**PROTOCOL TITLE:**

Group-based integrative pain management:
A pilot factorial randomized trial

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## PRÉCIS

### Study Title

Group-based integrative pain management in primary care safety net clinics: A pilot factorial randomized trial

### Objectives

The primary objective of this study is to evaluate the feasibility of key study design features for a randomized clinical trial of group-based integrative pain management in primary care safety clinics. Parameters of interest are feasibility of randomization and retention of participants, and intervention fidelity and adherence. A secondary objective of the study is to evaluate assessment procedures in preparation for a larger scale 2x2 factorial trial of group acupuncture and integrative group medical visits.

### Design and Outcomes

This is a pilot study using a 2x2 factorial randomized clinical trial design. The pilot tests two 12-week group-based models: group acupuncture and integrative group medical visits (IGMV). Our primary feasibility outcome is participant randomization, measured as the percentage of confirmed eligible patients who are randomized. Secondary feasibility outcomes include retention (percentage of participants who complete 3-month follow up survey), adherence to intervention, and intervention fidelity. Additional outcomes of interest are patient-reported outcomes that will be the primary focus of a larger trial. We will assess quality and variability of data at baseline and 3-month follow up for pain-related outcomes. Data will include patient-reported outcomes, electronic health record data, and qualitative interviews, focus groups and observations to assess multilevel individual, interpersonal and organizational outcomes.

### Interventions and Duration

All participants will receive usual care and be randomized to group acupuncture, IGMV, both, or waitlist control. Participants randomized to group acupuncture will receive 12 weeks of once weekly acupuncture treatments delivered in a group setting, which consists of a common space with multiple reclining chairs. Participants randomized to integrative group medical visits will receive 12 weeks of once weekly group sessions that include psychoeducation on pain topics, movement, mind-body skills practice, and facilitated discussion designed for social support.

### Sample Size and Population

Our target population is patients with chronic pain who receive care in primary care safety net clinics. For this pilot, we will recruit and enroll 40 English or Spanish-speaking adults with chronic pain for ≥3 months receiving care in San Francisco Department of Public Health primary care clinics are eligible for the trial.

## 1. STUDY OBJECTIVES

### 1.1 Primary Objective

Our primary objective is to pilot study procedures for a 2x2 randomized factorial trial of group acupuncture and integrative group medical visits for chronic pain among racially and ethnically diverse patients served by the San Francisco Department of Public Health. We will assess study feasibility based on the success of randomization of study participants (primary feasibility outcome: percentage randomized of confirmed eligible), retention, intervention fidelity, and intervention adherence.

### 1.2 Secondary Objectives

Secondary objectives of the study are to test quality and variability of longitudinal data for patient-reported, pain-related outcomes. We will collect data at baseline and three-month follow-up. Factorial analysis will be performed to assess differences from baseline to three-month follow-up at the margins and inside the table.

## 2. BACKGROUND AND RATIONALE

Clinical guidelines and a growing body of evidence endorse nonpharmacologic approaches as first line treatment for pain,[1] and as a core part of multimodal chronic pain management.[2-4] Primary care safety net clinics are a critical resource for the publicly insured, uninsured, and underserved, and are uniquely positioned for providing care to marginalized populations and addressing disparities.[5] However, significant barriers impede optimal pain assessment and treatment in primary care safety net clinics.

Group-based integrative pain management has emerged as a strategy to address time constraints and provide multimodal care in safety net clinics. Group-based models improve access by providing care to multiple patients simultaneously. Here, we focus on two group models involving clinician-delivered care: integrative group medical visits (IGMV) and group acupuncture. Numerous Federally Qualified Health Centers serving low income, publicly insured patients have implemented group models as a strategy to increase access to complementary and integrative health approaches such as nutrition, yoga, and mindfulness.[6] These IGMV programs have been implemented in geographically disperse locations in Spanish and English, documenting feasibility in safety net settings serving diverse health disparities populations including low-income people from multiple racial/ethnic backgrounds.[6] Existing IGMV programs share several common features. They are informed by clinical experiences, driven by patient-identified needs, and include multiple CIH therapies. While promising, a lack of coordinated efforts across programs limits our understanding of generalizable best practices for safety net clinics, scalability, and potential long-term sustainability. Our study addresses this gap during the R61 phase by manualizing IGMV with national experts.

Acupuncture is an evidence-based treatment for a range of pain conditions,[7-9] but it is rarely available to safety net patients due to lack of insurance reimbursement.[10] Group acupuncture – a well-established delivery model where multiple patients simultaneously receive treatment in a common space, seated in chairs or recliners – lowers costs and improves availability,[11,12] without compromising patient perceptions

of quality of care.[13] In low income primary care patients with chronic neck, back, or shoulder pain or osteoarthritis, group acupuncture is associated with decreased pain severity, pain interference, and depression based on a quasi-experimental study,[14] and with reduced chronic pain and improved physical function at 12 weeks based on a randomized clinical trial.[15] Beyond pain relief, group acupuncture is associated with improved quality of life, decreased stress, increased engagement in chronic disease self-care, [16-18] and reduced barriers to care through ease of scheduling and social learning (e.g., less fear of needles seeing others receiving treatment).[19] While evidence supports use of acupuncture, little is known about the benefits of acupuncture co-located in primary care as part of a comprehensive multimodal program. Our study addresses this gap by assessing group acupuncture with or without IGMV in a factorial trial in primary care safety net clinics.

