures and protocol were developed by experienced licensed oncology massage therapists in collaboration with Dr. Mao. This protocol is designed to treat musculoskeletal pain and is based on gold-standard textbooks in the field of oncology rehabilitation and medical massage. Versions of this protocol have been piloted in prior research to demonstrate efficacy in pain reduction and adequate safety in the cancer population.

Operating Procedure:

Prior to the treatment session, the massage therapist (MT) will:

- Greet patient/support members, escort them into private room, and sanitize hands.
- Take a focused history on pain and co-morbid symptoms.
- Review relevant medical history, laboratory results and imaging studies to rule out absolute contraindications and to ensure appropriate precautions are taken.
- Conduct a focused physical examination with close attention to medical equipment (e.g. intravenous lines, chemotherapy ports) and areas of swelling/infection/deformities that may affect treatment protocol. Visually assess posture and gait.
- Identify co-morbid complaints of the patient e.g. general aching, psychological distress, fatigue, or poor sleep.
- Assist patient onto table/chair. Establish comfortable body positioning that is appropriate for treatment approach. Offer blanket, pillow, and/or bolster to maximize comfort.
- Adjust patient's clothing per his/her preferences and as indicated for treatment.
- Identify patient's lubricant preference, i.e. oil or lotion.
- Dim lights and offer quiet music.

During the treatment session, the MT will:

- Follow the massage treatment protocol as described below in Table 1 and Table 2.
- Assess joints using active and/or passive pain-free range of motion. Use compression to identify and treat hypertonic muscles, tender/trigger points. Assess for trigger points with referral pattern to the site of pain. Use gentle fascial mobilizations to assess and treat fascial restriction in the area of pain, including surgical scars and tissues with a history of radiation treatment.
- Solicit and respond to patient feedback.

After the treatment session, the MT will:

- Assist patient to get off table/chair.
- Ask patient to re-assess pain and other symptoms, evaluate for adverse events, and invite feedback to be incorporated into future treatment sessions.
- Perform clinical/research documentation.

In subsequent treatment sessions, the MT will:

- Get patient feedback about the impact of the previous session in pain and co-morbid complaints.
- Adjust approach to respond to any shifts in primary area of pain if applicable.

Massage Treatment Protocol (Total Duration: 30 Minutes)

- Set silent timer for 5 minute intervals.
- Perform parasympathetic toning protocol for a minimum of 5 minutes. Assess breathing pattern. Provide verbal and physical cues for diaphragmatic breathing. Perform gentle release of

diaphragm and mobilization of ribs. Compress and muscle strip neck muscles. Perform OA release.

- Identify one focal body area that the patient considers to be the most painful (e.g. neck, shoulder, back, leg).
- Perform fascial release for a minimum of 5 minutes using techniques from the menu. Begin with indirect fascial release for tissues proximal to the site of pain. In subsequent sessions the treatment area may broaden in response to assessment and treatment outcomes.
- Perform tender point release for a minimum of 5 minutes using techniques from the menu. Begin with muscles proximal to the site of pain or with related referral patterns, in subsequent sessions the treatment area may broaden in response to assessment and treatment outcomes.
- Remaining time (2 - 3 minutes) can be used for integrative work distal to the pain site if indicated by gait and postural assessment or patient feedback during the treatment.
- End with effleurage (1-2 minutes) towards the heart, the therapist may use lubricant if necessary and appropriate.

Table 1: Recommended Massage Techniques

▪ Palmar Compression (PC) ▪ Digital Compression (DC) ▪ Lifting/Pincer Compression (LC) ▪ Muscle Stripping (MS) ▪ Active Range of Motion (AROM) ▪ Passive Range of Motion (PROM) ▪ Post-Isometric PROM (PI-PROM) ▪ Post-Isometric AROM (PI-AROM) ▪ Positional Release (PR) ▪ Effleurage (E) ▪ Indirect/Gathering Fascial Release (IFR) ▪ Direct/Stretching Fascial Release (DFR)	▪ Superficial Fascial Release (SFR) ▪ Muscular/Deep Fascial Release (MFR) ▪ Kinetic Fascial Release (KFR) ▪ Long Duration Fascial Release (LDFR) ▪ Short Duration Fascial Release (SDFR) ▪ Compression of trigger/tender point (CTP) ▪ Positional release of trigger/tender point (PRTP) ▪ Local stretch for trigger/tender point (LSTP) ▪ Global/Muscle stretch for trigger/tender point (GSTP)

