

Personalized Electro-acupuncture vs. Auricular-acupuncture Comparative Effectiveness
 PROTOCOL FACE PAGE FOR
 MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

OneMSK Sites	
Basking Ridge	All Protocol Activities
Bergen	All Protocol Activities
Commack	All Protocol Activities
Monmouth	All Protocol Activities
Rockville Centre	All Protocol Activities
Westchester	All Protocol Activities

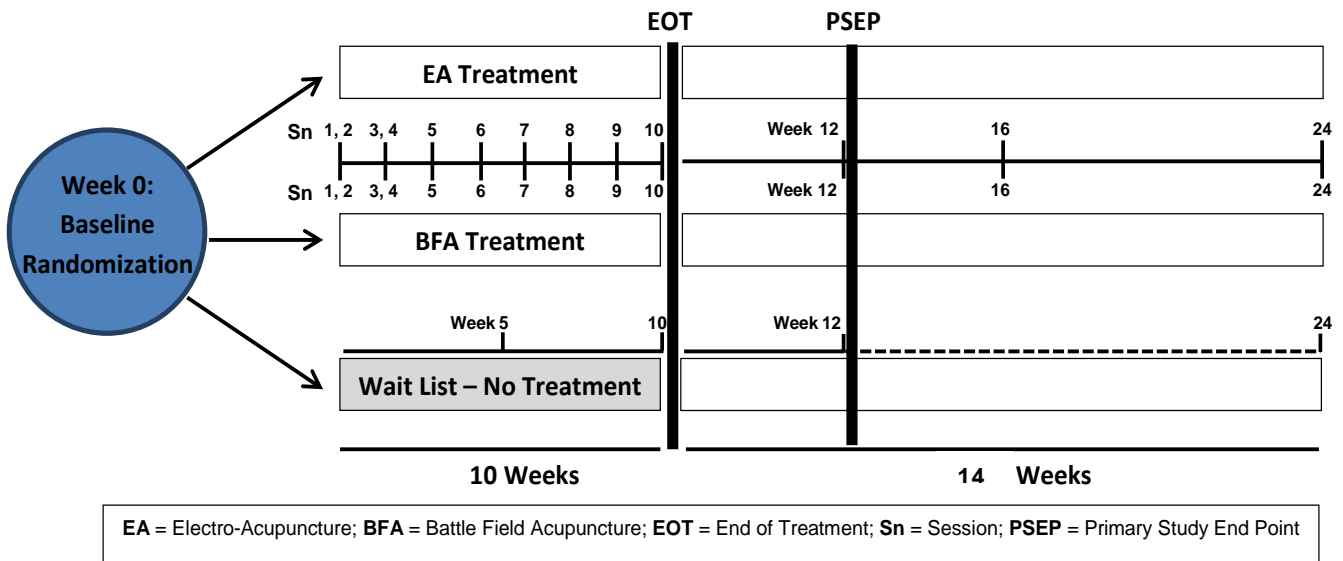
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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Study Title	Personalized E lectro-acupuncture vs. A uricular-acupuncture C omparative E ffectiveness (PEACE)
Specific Aim 1	To compare the effects of Electro-acupuncture (EA) vs. Battle Field Acupuncture (BFA) vs. Waitlist Control usual care (WLC) on patient-reported pain (primary outcome), physical functions, and co-morbid symptoms (fatigue, sleep disturbance, anxiety, depression, and PTSD) among patients experiencing chronic musculoskeletal pain
Specific Aims 2 and 3	To determine the interaction between outcome expectancy and type of needling delivery (EA vs. BFA) on pain reduction To evaluate the association between specific genetic polymorphisms and patients' responses to acupuncture
Patient Population	Patients experiencing chronic musculoskeletal pain for three months or greater
Number of Subjects	360
Study Design	Three-arm parallel (EA vs. BFA vs. WLC) randomized controlled trial
Treatment	Participants will receive 10 treatments of acupuncture (EA or BFA) over the course of 10 weeks (+/- 4 days), with a maximum of 2 treatments per week.
Time to Completion	Participants will be on the study for 24 weeks.

Figure 1 PEACE Study Schema



2.0 OBJECTIVES AND SCIENTIFIC AIMS

Building on identified scientific gaps in the literature and our promising preliminary data, we will conduct a randomized controlled trial (RCT) of Electro-acupuncture (EA) vs. Battle Field Acupuncture (BFA) vs. Waitlist Control usual care (WLC) on 360 patients with chronic musculoskeletal pain. We will also examine the effects of baseline outcome expectancy and genetic polymorphisms on pain reduction.

The overarching goal of the Personalized Electro-acupuncture vs. Auricular-acupuncture Comparative Effectiveness (PEACE) trial is to investigate EA and BFA (a form of auricular acupuncture) to guide the personalized delivery of treatment to improve pain and co-morbid symptoms. To achieve this overarching goal, the specific aims are:

Specific Aim 1: To compare the effects of Electro-acupuncture (EA) vs. Battle Field Acupuncture (BFA) vs. Waitlist Control usual care (WLC) on patient-reported pain (primary outcome), physical functions, and co-morbid symptoms (fatigue, sleep disturbance, anxiety, depression, and PTSD) among patients experiencing chronic musculoskeletal pain for three months or greater.

Primary Hypothesis 1(a): EA will produce greater reductions in average pain intensity (measured by the Brief Pain Inventory [BPI]) as compared to WLC usual care at 12 weeks after randomization.

Primary Hypothesis 1(b): BFA will produce greater reductions in average pain intensity (measured by the Brief Pain Inventory [BPI]) as compared to WLC usual care at 12 weeks after randomization.

Primary Hypothesis 1(c): BFA will be as effective as EA in reducing the average pain intensity at 12 weeks after randomization

Secondary Hypotheses:

- a) The effects of EA and BFA will be durable over the 24 week follow-up period among those who are randomized to receiving acupuncture (EA or BFA).
- b) EA and BFA will produce greater improvements than the WLC in co-morbid symptoms (i.e. fatigue, sleep disturbance, anxiety, depression, and PTSD).
- c) Both EA and BFA will produce greater improvements than the WLC in physical functions.

Specific Aim 2: To determine the interaction between outcome expectancy and type of needling delivery (EA vs. BFA) on pain reduction.

Primary Hypothesis 2: EA will produce clinically important percent pain-intensity reduction at 12 weeks after randomization regardless of baseline outcome expectancy; whereas BFA's pain reduction will be more dependent on baseline outcome expectancy.

Specific Aim 3: To evaluate the association between specific genetic polymorphisms and patients' responses to acupuncture.

Primary Hypothesis 3: Participants with either the AA alleles in COMT (rs4680) or GG/AG alleles in TCL1A (rs2369049) will be more likely than those without the genetic combination to respond to acupuncture treatments (EA or BFA).

Exploratory Hypothesis: Other genetic variants (e.g., TNF, IL-6, IL-1 β , and ADORA1) in pain processing and inflammation may predict response to EA, BFA, or both.

3.0 BACKGROUND AND RATIONALE

This protocol directly addresses a clinical issue that is of high public health and programmatic interest of the Department of Defense (DoD), Veterans Affairs (VA) and Memorial Sloan Kettering (MSK). If successful, this program of research will provide definitive evidence for the comparative effectiveness of Electro-acupuncture (EA) and Battle Field Acupuncture (BFA) for chronic pain management. In addition, it will guide the personalized delivery of acupuncture for patients with chronic pain. While this research is important for many individuals with chronic pain, it is of particular importance for the military and veteran population as many individuals who are actively serving or who have served our country suffer from chronic pain and are in need of effective non-pharmacological solutions to successfully manage it.

3.1. Acupuncture: A promising non-pharmacological therapy for managing chronic pain

Chronic pain affects approximately 100 million Americans and is the leading cause of disability in the general population.¹ It costs the United States \$600 billion each year in health care and loss of productivity.² Acupuncture, a therapy that is part of Traditional Chinese medicine (TCM), involves penetrating the skin with thin, solid, metallic needles that are manipulated by hand or electrical stimulation.³ Acupuncture is considered safe with few side effects (e.g., needling pain, bruising).⁴ It has both mechanistic and clinical plausibility as a treatment for the management of chronic pain in the veteran and military population. Based on animal research, acupuncture stimulation can regulate the neuro-substrates involved in both the ascending facilitatory pain pathways (e.g., substance P,^{5,6} N-methyl-D-aspartate receptors⁷) and the descending inhibitory pain pathways (e.g. opioid,⁸ serotonin⁹). These endogenous neurotransmitters play a central role in both chronic pain and comorbid mental health disorders (e.g., anxiety, depression). In recent years, novel functional neuroimaging techniques, including positron emission tomography (PET) scan¹⁰⁻¹² and functional magnetic resonance imaging (MRI),¹³⁻¹⁶ have increased our understanding of the neurological basis of acupuncture analgesia, which relies on complex neural networks involved in cognition, emotion, stress, and pain processing, including but not limited to the limbic system,^{13,17} hypothalamus, and brainstem networks.^{18,19} These translational research findings provide further support for biological plausibility in the management of chronic pain as well as other co-morbid conditions that frequently accompany chronic pain. With respect to the effectiveness of acupuncture for chronic pain, in a recent patient-level meta-analysis of

RCTs, including almost 18,000 patients with chronic non-malignant pain, acupuncture was found to be substantially better than usual care or standard care and significantly better than sham acupuncture.²⁰

Despite the growing evidence of acupuncture for treatment of chronic pain and associated co-morbidities, several important scientific gaps exist. First, trials of EA and BFA are few, have small sample sizes, and lack appropriate controls. These methodological limitations prevent drawing definitive conclusions about the effectiveness of these two types of acupuncture for chronic pain. Second, little research has focused on investigating the effect of acupuncture on pain-related mental health co-morbidities such as PTSD.²¹ Given that chronic pain and PTSD/depression commonly co-exist,^{22,23} a careful examination of the effect of acupuncture on pain and its co-morbid conditions is needed. Third, the practice of acupuncture involves many different techniques, including electro-acupuncture and auricular acupuncture; however, little research has been done to compare the relative effects between these two different types of acupuncture to guide specific delivery of acupuncture. Battle Field Acupuncture (BFA) is a form of auricular acupuncture developed in the military that is simple, requires only a four hour training, and can be used in a variety of acute and chronic pain settings with both popularity in the military and empirical success.^{24,25} However, clinical trials of BFA are very limited; thus, comparing BFA against WLC as well as EA will help inform the evidence base of BFA for chronic pain. Thus, building on the promising preliminary results described below, we seek to conduct a definitive trial of EA vs. BFA vs. WLC with long term follow up. If our results are consistent with our hypothesis, it will create a strong evidence base to guide the patient-centered integration of acupuncture for both cancer survivors and military and veteran populations to improve pain and co-morbid symptom management.