## 3. STUDY DESIGN

This study is funded through a R61/R33 phased award from the NIH HEAL Initiative. The R61 Phase 1 Specific Aims are as follows. In preparation for a larger scale, pragmatic 2x2 factorial trial, we aim to:

1. Refine and manualize IGMV in English and Spanish with stakeholder input and informed by relevant theory.
2. Test randomization procedures, contamination, and intervention fidelity in 40 patients with chronic pain.
3. Determine if there is preliminary evidence for our hypothesized mechanisms of action on improved pain management. We will collect and analyze data on pain outcomes, social isolation, and intersectional stigma.

Here we focus on procedures for specific aim 2, a pilot trial designed to assess the feasibility of key study design procedures for a larger trial.

- We will use a 2x2 factorial randomized clinical trial design.
- The primary feasibility outcome for the study is randomization of participants. The secondary feasibility outcomes include participant retention, intervention fidelity, and intervention adherence. We will also assess degree of bias and contamination between study groups.
- We will also assess quality and variability of data on patient-reported pain-related outcomes. These include is pain interference, social isolation, average weekly pain severity, social support for chronic pain, health-related quality of life, depressive symptoms, anxiety, sleep disturbance, internalized stigma of chronic pain, and pain self-efficacy.
- Study population will consist of adult patients 18 years of age and older who have painful diabetic neuropathy and have been seen for their diabetes at SFGH clinics within the past year. Forty participants will be enrolled and randomized to four arms (10 in each group): (a) usual care, waitlist comparison, (b) usual care combined with group acupuncture once weekly, (c) usual care with integrative group medical visits, (d) usual care with group

acupuncture and integrative group medical visits. Participants, practitioners, and assessors will not be blinded. The statistician will be blinded to participant assignment.

- All study procedures will take place at the UCSF Osher Center for Integrative Health and at the SFHN Castro Mission Health Center. Recruitment efforts will be through the Tom Waddell Urban Health Clinic, Castro Mission Health Center, and the Family Health Center.
- The full enrollment period for the study will take place in waves over 2-3 months depending on the rate of recruitment and the success of enrollment. Once the initial 6 participants are enrolled and consented, they will be randomized to the three treatment arms (randomization procedures are included in Section 4.3). Data collection and treatment will begin for the initial 6 participants while recruitment and enrollment continue on a rolling basis for the remaining study participants. The estimated duration of study involvement for each participant is approximately six months, which includes a 12-week intervention and a 3-month follow up interview post-intervention.
- Description of intervention and administration: All study participants will receive usual care. In addition, some participants will be randomized to receive group acupuncture for a period of 12 weeks, once per week. Some participants will be randomized to receive integrative group medical visits for a period of 12 weeks, once per week.

## 4. STUDY PROCEDURES

Our target population is low-income racially, ethnically, linguistically diverse individuals with chronic pain who receive primary care through public safety net clinics. This pilot feasibility study will be conducted at the San Francisco Department of Public Health.

### 4.1 Inclusion Criteria

To enroll in the study, participants must meet all of the following inclusion criteria:

1. Adults aged 18 years of age or older;
2. English or Spanish speaking;
3. Paneled to a primary care provider at one of the clinics of the study;
4. Diagnosis of chronic pain for 3 months or more;
5. Had a primary care visit for chronic pain within the past six months;
6. Ability to provide a phone number;
7. Intention to be available for up to 24 weeks.

### 4.2 Exclusion Criteria

All candidates meeting any of the exclusion criteria at baseline will be excluded from study participation.

1. Current anticoagulant use;

2. Active cancer treatment;
3. Inability to provide informed consent due to mental illness or cognitive impairment.

### 4.3 Study Enrollment Procedures

*Screening and Consent*

- We will use electronic health records to pre-screen patients who meet key eligibility criteria: age, chronic pain diagnosis, primary language, and empaneled with primary care provider at a study site.
- We will present a list of pre-screened patients to primary care providers to confirm eligibility and approval for enrollment.
- Clinical research coordinators (CRCs) will contact eligible patients by telephone to invite them to participate in a study to improve pain management in primary care.
- During the telephone call, CRCs will ask eligible patients about their preferred method of contact (i.e., phone, text message, and/or email) to schedule an orientation session and to receive reminders about the orientation session. The study team will also ask eligible patients for permission to send text message reminders and whether the study team can leave voicemail messages.
- We will also host orientations with eligible patients as an additional opportunity for them to learn about the study.
- CRCs will also be available to discuss the study in person with patients who are scheduled for upcoming appointments.
- CRCs will obtain informed consent from eligible patients who are interested in participating.

### 4.4 Data Collection and Randomization

- Following the consent process, CRCs will conduct a baseline assessment with study participants. Baseline data collection will include sociodemographic, pain symptoms, mood, daily activities and open-ended questions regarding social isolation, stigma, and experiences with pain care.
- After the baseline assessment, participants will be randomized to one of four groups (described in more detail below). To maintain participant flow and adequate staggering of acupuncture and IGMV, we will use computer-generated, randomly permuted blocks of 4 and 8, stratified by language. The database manager who will not be involved with enrollment will program the random allocation sequence; no other study staff will have access to generating the randomization sequence. The CRC will access the allocation

sequence using a programmed database that cannot be altered once the randomized condition is revealed.

