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Title Page

Emergency Department Acupuncture for Acute Musculoskeletal Pain Management: A Protocol for an Adaptive Pragmatic Randomized Controlled Trial

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Abstract

Introduction: Chronic musculoskeletal pain causes a significant burden on health and quality of life and may result from inadequate treatment of acute musculoskeletal pain. The Emergency Department (ED) represents a novel setting in which to test nonpharmacologic interventions early in the pain trajectory to prevent the transition from acute to chronic pain. Acupuncture is increasingly recognized as a safe, affordable and effective treatment for pain and anxiety in the clinic setting, but it has yet to be established as a primary treatment option in the ED.

Methods and analysis: This pragmatic clinical trial uses a two-stage adaptive randomized design to determine the feasibility, acceptability, and effectiveness of acupuncture initiated in the ED and continued in outpatient clinic for treating acute musculoskeletal pain. The objective of the first (treatment selection) stage is to determine the more effective style of ED-based acupuncture, auricular acupuncture or peripheral acupuncture, as compared to no acupuncture. All arms will receive usual care at the discretion of the ED provider blinded to treatment arm. The objective of the second (effectiveness confirmation) stage is to confirm the impact of the selected acupuncture arm on pain reduction. An interim analysis is planned at the end of Stage 1 based on probability of being the best treatment, after which adaptations will be considered including dropping the less effective arm, sample size re-estimation, and unequal treatment allocation ratio (e.g., 1:2) for Stage 2. Acupuncture treatments will be delivered by licensed acupuncturists in the ED and twice weekly for 1 month afterward in an outpatient clinic.

Ethics and dissemination: This study has been reviewed and approved by the Duke University Health System Institutional Review Board. Informed consent will be obtained from all participants. Results will be disseminated through peer review publications and public and conference presentations.

Trial registration number: ClinicalTrials.gov: NCT04290741

Article Summary

Strengths and limitations of this study

- The two-stage adaptive design of this clinical trial leverages findings from the first stage to inform adaptations in the second stage to increase likelihood of success with implementation and measuring the true effectiveness of acupuncture.

- This study uses two types of acupuncture by licensed acupuncturists: 1) an auricular acupuncture protocol and 2) acupuncture tailored to the individual that is reflective of how acupuncture is actually used clinically, to compare the efficacy, feasibility and acceptability of the two methods.

- The pragmatic design utilizes usual medical care in all arms and necessitates a control group with no sham acupuncture, to better replicate real-world conditions and assessment of acupuncture effectiveness. This design limits assessment of the specific vs non-specific effects of acupuncture on pain outcomes.

- This study extends the scope and assessment of acupuncture effectiveness to a more broadly representative emergency department (ED) population, and longitudinal delivery of acupuncture treatments in both the ED and outpatient clinic will better assess the benefit of multiple sessions for acute pain.

- The breadth of biopsychosocial outcome measures can contribute to a more comprehensive understanding of how acupuncture works for acute musculoskeletal pain and bridging the gap between eastern and western medicine.

Introduction

Over 40 million adults in the United States (US) suffer from chronic pain, which is pain lasting three months or longer.[1] Musculoskeletal pain, one of the largest subsets of chronic pain conditions, leads to high rates of healthcare utilization, increased opioid use, and poor physical, psychological, and cognitive health.[1] Musculoskeletal pain often results from an acute injury, and if not adequately treated, can transition to a chronic pain condition.[2,3] Significant challenges exist for adequately managing musculoskeletal pain due to the heterogenous nature of its causes and pain symptomatology, and standard treatments are often ineffective.[4,5] Additionally, numerous biological (e.g., inflammatory mediators), psychological (e.g., pain catastrophizing), and social (e.g., social support) factors (referred to collectively as "biopsychosocial" factors) contribute to the complexity of musculoskeletal pain development, severity, progression and disability.[6] Recent studies have begun to explore the role of biopsychosocial factors in the transition from acute to chronic pain and how they may serve as targets for intervention.[3,7] One strategy to prevent the transition from acute to chronic pain is early intervention using nonpharmacologic strategies that influence these biopsychosocial factors. The Emergency Department (ED) represents a novel setting in which to test nonpharmacologic interventions early in the pain trajectory with the goal of preventing the transition from acute to chronic musculoskeletal pain.

Acupuncture is a safe and cost-effective treatment for acute and chronic pain, particularly of the back, neck, and shoulder.[8,9] Furthermore, acupuncture has shown benefit in treating both pain and anxiety,[8] and acts on numerous neural, endogenous opioid and inflammatory pathways,[10] thereby representing a broader biopsychosocial intervention than other single pain treatment modalities. However, data on the use of acupuncture for pain management in the ED is limited since acupuncture practitioners are not currently standard or commonplace in US EDs.[11,12] A recent meta-analysis of ED studies has shown acupuncture to be superior to sham/placebo and equivalent or better than medications for pain reduction.[11,13] Only three small pilot studies have compared acupuncture combined with usual care to usual care alone, with results favoring acupuncture.[11,14] No study has compared different acupuncture protocols (e.g., battlefield/auricular acupuncture and peripheral acupuncture) to determine which is more efficacious, feasible or acceptable in the ED. Moreover, despite evidence that acupuncture is more effective with multiple sessions,[15] prior ED studies have not included a longitudinal outpatient acupuncture component for post-ED pain management or longer-term outcomes.

Therefore, the purpose of this study is to determine the effectiveness, feasibility and acceptability of acupuncture initiated in the Emergency Department (ED) and continued in a group clinic setting for treating acute musculoskeletal pain. The ED population is largely heterogeneous in sociodemographic composition and comprises populations previously excluded from acupuncture studies.[16] A **pragmatic randomized controlled trial** can determine the extent to which ED patients will attend and derive benefit from the full acupuncture experience, while extending the scope and assessment of treatment effectiveness to a more broadly representative patient population. We hypothesize that, when added to usual care, acupuncture initiated in the ED and continued in an outpatient setting for one month is more effective than usual care alone at reducing acute musculoskeletal pain at 1 hour while in the ED and at 1 month after ED visit.

METHODS AND ANALYSIS:

Study design

This pragmatic clinical trial uses a two-stage adaptive randomized design to determine the feasibility, acceptability, and effectiveness of acupuncture initiated in the Emergency Department (ED) for treating acute musculoskeletal pain. The objective of the first (treatment selection) stage is to determine the more effective style of ED-based acupuncture, i.e., Auricular Acupuncture (AA) or Peripheral Acupuncture (PA), as compared to no acupuncture (NA). The objective of the second (effectiveness confirmation) stage is to confirm the impact of the selected acupuncture arm on pain reduction. An interim analysis is planned at the end of Stage 1 based on probability of being the best treatment,[17] after which adaptations will be considered including dropping the less effective arm, sample size re-estimation, and unequal treatment allocation ratio such as 1:2 ratio for effectiveness in Stage 2. Acupuncture treatments will be delivered by licensed acupuncturists in the ED and up to 2 times per week for 1 month afterward in an outpatient clinic. In this pragmatic design, all study arms will receive usual care for pain management at the discretion of the ED provider who will be blinded to treatment arm.

Study setting and recruitment

Trial participants will be recruited from the Duke University Hospital Emergency Department (ED), an urban academic tertiary care referral center in North Carolina with 80,000 ED visits per year. All study screening, recruitment, informed e-consent, and enrollment procedures will be performed by trained clinical research coordinators. Study acupuncturists will be available during enrollment to explain acupuncture treatment to eligible patients. Outpatient acupuncture visits will be scheduled with the study acupuncturists using secure HIPAA-compliant scheduling software and take place at the Duke Integrative Medicine Clinic. Patient recruitment began in February 2020 and is ongoing.

Eligibility Criteria

Inclusion criteria

Participants must be adult (age 18 years or older) ED patients with pain in the neck, back, arms and/or legs and a clinical diagnosis of acute (≤7 days) musculoskeletal pain as determined by an ED provider, and able to read and understand the consent form in English. Participants with acute exacerbation of chronic pain in which the acute component is ≤7 days will be included, as this is a common ED presentation.[18]

Exclusion criteria

Patients will be excluded if they are: (1) suspected to have a non-musculoskeletal cause of pain, (2) unable to receive acupuncture due to injury, infection, or other contraindication to the use of needles at acupuncture sites; (3) not possible to attend outpatient clinic (e.g., visiting from out-of-state); (4) unable to provide informed consent or to comprehend or complete study measures or procedures due to cognitive impairment, including evidence of drug, medication or alcohol intoxication, or due to severe hearing or speech impairment; (5) unable to safely participate due to critical illness, obvious bony deformity, other serious medical condition (including active COVID-19 infection), and/or based on ED provider judgment.

Randomization and Blinding

Subjects will be randomized 1:1:1 to one of three treatment groups: 1) auricular acupuncture (AA), 2) peripheral acupuncture (PA), or 3) the control group with no acupuncture (NA). The randomization code will be computer-generated by the Biostatistics, Epidemiology and Research Design (BERD) Methods Core of the Department of Biostatistics and Bioinformatics, Duke University Medical Center. An unstratified block randomization method will be used to generate the random allocation sequence, which will be stored in a secure electronic file accessible only by the acupuncturists to ensure allocation concealment. The research coordinator enrolling eligible patients will be blinded to the allocation sequence and randomization assignments. After participant baseline measures and acupuncturist initial clinical assessment, the treating acupuncturist will open the randomization file and assign the participant to the treatment group corresponding to the next sequential entry.

The participants and the acupuncturists will not be blinded to their treatment allocation. All other members of the ED clinical and research teams will be blinded. Round stickers will be applied to the ears of all participants at the battlefield protocol sites to blind these members to patient assignment while in the ED. If the participant reports an adverse event, the research coordinator may become unblinded to record and address the event. Due to the adaptive nature of the statistical design, the statisticians and data safety monitoring committee (DSMC) will be unblinded to the control treatment arm in Stage 1 to perform the interim analysis; the statistician analyzing the data will remain blinded to the treatment arms. All other study investigators will remain blinded.

Interventions

Acupuncture will only be performed by licensed acupuncturists. For this study, two styles of acupuncture designed to increase feasibility in the ED will be employed. (1) Auricular acupuncture (AA) will involve the placement of needles in up to 5 sites on each ear corresponding to the previously developed battlefield acupuncture protocol to treat pain.[19,20] (2) Peripheral acupuncture (PA) will involve the placement of needles in head, neck, arms, legs, hands, and feet sites selected at the clinical discretion of the treating acupuncturist based upon acupuncture diagnosis as the primary mode of therapy.[21,22] Acupuncture sites on the torso (i.e., chest, back and abdomen) will not be used. Both acupuncture groups will receive acupuncture while in the ED. Afterwards, both groups will receive information and free access to acupuncture in an outpatient clinic for up to 2 times a week for 1 month after their ED visit. Our outpatient acupuncture clinic is designed as a group-based clinic modified for COVID-19-related social distancing to enhance access and affordability. All post-ED outpatient acupuncture treatments for both acupuncture groups will involve either PA, AA or both at the clinical discretion of the treating acupuncturist. The specific components of each acupuncture treatment will be recorded in details according to the revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) recommendations.[23] (3) The control group (no acupuncture = NA) will not receive acupuncture in the ED and will be asked not to seek acupuncture treatment for one month after their ED visit. Control group participants will complete assessments only, with the timing and content of their assessments matching those completed by the intervention groups.