3.2. Expectancy and response to acupuncture

Despite emerging evidence on the effect of acupuncture for chronic pain management,²⁶ the large effect seen in sham/placebo acupuncture groups introduces uncertainty in evaluating and interpreting the efficacy of acupuncture in placebo-controlled trials.²⁰ Indeed, a recent meta-analysis found that sham acupuncture (SA) was much more effective than sham oral pharmaceutical placebos for migraine prophylaxis.²⁷ The “powerful effect” of sham acupuncture requires more thoughtful investigation to evaluate the specific component that produces clinical benefit for patients so that we can utilize it effectively for clinical management of chronic pain. Response expectancy, defined as “expectations held by the individual about one’s own emotional and physiological response” to a treatment, is a critical component of the placebo response.²⁸ Expectancy can be based upon a prior stimulus (e.g. prior acupuncture or a similar intervention), the environment (e.g. confidence in the practitioner), or learned conditioning.²⁹ Evaluation of the association of expectancy with response to acupuncture has yielded mixed results,³⁰ but a large study in non-cancer clinical pain found baseline expectancy predicted treatment response.³¹ In a recent study using the third molar dental extraction model, Vas et al. found that expected pain reduction accounted for a large (up to 69.8%) variance in actual pain reduction.³² Unfortunately, the use of various and non-validated expectancy

measurements, different experimental designs, and study populations (healthy controls or clinical patients) create substantial challenges in defining the role of expectancy in acupuncture outcomes based on the current state of science.³⁰ Dr. Mao (PI) has developed a brief 4-item Acupuncture Expectancy Scale (AES) that has now been validated in Chinese,³³ English,³⁴ and Korean.³⁵ Our proposed Specific Aim 2 will use the AES to provide the most definitive information on how baseline expectancy predicts pain and other outcomes to both EA and BFA. This is built on our promising preliminary findings. If our preliminary results can be confirmed in the PEACE trial, they have the potential to guide **personalized** acupuncture needling techniques to optimize acupuncture outcome based on expectancy for those who suffer from chronic pain.

3.3. Genetic predictors of acupuncture response

Growing interest exists in the use of genetic biomarkers to personalize diagnosis and treatment for pain and other diseases.³⁶⁻³⁸ However, the research is extremely limited for acupuncture and pain. In our recent work, we have focused on the genetic polymorphisms Catechol-O-methyltransferase (COMT)³⁹ and T-cell leukemia 1A (TCL1A).⁴⁰ Previous work by Hall et al. found that Catechol-O-methyltransferase (COMT) val158met polymorphism was associated with placebo response in acupuncture for irritable bowel syndrome. COMT is an enzyme that regulates dopamine catabolism and plays a key role in processes associated with the placebo effect such as reward, pain, memory, and learning.³⁹ In animal models, acupuncture regulates dopamine release and transmission,^{41,42} and, in humans, acupuncture has been found to influence key regions of the brain in pain/memory and learning.^{15,17} This particular polymorphism was also found to be associated with lower pressure pain sensitivity.⁴³ In a genome-wide association study (GWAS), Ingle et al. identified four SNPs close to the TCL1A region that are associated with musculoskeletal pain.⁴⁰ Functional genomic studies then found that these SNPS were related to IL-17 production.⁴⁰ Recently, Bao et al. found that acupuncture appeared to reduce peripheral circulating IL-17 in breast cancer survivors with musculoskeletal pain.⁴⁴ Building on this preliminary scientific evidence, we examined genetic variants in COMT and TCL1A and found that they predicted response to acupuncture in breast cancer patients. If confirmed in the PEACE trial, these findings will be the first to confirm the potential value of **personalized** integration of acupuncture based on host genetic background to optimize pain management and to help us better understand the inherent genetic variability associated with acupuncture treatment response.

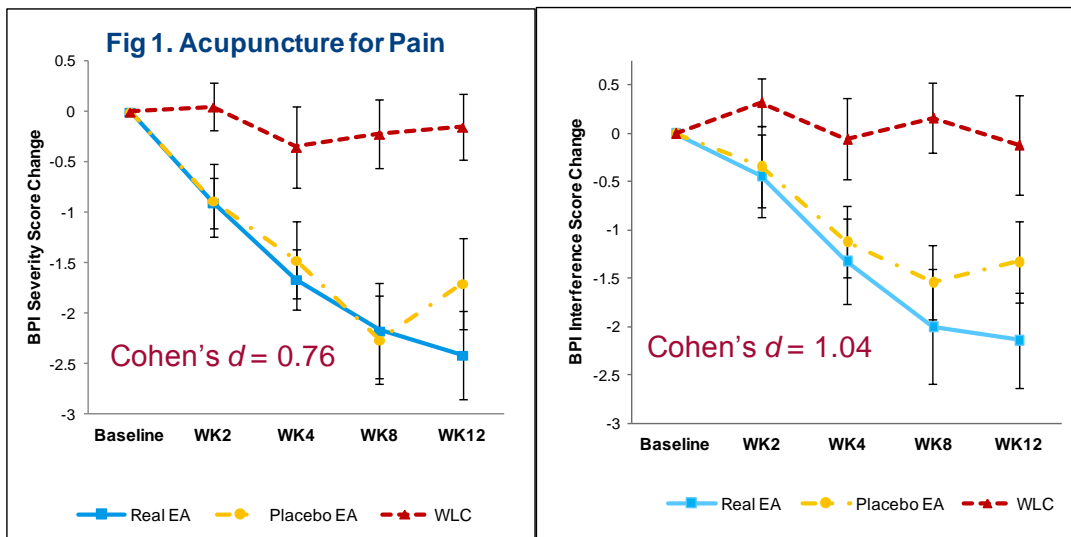
3.4. Preliminary studies

This study is a natural growth of our ongoing work over the past several years. Our preliminary work has provided a strong conceptual and methodological foundation that supports the study.

a) Electro-acupuncture (EA) for pain and co-morbid symptoms (see Specific Aim 1):

We recently completed an RCT of electro-acupuncture (EA) compared to sham acupuncture (SA) and waitlist control (WLC) in 67 breast cancer patients with joint pain (arthralgia) attributable to aromatase inhibitors.⁴⁵ Acupuncturists delivered 10 treatments of acupuncture

with 2 Hz electro-stimulation via a TENS unit. Sham acupuncture was conducted using non-penetrating Streitberger needles at non-traditional acupuncture points and sham electro-stimulation. The primary aim was pain intensity measured by the Brief Pain Inventory (BPI) between EA and WLC. Of the 67 patients randomized to the three arms, 71.6% were White and 23.8% were African American. Among participants, 21 (95.4%) in the EA group and 20 (90.5%) in the SA group received all 10 treatments. Only eight (12%) were lost to follow up by Week 12. Few minor adverse events, such as needling pain and bruises, were reported. At Week 8, the electro-acupuncture group had clinically and statistically significant reduction in joint pain intensity (-2.2 vs. -0.2, Cohen's $d=0.76$, $p=0.0004$) and pain-related interference (-2.0 vs. 0.2, Cohen's $d=1.04$, $p=0.0006$) compared with the WLC. Further, the improvement in pain intensity and interference appeared to be maintained 4 weeks following the last acupuncture treatment. Both EA and SA produced similar effects during the treatment; the study was not powered to detect statistically significant differences between the two acupuncture arms (Fig. 1). However, by Week 12 (4 weeks after the end of treatment) the pain intensity scores continued to improve for the EA group and got worse for the SA group, with a difference of 0.66 between EA and SA ($p=0.22$).

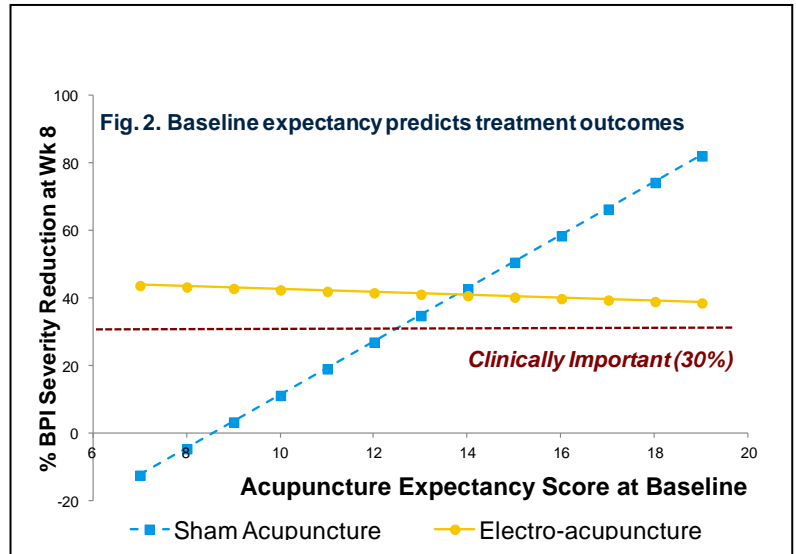


We also performed the analyses of pre-specified secondary outcomes and found that compared to WLC, EA produced significant improvement in fatigue ($p=0.0095$), anxiety ($p=0.044$), and depression ($p=0.015$), and non-significant but marginal improvement in sleep disturbance ($p=0.058$) during the 12 week intervention and follow up period. In contrast, SA did not produce significant reductions in fatigue and anxiety symptoms, but produced significant improvement in depression compared with WLC ($p=0.0088$).⁴⁶ Further, the EA group had non-significant improvement in the objective Physical Performance Test (PPT) score as compared to WLC (1.8 points, $p = 0.061$, Cohen's $d = 0.61$), while SA had very little impact on PPT as compared to WLC ($p=0.16$).⁴⁵ The Cohen's d s for pain and secondary outcomes suggest a moderate to large effect size for these outcomes, which demonstrates clinical utility. Our data suggest that our specific EA protocol may be effective in improving pain, co-morbid symptoms, and functional outcomes. If successfully confirmed in the PEACE

trial, this will have immediate and important clinical impact for those who suffer from chronic musculoskeletal pain. In addition, the data demonstrate our ability to successfully implement and complete an acupuncture trial with a low drop-out rate.