- Participants randomized to study interventions will participate in weekly sessions for twelve weeks and those randomized to Integrative Group Medical Visits have the option to participate in focus groups immediately following the final weekly session.
- Three months after baseline, participants will complete validated surveys about pain symptoms, social isolation, quality of life, and other pain-related symptoms and open-ended questions about pain management.
- Three months after baseline, participants will also complete semi-structured interviews on participants' experiences living with chronic pain, and their perspectives on non-pharmacologic pain treatment, including participation in the study.
- Interviews will focus on participants' experiences treating chronic pain, perspectives on non-pharmacologic treatment, and experiences referring patients to the Integrative Pain Management Program (i.e., the larger RCT component of this study). These interviews will last 45-60 minutes and take place in-person or virtually at a private location of the participant's preference (e.g., the participant's office, UCSF Osher Center for Integrative Health offices, or via Zoom). At the time of the interview, participants will complete a brief demographic form (including gender, racial and ethnic identity, years of clinical experience, and chronic pain treatment experience). No EHR data of any kind will be collected for providers participating in the provider interview subsample.

## 5. STUDY INTERVENTIONS

Study interventions are based on stakeholder input and patient preference, and the extent that they: (1) reflect real world practices that are viable options in primary care safety net settings, and (2) could be standardized to enhance replicability in future studies or in clinical practice. Study participants will be randomized to one of four experimental conditions:

i. Usual care. Participants will receive care as usual provided through their primary care providers. Usual care includes medical diagnostic evaluation, analgesic drug therapies, recommendations for physical activity, and sometimes referral to specialist physicians or physical therapy. Usual care was chosen as a comparison arm for this study because it is practical and clinically relevant. One challenge with using a usual care arm in a clinical trial is the potential variability in the care provided in clinical practices.[20] EHR data will be extracted and reviewed to accurately describe usual care for study participants.

ii. Integrative Group Medical Visits for Pain. IGMV will consist of a 12-week program that provides education on the biopsychosocial model of pain and multimodal treatments; physical movement; mindfulness training; and peer support. Non-pharmacologic approaches were chosen based on guidelines on chronic pain management; feedback of experts, staff, and patients;[21] and feasibility with the greatest potential to benefit participants. Participants will receive a binder with educational materials. Weekly IGMV sessions will be two hours in a group meeting space at the clinics. Sessions will start with a "check-in" where participants can share their emotions, thoughts, hopes, and fears related to their health and provide updates since the last session. Group sessions will be led by a primary care provider and a health educator and will include psychosocial support, tools for pain self-management, and psychoeducation for pain management.[22,23] Following the group "check-in," an invited guest (example: pharmacist, mindfulness expert) will provide information on educational topics, including neurobiology of pain, medication safety, and connections between mood and pain (see table 1 for sample content based on prior IGMV), as well as participatory activities such as therapeutic movement or mindfulness practice.

**Table 1. Sample IGMV Content**

| Week | Content | Facilitator(s)* |
|---|---|---|
| 1 | Orientation – goals, neurobiology of pain, pain stories, treatments & self-care | Health Educator & Program Coordinator (group facilitators) |
| 3 | Mindfulness, physical movement | Certified yoga instructor |
| 4 | Thoughts & pain, medication education | Clinical Pharmacist |
| 5 | Stress & pain, meditation/mindfulness | Mindfulness instructor |
| 6 | Emotions & pain | Clinical psychologist |
| 7 | Self-massage | Certified massage therapist |
| 8 | Pacing, physical movement | Certified yoga instructor |
| 9 | Nutrition, meditation/mindfulness | Nutritionist, mindfulness instructor |
| 10 | Sleep& pain | Clinical Pharmacist |
| 11 | Relationships & pain | Clinical psychologist, educator |
| 12 | Moving forward, graduation | Program Coordinator |

* Primary care provider present at all sessions

iii. Group Acupuncture. Acupuncture was selected based on: (1) strength of supporting evidence and inclusion in clinical guidelines,[8,9,24-26] (2) high acceptability and feasibility in our target population as demonstrated in our preliminary studies, and (3) substantial access barriers for socioeconomically disadvantaged patients due to lack of insurance coverage. Participants randomized to acupuncture will receive 12 weeks of acupuncture treatments delivered in a group setting, dosing similar to prior research.[15,16] Acupuncture point selection and other treatment details will follow responsive manualization, a protocol developed for the largest RCT of group acupuncture to date.[15,27] A licensed acupuncturist experienced with administering group acupuncture treatments will determine each participant's traditional Chinese medicine diagnosis and administer 8-10 acupuncture needles on distal points of participant's body (below the knees, from the elbows to the hands, and on the head). Duration of assessment, needle placement and retention will be 30-45 minutes. Details of acupuncture treatments (e.g., frequency and duration, TCM diagnosis, number of needles and points used) will be documented in standard EHR charting used by the Osher Center for Integrative Health.[28]

iv. Both group acupuncture and IGMV. Along with usual care, participants will be offered weekly group acupuncture treatments and integrative group medical visits as described above.

## 6. STUDY OUTCOMES

### 6.1 Feasibility Outcomes

Study feasibility includes multiple parameters. To assess the feasibility of conducting a 2x2 factorial trial of group-based integrative pain management in primary care safety net clinics, we have chosen key parameters, operational metrics, and goals for each metric as shown in Table 1.