Table 2: Massage Guide Organized by Primary Location of Musculoskeletal Pain

Primary Pain Location	Recommended Massage Guide
HEAD/JAW **Assess and treat local tissues first then progress to proximal and distal areas. See muscle guides.**	▪ Assess fascial mobility with superficial fascial release of tissues in the focal area with attention to local scars/fibrosis. ▪ Treat restriction with superficial indirect fascial release, tenting tissues over the painful area first. Progress to direct or kinetic fascial release where appropriate. ▪ Compress primary muscles to assess for tension, treat hypertonicity with compression and muscle stripping. ▪ Assess for trigger/tender points keeping in mind common referral patterns and treat with all appropriate elements of integrated TP release protocol. ▪ Assess A/PROM in joints in the area, treat with pain-free joint mobilizations. ▪ Effleurage with strokes directed toward the heart.
CERVICAL SPINE **Assess and treat local tissues first then progress**	▪ Assess fascial mobility with superficial fascial release of tissues in the focal area with attention to local scars/fibrosis.

to proximal and distal areas. See muscle guides.	▪ Treat restriction with superficial indirect fascial release, tenting tissues over the painful area first. Progress to direct or kinetic fascial release where appropriate. ▪ Compress primary muscles to assess for tension, treat hypertonicity with compression and muscle stripping. ▪ Assess for trigger/tender points keeping in mind common referral patterns and treat with all appropriate elements of integrated TP release protocol. ▪ Assess A/PROM in joints in the area, treat with pain-free joint mobilizations. ▪ Effleurage with strokes directed toward the heart.
THORACIC SPINE **Assess and treat local tissues first then progress to proximal and distal areas. See muscle guides.**	▪ Assess fascial mobility with superficial fascial release of tissues in the focal area with attention to local scars/fibrosis. ▪ Treat restriction with superficial indirect fascial release, tenting tissues over the painful area first. Progress to direct or kinetic fascial release where appropriate. ▪ Compress primary muscles to assess for tension, treat hypertonicity with compression and muscle stripping. ▪ Assess for trigger/tender points keeping in mind common referral patterns and treat with all appropriate elements of integrated TP release protocol. ▪ Assess A/PROM in joints in the area, treat with pain-free joint mobilizations. ▪ Effleurage with strokes directed toward the heart.
SHOULDER **Assess and treat local tissues first then progress to proximal and distal areas. See muscle guides.**	▪ Assess fascial mobility with superficial fascial release of tissues in the focal area with attention to local scars/fibrosis. ▪ Treat restriction with superficial indirect fascial release, tenting tissues over the painful area first. Progress to direct or kinetic fascial release where appropriate. ▪ Compress primary muscles to assess for tension, treat hypertonicity with compression and muscle stripping. ▪ Assess for trigger/tender points keeping in mind common referral patterns and treat with all appropriate elements of integrated TP release protocol. ▪ Assess A/PROM in joints in the area, treat with pain-free joint mobilizations. ▪ Effleurage with strokes directed toward the heart.
SHOULDER GIRDLE **Assess and treat local tissues first then progress to proximal and distal areas. See muscle guides.**	▪ Assess fascial mobility with superficial fascial release of tissues in the focal area with attention to local scars/fibrosis. ▪ Treat restriction with superficial indirect fascial release, tenting tissues over the painful area first. Progress to direct or kinetic fascial release where appropriate. ▪ Compress primary muscles to assess for tension, treat hypertonicity with compression and muscle stripping. ▪ Assess for trigger/tender points keeping in mind common referral patterns and treat with all appropriate elements of integrated TP release protocol.

	▪ Assess A/PROM in joints in the area, treat with pain-free joint mobilizations. ▪ Effleurage with strokes directed toward the heart.
CHEST/BREAST **Assess and treat local tissues first then progress to proximal and distal areas. See muscle guides.**	▪ Assess fascial mobility with superficial fascial release of tissues in the focal area with attention to local scars/fibrosis. ▪ Treat restriction with superficial indirect fascial release, tenting tissues over the painful area first. Progress to direct or kinetic fascial release where appropriate. ▪ Compress primary muscles to assess for tension, treat hypertonicity with compression and muscle stripping. ▪ Assess for trigger/tender points keeping in mind common referral patterns and treat with all appropriate elements of integrated TP release protocol. ▪ Assess A/PROM in joints in the area, treat with pain-free joint mobilizations. ▪ Effleurage with strokes directed toward the heart.
RIB CAGE **Assess and treat local tissues first then progress to proximal and distal areas. See muscle guides.**	▪ Assess fascial mobility with superficial fascial release of tissues in the focal area with attention to local scars/fibrosis. ▪ Treat restriction with superficial indirect fascial release, tenting tissues over the painful area first. Progress to direct or kinetic fascial release where appropriate. ▪ Compress primary muscles to assess for tension, treat hypertonicity with compression and muscle stripping. ▪ Assess for trigger/tender points keeping in mind common referral patterns and treat with all appropriate elements of integrated TP release protocol. ▪ Assess A/PROM in joints in the area, treat with pain-free joint mobilizations. ▪ Effleurage with strokes directed toward the heart.
UPPER EXTREMITY **Assess and treat local tissues first then progress to proximal and distal areas. See muscle guides.**	▪ Assess fascial mobility with superficial fascial release of tissues in the focal area with attention to local scars/fibrosis. ▪ Treat restriction with superficial indirect fascial release, tenting tissues over the painful area first. Progress to direct or kinetic fascial release where appropriate. ▪ Compress primary muscles to assess for tension, treat hypertonicity with compression and muscle stripping. ▪ Assess for trigger/tender points keeping in mind common referral patterns and treat with all appropriate elements of integrated TP release protocol. ▪ Assess A/PROM in joints in the area, treat with pain-free joint mobilizations. ▪ Effleurage with strokes directed toward the heart.
ABDOMINAL **Assess and treat local tissues first then progress to proximal and distal areas. See muscle guides.**	▪ Assess fascial mobility with superficial fascial release of tissues in the focal area with attention to local scars/fibrosis. ▪ Treat restriction with superficial indirect fascial release, tenting tissues over the painful area first. Progress to direct or kinetic fascial release where appropriate.