(b) Expectancy and response to acupuncture outcomes (see Specific Aim 2). The large placebo effect observed in prior acupuncture trials presents a substantial challenge for

interpretation of the specific effects of acupuncture treatment. We sought to evaluate the association between response expectancy, a key component of the placebo effect, and treatment outcome for EA and SA.⁴⁷ We analyzed data from the RCT described above.⁴⁵ We used the validated Acupuncture Expectancy Scale (AES)³⁴ to measure outcome expectancy from receiving acupuncture. The outcome was percent pain severity reduction at the end of treatment as compared to baseline. In the



multivariate model with Week 8 percent pain severity reduction as the dependent outcome, we found a baseline AES and treatment group interaction ($p=0.056$). For SA, each point increase in baseline expectancy was significantly associated with a greater percent pain reduction at Week 8 (regression coefficient = 7.9, standard error = 2.8, $p=0.007$). In contrast, we found no association between baseline AES and percent pain reduction in the EA group ($p=0.89$). Based on this model, we developed a calculated percent pain reduction based on baseline AES (Fig. 2). As illustrated, EA produced clinically important effects regardless of baseline expectancy; however, SA was only effective for those with higher baseline expectancy.⁴⁷ Because Battle Field Acupuncture (BFA) involves auricular points that are not proximal to body area where patients have pain,²⁴ we hypothesize that BFA response will be more likely driven by expectancy such as observed for SA. In this trial, we will test whether expectancy will predict outcome differently or similarly for EA and BFA. Such knowledge can help us tailor the delivery of acupuncture based on expectancy. For example, those with high baseline expectancy may benefit from starting with BFA rather than EA whereas those with lower baseline expectancy may benefit from proceeding to EA right away.

(c) Genetic predictors to acupuncture response (see Specific Aim 3). We evaluated the association between genetic variations and response to acupuncture in the pilot trial described above.⁴⁵ We genotyped rs4680 (Val158Met), rs4633 (His62His), rs4818 (Leu136Leu), rs6269 (1-98 A>G) variants in the COMT gene³⁹ and rs2369049 (A>G), and rs7158782 (A>G) variants in the TCL1A gene⁴⁰ using TaqMan SNP genotyping assays on a real-time HT-7900 PCR machine. Response to acupuncture was defined by a 30% reduction in end-of-treatment average pain-intensity score, measured by the BPI.⁴⁸ The Fisher exact

test was conducted to evaluate the association between a specific SNP single or in combination with treatment response. Among 38 subjects in the EA/SA groups who had both genotyping data and pain outcomes, 6 (15.8%) patients had AA on rs4680 and all responded to acupuncture, which was non-significantly higher than those without AA (53.1% response rate, $p=0.063$). Sixteen (42.1%) patients had AA/AG on rs2369049 and were non-significantly more likely to respond to acupuncture (both EA and SA) than those with AA (75% vs. 50%, $p=0.18$). Combining the effects of both SNPs, those subjects with either AA in rs4680 or GG/AG in rs2369049 (47.2%) were more likely to respond to acupuncture than those without (77.8% vs. 45.0%, $p=0.039$). Our research provides the first evidence that genetic variants in COMT and inflammation can predict response to acupuncture.⁴⁹ These preliminary findings need to be confirmed in the proposed PEACE trial to become actionable information to guide personalized integration of acupuncture into chronic pain management.

(d) Implementation of Battle Field Acupuncture (BFA) across the DoD and VA:

Timeliness of our research. Dr. Mao was involved in the *Acupuncture Training Across Clinical Settings (ATACS)* project that is funded by the DoD/VA Joint Incentive Fund. The goal of the project is to develop, pilot, evaluate, and implement a uniform tiered acupuncture education and training program for Military Health System (MHS) and Veterans Health Administration (VHA) providers in order to provide initial access and to expand this modality across MHS and VHA treatment facilities. The ATACS project will train 1,000 health care providers (e.g. physicians, nurse practitioners, physician assistants) in Battle Field Acupuncture (BFA) as well as 60 physicians in medical acupuncture. It will provide near-term, uniform implementation and integration of this modality across military and VA health care systems through a proven practical program of training and certification for providers. This will allow adoption and further development of acupuncture best practices across the MHS and VHA. It will provide a much needed alternative in cases where the initiation or continuation of opioid analgesics are deemed clinically risky, in cases where current medications and other therapies are not working, and in cases where the existence of and potential for substance abuse, addiction, and tolerance issues make opioid therapies impractical. Since the award of the Joint Incentive Fund (JIF) (November 2013 through August 19, 2014), 744 military and VA health care providers have been trained in BFA. Our PEACE trial is extremely timely as this national implementation project is being deployed. The scientific information learned from our study will inform the evidence-based and patient-centered delivery of acupuncture. In addition, the infrastructure developed by the ATACS will facilitate the dissemination of the findings of our PEACE trial. Once the results become available, Dr. Mao will work with DoD/VA pain management leadership to disseminate the findings.

3.5 Rationale and considerations for key design features

- We chose an RCT design because it is the most appropriate way to obtain a valid measure of efficacy, controlling for the large number of variables, whether known or unknown, measurable or immeasurable, that may confound the association between exposure and the primary outcome.
- We chose to use WLC usual care to provide a context to understand the overall magnitude of effect of EA and BFA for people with chronic musculoskeletal pain. We

seek to use the WLC group to control for the regression to the mean, Hawthorn effect, and natural history of disease in the standard care setting. WLC is also important for aims 2 and 3 to ensure we are investigating the predictors of response to acupuncture rather than predictors of change in the course of natural illnesses/standard care. We decided to provide acupuncture after the primary end point (12 week evaluation) to those in the WLC usual care because in our past experience, patients do not just want to get usual care without the possibility of receiving acupuncture. For patients with moderate to severe pain, we think the ethical implications of providing acupuncture for potential pain reduction outweigh the scientific value of having the patients wait for 24 weeks.

- We decided against sham/placebo controls as we are primarily interested in the overall effects of treatment processes for EA and BFA rather than to study the efficacy of the needling processes. We will also study the comparative effectiveness between EA and BFA. These results will provide actionable information that can change care. Acupuncture is currently being integrated into the DoD and VHA settings, but evidence of the magnitude of the effect is necessary to justify its continued use and clinical expansion.
- We have chosen to use the same EA we used in our pilot study⁴⁵ because 10 treatments of EA over 8 weeks led to significant pain and symptom reduction that persisted and continued to improve for the EA group even 4 weeks after the end of treatment.
- We chose BFA as a comparison because it is currently being implemented in the DoD and VA. Although BFA is a simple and safe form of acupuncture delivery that was developed in the military for soldiers and veterans,^{24,50} research is limited, especially its efficacy in managing chronic pain. As over 1,000 providers will be trained to deliver BFA in the DoD and VHA settings, an understanding of the overall and comparative effects of BFA will further its integration in a manner that is both patient-centered and effective.
- We have selected the BPI as the primary outcome measure because it is one of the most widely used pain instruments with excellent reliability and validity.⁵¹ The measure consists of pain intensity and pain interference domains.
- We chose change in the BPI intensity score between Week 12 and baseline as our primary endpoint because our preliminary data suggests that the effect of EA persisted.⁴⁵
- We chose an SNP genotyping approach because there are known potential mechanisms of acupuncture.³⁹ In addition, we identified a promising association in our R21 study that requires validation in the larger population with chronic musculoskeletal pain. Our approach is conservative, but will confirm our previous finding and result in actionable information that can potentially change clinical practice. Recognizing that other SNPs may predict either EA or BFA, we have carefully selected a list of additional SNPs that are involved in pain modulation or peripheral inflammation to be explored in the context of this trial.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

The PEACE study is a natural extension of the preliminary studies we have conducted in the last several years as summarized in the background section. The overarching long-term goal

is to inform the development of personalized integrative acupuncture for managing chronic pain by demonstrating the effects of two acupuncture techniques on both pain and co-mental health conditions. To accomplish our specific aims, we will conduct a 3-arm, parallel RCT comparing EA against BFA and WLC usual care among 360 people with chronic musculoskeletal pain. Patient volunteers will be randomly assigned to EA/BFA/WLC. We will deliver 10 sessions of acupuncture (EA or BFA) over the course of 10 weeks. For EA, we will use a standardized, semi-fixed protocol previously developed and tested by our group.⁴⁵ BFA is a technique that was developed by Colonel (Ret) Richard C. Niemtzow, MD^{24,25} and is currently being implemented in VA and DOD settings nationwide. Despite the empirical success in the military setting, clinical research evidence for efficacy is limited. Thus, comparing EA and BFA will inform the relative strengths and limitations of these two highly promising acupuncture techniques for chronic pain patients. Individuals in the WLC will receive either EA or BFA based on their personal treatment preference after the initial 12-week usual care waiting period. We will follow subjects in the EA and BFA groups at 12, 16, and 24 weeks from randomization to evaluate the persistence of the effects of acupuncture. The primary end-point will be the average pain intensity score change at Week 12 from Baseline measured via the BPI. Secondary endpoints will include the BPI pain-related interference and physical functions.⁵² We will use the Patient Global Impression of Change⁵³ to capture the patients' perceived clinical importance of improvement with acupuncture for pain. Because our preliminary study suggests that EA will also improve pain-associated comorbidities such as fatigue and psychological distress,⁵⁴ we will use previously validated patient reported outcomes for fatigue,⁵⁵ psychological distress,⁵⁶ PTSD,⁵⁷ and sleep disturbance.⁵⁸ To explore the health economic aspect of acupuncture, medical care costs will be evaluated at baseline and 12 weeks by using medical care resource consumption questions^{59,60} and health insurance direct costs related to chronic pain. To answer Specific Aim 2, we will incorporate the previously validated Acupuncture Expectancy Scale (AES)³⁴ to measure expectancy at Baseline and at key follow up visits. To answer Specific Aim 3, we will collect blood at baseline for DNA analyses.

4.2 Intervention

Participants will receive 10 treatments of acupuncture (EA or BFA) over the course of 10 weeks (+/- 4 days), with a maximum of 2 treatments per week. This level of intensity and duration of treatments is common in clinical practice and has been reported in published literature.^{61,62} In a meta-analysis, Ezzo et al. found that greater than 6 treatments of acupuncture in trial design is associated with positive outcomes.⁶³ This duration and treatment intensity has also been piloted in our study and found to be acceptable and desirable by patients, and it has led to clinical benefit.⁴⁵ Details of the treatment protocols are included in Appendix 1.

Electro-Acupuncture (EA) Procedure

During acupuncture treatments, patients will lie comfortably on a table and will then receive acupuncture. The acupuncturist will prep the skin with 75% alcohol wipe prior to needle insertion, and choose at least 4 local points around the body area with the most pain.