All participants in the control group and in both acupuncture groups will receive usual care for acute pain management at the discretion of their ED provider who will remain blinded to study arm. Usual care may include but is not limited to medications/analgesics, nonpharmacologic strategies (e.g., ice, heat, walking), and referrals to outpatient specialists and/or other nonpharmacologic treatment providers (e.g., physical therapy).

Outcomes

Outcome measures and biopsychosocial factors will be collected before randomization (ED baseline), 1 hour after randomization, and at 2 weeks and 1 month post-ED visit.

Primary Outcome Measures

The primary ED effectiveness endpoint will be the change in current pain score based on the 0-10 pain numeric rating scale (NRS) from ED baseline to 1 hour post-randomization. The primary combined ED-outpatient clinic effectiveness endpoint will be change in 24-hour average NRS pain score from ED baseline to 1 month post-ED visit.

Feasibility will be assessed based on patient recruitment and retention rates both in the ED and with subsequent one-month follow-up. Acceptability will be assessed based on patient-reported satisfaction as well as outpatient acupuncture clinic attendance rates, with attention to reasons for attrition or differential acceptance rates for different groups of participants. Safety will be evaluated by recording any adverse events (AEs), with common reasons to include bleeding, bruising, or pain at the needle sites. Serious adverse events (SAEs) are expected to be extremely rare given previous highly favorable safety data on acupuncture, and include infections, hospitalizations and deaths.[21,24]

Secondary Outcome Measures

Secondary outcomes will include patient function, quality of life, and biopsychosocial factors.

Function and quality-of-life will be measured at ED baseline, 2 weeks and 1 month across several different domains, including pain interference, fatigue, depression, anxiety, sleep disturbance, physical function, social function, and cognitive function, using the validated PROMIS-29 and Neuro-QoL instruments.[25,26] Given the acute time course of pain (7 days or less) for eligible participants, the timeframe for the PROMIS-29 questions will be modified from “over the past 7 days” to “over the past 24 hours (1 day)” for the ED baseline assessment only. We will also measure patient-reported medication use, including opioid and non-opioid medications. Opioid use will be assessed through patient report in the past 24 hours and in the past 7 days, as well as by electronic medical record (EMR) data extraction of prescriptions written during and up to one year after the ED visit.

A comprehensive set of biopsychosocial factors will be measured at ED baseline and one-month follow-up. These include:

(1) Patient demographics including age, sex, race, ethnicity, employment, marital status, education, income, and insurance status.

(2) Pain characteristics including anatomical location of pain, duration of current episode of musculoskeletal pain, and history of prior episodes of musculoskeletal pain.

(3) Degree and type of social support, including instrumental, informational, and emotional support, will be measured using the PROMIS Social Support 4-item scales.[27]

(4) All non-medical substance use, including opioid misuse, through the validated ASSIST tool.[28]
(5) Presence and severity of chronic pain using a recently validated simplified version of the graded chronic pain scale derived from the 3-item pain, enjoyment and general activity (PEG) score and degree of activity limitations.[29,30]
(6) Symptoms of systemic pathology will be measured using the validated Optimal Screening for Prediction of Referral and Outcome Review of Systems (OSPRO-ROS) tool, which predicts pain outcomes after musculoskeletal care in outpatient physical therapy settings.[31,32]
(7) Pain-related psychological distress using the validated concise Optimal Screening for Prediction of Referral and Outcome Yellow Flag (OSPRO-YF) tool, an assessment tool for measuring psychological response to pain including pain coping, catastrophizing, fear-avoidance and mood [32,33].
(8) Pain-related emotional distress based on the Perceived Stress Scale (PSS) tool.[34]
(7) Pain coping skills using the Coping Skills Questionnaire 2-item form (CSQ-2).[35]
(8) Pain self-efficacy using the Pain Self-Efficacy Questionnaire (PSEQ).[36]

Two additional measures will be collected in-person in the ED at baseline and 1 hour:
(9) Pressure pain threshold, a non-invasive quantitative test of pain sensitivity that measures the lowest applied pressure needed to evoke to an individual's perception of pain, will be performed on the bilateral trapezius muscles using slow progressive pressure (1 kg/cm^2/sec) with a standard hand-held algometer (Wagner Digital Force Gauge, Wagner Instruments, Greenwich, CT).[37,38]
(10) Blood samples will be collected and stored in a secure repository for future biomarker analysis of biochemical and genetic pathways involved in pain and response to acupuncture. Participants may opt out of the blood draw and still participate in the clinical trial.

Additional EMR data will be extracted by trained analysts and include medications administered and prescribed from the ED, opioids prescribed up to one year following index ED visit, return ED visits and hospitalizations up to 3 months following index ED visit, and ICD-10 codes for pain conditions and co-occurring diagnoses (e.g., medical and psychiatric comorbidities).

Data Collection and Management
Data will be collected at ED baseline, 1 hour post-randomization, and at 2 weeks and 1 month post-ED visit, with data entered directly into a REDCap secure electronic database.[39] All in-person biological measures including pressure pain threshold and blood draws for biomarkers will be obtained during the ED visit at baseline and 1 hour by research coordinators embedded in the ED. Pressure pain threshold will be recorded in REDCap. Blood samples will be coded with a unique study identifier and deidentified for storage.

ED baseline and 1-hour questionnaires to collect biopsychosocial factors and outcome measures will be completed by participants independently and entered directly into REDCap while they are in the ED (**Figure 1**). Research coordinators will be available for assistance with data entry if requested by participants. Participants will be contacted at 2 weeks and 1 month post-ED visit to complete online REDCap follow-up surveys (**Figure 1**) using follow-up procedures to facilitate maximum study retention. These procedures include up to three

automated electronic follow-up surveys sent via email, automated text message links to the surveys, follow-up phone calls by ED research assistants with the option to complete surveys by phone, and compensation for one-month follow-up assessment completion.

Acupuncturist assessments and treatment details in the ED and outpatient clinic will be entered directly into REDCap forms by the treating acupuncturist. ED medication data will be entered into REDCap forms by research coordinators. Acupuncture AEs and SAEs will be entered into REDCap forms by the study personnel notified of the event, and follow-up of the events will be completed within the same forms by the personnel completing follow-ups. Additional EMR data will be extracted by trained analysts and stored in a protected analytics environment. All data will be stored for at least 5 years after study completion for primary and ancillary studies, with access restricted to study staff, and is included in patient consent. To protect confidentiality, no personal information will be shared.

Sample size

For Stage 1, a total of 90 subjects (30 subjects per arm) will be used to (i) assess feasibility based on patient recruitment and retention rates, and (ii) determine the more effective arm at the ED one-hour timepoint for moving forward to Stage 2 for effectiveness confirmation. Sample size calculation for achieving Stage 2 study objectives assumed[17,40,41]: (1) a Stage 2 two-arm parallel design with 1:2 control:treatment allocation; (2) the primary endpoint is normally distributed; (3) with no acupuncture, a mean pain score of 6.5 with a standard deviation of 2.5;[42] (4) a minimally clinically meaningful difference in pain score of 1.3;[42] (5) a power of 90.0%; and (6) a 5% level of significance. This yielded a total sample size of 198 subjects (**Table 1**) at the end of Stage 2. To account for a possible 10% dropout rate requires increasing the total number enrolled to 220 subjects.

Table 1. Sample Size Estimation and Allocation

Stage	Randomization	Sample Size	Total
Stage 1	1:1:1	30 (NA), 30 (AA), 30 (PA)	90
Stage 2	1:2	36 (NA), 72 (AA or PA)	108
		Total	198

Data Analysis and Statistical Methods

Population: The primary analysis will be performed based on the intention-to-treat (ITT) population, which is defined as all randomized subjects who have at least one follow-up evaluation regardless of their compliance with the protocol. In case of a substantial number of protocol violations, additional per-protocol analyses may be performed to determine whether they influence the conclusions.

General Analysis Conventions/Rules: Descriptive statistics for continuous variables will be provided as: number of subjects, means and standard deviations, medians and interquartile ranges, and minima and maxima. Descriptive statistics for discrete (categorical) variables will be provided as the number and percentage of subjects in each category. Time to event variables will be provided using Kaplan-Meier survival curve estimates. Unless otherwise noted, any tests of hypotheses are two-sided, and the nominal level of significance will be 5%.

Handling of Missing Data: Imputation of missing data will be handled depending on the missingness mechanism.

Baseline Comparability: Number of subjects randomized, completing the study and reasons for discontinuation will be summarized by treatment group. Patient demographics and baseline characteristics including biopsychosocial factors will be tabulated and compared for treatment group differences. All comparisons will be performed by using the Cochran-Mantel-Haenszel (CMH) test for categorical variables and two-way analysis of variance for continuous variables.

Primary Analysis: The primary variable, change in pain score from ED baseline to 1 hour post-randomization, will be evaluated and compared between treatment groups. The corresponding 95% confidence interval for the difference in mean response rate between treatment groups will be obtained using analysis of variance (ANOVA).

Secondary Analyses: Responder analysis will also be performed using a logistic regression analysis that incorporates potential risk factors identified for response. Point estimate and the corresponding 95% confidence interval of odds ratios for the identified risk factors will also be obtained. In addition, the Stuart-Maxwell test may be performed to examine changes (or shifts) from baseline to follow-ups after ED discharge.

Exploratory Analyses: Exploratory analyses such as biomarker changes pre to one-hour post-randomization, subgroup analyses based on patient demographics and/or patient characteristics, and predictive model building, validation, and/or generalizability may be conducted as deemed appropriate by the principal investigator(s), biostatistician or as recommended by an internal established data safety monitoring committee (DSMC). These include secondary analyses of the impact on outcomes of the number of acupuncture needle sites or number of acupuncture pathways used, number of clinic visits attended, within treatment pain and/or anxiety reductions, among others. If possible, additional exploratory models predicting response to acupuncture based on biopsychosocial factors will be examined.

Safety Analysis: Table will show the AEs ordered by decreasing frequency for all participants. Separate tabulations will summarize the AEs by seriousness, severity, and possible association with study drug. If appropriate, the incidence rate of AEs will be compared by Fisher's Exact Test. Special attention will be given to those subjects who have discontinued due to AEs and those subjects who experienced a SAE.

Interim Analysis: There will be one planned interim analysis which will take place when two-thirds of subjects (i.e., 20 of 30 subjects per arm) have completed Stage 1. At interim analysis, the feasibility will be assessed based on patient recruitment and retention rates, and the more effective arm will be determined based on change in pain score at the one-hour ED timepoint based on probability of being the more effective treatment.[17] Some adaptations such as modifying current treatment arm, different randomization scheme, additional interim analyses, and/or sample size re-estimation may be applied as recommended by the DSMC.

Data Monitoring

A data safety monitoring committee (DSMC) comprised of an independent biostatistician, emergency medicine physician-researcher and a medical acupuncturist-pain medicine clinician will meet at least 2 times per year with ad hoc reports as needed, to monitor the safety and performance quality of the trial. The DSMC will also evaluate the interim analysis to make recommendations on adaptations for Stage 2 to the study investigators.

AEs and SAEs and their follow ups will be recorded in a secure REDCap file. AEs will be reviewed weekly, and SAEs will be reviewed immediately by the principal investigator and lead research coordinator and addressed as needed. All SAEs will be reported within 24 hours to the DSMC, IRB and study sponsor.