Table 1. Feasibility Parameters, Metrics and Goals

| Feasibility Parameter | Operational Metric | Goal |
|---|---|---|
| **Recruitment (primary feasibility outcome)** | Percent of confirmed eligible patients who are randomized | 40% of confirmed eligible patients |
| **Retention** | Percent of participants who completed 3-month follow up survey | 80% of randomized participants complete 3-month survey |
| **Adherence** | Average number of intervention sessions attended | Mean of six intervention sessions |

### 6.2 Patient-reported Outcomes

Pain-related outcomes of interest include:

- Pain interference from baseline to three months, measured using an eight-item survey of the NIH Patient Reported Outcomes Measurement Information System (PROMIS).[29] Items assess the extent that pain interferes with physical, cognitive, emotional, and recreational activities.
- Social isolation, collected using another NIH PROMIS measure, with an eight-item scale on lacking companionship, feeling left out, and feeling isolated.[30]
- We will also assess intervention effects on pain intensity, physical functioning, depression, and anxiety using NIH PROMIS measures.[31-34]
- Additional aspects of health-related quality of life associated with chronic pain will be collected using NIH PROMIS measures for sleep, social functioning, global physical, mental, and social well-being.
- Participant ratings of global improvement. A single item, 7 point rating on the Patient Global Impression of Change scale will assess minimal clinically important difference in changes in participants' pain.[35]
- Pain beliefs and attitudes will be assessed with scales for pain catastrophizing[36] and pain self-efficacy.[37,38]
- Social Support in Chronic Pain, a 6-item measure of perceived support related to pain.[39]
- Internalized Stigma of Chronic Pain (ISCP) scale, 21 items with five subscales on enacted and internalized chronic pain stigma: alienation, stereotype endorsement, discrimination experience, social withdrawal, and stigma resistance (Cronbach's $\alpha = 0.724$).[41] Prior research has documented an association between this measure and pain-related cognitive functioning, such as pain self-efficacy and pain catastrophizing.[41]
- Intersectional Discrimination Index measures anticipated, day-to-day, and major discrimination that do not focus on a single axis of discrimination (e.g., racism, homophobia) to capture intersectional categories.[42]
- Descriptive covariates collected at baseline will include: socio-demographic variables (age,

sex, race/ethnicity, place of birth, level of education, household income, marital status, employment status, and health insurance status) and a substance use screener (using HEAL CDE). Clinical data including chronic pain diagnosis, concomitant conditions, medications, and treatments received for pain will be obtained from participants' medical record.

- Use of non-pharmacologic approaches to pain management will also be collected to assess access, interest, and satisfaction with multimodal treatments.

## 7. SAFETY ASSESSMENTS

Participant safety will be continually monitored once an individual is enrolled in the study. Study staff will complete adverse event reporting on a weekly basis for all participants. Potential adverse experiences with group acupuncture include: agitation, anxiety, bleeding, bruising, contact dermatitis, dizziness/lightheadedness, fatigue, increased pain, redness/infection, soreness of muscles, swelling of arm/leg/other, tearfulness, weakness. Most risks associated with acupuncture are considered minimal side effects that resolve on their own.

Depending on the severity of an adverse event, modifications will be made to study participation. If an adverse event occurs that affects a participant's ability to come in for study treatments or assessments, study staff will gauge the participant's willingness to continue data collection in alternative ways such as over the phone or in-person at their home. If at any point in the study, participants report severe depressive symptoms or severe pain, research assistants will be instructed to refer participants to their primary care provider. In a situation that requires immediate attention, research assistants will notify a healthcare professional to follow-up with participants as needed. The medical team will follow standard protocol to ask appropriate follow up questions to assess the need for psychiatric evaluation for the participant.

### 7.1 Specification of Safety Parameters

Minor risks associated with acupuncture are anticipated to occur in less than 5% of participants. Over the course of the study, which will include 48 patients and a maximum of 576 acupuncture treatments, we might expect 5% of patients to have minor side effects and do not expect any serious adverse events. Any adverse event rate over 5% in 12 months will be reported to the UCSF IRB and NIH/NCCIH.

### 7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

The safe profile and low risks of acupuncture have been well documented in the literature.[43-45] A summary of key findings by severity of adverse events is listed below:

- Serious adverse events are very rare. Two prospective surveys conducted in the United Kingdom, which included over 65,000 acupuncture treatments reported no serious adverse events.[43,44] A prospective study in Germany of 229,230 patients who received a total of 2.2 million acupuncture treatments, reported two cases of pneumothorax.[45]
- Minor adverse event rates occur in less than 15 per 10,000 treatments.[43,44] The most common minor adverse events were bleeding or hematoma (estimates range from 2.1% to 6.1%), needling pain (< 2%), and aggravation

of symptoms (< 3%).

- Mild transient reactions include feeling relaxed (11.9%) or energized (6.6%), tiredness (2.6%), drowsiness (1.1%), dizziness (0.6%), nausea (0.3%), feeling faint (0.2%).

### 7.3 Adverse Events and Serious Adverse Events

An **adverse event (AE)** is defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events will be recorded regardless of their relationship to the study intervention.

A **serious adverse event (SAE)** is defined as any untoward medical occurrence that results in one or more of the following outcomes:

- Death
- A life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly or birth defect
- An important medical event based upon appropriate medical judgment

Information on minor adverse events will be collected as solicited events. These will be listed in alphabetical order on an electronic case report form. Study staff will collect this information at participants' weekly visits. Using an electronic data collection system, such as RedCap or Qualtrics, helps to assure that the reporting and data collection systems avoid double capture. Describe which AEs will be collected as solicited events. The adverse event form will also have items to capture any unsolicited events such as serious adverse events; these will be documented by study staff without direct input from participants. Adverse events will be reported on a monthly basis to the data and safety independent monitor. Serious adverse events will be reported immediately.