Additionally, the acupuncturist will choose at least 4 distant points to address the patient's baseline constitution. The acupuncturist will be asked to place between 10 and 20 Seirin acupuncture needles (30mm or 40mm and 0.16mm - 0.25mm gauge, Seirin-America Inc., Weymouth, MA). The acupuncture needles will be inserted to appropriate depths depending on the location on the body and body type of the patient.⁶⁴ The acupuncturist will manipulate the needles to achieve the "De Qi" sensation for the patients. "De Qi" is a local sensation of soreness, numbness, or distension that accompanies the insertion and manipulation of needles during acupuncture.⁶⁵ The needles at the four local points for pain will be electrically stimulated at 2 Hz by connecting to a TENS unit. Electro-stimulation of needles is a common procedure in acupuncture clinical practice.^{64,66} Our decision to use electro-stimulation of needles is based on physiological findings that low frequency electro-stimulation of acupuncture points stimulate the brain to release beta-endorphins.^{8,67} Additionally, this type of electric stimulation has been shown to produce substantial effects in trials of acupuncture for osteoarthritis.^{68,69} The acupuncturist will leave the needles in place for approximately 30 minutes with brief manipulation at the beginning and at the end of the treatment. After removing the needles, the acupuncturist will touch the needling points with a sterile cotton tipped applicator to absorb any blood. The acupuncturist will then assist the patient to get up slowly. In our pilot studies, this manualized protocol was found to be well tolerated with clinically important change in pain (greater than 2 point reduction in both pain-intensity and interference).^{45,70}

Battle Field Acupuncture (BFA) Procedure

The delivery of BFA is simple and not dependent on specific pain locations or diagnoses. The practitioner will help the patient to sit comfortably with his or her back well-supported. Each ear will be cleaned with an alcohol pad. The practitioner will place the ASP needle, using the correct technique, in the Cingulate Gyrus point on one ear with proper ear support and have the patient walk for a minute to assess him or her for any onset of dizziness or lightheadedness as an indication of a symptomatic vaso-vagal response. Upon returning from the walk, the practitioner will re-assess the patient's pain level. If the pain is greater than 0-1/10, and the patient is willing, the practitioner will place the Cingulate Gyrus needle in the other ear. The practitioner will repeat this process in the following sequence: Cingulate Gyrus, Thalamus, Omega 2, Point Zero, then Shen Men. For the first few needles, the practitioner will walk with the patient. In the event that the patient feels lightheaded, the practitioner will assist the patient to sit down. The practitioner will stop placing the needles for three reasons: 1) Pain decreased to 1 or 0; 2) patient asks needling to be stopped due to discomfort; or 3) significant vaso-vagal reaction observed. The total duration of BFA delivery is about 10 to 20 minutes depending how many points are used in the procedure.

Wait List Control (WLC) Usual Care Procedure

During the waiting period (12 weeks from randomization) for the patients in the WLC group, the research study assistant (RSA) will make contact with the patients at the same frequency as the acupuncture group with respect to data collection. Subjects in the WLC group continue to receive their standard medical care and pain management as prescribed by their physicians or other health care providers, including analgesic medications. After the 12 week

follow up period, patients in the WLC will receive up to ten treatments of either EA or BFA based on their personal preference as described above. Their outcomes will be tracked for an additional 12 weeks after the waiting period so the total duration of study participation is the same for all three groups.

Fidelity of Delivery of Interventions

All treatments will be delivered by licensed and experienced acupuncturists. All acupuncturists will be trained by Dr. Mao about the specific research protocol and educated on the importance of adherence to protocol methods. They will be observed and evaluated twice a year by an acupuncturist designated by Dr. Mao. If a new acupuncturist joins the study protocol, he/she will be trained by Dr. Mao. We have extensive experience in conducting acupuncture trials to ensure quality of interventions.^{45,46,71}

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Acupuncture Needles:

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

ASP needles are single-use, sterile, 2.5 mm semi-permanent, stainless steel auriculotherapy needles designed to stay in place for 3 to 4 days. ASP needles are FDA approved and commonly used in the Battle Field Acupuncture technique. The needles are purchased and distributed by Lhasa OMS in Weymouth, MA (<http://lhasaoms.com>).

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

The following sets of inclusion and exclusion criteria are based on our own research⁴⁵ and existing literature,^{72,73} informed by pain and primary care physicians and researchers who are familiar with pain management in ambulatory settings. We selected this criteria to ensure that: 1) the study is safe for the research participants; 2) the population is relevant to the eventual dissemination of the information with as wide as possible inclusion criteria; and 3) the population is relatively well-defined so that the change in outcomes among intervention groups can be appropriately measured and detected. No individuals will be excluded on the basis of race, ethnicity, or sex.

6.1 Subject Inclusion Criteria

- English speaking
- Age \geq 18 years or older
- Having musculoskeletal pain, defined as regional (joints, extremities, back, neck) or more generalized (fibromyalgia or chronic widespread pain)
- Having a pain rating of 4 or greater in worst pain on a 0-10 numerical rating scale in the preceding week (Patients with a neuropathic component to their pain that involves the extremities or back will be eligible);

- Having had pain for at least 3 months and at least 15 days with pain in the preceding 30 days;
- A diagnosis of cancer with no restrictions placed on type of cancer, other than that patients with metastatic disease will be excluded. Eligibility criteria are not restricted to MSK confirmed biopsy/diagnosis. Participating institution's testing is sufficient for other study sites.
- Completed active treatment (surgery, chemotherapy, and/or radiotherapy) at least one month prior to study initiation (patients on continued hormone treatment will not be excluded).

6.2 Subject Exclusion Criteria

- Have non-musculoskeletal pain syndromes (headache, facial pain, chest pain, visceral abdominal pain) if these are the sole source of pain, but can be present as co-morbid conditions as long as a patient has a primary musculoskeletal pain condition defined as above.
- Inflammatory arthritis that requires disease modifying drugs (e.g. rheumatoid arthritis)
- Phantom limb pain
- Patients with a history of metastatic cancer who are not currently NED
- Have a pending pain-related VA or social security or worker's comp disability claim by self-report
- Have an implanted electronically charged medical device

7.0 RECRUITMENT PLAN

Recruitment Plan (with Limited waiver of Authorization)

No restrictions are placed on cancer type. Patients with metastatic disease will be excluded. All other patients with a diagnosis of cancer, who completed active treatment, have chronic musculoskeletal pain, and meet the remaining eligibility criteria will be eligible for participation in the study. Our primary recruitment approach will be via sending recruitment letters to potential participants. Potential patients who meet basic eligibility criteria will be identified via querying of Dataline at MSK and sent a recruitment letter (See Appendix 5). The recruitment letter introduces the study to potential participants and states that we are conducting a study to compare the effectiveness of two acupuncture treatments for individuals diagnosed with musculoskeletal pain and if interested in learning more about the study, the patient should contact the research study assistant. The letter provides patients with an opt-out phone number and study e-mail address to contact if they do not wish to participate or be contacted further. We will also be identifying patients that meet basic eligibility criteria and have reports of pain on the MSK Engage symptom questionnaire through a dataline query. We have successfully used this recruitment method for similar studies.

In addition to sending recruitment letters, potential participants also can be identified and referred to the study RSA for accrual and consent by protocol investigators. The study PI and other members of the research team will reach out to colleagues about the study and present at Service meetings, including Breast Medicine, GI, Prostate, Head and Neck Services and

Psychiatry and Behavioral Sciences to introduce the study. Colleagues in Survivorship will be informed about the study, and recruitment materials will be provided to them. In addition to Integrative Medicine physicians, other Integrative Medicine therapists can also refer patients to the study. Study investigators and interested colleagues will be provided with study flyers and/or rack cards to provide to potential participants (See Appendix 6 and 7 for a study flyer and rack card). Potential participants may also be self-referred or referred by a clinician from other hospitals. Information about the protocol will appear in lay language on MSK's web site and on clinicaltrials.gov. Printed material will be posted in clinic areas where we have successfully posted study materials for other Integrative Medicine studies before (e.g., the Breast and Imaging Center, the Main Hospital, Kimmel, and the Rockefeller Outpatient Pavilion). Permission from the clinic sites will be obtained before posting in any location. Materials will also be distributed to potential referral sources who we have worked with on other research studies. All study recruitment materials will be submitted to, and approved, by the Institutional Review Board. We have used these recruitment strategies successfully to recruit participants to similar studies.

Initial contact with potential participants typically will be made by a member of the study team. The recruitment process presents no more than minimal risk to patient privacy, and minimal PHI will be maintained on screening logs. For these reasons, we seek a (partial) limited waiver of authorization to: (1) review MSK patient medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) converse with patients regarding possible enrollment; (3) handle PHI contained in those records and provided by potential subjects; and (4) maintain minimal PHI information in a screening log of patients approached.

In order to encourage adherence to the study procedures and to compensate for participants' time and travel during the study, all study participants will be compensated \$30 at each of the following visits: Baseline, Week 4, Week 10, Week 12, Week 16, and Week 24 for a total of \$180. Individuals who withdraw from the study will be compensated for the visits they have completed.

8.0 PRETREATMENT EVALUATION

8.1. Initial Screening

All potential participants will undergo an initial screening with an RSA in person or over the telephone. At this initial contact, research staff will explain the study goals and procedures and the research study assistant will ensure that participants meet basic eligibility criteria.

8.2. Screen Baseline Visit

Interested and potentially eligible patients will be seen by a clinician (physician, nurses/nurse practitioner, physician assistant, or study acupuncturist) for a screening visit to confirm eligibility, including a diagnostic interview for chronic pain, and a self-reported questionnaire about the patient's pain experience (Appendix 2). Appendix 2 may be completed online using REDCap (Research Electronic Data Capture) or over the phone with a member of the research staff within two weeks of enrollment. If deemed eligible, study staff will explain the study and review the written informed consent with the patient. After patients sign the

informed consent, they will complete a set of baseline questionnaires and a blood draw. Please refer to Table 2 below for questionnaires collected at baseline. After the baseline visit, participants will be provided with the initial installment (\$30) of the honorarium (\$180 total for 6 visits) for study participation.

Table 2: Data collection schema						
	Active Intervention¹			Follow Up¹		
Weeks	0	4	10	12	16	24
Pain						
Brief Pain Inventory (Pain)	X	X	X	X	X	X
Patient Global Impression of Change (Impression of Change in Pain)		X	X	X	X	X
Pain Catastrophizing Scale (Pain Coping)	X	X	X	X	X	X
Health Economics of Chronic Pain (Pain Medical Care Costs) ²	X			X		
Physical Functions						
WOMAC (Lower Extremity Function)	X	X	X	X	X	X
Quick DASH (Upper Extremity Function)	X	X	X	X	X	X
Co-symptoms and Quality of Life						
Brief Fatigue Inventory (Fatigue)	X	X	X	X	X	X
Hospital Anxiety and Depression Scale (Psychological Distress and Wellbeing)	X	X	X	X	X	X
PTSD – Checklist (Psychological Distress and Wellbeing)	X	X	X	X	X	X
Pittsburgh Sleep Quality Index (Sleep)	X	X	X	X	X	X
PROMIS-10 (Overall Health)	X	X	X	X	X	X
Predictive variables						
Acupuncture Expectancy Scale (Expectations of Acupuncture)	X	X	X			
Optional Blood Draw/ Saliva Sample	X ³			X		X

Co-variates						
Demographics and clinical	X					
Pain Medication Diary	X	X	X	X	X	X
Abbreviations: WOMAC: Western Ontario and McMaster Universities Osteoarthritis index; Quick DASH: quick-Disability Arm / Shoulder / Hand						
1. (+/-) 7 day window						
2. The health economic questions will be completed by enrolled patient 60 and on.						
3. Baseline blood draw will be collected prior to starting treatment for patients in Groups 1 and 2. Saliva is collected at baseline only.						