	▪ Compress primary muscles to assess for tension, treat hypertonicity with compression and muscle stripping. ▪ Assess for trigger/tender points keeping in mind common referral patterns and treat with all appropriate elements of integrated TP release protocol. ▪ Assess A/PROM in joints in the area, treat with pain-free joint mobilizations. ▪ Effleurage with strokes directed toward the heart.
LUMBAR **Assess and treat local tissues first then progress to proximal and distal areas. See muscle guides.**	▪ Assess fascial mobility with superficial fascial release of tissues in the focal area with attention to local scars/fibrosis. ▪ Treat restriction with superficial indirect fascial release, tenting tissues over the painful area first. Progress to direct or kinetic fascial release where appropriate. ▪ Compress primary muscles to assess for tension, treat hypertonicity with compression and muscle stripping. ▪ Assess for trigger/tender points keeping in mind common referral patterns and treat with all appropriate elements of integrated TP release protocol. ▪ Assess A/PROM in joints in the area, treat with pain-free joint mobilizations. ▪ Effleurage with strokes directed toward the heart.
SACRAL/PELVIC **Assess and treat local tissues first then progress to proximal and distal areas. See muscle guides.**	▪ Assess fascial mobility with superficial fascial release of tissues in the focal area with attention to local scars/fibrosis. ▪ Treat restriction with superficial indirect fascial release, tenting tissues over the painful area first. Progress to direct or kinetic fascial release where appropriate. ▪ Compress primary muscles to assess for tension, treat hypertonicity with compression and muscle stripping. ▪ Assess for trigger/tender points keeping in mind common referral patterns and treat with all appropriate elements of integrated TP release protocol. ▪ Assess A/PROM in joints in the area, treat with pain-free joint mobilizations. ▪ Effleurage with strokes directed toward the heart.
HIP **Assess and treat local tissues first then progress to proximal and distal areas. See muscle guides.**	▪ Assess fascial mobility with superficial fascial release of tissues in the focal area with attention to local scars/fibrosis. ▪ Treat restriction with superficial indirect fascial release, tenting tissues over the painful area first. Progress to direct or kinetic fascial release where appropriate. ▪ Compress primary muscles to assess for tension, treat hypertonicity with compression and muscle stripping. ▪ Assess for trigger/tender points keeping in mind common referral patterns and treat with all appropriate elements of integrated TP release protocol. ▪ Assess A/PROM in joints in the area, treat with pain-free joint mobilizations. ▪ Effleurage with strokes directed toward the heart.

LOWER EXTREMITY Assess and treat local tissues first then progress to proximal and distal areas. See muscle guides.	▪ Assess fascial mobility with superficial fascial release of tissues in the focal area with attention to local scars/fibrosis. ▪ Treat restriction with superficial indirect fascial release, tenting tissues over the painful area first. Progress to direct or kinetic fascial release where appropriate. ▪ Compress primary muscles to assess for tension, treat hypertonicity with compression and muscle stripping. ▪ Assess for trigger/tender points keeping in mind common referral patterns and treat with all appropriate elements of integrated TP release protocol. ▪ Assess A/PROM in joints in the area, treat with pain-free joint mobilizations. ▪ Effleurage with strokes directed toward the heart.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	13
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 15
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	4-5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5-6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9-11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9-11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Fig 1 and Table 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	5-7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5-9
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6-7, 9-11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	6-7, 11-12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11-12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11-12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11-12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9-11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9-11
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13-14
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	7
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.