### 7.4 Reporting Procedures

As part of training and orientation for the study, all research staff will be alerted to the importance and necessity of reporting of all adverse events that occur during the study. Forms for adverse event reporting will include sections to document relatedness and severity. Any adverse events will be immediately reported to the PI (Dr. Chao), dealt with immediately, and if necessary, discussed with mentors and advisors. If it is determined that a participant is experiencing a high level of distress, the activity will be stopped. Any small or large adverse events will also be discussed during weekly research meetings. Registered nurses and medical doctors will be available at the SFGH Clinical Research Center (CRC) to supervise and assist with procedures. Acute, adverse reactions to acupuncture or any other procedure will be treated by a physician. Reporting of adverse events will follow requirements mandated by the Committee on Human Research, with concurrent reporting to the Research Services Analyst (RSA) at the CRC. In addition, the RSA will receive a verbal or e-mail report of any serious adverse event (graded 3 or higher) that occurs during the conduct of the study within 48 hours. On-site SAEs and unexpected AEs of any grade that are both related to research and result in a change to risk/benefit or

require protocol and consent modifications will be reported to the UCSF IRB within 10 working days of PI awareness. All other AEs related to the research that are both non-serious (grades 1-2) and expected will be reported annually.

### 7.5 Follow-up for Adverse Events

Any adverse event reported by participants will be followed until resolved or considered stable. At subsequent acupuncture treatment visits, study staff will ask participants about the status of the reported adverse event at least once or until the participant reports that the adverse event has resolved.

### 7.6 Safety Monitoring

The Principal Investigator (PI) will be responsible for ensuring participants' safety on a daily basis. The full study team will monitor participant symptoms, performance status, and review questionnaires and clinical test results. Participants will be provided with a 24-hour contact number to report any persistent problems or emergencies. If any concerns arise, they will immediately be brought to the attention of study PI, Dr. Chao, who will consult with her mentors as needed. The PI will be responsible for reporting any adverse events and conducting the annual safety review of study data. Study data will be reviewed for adverse events, subject complaints, deviations from the protocol design, any unexpected incidents associated with the study procedures, and explanations for any subject withdrawals from the study.

## 8. INTERVENTION DISCONTINUATION

A subject may be discontinued from study treatment at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

Subject withdrawal of consent
Subject is not compliant with study procedures such as repeatedly not completing data collection
Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
Protocol violation requiring discontinuation of study treatment
Lost to follow-up
Sponsor request for early termination of study

Trained study staff will regularly assess whether participants meet criteria for discontinuation at acupuncture treatment visits, data collection visits, and follow-up phone calls.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. Refer to Section 10 for early termination procedures. Subjects who withdraw after Week 8 but prior to Week 12 should be encouraged to come in for a final visit (and the procedures to be followed would include those for their next scheduled visit).

Subjects who withdraw from the study will not be replaced.

## 9. STATISTICAL CONSIDERATIONS

### 9.1 Sample Size Rationale

The study will enroll 40 participants. As a small pilot study designed to pilot the refined intervention, we did not conduct a formal power calculation but instead used a confidence interval approach to determine sample size, based on current recommendations for small samples. Findings from the pilot study are intended to help plan for a future trial by estimating key parameters. However, small trials often overestimate treatment effects and the convention of basing power calculations on pilot trials has received considerable scrutiny (Kraemer, 2006). Our approach will be to determine whether the effect size from the pilot is clinically meaningful (i.e., within an 80% confidence interval of a pre-determined effect size) and justifies proceeding with future research. To determine this, Cocks and Torgenson (2013) recommend that a pilot sample size should be at least 9% of the sample size of the planned main study.

Based on data of minimally important differences for PROMIS pain measures, our main study would aim to detect a standardized effect size of 0.25. Using our pilot data to estimate within group correlation and a sample size calculator designed for individually randomized group trials, we estimated a sample size of 360. Using Cocks and Torgenson's method, the corresponding pilot sample size should be at least 32. Using an estimated attrition of 20%, we aim to enroll 40 participants. With 20 participants randomized to each of the study interventions, we will have sufficient power to determine if the effect size estimated from the pilot is within the range of clinical significance using a one-sided 80% confidence interval. If the estimated effect is zero or less, the upper 80% CI will not contain our target effect size of 0.25, and we would not proceed with a main study. If the estimated effect size from the pilot is larger than zero, and the study procedures are feasible and acceptable, then we would have sufficient preliminary data to proceed with the main study.

### 9.2 Statistical Analysis Plan

**Descriptive analyses**

Baseline characteristics of participants, including sociodemographics and health condition variables, will be summarized to determine sample generalizability, and compared to assess group equivalency. We will look at summary statistics for data cleaning (e.g., means, ranges)

and then consider distributions by randomized arm as a check of balanced distribution across groups.

Analysis of Feasibility. Feasibility outcomes will be analyzed by computing percentages, with 95% confidence intervals, of rates of retention and enrollment. We will also conduct a thematic analysis of qualitative responses on participants' experiences with the study and acceptability of group acupuncture.

Assessment of implementation, defined as quality and consistency of the intervention delivery across staff, will be focused on evaluating core components and content of IGMV and parameters in STRICTA guidelines for group acupuncture. IGMV facilitators will complete a short survey after each session documenting content and time spent on each component. Acupuncturists will complete charting for each treatment provided.

Analysis of Patient-Reported Outcome Measures. This study is powered to assess exploratory effects and pilot feasibility, not for confirmatory analysis. Nonetheless, we will analyze clinical outcomes in a manner similar to that planned for the main study to make a preliminary assessment of the strength of the effects; to identify any unexpected issues with missing data, skewed distributions, or outliers; and to refine the statistical analysis plan. Relative (mean ± SD) measures of effect sizes will be calculated as change from baseline to post-intervention for all outcome variables. Planned analyses include: within group changes from baseline to Week 12, group acupuncture vs. no acupuncture, and IGMV vs. no IGMV.