Blood Draw: Blood samples will be collected at baseline for DNA analyses to measure levels of the biomarker panel (e.g., COMT, TCL1A, TNF, IL-6, IL-1 β , and ADORA1). In preparation of a future grant submission, blood will also be collected at baseline, 12 weeks and 24 weeks to be banked for future correlative studies related to the intervention should we identify any literature during the conduct of the trial demonstrating that specific biomarkers are associated with symptoms or treatment responses. Blood samples will be collected and stored at -80°C until ready for processing (See Appendix 4 for details). If there is anything left over, it will be banked for future use under 06-107. If the subject declines to give blood (5% in our prior experience), we will offer a saliva collection kit as an alternative to blood collection, which will only be done at baseline.

8.3. Brief Laboratory Methods for DNA Analyses

Whole blood (4mL) will be collected in an EDTA tube and stored at -80°C until ready for processing. If the subject declines to give blood (5% in our prior experience), we will offer a saliva collection kit as an alternative to blood collection. The Integrated Genomics Operation core facility at MSK will perform all DNA extraction and genotyping for the proposed Specific Aim 3 (selection of SNPs are in Table 3 below). DNA will be extracted from the baseline whole blood using Qiagen QIAamp DNA Blood Kit as described by manufacturer's directions. Extracted DNA will then be quantified and qualified using respectively Spectramax Quant-it reader (Molecular Devices) and a Fragment Analyzer (Advanced Analytics) We will conduct genotyping using Applied Biosystems Inc. (ABI) pre-designed genotyping assays and custom designed genotyping assays.

Table 3. SNPs to be used in genotyping

Gene	Functional Class	rs number	Minor Allele Frequency (source 1000 Genomes)	Reference
COMT	Vall158Met Missense	rs4680	A=0.390/850	Associated with response to placebo acupuncture. Hall et al. PLoSOne 2012.
	1-98 A>G Promoter Region	rs6269	G=0.372/810	All SNPs associated with pain and affective pain impact; Shi et al. Qual Life Res. 2010; 19:1407.
	H62H Synonymous	rs4633	T=0.390/850	
	C>G Intragenic Region	rs7290221	G=0.495/1079	More central nervous system side effects of opioids; Shi et al. Qual Life Res. 2010; 19:1407.
TCLIA	A>G Intergenic Region	rs7158782	G=0.331/720	Associated with musculoskeletal pain; Ingle. Br Ca Res. 2010, 12(Suppl 4):S17.
	A>G Intergenic Region	rs2369049	G=0.285/620	
	A>G Intergenic Region	rs7159713	G=0.331/722	
TNF	-308 G>A Promoter Region	rs1800629	A=0.096/208	Worse pain, which is persistent in Lung cancer; Shi et al. Qual Life Res. 2010; 19:1407. Implicated in breast cancer related fatigue; Bower et al. J Clin Oncol. 2013; 31(13): 1656.
IL6	-174 C>G Promoter Region	rs1800795	C=0.1850/402	Implicated fatigue; Bower et al. J Clin Oncol. 2013; 31(13): 1656.
	-572 G>C Promoter Region	rs1800796	C=0.290/631	
	-597 G>A Promoter Region	rs1800797	A=0.182/396	
IL-1 β	-118 C>T Promoter Region	rs1143627	G=0.480/1046	Associated with pain severity and duration in pancreas cancer; Reyes-Gibby et al. J Pain Symptom Manage. 2009; 38: 894.
	-511 T>C Promoter Region	rs16944	A=0.465/1013	Implicated fatigue; Bower et al. J Clin Oncol. 2013; 31(13): 1656.
ADORA1	G>A Intragenic Region	rs12123037	A=0.219/476	Adenosine A1 receptors mediate local anti-nociceptive effects of acupuncture and may prolong the clinical benefit of acupuncture; Goldman et al. Nat Neurosci. 2010; 13(7):883.
	813 delT 3'Untranslated Region	rs11315020	T=0.094/204	

Grey highlighted and bolded SNPs are for confirmatory analyses. The other SNPs are for exploratory analyses.

8.4. Covariates

We will obtain age, gender, ethnicity, and other relevant medical and background information from standard study questionnaires. These variables will be entered into analyses as covariates as necessary. We will also obtain analgesic medication prescriptions by having participants bring in their medication bottles. Additionally, patients will be asked to complete 1 week of daily pain medication diaries at baseline (Week 0), one month after starting treatment (Week 4), at the end of treatment (Week 10), and at 3 time points post-treatment (Weeks 12, 16 and 24) to calculate weekly average pain medication usage throughout the study time period. IRB deviations will only be reported for these pain diaries if they are not returned, or are returned with 5 or more days missing.

8.5. Masking

For this trial, the statisticians are blinded to treatment assignment.

9.0 TREATMENT/INTERVENTION PLAN

Subjects will receive acupuncture treatments at MSK's Bendheim Integrative Medicine Center (1429 First Avenue at 74th Street) and/or at the Breast and Imaging Center (300 East 66th Street at 2nd Avenue) and/or MSK Westchester (500 Westchester Avenue) and/or MSK Commack (650 Commack Road) and/or MSK Basking Ridge (136 Mountain View Blvd), and/or MSK Monmouth (480 Red Hill Road), and/or Brooklyn Infusion Center (557 Atlantic Ave). Each participant will receive 10 treatments of acupuncture (EA or BFA) over the course of 10 weeks (with a maximum of 2 treatments per week). All Integrative Medicine Service acupuncturists are licensed, credentialed employees of MSK.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

The study schema and study schedule were presented in Section 1.0, Figure 1, and Section 8.0, Table 2, respectively. The following questionnaires will be collected according to the study schedule table (See Appendix 3). The average time to complete the PROs is approximately 30 to 40 minutes, which was judged to be acceptable to patients in our prior study.⁴⁵ To minimize missing data, RSAs will check all surveys right after completion. For subjects who miss a study visit, RSAs will mail survey instruments and call/email patients to complete them. Using this approach, our prior R21 only had 6% loss-to-follow-up during the intervention period and a total of 12% loss-to-follow-up by Week 12. The data collection schema can be seen in Section 8.0, Table 2.

(a) Primary Outcome: Brief Pain Inventory (BPI): The BPI will be used to quantify pain intensity and pain interference. The 4 pain intensity questions have response choices of 0 “no pain” to 10 “pain as bad as you can imagine” and its score is the arithmetic mean of the four pain severity items. This pain intensity score will be used as the **primary outcome**. The 7 pain interference questions have response choices of 0 “does not interfere” to 10 “completely interferes”, and the average of the 7 pain interference scores will be used as the **secondary outcome**. The psychometrics of the BPI is well-established with Cronbach’s alpha ranging from 0.77 to 0.91. The BPI is one of the most widely used instruments to measure pain in patients and has been demonstrated to be a reliable, valid, and responsive measure.⁵¹

(b) Other Validated Patient-Reported Outcomes (PROs):

Pain Catastrophizing Scale (PCS) is 13-item validated scale to measure the negative cognitive-emotional response (i.e., catastrophizing) to pain.⁷⁴ Patients are given a list of 13 statements describing different thoughts and feelings that may be associated with pain. They are asked the degree to which they experience each thought or feeling when they are in pain on a scale ranging from “0-not at all”, “1-to a slight degree”, “2-to a moderate degree”, “3-to a great degree” to “4-all the time”. The PCS yields a total score and three subscales scores assessing rumination, magnification, and helplessness.

Patients’ Global Impression of Change is a one item survey that will be used to define a clinically important change from the patient’s perspective.⁵³ Patients 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” and “very much improved” will be classified as responders.

Health Economics of Chronic Pain: Medical care costs associated with chronic pain will be measured by assessing the monetary value of the patient’s resource consumption during the 12-week period after randomization. This information will be collected from enrolled patient 60 and on. Information on resource use will be collected by medical care cost questions^{59,60} and by using health insurance direct costs related to physician office visits, hospital stays, prescription drugs, acupuncture sessions, etc, and indirect costs caused by patients’ work incapacity. For this study \$100 will be used as the cost of each acupuncture session, and

patients will receive 10 sessions for a total of \$1,000. Effectiveness will be measured using quality of life data collected from the PROMIS Global Health validated instrument and converted into EuroQoL (EQ-5D) index scores.

Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Physical Function subscale will be used to measure functional limitations in the lower extremity. The physical function subscale has 17 questions, which have excellent face, content, and construct validity. For each question, patients choose the degree of functional difficulty experienced ranging from “0 -none,” “1-mild,” “2-moderate,” “3-severe,” to “4-extreme”. To score, add up the numbers related to the response for each question, the total score ranges from 0 to 96; the higher the score, the more functional difficulty the patient is experiencing. The score has been shown to be reliable and responsive to therapeutic interventions.⁵² It has been used in multiple acupuncture intervention trials in patients with osteoarthritis of the knee.^{69,75}

Quick-Disability Arm / Shoulder / Hand (quick-DASH), an 11-item questionnaire, will be used to measure disability related to arm, shoulder, and hand symptoms. To calculate a *Quick DASH* score at least 10 of the 11 items must be completed. Each item has 5 response options and, from the item scores, scale scores are calculated, ranging from 0 (no disability) to 100 (most severe disability).⁷⁶ We recently validated this instrument in patients with musculoskeletal pain with excellent internal consistency, test-retest reliability, and construct validity.⁷⁷

Brief Fatigue Inventory (BFI) will be used to determine the effect of treatments on fatigue. This 9-item instrument was designed to assess one construct of fatigue severity in cancer and non-cancer populations. 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 assess the amount that fatigue has interfered with different aspects of the patient's life during the past 24 hours. The interference items are measured on a 0–10 scale, with 0 being “does not interfere” and 10 being “completely interferes.”⁵⁵ A composite fatigue severity score can be found by averaging the score obtained on each test item. The score of the scale was found to be reliable and valid in multiple languages and diverse populations.^{55,78}