Ethics considerations and Dissemination plan

The Duke University Health System Institutional Review Board has reviewed and approved this study (Protocol # Pro00104140). This trial was registered on 2/7/2020 with clinicaltrials.gov (registration # NCT04290741) and released to the public on 2/28/2020. We used the SPIRIT checklist when writing our report.[43] Upon completion of the trial, the results will be disseminated through peer review publications as well as presentations at professional organization conferences and to the public including healthcare organizations.

Patient and Public Involvement

Patients and the public were not involved in the original design of the study. However, patient participants will be interviewed for feedback on their acupuncture and research experience to potentially inform future adaptations.

Discussion

Adaptive design: The innovative adaptive design of this study enables findings from the first stage to be used to increase the likelihood of success in the second stage for measuring the true effectiveness of acupuncture in an ED population. Adaptations to drop the least effective arm and/or mitigate issues that arise in Stage 1 are designed to optimize implementation of acupuncture for both the study and its broader applicability to other settings.[44] Efforts will be made to limit potential bias from adaptations and maintain trial integrity and validity by utilizing an independent DSMC to decide on any adaptations.

Novel care pathways: This will be one of the first randomized trials to integrate acupuncture into ED care and to establish linkages to outpatient acupuncture treatment. It will also be one of the first acupuncture studies to include a diverse sociodemographic population and to utilize a group-based clinic to enhance access and affordability of this treatment option.[16] Patient knowledge of, access to, and availability of nonpharmacologic therapies are frequent barriers to use.[16,45] Post-ED follow-up can be particularly challenging among ED patients due to cost and time constraints, so lowering these barriers are key to improving access to care. Furthermore, initial therapeutic experience with acupuncture has been shown to increase patient follow-through with continued acupuncture,[46] highlighting the benefit of combining ED with outpatient care. Goals of the study include reducing patient need for pain medications,

particularly opioids, and return ED visits for pain control through use of acupuncture. Our findings will inform future ED and follow-up acupuncture treatment recommendations.

Tailoring Acupuncture to the ED environment: Comparing auricular acupuncture (AA) to peripheral acupuncture (PA) in the ED setting is a key component of our study, as it allows further exploration of the feasibility and acceptability of ED-based acupuncture through two different patient experiences. AA can be delivered quickly, easily, and without removal of clothing, thus fitting well within the space and time constraints of the ED environment.[19] Furthermore, specific types of auricular needles can be left in place for later self-stimulation by patients to provide additional pain relief for an additional 1-5 days.[19,47] Use of AA can be limited by patient discomfort with needles in the ear, potential compatibility issues with obtaining CT and MRI imaging while needles are in place, and lack of clinical guidelines for its use.

Peripheral acupuncture (PA) allows for greater personalization of treatment than AA by offering a much larger number of meridians or channels that the acupuncturist can access for pain relief.[48,49] PA also offers the flexibility to adapt treatments for very anxious or needle-sensitive patients because needle depth and level of stimulation can be modified to suit individual needs. While tight clothing may limit the number of accessible acupuncture points, this is typically not a major barrier for experienced acupuncturists.

While PA can take longer for the patient, 20-45 minutes for PA compared with 10-20 minutes for AA, spending more time with the acupuncturist can contribute to their increased sense of support and better anxiety relief. In addition, PA can be more efficient for the acupuncturist than AA when treating multiple patients, as the acupuncturist can leave one patient while needles are in place to tend to the next patient, returning later for needle removal and session completion. By contrast, AA involves frequent patient reassessments between each needle insertion requiring the acupuncturist's full attention until session completion before proceeding to the next patient. Lastly, while the battlefield protocol was developed and used by the military and VA to be simple enough to train non-acupuncturists to use it, outside of the military both AA and PA can only be performed by licensed and trained acupuncturists.[20–22]

Usual care for ED pain management: The choice of usual care for all treatment arms was based on the goal of developing a practical and feasible intervention in the ED setting where medications are expected by patients but can be variably prescribed among providers.[50,51] Therefore, restriction of medications from any one arm could be perceived as undesirable or unethical by ED patients seeking care. In addition, choice of medication can depend on many factors, including provider and patient preferences, and allergies, adverse reactions, or contraindications to specific medications. Therefore, in order to increase the applicability of our findings, the decision was made to allow provider judgement to dictate medication choice as well as dosing. This has the added benefit of managing breakthrough pain through usual ED provider reassessment and repeat dosing as deemed clinically appropriate. ED providers were kept blinded to treatment arm so that their usual clinical judgement determined usual care treatment. Thus, the results of this trial will reflect the results expected in actual clinical practice in an academic ED.

The choice of no acupuncture for the control group as compared with sham or other placebo was based on the goal of studying the effect of acupuncture in a pragmatic setting. Given the

high volume, high throughput environment of most US EDs, there is not a typical usual care option that would equate to a placebo or sham intervention. For instance, most EDs do not have the time or resources to routinely provide another nonpharmacologic practitioner or additional ED staff member who could devote extra time for patient support. Thus, the alternative to acupuncture in most settings would simply be no acupuncture, with a focus on medication prescriptions, supportive care, and/or, less commonly, outpatient referrals (e.g., primary care, physical therapist, orthopedist) for further management.

Breadth of Study Outcomes: This study will also generate data on biopsychosocial factors to better characterize the population of patients seen in the ED for acute musculoskeletal pain. Exploration of these factors may also identify mediators of the patient response to acupuncture. These mediators may help identify patients more likely to improve with acupuncture and/or better elucidate potential mechanisms of acupuncture's therapeutic effects. Findings from this study will further our understanding of acute pain and its nonpharmacologic management through acupuncture, as well as their associations with the comprehensive set of biopsychosocial factors.

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Author contributions
SAE drafted the study protocol manuscript. OG, CAS, and MRK participated in the design of the study and revising the protocol manuscript. SC, MK and AG were responsible for the statistical design of the study and revising the protocol manuscript. CDL, MM, AD, AMM and ATL provided clinical advice and made critical revisions to the protocol and manuscript. EW, AO, OCT and JD were involved as clinical research coordinators in revising and editing the protocol and manuscript. SAE is principal investigator of the study and is responsible for making final decisions on the trial design and manuscript preparation. All authors approved the final manuscript.

Protocol version: 1.27, Date 02/25/2021

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The study funders had no role in the study design, collection or analysis of data.

Competing interests
None declared.

Patient consent
Obtained.

Ethics approval
The Duke University Health System Institutional Review Board has reviewed and approved this study on January 29, 2020 (Protocol No: Pro00104140).

Data availability statement
Not applicable.

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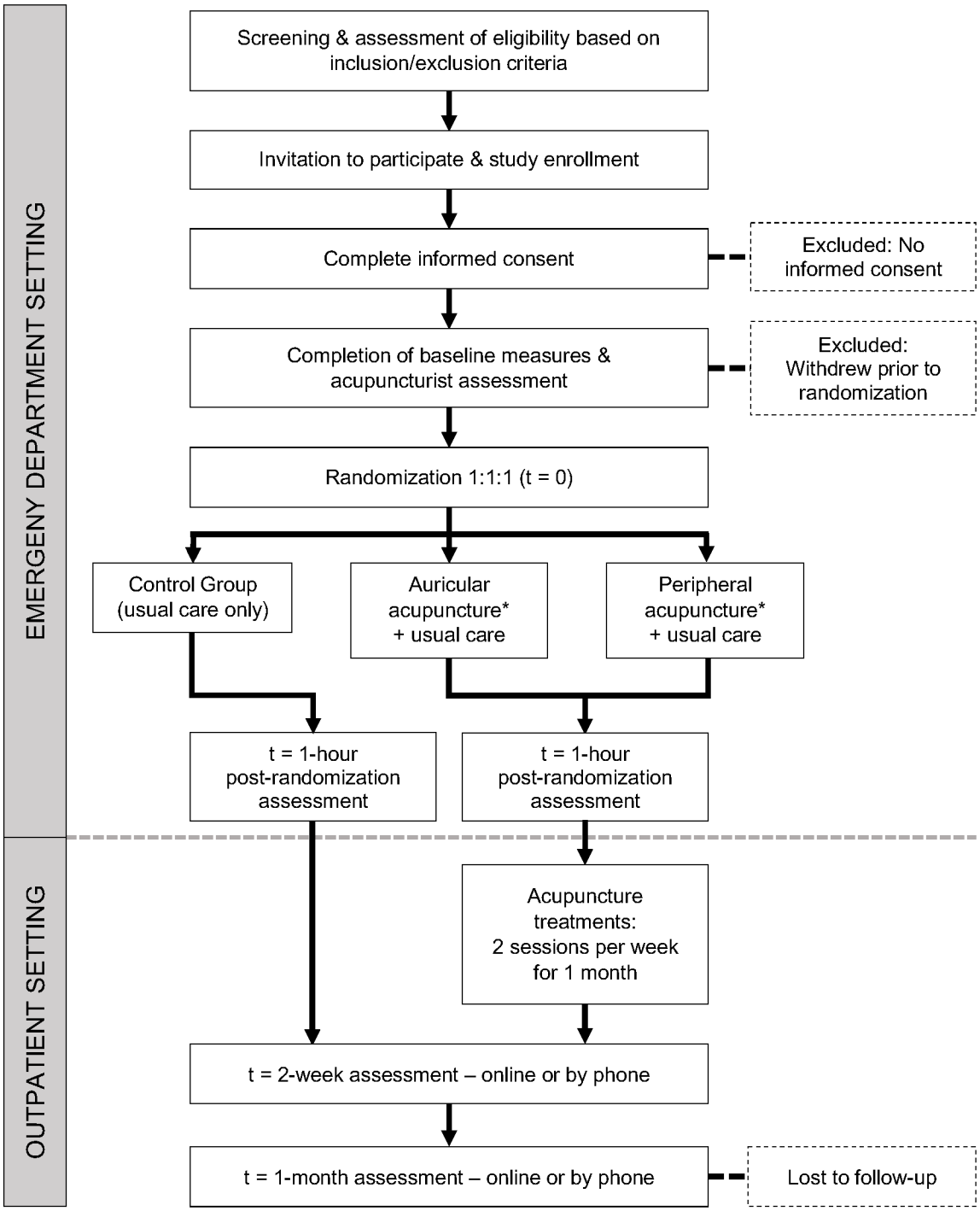
Figure captions:

Figure 1. Trial flowchart. After interim analysis in Stage 1, the less effective acupuncture arm will be dropped.

Appendix 1. Example informed consent form

Figure 1. Trial flowchart



Form M0345

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
Emergency Department Acupuncture for Musculoskeletal Pain Management

CONCISE SUMMARY

The purpose of this study is to measure how well acupuncture (the insertion of very thin needles through your skin at strategic points on your body) improves pain and function, as well as its feasibility, acceptability, and safety in the Emergency Department (ED).

If you agree to participate in this study, you will have an initial assessment with a pain threshold test, study questionnaires, and optional blood draw. You will be randomly assigned to receive either one of two types of acupuncture or no acupuncture. Acupuncture will be performed by a North Carolina Licensed Acupuncturist while in the ED. One hour after your group assignment you will complete a second pain threshold test, study questionnaires, and optional blood draw. After your ED visit, if you are assigned to acupuncture you will attend acupuncture at an outpatient clinic twice a week for 4 weeks. You will be asked to complete questionnaires at 2 and 4 weeks after your ED visit. If you are assigned no acupuncture, you will be asked not to receive any acupuncture for 4 weeks after your ED visit, and you will only complete the questionnaires. Your data and samples collected for this study may be stored and shared for future research.