Treatment effects will be estimated using a repeated measures ANCOVA approach. The framework is similar to a linear mixed models but it includes the baseline of the outcome as a covariate (and omits the baseline from the outcome vector), and the models will include indicators for assignment to acupuncture, IGMV, a categorical variable for time, and interactions between treatment indicators and time, as well as random intercepts for person nested within group to account for within-group and within-patient correlation of the repeated measures. Models with a three-way interaction between the two treatment indicators and time will be evaluated as a first step to assess for synergy between IGMV and group acupuncture. We will also calculate an interaction ratio to assess clinically meaningful antagonism or synergy between the two interventions, specified as interaction ratios of ≤0.80 or ≥1.25.[46] If there is evidence of interaction, we will assess marginal effects of each intervention. If no evidence of synergy is identified, we will proceed with models that omit the three-way interaction term, to instead focus on main effects of each treatment type. This approach will optimally weight data for patients with different numbers of responses, and will provide valid estimates in the presence of missing data under relatively mild assumptions about how the missing data arise.[47] We will conduct intent-to-treat, per protocol, and complier average causal effects analyses; and exploratory as treated analysis (receipt of any group integrative health intervention and dose-response based on number of sessions attended). Outcomes will be normalized as needed to meet model assumptions; for outcomes which do not meet distributional assumptions of normality, other generalized linear mixed models or non-parametric approaches such as Kruskal-Wallis tests will be used. Secondary outcomes will also be analyzed using this approach.

## 10. DATA COLLECTION AND QUALITY ASSURANCE

### 10.1 Data Collection Forms

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject in the

study. Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a subject number. If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator.

## 10.2 Data Management

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

## 10.3 Quality Assurance

### 10.3.1 Training

All UCSF Key Personnel conducting human research are required to complete human subjects protection training through an online program called the Collaborative Institutional Training Initiative (CITI). UCSF Key Personnel are defined as all individuals who contribute in a substantive way to the scientific development or execution of the study at or on behalf of UCSF. In addition, UCSF IRB considers individuals who obtain informed consent to be Key Personnel. The CITI course includes an overview of the regulations that govern human subjects research, as well as training modules on the Health Insurance Portability and Accountability Act as it applies to research. To supplement CITI modules, study staff will also receive online training in Good Clinical Practice, Responsible Conduct in Research, and more detailed HIPAA privacy and information security training.

### 10.3.2 Quality Control Committee

The quality control committee will consist of Dr. Chao (PI), Dr. Hartogensis (study statistician) and Julia Wu (project manager). Ms. Wu will report on metrics described in 10.3.3 on a weekly basis with study staff. Dr. Chao, Dr. Hartogensis, and Ms. Wu will regularly review quality control reports on a quarterly basis and more frequently as needed should any issues or questions arise.

### 10.3.3 Protocol Deviations

At each study encounter, study staff will complete forms documenting adherence and deviation with key aspects of the study protocol. The Principal Investigator will review the forms on a monthly basis to evaluate any deviations from the study protocol. In addition, protocol deviations will be discussed at regularly scheduled study meetings.

Practitioner adherence to the study manual will also be evaluated by review of practitioner clinic notes, observation of clinic visits, and interviews with practitioners

at the completion of each cohort. We will observe three study visits per cohort (i.e., monthly over the twelve weeks of acupuncture visits). Deviation from the study protocol will be defined as any diagnosis or acupuncture point that is not described in the study manual. All deviations will be documented in the Manual of Procedures.

#### 10.3.4 Monitoring

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the Electronic Data Capture system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database. At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

## 11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

### 11.1 Institutional Review Board (IRB) Review

All study procedures, informed consent documents, and any subsequent modifications will be reviewed and approved by the Institutional Review Board of the University of California, San Francisco.

### 11.2 Informed Consent Forms

A signed consent form will be obtained from each participant. For participants who cannot consent for themselves, such as those with a legal guardian (e.g. person with power of attorney), this individual must sign the consent form. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant or legal guardian and this fact will be documented in the participant's record. Detailed procedures for obtaining consent, including of non-English speakers is described in Section 4.3. The informed consent form is attached as Appendix A.

### 11.3 Participant Confidentiality

In order to maintain confidentiality, any data, specimens, forms, reports, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. Study materials will be marked with codes. Only study researchers will have access to the data key that links codes with participant names. The data key will be kept in a locked filing drawer in a secure office at UCSF accessible only by research staff. At the end of the study, the data key will be destroyed. All electronic data collected will be password protected using REDCap or a comparable system with a secure, web-based application with features to support HIPAA compliance, including a full audit trail, user-based privileges, and integration with the institutional LDAP server. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the

FDA, the NIH, and the OHRP.

### 11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NIH, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

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# UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
# CONSENT TO PARTICIPATE IN A RESEARCH STUDY

**Study Title: Group-based Integrative Pain Management**

| | |
|---|---|
| Principal Investigator: | Maria Chao, DrPH, MPA, Associate Professor, Medicine<br>1545 Divisadero Street San Francisco CA 94115<br>Phone: 415-353-7749; e-mail: maria.chao@ucsf.edu |

| | |
|---|---|
| Study Coordinator: | Denise Ruvalcaba, Phone: 415-514-0577<br>Denise.Ruvalcaba@ucsf.edu |

This is a clinical research study. The Principal Investigator, who is the person in charge of this study, or a member of the study team from the UCSF Osher Center for Integrative Health will explain the study to you.

Research studies include only people who choose to take part. Please take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask the study coordinator.