Pittsburgh Sleep Quality Index (PSQI) will be used to determine the effect of acupuncture on sleep. This 19-item instrument produces a global sleep quality score and 7 specific component scores: quality, latency, duration, disturbance, habitual sleep efficiency, use of sleeping medications, and daytime dysfunction. These self-rated questions are scored on a 0 to 3 scale over a period of one month. The sum of these seven components yield one global score that will be used as the patient-reported outcome for sleep disturbance. Global scores range from 0-21 and reflect the number and severity of sleep problems. Global scores of 5 or greater indicate poor sleep quality and high sleep disturbance.⁵⁸ The psychometric properties of the PSQI have been supported widely in a variety of populations.⁷⁹

Hospital Anxiety and Depression Scale (HADS) will be used to explore the effect of treatments on psychological distress. HADS is a 14-item scale with 7 items measuring depression and 7 items measuring anxiety. 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. Established cutoffs are: 0–7 not significant; 8–10 subclinical; and 11-21 clinically significant depression/anxiety.⁵⁶ The scale uses varying response items. Factor analysis showed two distinct but correlated factors of anxiety and depression.⁸⁰ The score of the scale has been shown to be both reliable and valid.⁸¹

PTSD Check List – Civilian (PCL-C) is a 17-item continuous severity measure that corresponds to the 17 Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria for PTSD. Civilians indicate the extent to which they have been bothered by each symptom in the past month using a 5-point scale, from 1 “Not at all” to 5 “Extremely”. To score, add up the numbers related to the response for each question, the total score ranges from 17 to 85; the higher the score, the more stress the patient is experiencing. For civilian primary care settings, the suggested cut-point score for PTSD ranges from 30 to 35. It has demonstrated excellent reliability and validity.⁵⁷

PROMIS Global Health Measure is a brief instrument composed of 10 items that demonstrates adequate reliability and validity^{82,83} as a measure of health related QOL in general and clinical populations.^{84,85} Patients are asked to respond to questions 1-8 and 10 on a scale of 1-5. Question 9 is on a 0-10 scale (average pain rating). The measure results in two global physical and mental health scores that will be used as secondary outcomes to evaluate the effect of acupuncture on QOL.⁸²

(c) Acupuncture Expectancy Scale (AES): This 4-item instrument was developed by Mao et al. (PI) and has demonstrated reliability (Cronbach’s α of 0.82) and validity by positive correlation to patient self-reported efficacy and satisfaction.³³ For each question, subjects are asked to rate from 1 to 5 on a five-point Likert scale, with 1 indicating “Not at all agree” and 5 indicating “Completely agree” with the expected improvement as result of acupuncture. The score ranges from 4 to 20, with higher scores indicating greater expectancy. We validated this measurement in a second study and found the scale to be reliable and valid with sensitivity to change over time in response to acupuncture treatment.³⁴ In our R21 study, we found that the expectancy score was stable over time in the WLC group. Baseline expectancy predicted treatment outcomes differently for EA versus SA.⁴⁷

11.0 TOXICITIES/SIDE EFFECTS

Potential Risks: Patients will be monitored for side effects at each visit. Adverse effects related to the administration of acupuncture will be collected each week before and after each treatment by the acupuncturist/therapist or research study assistant.

Although the risks associated with participation in the proposed study are minimal, all potential risks that might occur as a result of participation will be detailed in the informed consent, and will be fully discussed with each subject prior to enrollment. It will be further explained that while some risks are not predictable, every precaution consistent with the best

medical practice to protect the health and safety of subjects will be taken. We will document all adverse events and report any related serious adverse events promptly to the IRB.

Risk of Acupuncture: The risks associated with electro-acupuncture (EA) and Battle Field Acupuncture (BFA) are minor. The most common side effects are mild pain on insertion of the needle. There is a possibility of a small amount of bleeding or bruising. Sometimes, pain in joints and muscles may get worse with acupuncture shortly after treatment. Since, on rare occasion, chest needling can lead to a pneumothorax, no needles will be placed in the chest region for the proposed study. Licensed acupuncturists who have at least five years of clinical experience will administer the acupuncture. We will make every effort to ensure the safety and comfort of the research subjects, including wiping the needling site with alcohol before the procedure and wiping the needling site with sterile cotton tipped applicator. Acupuncturists will record any adverse events during each clinical visit. We will promptly report any related SAEs to the IRB following institutional guidelines.

Risk of Blood Draw: A small number of people find blood draws very uncomfortable. Risks and discomforts involved in having blood drawn are pain and bruising where the needle enters the skin and the possibility of infection or fainting. Standard of care procedures will be followed to minimize these risks.

Confidentiality Risks: Information about study subjects will be kept confidential and managed according to the requirements of the Health Information Portability and Accountability Act (HIPAA). The paper data files will be kept in locked cabinets and electronic files will be kept in password-protected personal computers. All identifiers will be stripped after completion of the trial. The data will be disclosed to the IRB upon request for data safety monitoring. Secondary use of the data will not be attempted after the study ends without subsequent IRB approval.

Risks Associated with Genetic Testing: The use of a subject's sample for genetic testing raises special issues of confidentiality, because it is conceivable that information about his/her genes could be used against him/her if the wrong people obtain this information. For example, an insurance company could try denying benefits or an employer could try denying employment if it was known that s/he carried certain genes. In addition, if information that a subject carried certain genes became known to him/her or to his/her family members, it may cause him/her to feel upset or stigmatized. To reduce this possibility, the following specific measures will be taken to protect each subject's confidentiality:

- In the laboratory, each subject's blood samples and genetics sample will be labeled with a number only. The subject's name or any other identifying information will not be attached to the samples in the research laboratory.
- The genetic testing of each subject's sample is for research purposes only. No results of genetic testing from this study will appear in a subject's medical record.
- Genetic test results will not be made available to subjects, their doctors, other clinicians or any other clinical staff. If a subject wants to know more about his/her risks for diseases in which genes play a role, we recommend that s/he speaks with a genetic counselor. We will provide subjects with names of genetic counselors in the area if they wish to speak with one.

- To protect subjects' confidentiality as much as possible, no computer records will be created that could be used to identify their genetic or medical information individually. Thus, even if a "hacker" breaks into the laboratory computer system, there will be no information stored there that can identify a subject as an individual.

Risk of psychological distress: It is possible that subjects may be upset to find out that they are randomized to their non-preferred arm of the study. With appropriate consent and the debriefing process, such risks are minimized. Subjects will be informed that they are participating in an experimental study to determine the effectiveness of acupuncture for chronic pain. They have the chance to be randomized to either electro-acupuncture, battle field acupuncture, or the waitlist control group. Subjects in the waitlist control group may choose to have 10 treatments of either electro-acupuncture or battle field acupuncture at 12 weeks after randomization. At the end of the study, subjects will be offered the opportunity to discuss the findings with the PI. In addition, some of the questions in the questionnaire may elicit distress among subjects. At baseline examination, patients will be screened for any elevated anxiety and depression or suicidal ideation/plan. If the subject demonstrates clinically significant distress, s/he will be referred to the appropriate clinical and psychosocial services if they are a patient of MSK. Dr. Mao, the PI, has extensive clinical experience in treating physical and psychological distress. During the study period, if the research staff identifies any patients who are psychologically distressed they will notify Drs. Mao or Bao immediately to facilitate appropriate evaluation and treatment.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Our primary outcome measure is the Brief Pain Inventory (BPI), which will be measured at baseline and 4, 10, 12, 16 and 24 weeks post-treatment. Our primary hypothesis is that both EA and BFA will produce greater reductions in average pain intensity as compared to WLC usual care at 12 weeks after randomization. Our secondary hypotheses are that EA and BFA will produce greater improvements in physical functions, co-morbid symptoms (fatigue, sleep disturbance, anxiety/depression, PTSD), and QOL at 12 weeks after randomization and that these effects will be durable over the 24 week follow-up period.

The purpose of Specific Aim 2 is to determine the interaction between outcome expectancy and type of needling delivery/stimulation (EA vs. BFA) on pain reduction. We hypothesize that EA will produce clinically important percent pain-intensity reduction at 12 weeks after randomization regardless of baseline outcome expectancy whereas BFA's pain reduction will be more dependent on baseline outcome expectancy. To answer Specific Aim 2, we will use the Acupuncture Expectancy Scale (AES) to measure expectancy at baseline and at key follow up visits (weeks 4 and 10).

For Specific Aim 3, we will evaluate the association between genetic polymorphisms and patients' responses to acupuncture. Our primary hypothesis is that participants with either the AA alleles in COMT (rs4680) or GG/AG alleles in TCL1A (rs2369049) will be more likely than those without the genetic combination to respond to acupuncture treatments

(EA or BFA). Our Exploratory Hypothesis is that other genetic variants (e.g., TNF, IL-6, IL-1B, and ADORA1) in pain processing and inflammation may predict response to EA, BFA, or both. To answer Specific Aim 3, we will collect blood at baseline for DNA analyses.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Any subjects experiencing a serious adverse event (SAE) felt to be related to the study intervention will be removed from receiving further acupuncture treatment. Patients also will be removed from receiving further acupuncture treatment if they miss two consecutive acupuncture visits without notification of study staff, or if discontinuation from the treatment is deemed by the principal investigator to be in their best interest. Subjects discontinued from the treatment aspects of the clinical trial will be scheduled for the 12 and 24 week evaluations and given appropriate treatment referrals. For the 12 and 24 week visits, subjects will receive all assessments that were scheduled for these study visits. Any subject withdrawing their consent to participate in the study or their authorization to use their protected health information will be withdrawn from the study.

Subjects will be informed during the consent discussion that treatment may be discontinued due to:

- 1) Intolerable side effects (side effects felt by the patient, acupuncturist, or physician to be of greater severity than the potential benefit from treatment);
- 2) Failure to attend 2 consecutive acupuncture visits without notification of study staff.

If patients fail to attend sessions with notification, every effort will be made to reschedule the patient such that they can receive the maximum number of treatments.

Reasons for subject discontinuation from the clinical trial will be documented on the Study Termination Form, along with any referrals that are made. We will make every effort to continue to collect data on every subject for the entire study duration regardless of whether or not the subject continues to adhere to the study interventions, assuming the subject has not withdrawn his/her authorization to obtain such information.

14.0 BIOSTATISTICS

14.1. Data Analyses

We will perform analysis according to the intention-to-treat (ITT) principle (i.e. subjects will be analyzed according to the treatment group to which they were randomly allocated).