Risks associated with acupuncture include pain at the site of needle insertion, bruising, and bleeding. There are risks related to loss of confidentiality, but every effort will be made to safeguard your information.

If you are interested in learning more about this study, please continue reading below.

You are being asked to take part in this research study because you presented to the Emergency Department with a musculoskeletal pain (pain that affects the muscles, bones, and/or tissues that connect them).

Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

Please tell the study doctor or staff if you are taking part in another research study.

WHO WILL BE MY DOCTOR ON THIS STUDY?
If you decide to participate, Dr. Stephanie Eucker will be your doctor for the study and will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed. This study is sponsored by the Duke Endowment and the Substance Abuse and Mental Health Services Administration (SAMHSA).

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Consent to Participate in a Research Study
Emergency Department Acupuncture for Musculoskeletal Pain Management

WHY IS THIS STUDY BEING DONE?
Musculoskeletal pain is one of the most common reasons for doctors' office and emergency department visits. Painful episodes can lead to significant disability and ongoing disruption of daily functioning.

Acupuncture involves the insertion of very thin needles through your skin at strategic points on your body. It is not well-understood how acupuncture works, but there is some evidence that it is safe and cost-effective in outpatient settings for management of acute and chronic pain, particularly of the back, neck, and shoulder. Acupuncture is most often used to treat pain and anxiety in the clinic setting, but has not routinely been used in the ED.

The goal of this study is to measure how well acupuncture relieves pain and improves function, as well as its feasibility, acceptability, and safety in the ED.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
Approximately 750 people will take part in this study at Duke.

WHAT IS INVOLVED IN THE STUDY?
If you agree to be in this study, you will be asked to sign and date this consent form. If you sign this form electronically, you will be asked to provide your email address so that a copy of it can be emailed to you. By providing your email address for use in the consent process, you are at potential risk for a loss of confidentiality because email is not a secure means of communication.

You will undergo an Initial Assessment that includes the following:

- Pressure Pain Threshold test. This is a non-invasive test that uses a device that applies pressure to your body (shoulder muscle) to measure the amount of pressure that causes mild pain.
- Blood draw for biomarker measurements that is optional (approximately 3-4 teaspoons)
- Completion of questionnaires

You will be randomly assigned, like drawing numbers from a hat, to one of three groups listed below. You have an equal chance of being assigned to each group and a 2 out of 3 chance of getting acupuncture.

- Ear (auricular) acupuncture – placement of needles in up to 10 sites total in both ears
- Peripheral acupuncture – placement of needles in up to 30 specific sites in the head, neck, arms from the shoulders to the hands, and legs from the knees to the feet
- Control – no acupuncture

The acupuncture treatments will be performed in an Emergency Department examination room by a North Carolina Licensed Acupuncturist. Acupuncture consists of inserting single use, sterile, acupuncture needles, measuring 0.16-0.22mm in thickness (about the thickness of a hair) and varying in length from 1.5-5cm (0.5-2 inches). The skin will be cleansed prior to needle insertion, and needles will be placed utilizing clean needle technique. Needle insertion depth will vary between 0.5 cm (0.2 inches) and 4.5 cm (1.8 inches) (through the skin and sometimes muscle layers only), depending on the area of

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treatment. Needles will be retained for up to 30 minutes. Auricular acupuncture needles are much smaller, 0.15 cm (0.06 inches) in length (only through the skin), attached to a bandaid adhesive so they can be retained for up to 4 days. All needles can be removed earlier at your request. All acupuncture performed adheres to the guidelines of Clean Needle Technique as required by North Carolina law.

Regardless of which group you are assigned to, you will also receive the usual care for musculoskeletal pain, including medications and other non-medication pain treatments such as ice/heat at the discretion your ED doctor.

You will receive the usual care for acute pain management as determined by your ED doctor.
If you are assigned to the control group you will not receive acupuncture. If you are assigned to one of the acupuncture groups, you will receive acupuncture in the ED. The session will last approximately 15-30 minutes.

One hour after you have been assigned to a treatment group you will be asked to complete a brief questionnaire, a pressure pain threshold test, and have an optional second blood draw (3-4 teaspoons) for research for future biomarker analysis.

Blood collection for biomarkers in this study is optional. Biomarkers are substances in the body that can be indicators of a disease. You do not have to allow for research blood draws to participate in this study. If you agree to blood collection, samples will be taken during and one hour after completion of the initial assessment in the ED.

Please initial below indicating whether or not you agree to research blood draws.

_____ Yes, I agree to undergo a blood draw for research purposes.

_____ No, I do not want to undergo a blood draw for research purposes.

If you are assigned to an acupuncture group, we will provide you with information and free access to group-based acupuncture in the outpatient Integrative Medicine clinic for the next 4 weeks. There will be two sessions per week, and each session will last approximately 30 minutes. You will be asked to provide your phone number and email address to schedule your acupuncture visits. Your name and contact information will be entered into an online scheduling program, Microsoft Bookings. This program will be used to schedule your acupuncture appointments and send appointment reminders.

If you are assigned to the control group, you will not receive acupuncture in the ED, and we ask that you not receive acupuncture for 4 weeks after you sign this consent form. Current research supports that acupuncture will still be effective in treating pain after that time, should you choose to seek acupuncture treatment after participation in the study.

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Regardless of which group you are assigned to, you will be asked to complete questionnaires about your pain, pain management, and quality of life at 2 and 4 weeks after your ED visit. You will receive emails at these time points with a link to the study questionnaires. If you have not completed these within a few days of receiving the email you may be contacted by a member of the study team via text message and/or phone to ensure you are able to access the link. If you have trouble with the link or prefer to answer by phone the questionnaires may be completed via phone.

You may be asked to complete an interview via phone. Interviews will be conducted by a member of the study team. We will ask you questions about your experience with the study and research study materials. This interview will last approximately 15 to 30 minutes. The interviews will be recorded. Recordings may contain your name and age. Your interview will be transcribed within 2 to 3 months and any identifying information will be deleted. Recordings will be stored until the data analysis for this study is complete, approximately 2 years, at which time they will be deleted. Recordings and transcriptions of interviews will be stored in a secure folder that only the study team has access to.

HOW LONG WILL I BE IN THIS STUDY?
If you agree to be in this study, your participation will last approximately 4 weeks. You can choose to stop participating at any time without penalty or loss of any benefits to which you are entitled. However, if you decide to stop participating in the study, we encourage you to talk to your doctor first.

WHAT ARE THE RISKS OF THE STUDY?
Acupuncture may occasionally result in slight bruising, pain at the site of needle insertion, and bleeding, dizziness, and numbness or tingling near the needling sites that may last a few days.
Infection, excess bleeding, or fainting are also possible, although unlikely.

Risks associated with drawing blood from your arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

There is also a risk of loss of confidentiality of your private information. Every effort will be made to protect your information, but this cannot be guaranteed. By providing your email address you are at potential risk for a loss of confidentiality because email is not a secure means of communication.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
There may be direct medical benefits to you for participating in this study. If you are assigned to an acupuncture group, you may have decreased pain but that cannot be guaranteed. A potential benefit of this study is to gain knowledge that may lead to improved pain management in the ED in the future. If you are randomized to the no acupuncture group there is no expected benefit above standard of care.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total confidentiality. By providing your email address for use in the consent process, you are at risk for a loss of confidentiality because

Subject Initials _____

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email is not a secure means of communication. Your personal information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding, and regulating the study. Your date of birth, dates related to your ED visit, acupuncture visits, and any tests or procedures you have had will be collected for this study. Your name, phone number, and email address will be shared with Microsoft Bookings. We will share only the minimum necessary information in order to conduct the research. Your personal information may also be shared if required by law.

Your records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration, the Substance Abuse and Mental Health Services Administration (SAMHSA), the Duke University Health System Institutional Review Board, and others as appropriate. If any of these groups review your research record, they may also need to review your entire medical record.

The study results will be retained in your research record for at least six years after the study is completed.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your identity will not be revealed.

Some recipients who receive your health information might not have to follow the same privacy rules. Once your information is shared outside of DUHS, we cannot guarantee that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect your health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

WHAT ARE THE COSTS TO YOU?
You or your insurance provider will be responsible and billed for all costs related to your routine medical care, including copayments and deductibles. Routine medical care services are those that you would have received for your condition if you were not participating in this research study. Not all services are covered by insurance. The amount of your out-of-pocket expense will depend on your insurance plan.

Services and procedures that are done solely for research purposes will be paid for by the study. This includes the cost of both inpatient and outpatient acupuncture and costs related to blood draws (if applicable). Please talk with the PI/study team about the specific services and procedures that will be paid for, and the ones for which you or your insurance will be responsible.

We will monitor your DUHS patient care charges to make sure that costs are directed appropriately. If you have any questions or concerns about appropriate billing, contact your study team coordinator so that he/she can help find a resolution.

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WHAT ABOUT COMPENSATION?
You will receive a $30 Amazon gift card after you complete the 4-week follow up survey. Gift cards may be sent via email or text message after the surveys have been completed.

WHAT ABOUT RESEARCH RELATED INJURIES?
Immediate necessary medical care is available at Duke University Medical Center in the event that you are injured as a direct result of your participation in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., or your Duke physicians to provide monetary compensation or free medical care to you in the event of a study-related injury.

For questions about the study or research-related injury, contact Dr. Eucker at 919-684-5537 during regular business hours and at 919-684-8111 after hours and on weekends and holidays and ask that she be paged.

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?
You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concerns an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record. All data that has already been collected will be maintained.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled and will not affect your access to health care at Duke. If you do decide to withdraw from the research study, we ask that you contact Dr. Eucker in writing and let her know that you are withdrawing from the study. Her mailing address is DUMC Box 3096, Durham, NC, 27710.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

Your study doctor may decide to take you off this study if she determines that it is no longer in your best interest to continue.

If you agree to allow your blood to be kept for future research with identifying information that could link your sample to you, you are free to change your mind at any time. We ask that you contact Dr. Eucker in writing and let her know you are withdrawing your permission for your identifiable blood samples to be used for future research. Her mailing address is listed above. At that time, we will ask you to indicate in writing if you want the unused identifiable blood destroyed or if your samples (having all identifying information removed that would link the sample to you) could be used for other research.

Your samples and data may be stored and shared for future research without additional informed consent if identifiable private information, such as your name and medical record number, are removed. If your

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identifying information is removed from your samples or data, we will no longer be able to identify and destroy them.

A description of this clinical trial will be available on https://clinicaltrials.gov/ as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or a research-related injury, or if you have problems, concerns, questions or suggestions about the research, contact Dr. Eucker at 919-684-5537 during regular business hours and at 919-684-8111 after hours and on weekends and holidays and ask that she be paged.

For questions about your rights as a research participant, to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

STATEMENT OF CONSENT
"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form."