You are being asked to take part in this study because you have chronic pain.

**Why is this study being done?**

The purpose of this study is to understand what kinds of healthcare work best for people living with chronic pain. This study will compare the effects, good and/or bad, of group pain management, group acupuncture, and usual care for chronic pain. We want to see if adding non-medication treatments to usual care is better than usual care alone for patients with chronic pain. In this study, you will be randomly assigned to either A) usual care for chronic pain, B) group acupuncture, C) group pain management, or D) group acupuncture *and* group pain management.

The National Institutes of Health pays for the conduct of this study.

**What is the usual care for my condition?**

The usual care for your condition includes pain medications, surgical procedures, and sometimes physical therapy or other non-medication treatment options.

**How many people will take part in this study?**

About 400 people will take part in this study. This includes 40 people in a pilot phase and then 360 people in a larger study. This consent is for the pilot phase with 40 people.

**What will happen if I take part in this research study?**
If you agree, the following procedures will occur:

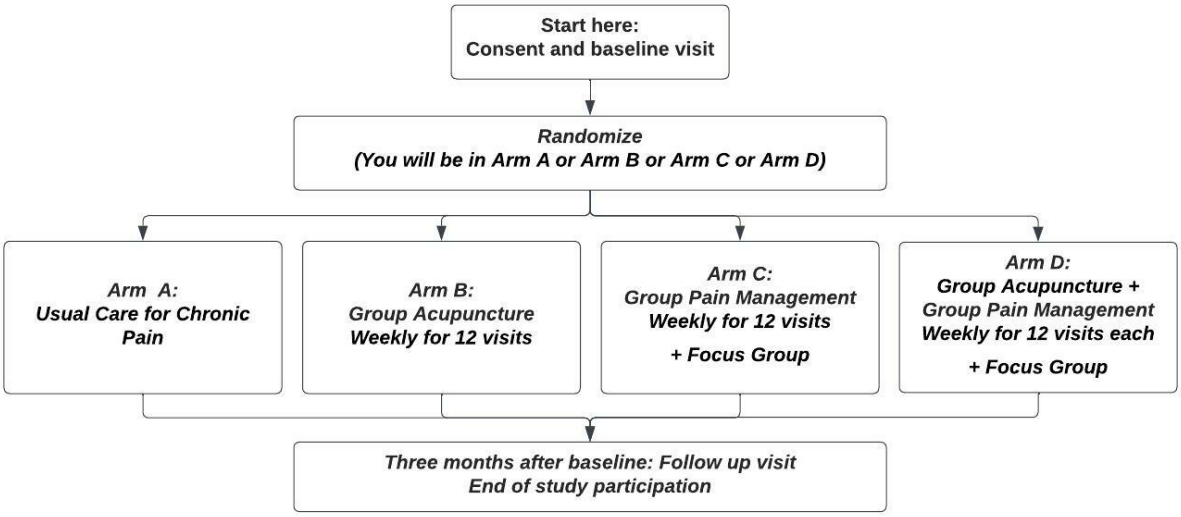
- Baseline Visit. If you choose to participate you will sign this consent form. After you have signed the consent form, you will be asked to participate in an initial interview and complete forms about your chronic pain symptoms, mood, and daily activities. It should take about 60 minutes to complete these forms.
- Medical Record Review. Study staff will access your medical record to collect information on your health and your use of healthcare services and medication. You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.
- You will be "randomized" into one of the study groups described below. Randomization means that you are put into a study arm by chance. A computer program will place you in one of the arms. Neither you nor your primary care provider can choose the arm you will be in. You will have an equal chance of being placed in any arm. If you are in Arm B, C, or D, the group programs will include discussions of confidentiality and privacy to support comfortable participation:
  - **If you are in Arm A,** you will receive usual care for chronic pain from your primary care provider. You will have the option of being on a waiting list to participate in group acupuncture or group pain management 3 months after starting the study.
  - **If you are in Arm B, you will participate in weekly acupuncture treatment for 12 weeks**. Acupuncture treatments will take place in a group setting with 6-8 other patients, in a common space with multiple reclining chairs located at the clinic. A licensed acupuncturist will perform a brief interview with you about your symptoms. The acupuncturist will then place thin, sterile acupuncture needles in certain points of your body in accordance with traditional Chinese medicine principles. You will then relax with needles in place for 20-40 minutes in a quiet, communal space.
  - **If you are in Arm C, you will participate in a weekly, 2-hour group pain management program for 12 weeks.** The pain management group will include 8-12 other patients living with chronic pain. include education about chronic pain; physical movement; mindfulness practice; peer support. Group sessions will meet at either Tom Waddell Urban Health Clinic or at San Francisco General Hospital. They will be facilitated by clinic staff.
  - **If you are in Arm D, you will participate in both group acupuncture and group pain management as described above, each once a week for 12 weeks.**
- **Follow-up Visit:** After 12 weeks**,** you will be asked to complete a brief interview with a study staff member and complete forms about your chronic pain symptoms, mood, and daily activities. This visit should take up to 60 minutes. If you are randomized to group pain management, you will be invited to participate in a two-hour focus group discussion about your experiences with the program.

**Study location:** All acupuncture, group pain management and usual care visits will take place at the Castro-Mission Health Center, the Tom Waddell Health Clinic or the Family Health Center at San Francisco General Hospital. Visits with the study staff will take place at these clinics or if you prefer can be done via Zoom videoconference.

For in person visits for this study, you will first complete COVID-19 screening procedures. Study activities will follow UCSF institutional policies for COVID-19, including guidelines for masking, social distancing, and population distancing.

## Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.




### How long will I be in the study?

You will be asked to participate in the study for a total of 3 months. Your total time participating in the study will depend on the study arm you are assigned to: about 2 hours if you are in Arm A (usual care), about 10 hours if you are in Arm B (group acupuncture), about 28 hours if you are in Arm C (group pain management), and about 36 hours if you are in group D (group acupuncture and group pain management).

### Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study staff and your primary care provider if you are thinking about stopping or decide to stop. They will tell you how to stop your participation safely. It is important to tell your primary care provider that you are thinking about stopping to discuss what follow-up care could be most helpful for you.

If you withdraw from the study, any data we have already collected from you will remain part of the study records. After you withdraw, the researchers may still get information from your medical records if it is relevant to the study. You must tell the study team you do not want this information to be collected when you withdraw, otherwise it will be collected.

The study team may stop you from taking part in this study at any time if they believe it is in your best interest, if you do not follow the study rules, or if the study is stopped.

### What side effects or risks can I expect from being in the study?

There are some possible risks from taking part in this study. You may have side effects while on the study depending on which group you are in. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. You should talk to the study staff about any side effects you experience while taking part in the study.

Risks and side effects related to the study include:

- **Randomization risks:** You will be assigned to a treatment group by chance, and the treatment you receive may prove to be less effective or to have more side effects than the other study treatment(s) or other available treatments.
- Some of the questions on the forms or interviews may make you uncomfortable or upset. You are free to decline to answer any questions you do not wish to answer.
- **Risks to privacy:** Participating in group sessions comes with a risk of potential loss of privacy from receiving treatment with other people present. All group participants will agree with maintaining other people's medical and personal information completely confidential and participants will only share information with others that they choose to share. However, confidentiality cannot be guaranteed.
- **Unknown Risks:** There may be side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.
- Risks and side effects related to **acupuncture** include those which are:
    - **Likely**
        - A slight pinch, tingling, or numbness at the site of needle insertion
        - Sensation of feeling sleepy or relaxed
    - **Less Likely**
        - Bleeding or hematoma (6% of patients)
        - Slight pain at site of needle insertion (< 2% of patients)
        - Sweating, dizziness, nausea, or fainting (< 1% of patients)
    - **Rare but serious**
        - Pneumothorax and systemic infection have been reported in the literature but are very rare (less than 1 out of 10,000).

**Are there benefits to taking part in the study?**
You may or may not benefit from participating in the study.

**What other choices do I have if I do not take part in this study?**

Your other choices may include:

- Getting treatment or care for your pain without being in a study.
- Taking part in another study.
- Getting no treatment.

Please talk to your primary care provider about your choices before deciding if you will take part in this study.

**How will my information be used?**

Researchers will use your information to conduct this study. Once the study is done using your information, we may use the information collected for future research studies or share them with other researchers so they can use them for other studies in the future. We will not share your name or any other personal information. We cannot guarantee that this will prevent future researchers from determining who you are. We will not ask you for additional permission to share this de-identified information.

**How will information about me 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 privacy. Some information from your medical records will be collected and used for this study. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Authorized representatives from the following organizations may review your research data for the purpose of monitoring or managing the conduct of this study:

- San Francisco Department of Public Health
- Representatives of the National Institutes of Health
- Representatives of the University of California
- Representatives of the Office of Human Research Protections (OHRP)

**Are there any costs to me for taking part in this study?**

No. The sponsor has agreed to pay for all items associated with this research study; you or your insurer will not be billed.

**Will I be paid for taking part in this study?**

In return for your time and effort, you will be paid for taking part in this study. You will receive payment through gift cards or cash.

You can receive up to $90 for completing interview visits. This includes:

- $40 for the baseline visit and $50 for the 12-week follow-up visit

If you are in an arm receiving group acupuncture or group pain management, you can receive an additional $25 for completing all acupuncture or group pain management sessions.

If you are in an arm receiving group pain management, you can receive $25 for the focus group.

**Will I be reimbursed if I pay expenses related to my participation in this study?**

You may be reimbursed up to $25 for parking or transportation if you take part in this study.

**What happens if I am injured because I took part in this study?**

It is important that you tell the researcher Dr. Maria Chao, if you feel that you have been injured because of taking part in this study. You can tell the researcher in person or call her at 415-353-7749.

Treatment and Compensation for Injury: If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California or the study sponsor, the National Institute of Health, depending on a number of factors. The University and the study sponsor do not normally provide any other form of compensation for injury. For further information about this, you may call the office of the Institutional Review Board at 415- 476-1814.

**What are my rights if I take part in this study?**

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you, and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

**Who can answer my questions about the study?**

You can contact the research team with any questions, concerns, or complaints you have about this study at 415-353-7749.

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please call the office of the Institutional Review Board at 415-476-1814.

A description of this clinical trial will be available on http://www.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.

The National Clinical Trial (NCT) number for this study is not yet assigned.

**CONSENT**

You have been given copies of this consent form and the Experimental Subject's Bill of Rights to keep.

You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you wish to participate in this study, you should sign below.

| | |
|---|---|
| _____ | _____ |
| Date | Participant's Signature for Consent |
| _____ | _____ |
| Date | Person Obtaining Consent |

Future contact with this study:

☐ This consent form only covers assessments for the months that you are in the study. If you initial this box, you are agreeing to allow researchers to contact you for follow-up regarding this study after that time.

Future contact with other studies:

☐ There may be other research studies at UCSF for which you may be qualified. If you initial this box, you are agreeing to allow researchers to contact you to give you information about other studies.