Specific Aim 1: To compare the effects of acupuncture on patient-reported pain (primary outcome), physical functions, and co-morbid symptoms (fatigue, sleep disturbance, anxiety, depression, and PTSD) at week 12, we will use linear mixed models (LMMs)⁸⁶ to test differences between treatment arms in score changes from baseline to Week 12, with randomization strata as covariates. Specifically, in addition to the randomization strata, the models will adjust for baseline score⁸⁶ and will contain assessment time, treatment

arm, and the time-by-treatment arm interaction. The interaction term will be used to test whether the treatment arms significantly differ in their changes from baseline. The change in BPI pain intensity at week 12 from randomization is the primary endpoint for this trial. We will first separately compare BFA to control and EA to control. If at least one acupuncture group is significantly superior to control at significance threshold $p < 0.025$ (to maintain overall Type 1 error at 5% for the two tests), we will compare BFA to EA using a non-inferiority approach, calculating a one-sided, 95% confidence interval. This testing strategy is considered a “gate-keeping” approach⁸⁷ to managing multiple statistical comparisons, and it maintains the overall Type 1 error level at 5% for testing the primary endpoint of the trial.

To determine the durability of treatment effect, we will first model the change between week 12 and week 24 using LMMs in the BFA and EA group separately. To determine whether there are differences between BFA and EA in the durability of their treatment effects, we will use LMMs containing the randomization strata, assessment time, and treatment arm, , where time zero is week 12. For secondary outcomes, we will use similar analytical strategies for physical functions, co-morbid symptoms (fatigue, sleep disturbance, anxiety/depression, PTSD), and QOL. Additionally, we will use the weekly pain medication diaries to calculate average pain medication usage across the study time period for each study participant to determine if acupuncture decreased the use of pain medication.

The BPI average pain intensity score is the mean of 4 items, one of which asks respondents to rate their pain at its LEAST in the past 24 hours. Some pain researchers have argued to use the BPI Worst Pain item or the Average Pain item as a more appropriate end point for pain clinical trials; as such, we will perform secondary analyses to aid the interpretation of our findings. Furthermore, to enhance clinical interpretation of our results, we will use 30% or greater reduction in pain intensity as definition for responders (ref. Farrar paper)⁸⁸, and present the proportion of responders in each arm at week 12 (primary end point), and week 26.

Specific Aim 2: To determine the interaction between outcome expectancy and type of needling delivery/stimulation (EA vs. BFA) on pain reduction, we will define response to acupuncture therapy as a continuous outcome measured as percent change of pain intensity score of the BPI and calculated by $(BPI[wk0] - BPI[wk12])/BPI[wk0]$. Similar to our approach in our previous study,⁴⁷ we will then build a multiple linear regression model with percent reduction in BPI severity as the dependent variable, and baseline expectancy and treatment group (EA or SA) as independent variables, including the expectancy and treatment group interaction term. The regression coefficient for the interaction term represents the between-group difference of percent reduction in BPI for one unit change in the expectancy score.

Specific Aim 3: To evaluate the association between genetic polymorphisms in COMT and TCL1A genes and patients’ responses to acupuncture. We hypothesize that those

participants with either AA in COMT (rs4680) or GG/AG in TCL1A (rs2369049) will be more likely than those without the genetic combination to respond to acupuncture treatments (EA or BFA). To ensure our findings can result in actionable information to guide clinical care, we will calculate percent pain intensity reduction between Week 12 and Baseline for each patient, and we will define a binary variable for clinical response to acupuncture as 30% pain reduction between Week 12 and baseline. This binary response variable is consistent with that established by Farrar et al. to be a clinically important change in pain trials.⁸⁸ We will perform rigorous quality control for the genotype data and will exclude genotypes that are missing for >15% subjects and subjects with >15% missing SNPs from subsequent analyses. We will tabulate genotype frequencies and perform tests of Hardy-Weinberg Equilibrium (HWE) separately for each race/ethnicity subgroup. To test our primary hypothesis that polymorphisms in COMT and TCL1A are associated with acupuncture response, we will develop multivariable linear regression models with the genotype for each SNP and treatment indicator (EA vs BFA) included as independent variables. A significant association will be claimed if the p-value for the genotype variable is less than 0.025 (since we are testing two SNPs). We will then use the “case-only” approach⁸⁸ to perform logistic regression with binary response as the independent variable and genotype as the dependent variable. Such “case-only” analysis is the most powerful analysis for gene-treatment interactions with a binary dependent variable.⁸⁹ Recognizing that other genetic variants (e.g., TNF, IL-6, IL-1 β , and ADORA1) could influence acupuncture outcomes, we included additional SNPs as listed in Table 3 above for exploratory analyses in a similar way as our primary SNPs. In addition to assessing associations with binary pain response, we will also explore associations with changes in the raw scores and percent change. For SNPs that are significantly associated and not in strong linkage disequilibrium, we will examine if they interact with each other in association with response to acupuncture. We will further examine gene-treatment interactions in race/ethnicity subgroups. We will also explore whether genes identified in this aim will interact with expectancy in predicting outcomes. We will code each genotype as the count of minor alleles in all association testing.

14.2. Sample Size

Aim 1: We plan to enroll and randomize 360 participants (2:2:1) to EA, BFA, and WLC groups. For our sample size/power considerations for comparisons between EA vs. WLC and BFA vs. WLC, we calculated the smallest standardized effect size (aka, Cohen’s d) we will be able to detect with 80% power, given our sample sizes of 144 in each of the acupuncture arms and 72 in WLC. To estimate this smallest detectable effect size, we used the methods of Lu, Luo, & Chen (2008)⁹⁰, which describes sample size calculations for a class of analyses called the “mixed model for repeated measures” (MMRM) in randomized clinical trials with participant attrition. Our LMM analyses fall under this MMRM class of analyses. Using the “power.mmrn” function from the R package “longpower”, we applied the formulas in Lu et al. (2008)⁹⁰ to our study design and assumptions to derive the smallest detectable effect size for the coefficient of the time-by-arm interaction term in our LMM (see Section 14.1), which we transformed to represent the standardized mean difference (aka, Cohen’s d) of the changes in pain intensity from baseline between two arms at 12 weeks post-randomization.

Assuming a 20% attrition rate (higher than in our prior trial) across all arms by week 12, an α of 2.5%, a correlation between baseline and post-treatment assessments of 0.5, and power of 80%, we will be able to detect an effect size of 0.48 or greater between either EA vs. WLC or BFA vs. WLC. This is a moderate effect size which is less than that found in our prior pilot trial (effect size of 0.76) and that detected by the meta-analysis conducted by Vickers et al (0.5 between acupuncture and standard care)²⁰. Thus, our trial is adequately powered to detect such as difference.

As part of our gatekeeping multiple testing procedure, we split our overall type I error rate of 5% evenly between the test of EA vs. WLC and the test of BFA vs. WLC. If neither, or only one of, EA or BFA is better than WLC at the $p < 0.025$ threshold, then there is no need for us to evaluate whether BFA is non-inferior to EA. On the other hand, if both EA and BFA have significant improvements in pain intensity compared to WLC at the $p < 0.025$ threshold, then we will proceed to evaluate whether BFA is non-inferior to EA. In this gatekeeping scenario, the alphas from both of the comparisons with WLC will propagate to our non-inferiority comparison and our overall type I error rate for testing our primary endpoint will be preserved at 5%. Given our sample size, we will have 80% power to find BFA non-inferior to EA with respect to change in BPI pain intensity within a margin of .33 change-score standard deviations (SDs), assuming a one-sided significance threshold of $p < 0.05$. We expect this SD to be between 2-3, so this margin translates to between a 0.67 and 1 point difference in BPI pain intensity reduction. If we are able to demonstrate this, the interpretation would be that BFA is as good as EA with the caveat that we cannot exclude the possibility that EA is slightly better but not to the degree of clinical importance.

We do not plan to adjust for multiple testing across our analyses of our secondary endpoints (e.g., physical function, fatigue, sleep disturbance, anxiety, depression, and PTSD). Our view is that strict control of alpha is necessary and appropriate for studies of novel agents, where decisions on licensing need to be made by consistent criteria. In the case of intervention which is already widely available and used for chronic pain, we believe that general scientific judgment for interpretation of p values is superior to formal adjustment. We will interpret the data incorporating the effect sizes with 95% confidence intervals among comparisons in addition to the p-values.

Aim 2:

This aim hypothesizes that there is a significant interaction between treatment and baseline AES on percent pain intensity reduction. Our preliminary data demonstrates that the regression coefficient for the interaction term between treatment and AES is 8.31 (standard error =4.21) using percent change in BPI-severity as the dependent variable in a linear regression model including treatment, baseline AES, and their interaction. Using a conservative estimate of correlation (0.2) between the interaction term and the dependent variable, we need a total of 191 subjects to detect this observed interaction effect with 80% power. Thus our proposed sample size (288 subjects in both EA and BFA groups) is sufficient to detect this observed interaction effect.

Aim 3: We provide power calculation to compare response to acupuncture in carriers of AA in rs4680 or GG/AG in rs2369049 versus non-carriers in the EA group. In the preliminary study, 47.2% of 38 patients were carriers; the response rates were 45% in non-carriers and ~78% in carriers. Therefore, assuming 45% carrier rate, there will be 52 carriers (~45% of 116 patients) and 64 non-carriers. Assuming a 45% response rate in non-carriers as in the preliminary study, we will have at least 90% power at 5% significance level to detect at least 30% difference in response rates between 52 carriers and 64 non-carriers. Similar power calculation applies to comparison of response to acupuncture in carriers and non-carriers in the BFA group. These analyses are confirmatory rather than exploratory.

We will not have adequate power to conduct comparisons in the WLC group since there are only 58 patients. Nonetheless, we will obtain descriptive statistics within this group. With 45% carrier rate, we will have 26 carriers and 32 non-carriers. We can estimate the response rate in 26 carriers to within +/- 19% standard deviation, and estimate the response rate in 32 non-carriers to within +/- 17% standard deviation.

We will not have adequate power to conduct comparisons of response rates in carriers (or non-carriers) receiving EA or BFA versus carriers receiving WLC due to the limited number of carriers receiving WLC. Nonetheless, we will pursue exploratory comparisons. With 26 carriers receiving WLC and 52 carriers receiving EA (or BFA) and assuming the WLC group to have a 45% response rate and the EA (or BFA) group to have at least 80% response rate, we will have at least 80% power at 5% significance level to detect the difference of at least 35% between these response rates. Similar power calculation applies to an exploratory comparison of response rates in non-carriers.