_____	_____	_____
Signature of Subject	Date	Time
_____	_____	_____
Signature of Witness (if applicable)	Date	Time
_____	_____	_____
Signature of Person Obtaining Consent	Date	Time

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1-15
Protocol version	#3	Date and version identifier	14
Funding	#4	Sources and types of financial, material, and other support	14-15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	14

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	14-15
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	6

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	12
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9-10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-10, Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-10
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9-10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9-10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10-11
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10-12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	14
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	9

Notes:

- 13: 9-10, Figure 1 The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 07. April 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

Acupuncture for Acute Musculoskeletal Pain Management in the Emergency Department and Continuity Clinic: A Protocol for an Adaptive Pragmatic Randomized Controlled Trial

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Title Page

Acupuncture for Acute Musculoskeletal Pain Management in the Emergency Department and Continuity Clinic: A Protocol for an Adaptive Pragmatic Randomized Controlled Trial

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Abstract

Introduction: Chronic musculoskeletal pain causes a significant burden on health and quality of life and may result from inadequate treatment of acute musculoskeletal pain. The Emergency Department (ED) represents a novel setting in which to test nonpharmacologic interventions early in the pain trajectory to prevent the transition from acute to chronic pain. Acupuncture is increasingly recognized as a safe, affordable and effective treatment for pain and anxiety in the clinic setting, but it has yet to be established as a primary treatment option in the ED.

Methods and analysis: This pragmatic clinical trial uses a two-stage adaptive randomized design to determine the feasibility, acceptability, and effectiveness of acupuncture initiated in the ED and continued in outpatient clinic for treating acute musculoskeletal pain. The objective of the first (treatment selection) stage is to determine the more effective style of ED-based acupuncture, auricular acupuncture or peripheral acupuncture, as compared to no acupuncture. All arms will receive usual care at the discretion of the ED provider blinded to treatment arm. The objective of the second (effectiveness confirmation) stage is to confirm the impact of the selected acupuncture arm on pain reduction. An interim analysis is planned at the end of Stage 1 based on probability of being the best treatment, after which adaptations will be considered including dropping the less effective arm, sample size re-estimation, and unequal treatment allocation ratio (e.g., 1:2) for Stage 2. Acupuncture treatments will be delivered by licensed acupuncturists in the ED and twice weekly for 1 month afterward in an outpatient clinic.

Ethics and dissemination: This study has been reviewed and approved by the Duke University Health System Institutional Review Board. Informed consent will be obtained from all participants. Results will be disseminated through peer review publications and public and conference presentations.

Trial registration number: ClinicalTrials.gov: NCT04290741

Article Summary

Strengths and limitations of this study

- Two-stage adaptive design balances improved implementation with statistical power to measure effectiveness of acupuncture.
- Two types of acupuncture, (battlefield) auricular and peripheral, enable efficient emergency department treatment and are compared to control.
- Pragmatic design better replicates real-world conditions but limits assessment of specific vs non-specific effects of acupuncture on pain outcomes.
- Includes longitudinal delivery of acupuncture treatments in both the emergency department and outpatient clinic for one month to treat acute musculoskeletal pain.
- Breadth of biopsychosocial outcomes to assess how acupuncture works and help bridge the gap between eastern and western medicine.

Introduction

Over 40 million adults in the United States (US) suffer from chronic pain, which is pain lasting three months or longer.[1] Musculoskeletal pain, one of the largest subsets of chronic pain conditions, leads to high rates of healthcare utilization, increased opioid use, and poor physical, psychological, and cognitive health.[1] Musculoskeletal pain often results from an acute injury, and if not adequately treated, can transition to a chronic pain condition.[2,3] Significant challenges exist for adequately managing musculoskeletal pain due to the heterogenous nature of its causes and pain symptomatology, and standard treatments are often ineffective.[4,5] Additionally, numerous biological (e.g., inflammatory mediators), psychological (e.g., pain catastrophizing), and social (e.g., social support) factors (referred to collectively as "biopsychosocial" factors) contribute to the complexity of musculoskeletal pain development, severity, progression and disability.[6] Recent studies have begun to explore the role of biopsychosocial factors in the transition from acute to chronic pain and how they may serve as targets for intervention.[3,7] One strategy to prevent the transition from acute to chronic pain is early intervention using nonpharmacologic strategies that influence these biopsychosocial factors. The Emergency Department (ED) represents a novel setting in which to test nonpharmacologic interventions early in the pain trajectory with the goal of preventing the transition from acute to chronic musculoskeletal pain.

Acupuncture is a safe and cost-effective treatment for acute and chronic pain, particularly of the back, neck, and shoulder.[8,9] Furthermore, acupuncture has shown benefit in treating both pain and anxiety,[8] and acts on numerous neural, endogenous opioid and inflammatory pathways,[10] thereby representing a broader biopsychosocial intervention than other single pain treatment modalities. However, data on the use of acupuncture for pain management in the ED is limited since acupuncture practitioners are not currently standard or commonplace in US EDs.[11,12] A recent meta-analysis of ED studies has shown acupuncture to be superior to sham/placebo and equivalent or better than medications for pain reduction.[11,13] Only three small pilot studies have compared acupuncture combined with usual care to usual care alone, with results favoring acupuncture.[11,14] No study has compared different acupuncture protocols (e.g., battlefield/auricular acupuncture and peripheral acupuncture) to determine which is more efficacious, feasible or acceptable in the ED. Moreover, despite evidence that acupuncture is more effective with multiple sessions,[15] prior ED studies have not included a longitudinal outpatient acupuncture component for post-ED pain management or longer-term outcomes.

Therefore, the purpose of this study is to determine the effectiveness, feasibility and acceptability of acupuncture initiated in the Emergency Department (ED) and continued in a group clinic setting for treating acute musculoskeletal pain. The ED population is largely heterogeneous in sociodemographic composition and comprises populations previously excluded from acupuncture studies.[16] A **pragmatic randomized controlled trial** can determine the extent to which ED patients will attend and derive benefit from the full acupuncture experience, while extending the scope and assessment of treatment effectiveness to a more broadly representative U.S. patient population. We hypothesize that, when added to usual care, acupuncture initiated in the ED and continued in an outpatient setting for one month is more effective than usual care alone at reducing acute musculoskeletal pain at 1 hour while in the ED and at 1 month after ED visit.

METHODS AND ANALYSIS:

Study design

This pragmatic clinical trial uses a two-stage adaptive randomized design to determine the feasibility, acceptability, and effectiveness of acupuncture initiated in the Emergency Department (ED) for treating acute musculoskeletal pain. The objective of the first (treatment selection) stage is to determine the more effective style of ED-based acupuncture, i.e., Auricular Acupuncture (AA) based on the Battlefield Acupuncture protocol, or Peripheral Acupuncture (PA), as compared to no acupuncture (NA). The objective of the second (effectiveness confirmation) stage is to confirm the impact of the selected acupuncture arm on pain reduction. An interim analysis is planned at the end of Stage 1 based on probability of being the best treatment,[17] after which adaptations will be considered including dropping the less effective arm, sample size re-estimation, and unequal treatment allocation ratio such as 1:2 ratio for effectiveness in Stage 2. Acupuncture treatments will be delivered by licensed acupuncturists in the ED and up to 2 times per week for 1 month afterward in an outpatient clinic. In this pragmatic design, all study arms will receive usual care for pain management at the discretion of the ED provider who will be blinded to treatment arm.

Study setting and recruitment

Trial participants will be recruited from the Duke University Hospital Emergency Department (ED), an urban academic tertiary care referral center in North Carolina with 80,000 ED visits per year. All study screening, recruitment, informed e-consent (Appendix 1), and enrollment procedures will be performed by trained clinical research coordinators. Study acupuncturists will be available during enrollment to explain acupuncture treatment to eligible patients. Outpatient acupuncture visits will be scheduled with the study acupuncturists using secure HIPAA-compliant scheduling software and take place at the Duke Integrative Medicine Clinic. Patient recruitment began in February 2020 and is ongoing. The study start date is February 10, 2020, and planned end date is February 28, 2023.

Eligibility Criteria

Inclusion criteria

Participants must be adult (age 18 years or older) ED patients with pain in the neck, back, arms and/or legs and a clinical diagnosis of acute (≤7 days) musculoskeletal pain as determined by an ED provider, and able to read and understand the consent form in English. Participants with acute exacerbation of chronic pain in which the acute component is ≤7 days will be included, as this is a common ED presentation.[18]

Exclusion criteria

Patients will be excluded if they are: (1) suspected to have a non-musculoskeletal cause of pain, (2) unable to receive acupuncture due to injury, infection, or other contraindication to the use of needles at acupuncture sites; (3) not possible to attend outpatient clinic (e.g., visiting from out-of-state); (4) unable to provide informed consent or to comprehend or complete study measures or procedures due to cognitive impairment, including evidence of drug, medication or alcohol intoxication, or due to severe hearing or speech impairment; (5) unable to safely participate due

to critical illness, obvious bony deformity, other serious medical condition (including active COVID-19 infection), and/or based on ED provider judgment.

Randomization and Blinding

Subjects will be randomized 1:1:1 to one of three treatment groups: 1) auricular acupuncture (AA), 2) peripheral acupuncture (PA), or 3) the control group with no acupuncture (NA). The randomization code will be computer-generated by the Biostatistics, Epidemiology and Research Design (BERD) Methods Core of the Department of Biostatistics and Bioinformatics, Duke University Medical Center. An unstratified block randomization method will be used to generate the random allocation sequence, which will be stored in a secure electronic file accessible only by the acupuncturists to ensure allocation concealment. The research coordinator enrolling eligible patients will be blinded to the allocation sequence and randomization assignments. After participant baseline measures and acupuncturist initial clinical assessment, the treating acupuncturist will open the randomization file and assign the participant to the treatment group corresponding to the next sequential entry.

The participants and the acupuncturists will not be blinded to their treatment allocation. All other members of the ED clinical and research teams will be blinded. Round stickers will be applied to the ears of all participants at the battlefield protocol sites to blind these members to patient assignment while in the ED. If the participant reports an adverse event, the research coordinator may become unblinded to record and address the event. Due to the adaptive nature of the statistical design, the statisticians and data safety monitoring committee (DSMC) will be unblinded to the control treatment arm in Stage 1 to perform the interim analysis; the statistician analyzing the data will remain blinded to the treatment arms. All other study investigators will remain blinded.

Interventions

Acupuncture will only be performed by licensed acupuncturists. For this study, two styles of acupuncture designed to increase feasibility in the ED will be employed. (1) Auricular acupuncture (AA) will involve the placement of pyonex needles in up to 5 sites on each ear based on the previously developed battlefield acupuncture protocol to treat pain.[19,20] (2) Peripheral acupuncture (PA) will involve the placement of needles in head, neck, arms, legs, hands, and feet sites selected at the clinical discretion of the treating acupuncturist based upon acupuncture diagnosis as the primary mode of therapy.[21,22] Acupuncture sites on the torso (i.e., chest, back and abdomen) will not be used, as accessing these sites is often logistically challenging in a busy ED environment. Both acupuncture groups will receive acupuncture while in the ED. Afterwards, both groups will receive information and free access to acupuncture in an outpatient clinic for up to 2 times a week for 1 month after their ED visit. Our outpatient acupuncture clinic is designed as a group-based clinic modified for COVID-19-related social distancing to enhance access and affordability. All post-ED outpatient acupuncture treatments for both acupuncture groups will involve either PA, AA or both at the clinical discretion of the treating acupuncturist. The specific components of each acupuncture treatment will be recorded in details according to the revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) recommendations.[23] (3) The control group (no acupuncture = NA) will not receive acupuncture in the ED and will be asked not to seek acupuncture treatment for

one month after their ED visit. Control group participants will complete assessments only, with the timing and content of their assessments matching those completed by the intervention groups.