14.3. Missing Data

As the only certain way to avoid biases from missing data is to collect complete data,⁹¹ our first line of defense will be to minimize the occurrence of missing observations by using a well-piloted clinical trial design and protocol and by using well-trained research staff and an acceptable subject burden.⁹² Our prior trial had only 12% missing data.⁴⁵ We will ask those who voluntarily withdraw from the trial to continue to provide data and reimburse them for completing the evaluation. Lastly, for those who voluntarily withdraw from the study, we will record their reasons for withdrawing. Because missing data is inevitable in a prospective study like this, our second line of defense is to apply data analysis strategies that are as robust as possible to data losses. We will first explore whether missingness is associated with observed variables (particularly randomization arm and the baseline outcome measures) by comparing patients with complete and incomplete data. Of note, the LMMs described above validly include patients with incomplete data under the missing at random assumption. However, our exploration of the data may deem the missing at random assumption to be inappropriate. In this case, we will conduct sensitivity analyses using multiple imputation as well as consider pattern mixture models to help us deal with these issues.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2 Randomization

Patients will be randomized using the Clinical Research Database (CRDB). Randomization will be 2:2:1 (EA:BFA:WLC) using randomly permuted blocks of random length stratified by accrual site (main campus vs. each regional site). Because patients who use opioid medications may have different responses to treatment, we will also stratify on whether a participant is on opioids or not. CRDB is a password protected database ensuring full allocation concealment. Information on group assignments will be communicated to the acupuncturists and RSAs who schedule treatment and follow up visits. The study statisticians will remain blinded. We will accomplish the randomization in two steps. First, the RSA will inform the subject whether s/he is randomized to an acupuncture or WLC group after the baseline visit. Second, the RSA will inform the treating acupuncturist about subject randomization assignment.

16.0 DATA MANAGEMENT ISSUES

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

The data collected for this study will be entered into either CRDB, Excel, Access or REDCap secure study databases based on the database functionality. A minimal dataset will be entered into CRDB, and a study tracker will be in Excel. Participants will be asked to complete patient reported outcomes assessments online using REDCap, as described below. If they prefer, patients will have the option to complete the measures via pencil and

paper on scannable forms or over the phone with an RSA to reduce participant burden and ensure timely completion.

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

Microsoft Access databases will be used to store scannable forms associated with the AutoData Scannable Office software described below. The scannable questionnaires that patients fill out for this protocol will not be IRB stamped documents. The questionnaires will not be changed from their IRB stamped counterparts, but in order to use these questionnaires, we need to have them in Microsoft Word format. The software (AutoData Scannable Office) takes the questionnaires in a Microsoft Word documents and prints them with a patient specific barcode at the bottom. After the patient fills it out, the original questionnaire can be scanned into this software, and the software reads and records the patients' answers in a Microsoft Access database.

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

16.1 Quality Assurance

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

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: <http://cancertrials.nci.nih.gov/researchers/dsm/index.html>. The DSM Plans at MSK were established and are monitored by the Clinical Research Administration. The MSK Data and Safety Monitoring Plans can be found on the MSK Intranet at: <http://mskweb2.mskcc.org/irb/index.htm>

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

Risks/Benefits Assessment

Although the risks associated with participation in the proposed study are minimal, all potential risks that might occur as a result of participation will be detailed in an informed consent form, and will also be fully discussed with each subject prior to enrollment. We will also explain to each subject that in the unlikely event of physical injury directly resulting from the research procedures, every effort will be made to make available the facilities and professional skills of MSK. It will be further explained that while some risks are not predictable, every precaution consistent with the best medical practice to protect the health and safety of subjects will be taken. We will document all related adverse events and report any related serious adverse event promptly to IRB.

Risk of Acupuncture: The risks associated with electro-acupuncture (EA) and Battle Field Acupuncture (BFA) are minor. The most common side effects are mild pain on insertion of the needle. There is a possibility of a small amount of bleeding or bruising. Sometimes, pain in joints and muscles may get worse with acupuncture shortly after treatment. Since, on rare occasion, chest needling can lead to a pneumothorax, no needles will be placed in the chest region for the proposed study. Licensed acupuncturists who have at least five years of clinical experience will administer the acupuncture. We will make every effort to ensure the safety and comfort of the research subjects, including wiping the needling site with alcohol before the procedure and wiping the needling site with sterile cotton tipped applicator.

Adverse events will be recorded during each clinical visit. Any related SAEs will be reported to the IRB.

Risk of Venipuncture: There is a small risk to the subject during the blood draw, which may include bruising, bleeding, fainting, and/or local infection. The PI will be available to handle any subject safety concerns.

Confidentiality Risks: Every effort will be made to maintain confidentiality of the study subjects according to the requirements of the Health Information Portability and Accountability Act (HIPAA). Research and hospital records are confidential. Subject's names or any other personally identifying information will not be used in reports or publications resulting from this study. Authorized agencies (e.g., qualified monitors from DoD, etc.), and appropriate personnel may review subject's records as required. All forms are kept in a locked file cabinet when not in use. Clinical data will be kept in a centralized database with restricted access to study personnel. Data will be entered into MSK's clinical research database (CRDB), a study excel file, and study Access and REDCap databases on a secure MSK shared drive. Individual identifying information will be omitted from figures used in publications resulting from this research.

Risk of psychological distress: It is possible that subjects may be upset to find out that they are randomized to their non-preferred arm of the study. With appropriate consent and the debriefing process, such risks are minimized. Subjects will be informed that they are participating in an experimental study to compare the effects of two types of acupuncture or usual care for chronic pain. They have the chance to be randomized to 1 of the 3 groups. At the end of the study, subjects will be offered the opportunity to discuss the findings with the PI. In addition, some of the questions in the questionnaire may elicit distress among subjects. During the study period, if the research staff identifies any patients who are psychologically distressed they will notify the study PI immediately to facilitate appropriate evaluation and treatment.

Risks Associated with Genetic Testing: The use of a subject's sample for genetic testing raises special issues of confidentiality, because it is conceivable that information about his/her genes could be used against him/her if the wrong people obtain this information. For example, an insurance company could try denying benefits or an employer could try denying employment if it was known that s/he carried certain genes. In addition, if information that a subject carried certain genes became known to him/her or to his/her family members, it may cause him/her to feel upset or stigmatized. To reduce this possibility, the following specific measures will be taken to protect each subject's confidentiality:

- In the laboratory, each subject's blood samples and genetics sample will be labeled with a number only. The subject's name or any other identifying information will not be attached to the samples in the research laboratory.
- The genetic testing of each subject's sample is for research purposes only. No results of genetic testing from this study will appear in a subject's medical record.
- Genetic test results will not be made available to subjects, their doctors, other clinicians or any other clinical staff. If a subject wants to know more about his/her risks for diseases in which genes play a role, we recommend that s/he speaks with a genetic counselor. We will provide subjects with names of genetic counselors in the area if they wish to speak with one.
- To protect subjects' confidentiality as much as possible, no computer records will be created that could be used to identify their genetic or medical information individually.

Thus, even if a “hacker” breaks into the laboratory computer system, there will be no information stored there that can identify a subject as an individual.

Costs: Study related procedures and visits will be provided to the subjects at no cost. To encourage adherence to the study procedures, we will provide \$30 at each of the following visits: Baseline, Week 4, Week 10, Week 12, Week 16 and Week 24 (total of \$180 per participant).

Risk management and emergency response:

- All potential risks that might occur as a result of participation will be detailed in an informed consent form, and will also be fully discussed with each subject prior to enrollment. We will also explain to each subject that in the unlikely event of physical injury directly resulting from the research procedures, every effort will be made to make the facilities and professional skills of the MSK available to them. While some risks are unpredictable, every precaution consistent with the best medical practices to protect the health and safety of subjects will be taken.
- At each study visit, the acupuncturist and/or RSA will ask the subjects if they have experienced any adverse events during the past weeks. All related AEs will be recorded in an AE log which includes the date of onset and cessation of the AE, severity of AE (i.e., mild, moderate, severe), and relationship to study intervention (i.e., none, possible, probable, definite). The PI will review all recorded AEs in a timely manner. Any related serious adverse event (SAE) will be promptly reported to the IRB.
- All subjects will be instructed to contact the RSAs immediately if they experience any troubling side effects or worsening of symptoms. Patients will be instructed to return to the clinic for an unscheduled study visit for further evaluation and treatment (if clinically warranted). Any patient, who experiences an AE that, in the opinion of the PI, would warrant discontinuing treatment, will be discontinued from the trial. Given this level of safety monitoring, it is anticipated that potentially dangerous AEs resulting from the study intervention will be detected and treated in a timely manner. All related AEs will be followed up until the AE has resolved.

Potential Benefits:

- Preliminary research based on our previous study has suggested that acupuncture may reduce joint pain in addition to improving fatigue, sleep disturbance, and psychological distress; however, acupuncture may or may not be effective for any given patient. The research will help future patients and health care providers to determine whether they should consider use acupuncture to treat chronic pain. The risks to subjects are small in comparison to the scientific information and potential benefit to patients that will result from the conduct of this study.
- The proposed study can directly inform not only the effectiveness of two types of acupuncture for the treatment of chronic pain and symptom co-morbidity, but also identify for whom each type of acupuncture would be beneficial, and how to tailor acupuncture delivery based on patient characteristics to enhance therapeutic benefit. The result of this study will help advance the existing science and the practice of acupuncture and accelerate the development of personalized integrative pain management strategies to improve symptoms, physical functions, and quality of life (QOL) for millions of people who suffer from chronic pain.

Alternatives to Participation:

- If patients do not enroll in this study, they may contact their personal physicians to discuss other treatments for chronic musculoskeletal pain.

Risk/Benefit Ratio:

- The potential benefits of this study far outweigh the potential risks. Chronic pain is a common and debilitating symptom that is experienced by many individuals. The results of the proposed study will have an immediate impact to help those suffering from chronic pain make informed and evidence-based decisions about how to most effectively address chronic musculoskeletal pain and co-occurring symptoms. Thus, this study has the potential to improve symptom burden and wellbeing for millions of individuals whose life is impacted by chronic pain. This research also has the potential to generalize to other chronic conditions and the population at large. We will carefully monitor any adverse events related to acupuncture, and minimize the risks for research subjects.

17.1 Privacy

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

17.2 Serious Adverse Event (SAE) Reporting

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

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

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. SAEs classified as unrelated to the study intervention (per section 11.0) will not be considered reportable to the IRB and will not have a corresponding Clinical Research Database (CRDB) SAE report generated. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
 - A explanation of how the AE was handled
 - A description of the subject's condition
 - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:

The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.2.1 Not Applicable

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

Appendix 1: Acupuncture Intervention (EA and BFA) Protocol

Appendix 2: Screening Eligibility Document

Appendix 3: Patient Reported Outcome Measures

Appendix 4: Blood Processing

Appendix 5: Recruitment Letter

Appendix 6: Recruitment Flyer

Appendix 7: Recruitment Rack Card

Appendix 8: No Contact Letter

Appendix 9: DOD Research Summary Sheet

Appendix 10: Recruitment Letter - Breast

Appendix 11: Recruitment Letter - Colorectal

Appendix 12: Recruitment Letter - Lung

Appendix 13: Recruitment Letter - Lymphoma

Appendix 14: Recruitment Letter - Prostate

Appendix 15: Recruitment Letter - Testicular

Appendix 16: Recruitment Letter – Men

Appendix 17: Recruitment Letter - Updated