All participants in the control group and in both acupuncture groups will receive usual care for acute pain management at the discretion of their ED provider who will remain blinded to study arm. Usual care may include but is not limited to medications/analgesics, nonpharmacologic strategies (e.g., ice, heat, walking), and referrals to outpatient specialists and/or other nonpharmacologic treatment providers (e.g., physical therapy).

Outcomes

Outcome measures and biopsychosocial factors will be collected before randomization (ED baseline), 1 hour after randomization, and at 2 weeks and 1 month post-ED visit.

Primary Outcome Measures

The primary ED effectiveness endpoint will be the change in current pain score based on the 0-10 pain numeric rating scale (NRS) from ED baseline to 1 hour post-treatment. The primary combined ED-outpatient clinic effectiveness endpoint will be change in 24-hour average NRS pain score from ED baseline to 1 month post-ED visit.

Feasibility will be assessed based on patient recruitment and retention rates both in the ED and with subsequent one-month follow-up. Acceptability will be assessed based on patient-reported satisfaction as well as outpatient acupuncture clinic attendance rates, with attention to reasons for attrition or differential acceptance rates for different groups of participants. Safety will be evaluated by recording any adverse events (AEs), with common reasons to include bleeding, bruising, or pain at the needle sites. Serious adverse events (SAEs) are expected to be extremely rare given previous highly favorable safety data on acupuncture, and include infections, hospitalizations and deaths.[21,24]

Secondary Outcome Measures

Secondary outcomes will include patient function, quality of life, and biopsychosocial factors.

Function and quality-of-life will be measured at ED baseline, 2 weeks and 1 month across several different domains, including pain interference, fatigue, depression, anxiety, sleep disturbance, physical function, social function, and cognitive function, using the validated PROMIS-29 and Neuro-QoL instruments.[25,26] Given the acute time course of pain (7 days or less) for eligible participants, the timeframe for the PROMIS-29 questions will be modified from “over the past 7 days” to “over the past 24 hours (1 day)” for the ED baseline assessment only. We will also measure patient-reported medication use, including opioid and non-opioid medications. Opioid use will be assessed through patient report in the past 24 hours and in the past 7 days, as well as by electronic medical record (EMR) data extraction of prescriptions written during and up to one year after the ED visit.

A comprehensive set of biopsychosocial factors will be measured at ED baseline and one-month follow-up. These include:

(1) Patient demographics including age, sex, race, ethnicity, employment, marital status, education, income, and insurance status.

(2) Pain characteristics including anatomical location of pain, duration of current episode of musculoskeletal pain, and history of prior episodes of musculoskeletal pain.
(3) Degree and type of social support, including instrumental, informational, and emotional support, will be measured using the PROMIS Social Support 4-item scales.[27]
(4) All non-medical substance use, including opioid misuse, through the validated ASSIST tool.[28]
(5) Presence and severity of chronic pain using a recently validated simplified version of the graded chronic pain scale derived from the 3-item pain, enjoyment and general activity (PEG) score and degree of activity limitations.[29,30]
(6) Symptoms of systemic pathology will be measured using the validated Optimal Screening for Prediction of Referral and Outcome Review of Systems (OSPRO-ROS) tool, which predicts pain outcomes after musculoskeletal care in outpatient physical therapy settings.[31,32]
(7) Pain-related psychological distress using the validated concise Optimal Screening for Prediction of Referral and Outcome Yellow Flag (OSPRO-YF) tool, an assessment tool for measuring psychological response to pain including pain coping, catastrophizing, fear-avoidance and mood [32,33].
(8) Pain-related emotional distress based on the Perceived Stress Scale (PSS) tool.[34]
(7) Pain coping skills using the Coping Skills Questionnaire 2-item form (CSQ-2).[35]
(8) Pain self-efficacy using the Pain Self-Efficacy Questionnaire (PSEQ).[36]

Two additional measures will be collected in-person in the ED at baseline and 1 hour:
(9) Pressure pain threshold, a non-invasive quantitative test of pain sensitivity that measures the lowest applied pressure needed to evoke to an individual's perception of pain, will be performed on the bilateral trapezius muscles using slow progressive pressure (1 kg/cm^2/sec) with a standard hand-held algometer (Wagner Digital Force Gauge, Wagner Instruments, Greenwich, CT).[37,38]
(10) Blood samples will be collected and stored in a secure repository for future biomarker analysis of biochemical and genetic pathways involved in pain and response to acupuncture. Participants may opt out of the blood draw and still participate in the clinical trial.

Additional EMR data will be extracted by trained analysts and include medications administered and prescribed from the ED, opioids prescribed up to one year following index ED visit, return ED visits and hospitalizations up to 3 months following index ED visit, and ICD-10 codes for pain conditions and co-occurring diagnoses (e.g., medical and psychiatric comorbidities).

Data Collection and Management

Data will be collected at ED baseline, 1 hour post-treatment, and at 2 weeks and 1 month post-ED visit, with data entered directly into a REDCap secure electronic database.[39] All in-person biological measures including pressure pain threshold and blood draws for biomarkers will be obtained during the ED visit at baseline and 1 hour by research coordinators embedded in the ED. Pressure pain threshold will be recorded in REDCap. Blood samples will be coded with a unique study identifier and deidentified for storage.

ED baseline and 1-hour questionnaires to collect biopsychosocial factors and outcome measures will be completed by participants independently and entered directly into REDCap

while they are in the ED (**Figure 1**). Research coordinators will be available for assistance with data entry if requested by participants. Participants will be contacted at 2 weeks and 1 month post-ED visit to complete online REDCap follow-up surveys (**Figure 1**) using follow-up procedures to facilitate maximum study retention. These procedures include up to three automated electronic follow-up surveys sent via email, automated text message links to the surveys, follow-up phone calls by ED research assistants with the option to complete surveys by phone, and compensation for one-month follow-up assessment completion.

Acupuncturist assessments and treatment details in the ED and outpatient clinic will be entered directly into REDCap forms by the treating acupuncturist. ED medication data will be entered into REDCap forms by research coordinators. Acupuncture AEs and SAEs will be entered into REDCap forms by the study personnel notified of the event, and follow-up of the events will be completed within the same forms by the personnel completing follow-ups. Additional EMR data will be extracted by trained analysts and stored in a protected analytics environment. All data will be stored for at least 5 years after study completion for primary and ancillary studies, with access restricted to study staff, and is included in patient consent. To protect confidentiality, no personal information will be shared.

Sample size

For Stage 1, a total of 90 subjects (30 subjects per arm) will be used to (i) assess feasibility based on patient recruitment and retention rates, and (ii) determine the more effective arm at the ED one-hour timepoint for moving forward to Stage 2 for effectiveness confirmation. Sample size calculation for achieving Stage 2 study objectives assumed[17,40,41]: (1) a Stage 2 two-arm parallel design with 1:2 control:treatment allocation; (2) the primary endpoint is normally distributed; (3) with no acupuncture, a mean pain score of 6.5 with a standard deviation of 2.5;[42] (4) a minimally clinically meaningful difference in pain score of 1.3;[42] (5) a power of 90.0%; and (6) a 5% level of significance. This yielded a total sample size of 198 subjects (**Table 1**) at the end of Stage 2. To account for a possible 10% dropout rate requires increasing the total number enrolled to 220 subjects.

Table 1. Sample Size Estimation and Allocation

Stage	Randomization	Sample Size	Total
Stage 1	1:1:1	30 (NA), 30 (AA), 30 (PA)	90
Stage 2	1:2	36 (NA), 72 (AA or PA)	108
		Total	198

Data Analysis and Statistical Methods

Population: The primary analysis will be performed based on the intention-to-treat (ITT) population, which is defined as all randomized subjects who have at least one follow-up evaluation regardless of their compliance with the protocol. In case of a substantial number of protocol violations, additional per-protocol analyses may be performed to determine whether they influence the conclusions.

General Analysis Conventions/Rules: Descriptive statistics for continuous variables will be provided as: number of subjects, means and standard deviations, medians and interquartile

ranges, and minima and maxima. Descriptive statistics for discrete (categorical) variables will be provided as the number and percentage of subjects in each category. Time to event variables will be provided using Kaplan-Meier survival curve estimates. Unless otherwise noted, any tests of hypotheses are two-sided, and the nominal level of significance will be 5%.

Handling of Missing Data: Imputation of missing data will be handled depending on the missingness mechanism.

Baseline Comparability: Number of subjects randomized, completing the study and reasons for discontinuation will be summarized by treatment group. Patient demographics and baseline characteristics including biopsychosocial factors will be tabulated and compared for treatment group differences. All comparisons will be performed by using the Cochran-Mantel-Haenszel (CMH) test for categorical variables and two-way analysis of variance for continuous variables.

Primary Analysis: The primary variable, change in pain score from ED baseline to 1 hour post-treatment, will be evaluated and compared between treatment groups. The corresponding 95% confidence interval for the difference in mean response rate between treatment groups will be obtained using analysis of variance (ANOVA).

Secondary Analyses: Responder analysis will also be performed using a logistic regression analysis that incorporates potential risk factors identified for response. Point estimate and the corresponding 95% confidence interval of odds ratios for the identified risk factors will also be obtained. In addition, the Stuart-Maxwell test may be performed to examine changes (or shifts) from baseline to follow-ups after ED discharge.

Exploratory Analyses: Exploratory analyses such as biomarker changes pre to one-hour post-treatment, subgroup analyses based on patient demographics and/or patient characteristics, and predictive model building, validation, and/or generalizability may be conducted as deemed appropriate by the principal investigator(s), biostatistician or as recommended by an internal established data safety monitoring committee (DSMC). These include secondary analyses of the impact on outcomes of the number of acupuncture needle sites or number of acupuncture pathways used, number of clinic visits attended, within treatment pain and/or anxiety reductions, among others. If possible, additional exploratory models predicting response to acupuncture based on biopsychosocial factors will be examined.

Safety Analysis: Table will show the AEs ordered by decreasing frequency for all participants. Separate tabulations will summarize the AEs by seriousness, severity, and possible association with study drug. If appropriate, the incidence rate of AEs will be compared by Fisher's Exact Test. Special attention will be given to those subjects who have discontinued due to AEs and those subjects who experienced a SAE.

Interim Analysis: There will be one planned interim analysis which will take place when two-thirds of subjects (i.e., 20 of 30 subjects per arm) have completed Stage 1. At interim analysis, the feasibility will be assessed based on patient recruitment and retention rates, and the more

effective arm will be determined based on change in pain score at the one-hour ED timepoint based on probability of being the more effective treatment.[17] Some adaptations such as modifying current treatment arm, different randomization scheme, additional interim analyses, and/or sample size re-estimation may be applied as recommended by the DSMC.

Data Monitoring

A data safety monitoring committee (DSMC) comprised of an independent biostatistician, emergency medicine physician-researcher and a medical acupuncturist-pain medicine clinician will meet at least 2 times per year with ad hoc reports as needed, to monitor the safety and performance quality of the trial. The DSMC will also evaluate the interim analysis to make recommendations on adaptations for Stage 2 to the study investigators.

AEs and SAEs and their follow ups will be recorded in a secure REDCap file. AEs will be reviewed weekly, and SAEs will be reviewed immediately by the principal investigator and lead research coordinator and addressed as needed. All SAEs will be reported within 24 hours to the DSMC, IRB and study sponsor.

Ethics and Dissemination

The Duke University Health System Institutional Review Board has reviewed and approved this study (Protocol # Pro00104140). This trial was registered on 2/7/2020 with clinicaltrials.gov (registration # NCT04290741) and released to the public on 2/28/2020. We used the SPIRIT checklist when writing our report.[43] Upon completion of the trial, the results will be disseminated through peer review publications as well as presentations at professional organization conferences and to the public including healthcare organizations.

Patient and Public Involvement

Patients and the public were not involved in the original design of the study. However, patient participants will be interviewed for feedback on their acupuncture and research experience to potentially inform future adaptations.

Discussion

Adaptive design: The innovative adaptive design of this study enables findings from the first stage to be used to increase the likelihood of success in the second stage for measuring the true effectiveness of acupuncture in an ED population. Adaptations to drop the least effective arm and/or mitigate issues that arise in Stage 1 are designed to optimize implementation of acupuncture for both the study and its broader applicability to other settings.[44] Efforts will be made to limit potential bias from adaptations and maintain trial integrity and validity by utilizing an independent DSMC to decide on any adaptations.

Novel care pathways: This will be one of the first randomized trials to integrate acupuncture into ED care and to establish linkages to outpatient acupuncture treatment. It will also be one of the first acupuncture studies to include a diverse sociodemographic population and to utilize a group-based clinic to enhance access and affordability of this treatment option.[16] Patient knowledge of, access to, and availability of nonpharmacologic therapies are frequent barriers to use.[16,45] Post-ED follow-up can be particularly challenging among ED patients due to cost

and time constraints, so lowering these barriers are key to improving access to care. Furthermore, initial therapeutic experience with acupuncture has been shown to increase patient follow-through with continued acupuncture,[46] highlighting the benefit of combining ED with outpatient care. Goals of the study include reducing patient need for pain medications, particularly opioids, and return ED visits for pain control through use of acupuncture. Our findings will inform future ED and follow-up acupuncture treatment recommendations.

Tailoring Acupuncture to the ED environment: Comparing auricular acupuncture (AA) to peripheral acupuncture (PA) in the ED setting is a key component of our study, as it allows further exploration of the feasibility and acceptability of ED-based acupuncture through two different patient experiences. AA can be delivered quickly, easily, and without removal of clothing, thus fitting well within the space and time constraints of the ED environment.[19] Furthermore, specific types of auricular needles can be left in place for later self-stimulation by patients to provide additional pain relief for an additional 1-5 days.[19,47] Use of AA can be limited by patient discomfort with needles in the ear, potential compatibility issues with obtaining CT and MRI imaging while needles are in place, and lack of clinical guidelines for its use.

Peripheral acupuncture (PA) allows for greater personalization of treatment than AA by offering a much larger number of meridians or channels that the acupuncturist can access for pain relief.[48,49] PA also offers the flexibility to adapt treatments for very anxious or needle-sensitive patients because needle depth and level of stimulation can be modified to suit individual needs. While tight clothing may limit the number of accessible acupuncture points, this is typically not a major barrier for experienced acupuncturists.

While PA can take longer for the patient, 20-45 minutes for PA compared with 10-20 minutes for AA, spending more time with the acupuncturist can contribute to their increased sense of support and better anxiety relief. In addition, PA can be more efficient for the acupuncturist than AA when treating multiple patients, as the acupuncturist can leave one patient while needles are in place to tend to the next patient, returning later for needle removal and session completion. By contrast, AA involves frequent patient reassessments between each needle insertion requiring the acupuncturist's full attention until session completion before proceeding to the next patient.

Usual care for ED pain management: The choice of usual care for all treatment arms was based on the goal of developing a practical and feasible intervention in the ED setting where medications are expected by patients but can be variably prescribed among providers.[50,51] Therefore, restriction of medications from any one arm could be perceived as undesirable or unethical by ED patients seeking care. In addition, choice of medication can depend on many factors, including provider and patient preferences, and allergies, adverse reactions, or contraindications to specific medications. Therefore, in order to increase the applicability of our findings, the decision was made to allow provider judgement to dictate medication choice as well as dosing. This has the added benefit of managing breakthrough pain through usual ED provider reassessment and repeat dosing as deemed clinically appropriate. ED providers were kept blinded to treatment arm so that their usual clinical judgement determined usual care treatment. Thus, the results of this trial will reflect the results expected in actual clinical practice in an academic ED.

The choice of no acupuncture for the control group as compared with sham or other placebo was based on the goal of studying the effect of acupuncture in a pragmatic setting. Given the high volume, high throughput environment of most US EDs, there is not a typical usual care option that would equate to a placebo or sham intervention. For instance, most EDs do not have the time or resources to routinely provide another nonpharmacologic practitioner or additional ED staff member who could devote extra time for patient support. Thus, the alternative to acupuncture in most settings would simply be no acupuncture, with a focus on medication prescriptions, supportive care, and/or, less commonly, outpatient referrals (e.g., primary care, physical therapist, orthopedist) for further management.

Breadth of Study Outcomes: This study will also generate data on biopsychosocial factors to better characterize the population of patients seen in the ED for acute musculoskeletal pain. Exploration of these factors may also identify mediators of the patient response to acupuncture. These mediators may help identify patients more likely to improve with acupuncture and/or better elucidate potential mechanisms of acupuncture's therapeutic effects. Findings from this study will further our understanding of acute pain and its nonpharmacologic management through acupuncture, as well as their associations with the comprehensive set of biopsychosocial factors.

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Author contributions
SAE drafted the study protocol manuscript. OG, CAS, and MRK participated in the design of the study and revising the protocol manuscript. SC, MK and AG were responsible for the statistical design of the study and revising the protocol manuscript. CDL, MM, AD, AMM and ATL provided clinical advice and made critical revisions to the protocol and manuscript. EW, AO, OT and JD were involved as clinical research coordinators in revising and editing the protocol and manuscript. SAE is principal investigator of the study and is responsible for making final decisions on the trial design and manuscript preparation. All authors approved the final manuscript.

Protocol version: 1.27, Date 02/25/2021

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The study funders had no role in the study design, collection or analysis of data.

Competing interests
None declared.

Patient consent
Obtained. See Appendix 1.

Ethics approval
The Duke University Health System Institutional Review Board has reviewed and approved this study on January 29, 2020 (Protocol No: Pro00104140).

Data availability statement
Not applicable.

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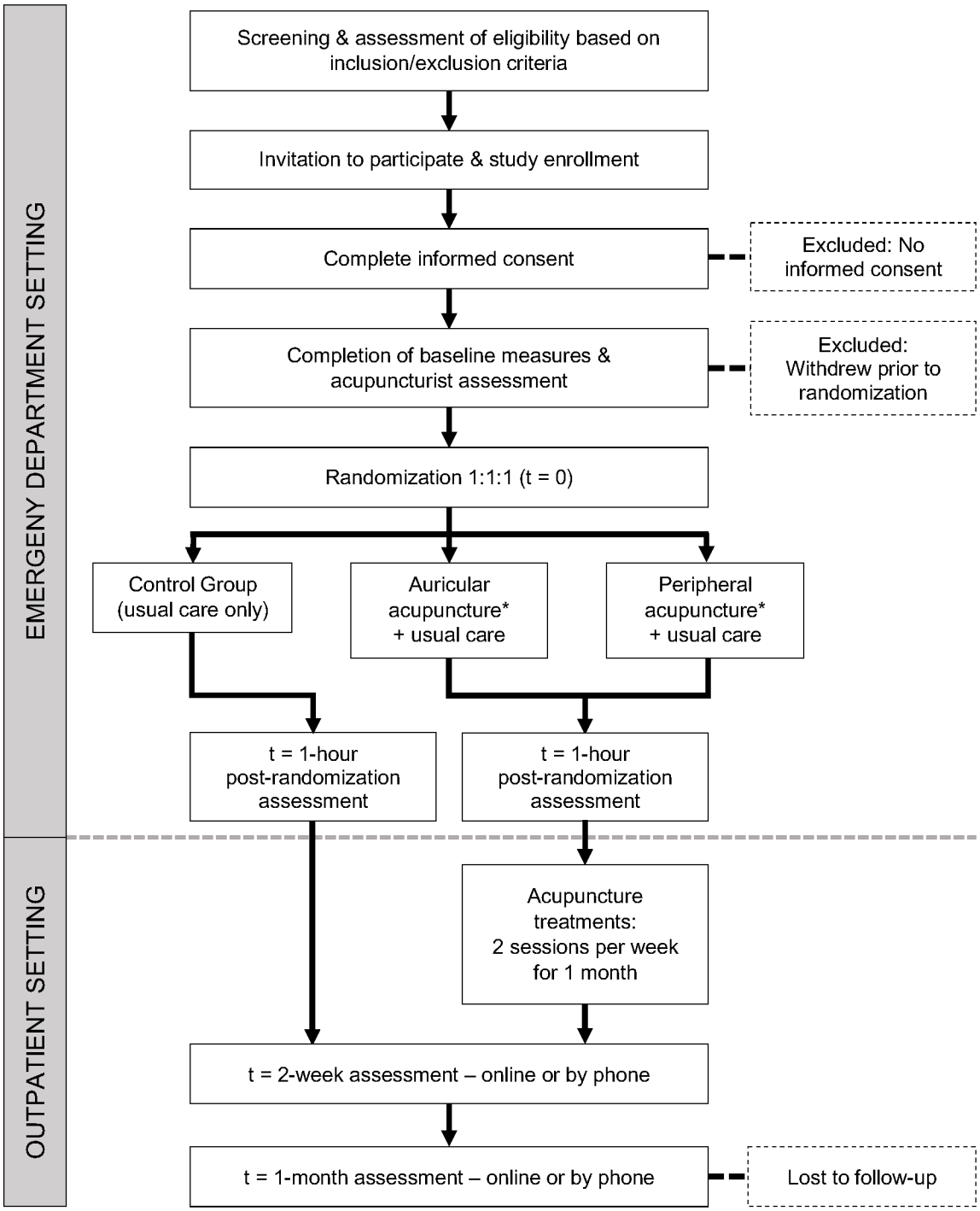
Figure captions:

Figure 1. Trial flowchart. After interim analysis in Stage 1, the less effective acupuncture arm will be dropped.

Appendix 1. Example informed consent form

Figure 1. Trial flowchart



Form M0345

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
Emergency Department Acupuncture for Musculoskeletal Pain Management

CONCISE SUMMARY

The purpose of this study is to measure how well acupuncture (the insertion of very thin needles through your skin at strategic points on your body) improves pain and function, as well as its feasibility, acceptability, and safety in the Emergency Department (ED).

If you agree to participate in this study, you will have an initial assessment with a pain threshold test, study questionnaires, and optional blood draw. You will be randomly assigned to receive either one of two types of acupuncture or no acupuncture. Acupuncture will be performed by a North Carolina Licensed Acupuncturist while in the ED. One hour after your group assignment you will complete a second pain threshold test, study questionnaires, and optional blood draw. After your ED visit, if you are assigned to acupuncture you will attend acupuncture at an outpatient clinic twice a week for 4 weeks. You will be asked to complete questionnaires at 2 and 4 weeks after your ED visit. If you are assigned no acupuncture, you will be asked not to receive any acupuncture for 4 weeks after your ED visit, and you will only complete the questionnaires. Your data and samples collected for this study may be stored and shared for future research.

Risks associated with acupuncture include pain at the site of needle insertion, bruising, and bleeding. There are risks related to loss of confidentiality, but every effort will be made to safeguard your information.

If you are interested in learning more about this study, please continue reading below.

You are being asked to take part in this research study because you presented to the Emergency Department with a musculoskeletal pain (pain that affects the muscles, bones, and/or tissues that connect them).

Research studies are voluntary and include only people who choose to take part. Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

Please tell the study doctor or staff if you are taking part in another research study.

WHO WILL BE MY DOCTOR ON THIS STUDY?
If you decide to participate, Dr. Stephanie Eucker will be your doctor for the study and will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed. This study is sponsored by the Duke Endowment and the Substance Abuse and Mental Health Services Administration (SAMHSA).

Form M0345

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
Emergency Department Acupuncture for Musculoskeletal Pain Management

WHY IS THIS STUDY BEING DONE?
Musculoskeletal pain is one of the most common reasons for doctors' office and emergency department visits. Painful episodes can lead to significant disability and ongoing disruption of daily functioning.

Acupuncture involves the insertion of very thin needles through your skin at strategic points on your body. It is not well-understood how acupuncture works, but there is some evidence that it is safe and cost-effective in outpatient settings for management of acute and chronic pain, particularly of the back, neck, and shoulder. Acupuncture is most often used to treat pain and anxiety in the clinic setting, but has not routinely been used in the ED.

The goal of this study is to measure how well acupuncture relieves pain and improves function, as well as its feasibility, acceptability, and safety in the ED.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
Approximately 750 people will take part in this study at Duke.

WHAT IS INVOLVED IN THE STUDY?
If you agree to be in this study, you will be asked to sign and date this consent form. If you sign this form electronically, you will be asked to provide your email address so that a copy of it can be emailed to you. By providing your email address for use in the consent process, you are at potential risk for a loss of confidentiality because email is not a secure means of communication.

You will undergo an Initial Assessment that includes the following:

- Pressure Pain Threshold test. This is a non-invasive test that uses a device that applies pressure to your body (shoulder muscle) to measure the amount of pressure that causes mild pain.
- Blood draw for biomarker measurements that is optional (approximately 3-4 teaspoons)
- Completion of questionnaires

You will be randomly assigned, like drawing numbers from a hat, to one of three groups listed below. You have an equal chance of being assigned to each group and a 2 out of 3 chance of getting acupuncture.

- Ear (auricular) acupuncture – placement of needles in up to 10 sites total in both ears
- Peripheral acupuncture – placement of needles in up to 30 specific sites in the head, neck, arms from the shoulders to the hands, and legs from the knees to the feet
- Control – no acupuncture

The acupuncture treatments will be performed in an Emergency Department examination room by a North Carolina Licensed Acupuncturist. Acupuncture consists of inserting single use, sterile, acupuncture needles, measuring 0.16-0.22mm in thickness (about the thickness of a hair) and varying in length from 1.5-5cm (0.5-2 inches). The skin will be cleansed prior to needle insertion, and needles will be placed utilizing clean needle technique. Needle insertion depth will vary between 0.5 cm (0.2 inches) and 4.5 cm (1.8 inches) (through the skin and sometimes muscle layers only), depending on the area of

Form M0345

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study
Emergency Department Acupuncture for Musculoskeletal Pain Management

treatment. Needles will be retained for up to 30 minutes. Auricular acupuncture needles are much smaller, 0.15 cm (0.06 inches) in length (only through the skin), attached to a bandaid adhesive so they can be retained for up to 4 days. All needles can be removed earlier at your request. All acupuncture performed adheres to the guidelines of Clean Needle Technique as required by North Carolina law.

Regardless of which group you are assigned to, you will also receive the usual care for musculoskeletal pain, including medications and other non-medication pain treatments such as ice/heat at the discretion your ED doctor.

You will receive the usual care for acute pain management as determined by your ED doctor.
If you are assigned to the control group you will not receive acupuncture. If you are assigned to one of the acupuncture groups, you will receive acupuncture in the ED. The session will last approximately 15-30 minutes.

One hour after you have been assigned to a treatment group you will be asked to complete a brief questionnaire, a pressure pain threshold test, and have an optional second blood draw (3-4 teaspoons) for research for future biomarker analysis.

Blood collection for biomarkers in this study is optional. Biomarkers are substances in the body that can be indicators of a disease. You do not have to allow for research blood draws to participate in this study. If you agree to blood collection, samples will be taken during and one hour after completion of the initial assessment in the ED.

Please initial below indicating whether or not you agree to research blood draws.

_____ Yes, I agree to undergo a blood draw for research purposes.

_____ No, I do not want to undergo a blood draw for research purposes.

If you are assigned to an acupuncture group, we will provide you with information and free access to group-based acupuncture in the outpatient Integrative Medicine clinic for the next 4 weeks. There will be two sessions per week, and each session will last approximately 30 minutes. You will be asked to provide your phone number and email address to schedule your acupuncture visits. Your name and contact information will be entered into an online scheduling program, Microsoft Bookings. This program will be used to schedule your acupuncture appointments and send appointment reminders.

If you are assigned to the control group, you will not receive acupuncture in the ED, and we ask that you not receive acupuncture for 4 weeks after you sign this consent form. Current research supports that acupuncture will still be effective in treating pain after that time, should you choose to seek acupuncture treatment after participation in the study.

Form M0345

DUKE UNIVERSITY HEALTH SYSTEM

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Regardless of which group you are assigned to, you will be asked to complete questionnaires about your pain, pain management, and quality of life at 2 and 4 weeks after your ED visit. You will receive emails at these time points with a link to the study questionnaires. If you have not completed these within a few days of receiving the email you may be contacted by a member of the study team via text message and/or phone to ensure you are able to access the link. If you have trouble with the link or prefer to answer by phone the questionnaires may be completed via phone.

You may be asked to complete an interview via phone. Interviews will be conducted by a member of the study team. We will ask you questions about your experience with the study and research study materials. This interview will last approximately 15 to 30 minutes. The interviews will be recorded. Recordings may contain your name and age. Your interview will be transcribed within 2 to 3 months and any identifying information will be deleted. Recordings will be stored until the data analysis for this study is complete, approximately 2 years, at which time they will be deleted. Recordings and transcriptions of interviews will be stored in a secure folder that only the study team has access to.

HOW LONG WILL I BE IN THIS STUDY?
If you agree to be in this study, your participation will last approximately 4 weeks. You can choose to stop participating at any time without penalty or loss of any benefits to which you are entitled. However, if you decide to stop participating in the study, we encourage you to talk to your doctor first.

WHAT ARE THE RISKS OF THE STUDY?
Acupuncture may occasionally result in slight bruising, pain at the site of needle insertion, and bleeding, dizziness, and numbness or tingling near the needling sites that may last a few days.
Infection, excess bleeding, or fainting are also possible, although unlikely.

Risks associated with drawing blood from your arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

There is also a risk of loss of confidentiality of your private information. Every effort will be made to protect your information, but this cannot be guaranteed. By providing your email address you are at potential risk for a loss of confidentiality because email is not a secure means of communication.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
There may be direct medical benefits to you for participating in this study. If you are assigned to an acupuncture group, you may have decreased pain but that cannot be guaranteed. A potential benefit of this study is to gain knowledge that may lead to improved pain management in the ED in the future. If you are randomized to the no acupuncture group there is no expected benefit above standard of care.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total confidentiality. By providing your email address for use in the consent process, you are at risk for a loss of confidentiality because

Subject Initials _____

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email is not a secure means of communication. Your personal information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding, and regulating the study. Your date of birth, dates related to your ED visit, acupuncture visits, and any tests or procedures you have had will be collected for this study. Your name, phone number, and email address will be shared with Microsoft Bookings. We will share only the minimum necessary information in order to conduct the research. Your personal information may also be shared if required by law.

Your records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration, the Substance Abuse and Mental Health Services Administration (SAMHSA), the Duke University Health System Institutional Review Board, and others as appropriate. If any of these groups review your research record, they may also need to review your entire medical record.

The study results will be retained in your research record for at least six years after the study is completed.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your identity will not be revealed.

Some recipients who receive your health information might not have to follow the same privacy rules. Once your information is shared outside of DUHS, we cannot guarantee that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect your health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

WHAT ARE THE COSTS TO YOU?
You or your insurance provider will be responsible and billed for all costs related to your routine medical care, including copayments and deductibles. Routine medical care services are those that you would have received for your condition if you were not participating in this research study. Not all services are covered by insurance. The amount of your out-of-pocket expense will depend on your insurance plan.

Services and procedures that are done solely for research purposes will be paid for by the study. This includes the cost of both inpatient and outpatient acupuncture and costs related to blood draws (if applicable). Please talk with the PI/study team about the specific services and procedures that will be paid for, and the ones for which you or your insurance will be responsible.

We will monitor your DUHS patient care charges to make sure that costs are directed appropriately. If you have any questions or concerns about appropriate billing, contact your study team coordinator so that he/she can help find a resolution.

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WHAT ABOUT COMPENSATION?
You will receive a $30 Amazon gift card after you complete the 4-week follow up survey. Gift cards may be sent via email or text message after the surveys have been completed.

WHAT ABOUT RESEARCH RELATED INJURIES?
Immediate necessary medical care is available at Duke University Medical Center in the event that you are injured as a direct result of your participation in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., or your Duke physicians to provide monetary compensation or free medical care to you in the event of a study-related injury.

For questions about the study or research-related injury, contact Dr. Eucker at 919-684-5537 during regular business hours and at 919-684-8111 after hours and on weekends and holidays and ask that she be paged.

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?
You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concerns an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record. All data that has already been collected will be maintained.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled and will not affect your access to health care at Duke. If you do decide to withdraw from the research study, we ask that you contact Dr. Eucker in writing and let her know that you are withdrawing from the study. Her mailing address is DUMC Box 3096, Durham, NC, 27710.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

Your study doctor may decide to take you off this study if she determines that it is no longer in your best interest to continue.

If you agree to allow your blood to be kept for future research with identifying information that could link your sample to you, you are free to change your mind at any time. We ask that you contact Dr. Eucker in writing and let her know you are withdrawing your permission for your identifiable blood samples to be used for future research. Her mailing address is listed above. At that time, we will ask you to indicate in writing if you want the unused identifiable blood destroyed or if your samples (having all identifying information removed that would link the sample to you) could be used for other research.

Your samples and data may be stored and shared for future research without additional informed consent if identifiable private information, such as your name and medical record number, are removed. If your

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identifying information is removed from your samples or data, we will no longer be able to identify and destroy them.

A description of this clinical trial will be available on https://clinicaltrials.gov/ as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or a research-related injury, or if you have problems, concerns, questions or suggestions about the research, contact Dr. Eucker at 919-684-5537 during regular business hours and at 919-684-8111 after hours and on weekends and holidays and ask that she be paged.

For questions about your rights as a research participant, to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

STATEMENT OF CONSENT
"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form."

_____	_____	_____
Signature of Subject	Date	Time
_____	_____	_____
Signature of Witness (if applicable)	Date	Time
_____	_____	_____
Signature of Person Obtaining Consent	Date	Time

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1-15
Protocol version	#3	Date and version identifier	14
Funding	#4	Sources and types of financial, material, and other support	14-15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	14

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	14-15
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	6

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	12
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	9-10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-10, Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-10
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9-10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9-10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10-11
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10-12
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	14
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	9

Notes:

- 13: 9-10, Figure 1 The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 07. April 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai