NIH Collaboratory Rethinking Clinical Trials™
Health Care Systems Research Collaboratory

Regulatory/Ethics Consultation Call

Pragmatic Trial of Acupuncture for Chronic Low Back Pain in Older Adults (AcuOA)

Monday, December 9, 2019
Meeting Participants

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AGENDA ITEMS	DISCUSSION	ACTION ITEMS

Overview of Demonstration Project	• **Overview:** The AcuOA pragmatic trial will evaluate the feasibility of acupuncture treatment compared with usual care for older adults with chronic low back pain. AcuOA will be a three-arm trial with patients recruited from four diverse health plans to represent the ethnic and racial composition of Medicare enrollees as well as the most common ways acupuncture is incorporated in insurance-based care for chronic pain. The acupuncture care delivery model varies across the four health systems (i.e., internal vs external delivery).
	• **Collaborative network partners:**
	  ○ Kaiser Permanente Washington (KPWA), Seattle, WA
	  ○ Kaiser Permanente Northern California (KPNC), Oakland, CA
	  ○ Sutter Health (SH), Palo Alto, CA
	  ○ Institute for Family Health (IFH), New York, NY
	• **NIH Institute:** National Center for Complementary and Integrative Health (NCCIH)
	• **Study design:** AcuOA is a three-arm trial of approximately 789-840 adults aged 65 years or older with chronic low back pain, comparing a standard 12-week course of acupuncture or an enhanced course of acupuncture (12-week standard course, plus
		The Ethics and Regulatory Core need to examine whether acupuncturists are properly considered as engaged in research.

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	12-week maintenance course) to usual medical care for chronic low back pain. Patients will be randomized individually. At KPWA, KPNC, and SH, participants will be recruited through the EHR; at IFH patients will be referred to the study by their primary care physician (PCP). The recruitment period is expected to take about 12-15 months. • **Primary and secondary outcomes:** The primary outcomes will be back-related function at 6 months. Secondary outcomes include pain intensity and pain interference as well as clinically meaningful improvement. These and other biopsychosocial measures will be collected at 3-, 6-, and 12-months post-randomization. o The study team hypothesizes that back-related function in older adults with chronic low back pain will be most improved among participants in the enhanced acupuncture arm, followed by the standard acupuncture arm, with the least improvement among those receiving only usual care. o A short battery of measures will be used to evaluate physical function, pain interference, and pain intensity at monthly intervals. The study team will collect patient-reported outcome measures. o The team will collect data from electronic health records and Medicare in order to assess cost-effectiveness. • **Other important notes about the study:** o The Center for Medicare and Medicaid Services (CMS) is currently conducting a national coverage analysis on acupuncture for chronic low back pain (see section below on "Issues beyond the study"). If CMS determines these costs may be covered, the Medicare reimbursement framework may impact participant reimbursement/payment, as some participants will be seen at health care system facilities (with Medicare reimbursement) and others will be referred to acupuncturists practicing in the community (which may not meet Medicare reimbursement rules). o The participating sites are structured differently for acupuncture services, so part of the UG3 pilot phase is to assess what intervention adaptations will be made within each setting.	

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Status of IRB approval	• For the UG3 phase, IRB approval will be obtained at each collaborating site. • During the first year, the team plans to develop materials for submission to a single IRB of record for the UH3 phase, which will be the Kaiser Permanente Northern California IRB.	
Risk classification	• From the study protocol (attached supplemental material): ○ Risks of acupuncture: In general, acupuncture is a very safe procedure. Because the needles are thin, they usually cause little or no pain although severe discomfort may occur on rare occasions. Occasionally, up to a week of increased pain or discomfort may occur after treatment. There have also been reports of bruising, fatigue, fainting, nausea, and infection at the insertion sites, but these also occur infrequently. Both specific and generalized side effects may occur with acupuncture therapy. • The study team indicated that they consider acupuncture in this population to be a minimal risk procedure. • Those on the call discussed the regulatory definition of minimal risk and the differences between a relative risk standard (the risk to someone who has the condition, chronic lower back pain) or absolute risk standard (the risk to a "healthy person"). Some IRBs allow a relative risk standard while others use an absolute risk standard. • While the team anticipates the study to be minimal risk to participants under both of these standards, those on the call suggested that the team be explicit in the IRB materials about why this study would qualify as minimal risk, but ultimately it is the IRB that will make this determination. • At KPWA, acupuncture has been deemed to meet the criteria for minimal risk in prior studies.	Dr. Ali planned to send language around minimal risk as defined in the revised common rule (sent Dec 9 but later retracted as it applied only to prisoners)
Consent	• At KPWA, KPNC, and SH, the study team will contact the PCP to confirm that the patient can be contacted. Patients are then mailed an invitation letter with an information sheet. Patients are asked to complete an online screener (or contact the study team). For patients who contact the study team for screening, oral consent is obtained before the screening questions are asked. For patients who are screened	Members of the Ethics and Regulatory Core need to examine the issue of consent in this trial further.

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	study-eligible, oral consent for the trial is obtained, and a baseline interview is completed, and then the participant is randomized to one of the three arms. • At IFH, PCPs will directly refer potentially eligible patients to study staff for screening. Written consent for the trial will be obtained at IFH. • The study team was asked why they did not plan to obtain written consent since participants will be seen for the acupuncture treatment. They explained that the acupuncturists are not study team members who would be able to obtain consent. In addition, not all participants would receive acupuncture treatment (one-third will receive usual medical care). They also described the logistical difficulties of sending a consent form to participants and getting it signed and sent back. • The regulatory requirements for oral consent (waiver of documentation of consent) were discussed. Under 45 CFR 46.117, a waiver of documentation is permissible when the research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside the research context. The reviewing IRB would need to determine that these criteria are met to approve an oral consent process for the study. • Those on the call suggested that a written consent process might be preferable to eliminate questions about whether the study meets the criteria for waiver. • Additional research is needed on the CMS issue (described below), including whether there are any special requirements related to consent when doing research under a CED (coverage with evidence determination), which may be the case as this trial is implemented.	
Privacy/HIPAA	• From the study protocol (attached supplemental material): o A HIPAA waiver of authorization will be obtained for the EHR record review. Patient health care utilization and administrative data will be used for the identification of patients who are potentially eligible for the study and to examine pertinent health care utilization patterns among study participants (including healthcare encounters and pharmacy-related outcomes). All data will be extracted from EHR and administrative databases in each of the healthcare systems participating in the study. Prior to consent, select variables will be extracted (to determine eligibility, as described	

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	above) and uploaded into the site's recruitment tracking system, which will be password protected and accessible only to authorized study staff. ○ In previous PCTs conducted by the study team in which the need for written consent was waived and oral consent obtained, similar sources of data (PROs and EHR data) were used without a written HIPAA authorization; however, this required a Privacy Board approval of an alteration of HIPAA. If we determine that written consent is indicated for this trial, a written HIPAA authorization will be obtained. • Those on the call felt that in the context of CMS rules about coverage, there are other factors and more complexity to carefully consider. • It was thought that whatever waiver is granted for consent, the HIPPA authorization would follow the same path.	
Monitoring and oversight	• From the study protocol (supplemental material): ○ An Independent Monitoring Committee (IMC), to be established in the UG3 year, will oversee the trial and conduct reviews to evaluate the accumulated study data for participant safety, study conduct and progress. The monitoring plan will be finalized in the UG3 year by the Multiple PIs in collaboration with the Collaboratory Coordinating Center and NCCIH. The IMC will review the study protocol and materials prior to implementation; review Adverse Events (AEs)/Serious Adverse Events (SAEs) and data on recruitment and retention efforts every six months during the conduct of the trial (or at the frequency deemed necessary by NCCIH). Outcomes from each IMC meeting will be shared with the IRB of record and appropriate NIH program staff. • The AcuOA study has established a protocol review committee, which has been approved by NCCIH. This committee consists of experts in pain, chronic pain, internal medicine, family medicine, qualitative research, and clinical trials, and will review all planning materials developed during the UG3 phase. It is expected that this committee will transition into the IMC in the UH3 phase.	

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Issues beyond the study	• A certificate of confidentiality will be automatically provided per recent NIH policy. This certificate adds provisions for future research uses and confidentiality obligations for future data sharing.
	• CMS has opened a national coverage analysis (NCA) to determine whether acupuncture for chronic low back pain is reasonable and necessary under the Medicare program. CMS is currently soliciting public comment on this topic. If Medicare will cover acupuncture on chronic low back pain in the context of clinical trials, the issue will be how many participants can be treated within the Medicare reimbursement framework, as some will be seen at health care system facilities and others will be referred to acupuncturists practicing in the community (which may not meet Medicare reimbursement rules). CMS planned to issue a final determination of coverage in October 2019 but instead provided notice that a decision is forthcoming. Further analysis of the impact on this trial is required.
	• Potential CMS-related issues:
	  ○ There are special rules for CMS around criteria for evidence development. CMS is particularly interested in the direct supervision of acupuncture needling (i.e., by an MD or NP).
	  ○ While AcuOA will proceed even without CMS coverage, it is expected the results of the trial will inform future coverage determination.
		The Ethics and Regulatory Core will discuss and examine any special consideration for conducting pragmatic clinical trials in the setting of CEDs.*

*Medicare released a decision memo on January 21, 2020, that they will cover acupuncture for chronic low back pain under section 1862(a)(1)(A) of the Social Security Act (https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=295).

Pragmatic Trial of Acupuncture for Chronic Low Back Pain in Older Adults

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OVERVIEW

A critical gap exists in the evidence on the safety and effectiveness of treatments for older adults with chronic low back pain (cLBP). This gap is of particular concern because about 12% of adults over age 65 suffer from impairing cLBP,[1] the prevalence is increasing[2] and older adults commonly have more disabling back pain than younger adults.[3] Many treatments considered appropriate for younger adults may not be appropriate for older adults given their greater prevalence of comorbidities with attendant polypharmacy.[4] In addition, burgeoning imaging rates reveal incidental pathology in many cases, placing older adults at risk for inappropriate invasive treatments.[2,5] Because of normal physiological changes with aging (e.g., reduced tolerance of medications and increased prevalence of osteoporosis), older adults are at substantially increased risk of adverse effects of commonly used LBP treatments[1,6-8] including medications (e.g., non-steroidal anti-inflammatory drugs [NSAIDs], muscle relaxants, and opioids) and complementary and integrative (CIM) treatments such as high velocity spinal manipulation techniques. While numerous randomized clinical trials (RCTs) have evaluated treatments for chronic pain, their applicability to older adults is ***unclear*** because most of these RCTs included few, if any, older adults.

Evidence-based guidelines from 2017 recommended 9 nonpharmacological treatments for cLBP including acupuncture, which is considered to have moderate evidence of effectiveness for improving pain and function compared to usual care.[9] These therapies are now recommended as first-line therapy for cLBP. Acupuncture has been found effective for cLBP in younger adults, with little diminution of effectiveness over 12 months of follow-up.[10] However, few studies of acupuncture have included adults over 64. Acupuncture is not routinely covered by Medicare, and thus not available to most older adults. However, older adults are interested in acupuncture and Medicare is interested in data on the value of acupuncture for older adults with cLBP to inform coverage decisions and efficient implementation. Our pragmatic clinical trial is designed to test the value of a standard course of acupuncture and a standard course of acupuncture supplemented with a maintenance course compared to usual medical care. If successful, this pragmatic RCT will offer clear guidance about the value of acupuncture for improving functional status and reducing pain intensity and pain interference for older adults with cLBP. This evidence will provide essential information for Medicare regarding coverage decisions and for individual physicians and patients deciding on a course of treatment.

STUDY AIMS

UG3 Aim 1: In the UG3 year, conduct the necessary preliminary work to ensure our ability to conduct an effective and robust pragmatic trial of acupuncture for cLBP in older adults. We will work closely with the NIH Health Care Systems Collaboratory Coordinating Center (HCS-CCC) and its affiliate working groups to ensure that the final trial design is feasible and efficient, by: a) refining plans for patient recruitment, intervention protocols, and process and outcome measures; and b) ensuring adequate electronic health record (EHR)/information technology (IT) infrastructure and clinical data quality to conduct the trial. We will work with stakeholder advisors and collective formative data from older adults with cLBP and acupuncturists to ensure study implementation processes and materials include their perspectives.

UH3 Aim 1: Conduct a pragmatic RCT evaluating acupuncture and maintenance acupuncture for older adults with cLBP in four health care systems (HCSs). We will implement the procedures and protocols finalized in the UG3 period to conduct a pragmatic trial of 828 older adults (≥65 years of age) with cLBP comparing standard acupuncture (SA;12 weeks of acupuncture) or enhanced acupuncture (EA; 12 weeks of SA, 12 weeks maintenance) to usual care (UC) (all groups, N=276). Primary

outcomes will be back-related function at 26 weeks. Key secondary outcomes will include pain intensity and pain interference and clinically meaningful improvement. Outcomes will also be collected at 12 and 52 weeks.

<u>UH3 Aim 2:</u> Conduct a cost-effectiveness analysis of EA and SA compared to UC.

<u>UH3 Aim 3:</u> Conduct formative and summative evaluations to understand, describe and explain barriers and facilitators to adoption, implementation, and sustainability of acupuncture treatment for older adults. Identify health care administration and clinical work flow factors important for integrating acupuncture referral and treatment into a broad array of HCSs including fee for service environments.

Our team's collaborative history and substantive experience conducting pragmatic research and clinical trials on acupuncture and other non-pharmacotherapy approaches to the treatment of chronic pain provides a strong foundation for the proposed research.

AMENDMENT: Our sample size may be slightly different, based on some power calculations completed after the grant application was submitted. We have not made any changes to that sample size as we plan to revisit the assumptions for the calculations during the UG3 year. We believe our sample size will vary between 789 and 840.

UG3 Clinical Trial Planning Phase

During phase 1 (UG3), we will conduct the necessary preliminary work to ensure we can conduct an effective and robust pragmatic trial of acupuncture for cLBP in older adults. To achieve each of the milestones, we will work closely with the NIH HCS-CCC and its affiliate core working groups to ensure the strongest possible approach, that measures and approaches are harmonized where feasible with other Collaboratory trials, and that we take advantage of the substantial experience of the HCS Collaboratory.

We worked closely with performance site collaborators to ascertain that each site has sufficient numbers of potentially eligible older adults to exceed projected recruitment goals by a wide margin. The sites are described below and expected recruitment yields are in Table 1.

Kaiser Permanente Washington (KPWA) is an integrated HCS that provides both health insurance and care. About 60% of its 710,000 members receive care at 29 KPWA owned-and-operated medical centers with the other 40% see network-affiliated providers. Although most members live in the heavily populated Seattle-Olympia corridor, the health plan has members from across the state, including more rural and medically underserved areas. KPWA allow patients with appropriate insurance to self-refer to acupuncturists within the HCS network and limits the number of allowed reimbursable visits. ***Kaiser Permanente Northern California*** (KPNC) is also an integrated HCS that provides health insurance and care to approximately 4,000,000 members (1/3 of Northern California residents); it owns and operates 21 hospitals and over 200 outpatient clinics. Both KPWA and KPNC are integrated health care and insurance systems. KPNC allows physicians to refer patients with cLBP to acupuncture as a specialty after 3 months with no improvement using another treatment. KPNC, however, has very limited capacity to meet demand for acupuncture services internally so we plan to contract with community providers for the acupuncture provided in this study. ***Sutter Health*** (SH) is a large non-profit HCS with a network of medical groups (5,500 physicians in primary care and ambulatory care practices) and 24 hospitals located throughout Northern California in areas that complement with the geographic distribution of the KPNC clinics. SH accepts multiple forms of insurance thereby representing an important and common sector of the US health care marketplace. The options for acupuncture services for patients at SH vary by the type of insurance they have. The ***Institute for Family Health*** (IFH) is a freestanding federally qualified health center (FQHC) network operating 23 full-time health centers and seven part-time centers in New York City and New York State's Mid-Hudson Valley. IFH provides a full range of primary medical care, specialty care, dental services, mental health, and other services at each of its sites, either directly, by contract or referral and serves a broad range of patients (age, sex, race) regardless of their ability to pay. Counting all sites, IFH serves about 98,000 patients. IFH offers limited acupuncture performed by supervised acupuncture students but is testing acupuncture delivered by licensed acupuncturists in a large-room "group setting" within their clinics in a current trial. These systems were selected to ensure that our population mirrors that of Medicare and represents several ways to incorporate acupuncture into care.

AMENDMENT: IFH will deliver individualized acupuncture treatment sessions with screens between patients. We will explore having some acupuncture treatments delivered in medical clinics in the other three locations. More work on that is expected once Medicare releases their final ruling on reimbursement of acupuncture for chronic low back pain during trials of older adults.

Table 1 summarizes the locations of our selected performance sites and the forecasted number of eligible patients based on preliminary electronic health record information and provides the targeted enrollment for each site. In general, our target enrollment requires only a very small proportion (1-3% at KPWA, KPNC, and SH) of potentially eligible patients suggesting that we should have no problem meeting enrollment targets. Within these HCSs in 2017, roughly 55,000 adults over 65 years of age made visits for LBP. In each of these three sites, we plan to use a population-based approach to recruit patients, reaching out to primary care providers shortly after any ambulatory care visit in which LBP was included as a diagnosis to let them know our intention to invite their patient to participate in the trial. Unless the PCP suggests we not contact a particular patient, we will reach out to invite them to complete a screening to determine their eligibility for the study and the potential receipt of acupuncture services. Using such recruitment methods on many occasions in these settings, we have consistently met and exceeded enrollment targets and we are confident we have ample population base to successfully recruit for this trial. Assuming that 15% of patients with a visit for back pain will be eligible and willing to be screened, as was found in the BOLD study (a study of older adults with cLBP in which KPNC participated),[88] we will have 1480 patients from KPWA, 5462 patients from KPNC, and 1200 from Sutter (with additional Sutter recruitment possible if necessary), suggesting more than sufficient sample to reach the target samples of 180, 300, and 219 in the respective sites. Our recruitment approach in these sites uses EHR information to identify and directly recruit patients whose pattern of healthcare utilization indicates a potential treatment need that our interventions target. This strategy reduces burden on primary care and uses a population-management approach available and used by many healthcare systems. Our patient recruitment process at the IFH-affiliated clinics will proceed somewhat differently and is based on a process successfully employed in a recent PCORI-sponsored trial (NCT024356727) comparing group to individual acupuncture in demographically similar clinics. For that study, PCPs connected their eligible patients to the study and 58% of those referred were interested and willing to participate. Hence, if PCPs connect roughly a third of their eligible patients to the study, we will be able to reach recruitment targets at IFH. During the UG3 year, KPWA qualitative and recruitment experts will support the IFH team in refining recruitment processes to optimize yields during the main trial. If we determine that IFH will not be able to reach these goals, we will reduce the expected sample at that performance site and enhance sampling at our other sites. The EHR data system cannot be rapidly accessed at IFH as necessary to support the population-level process employed in our other sites. Even though the recruitment process is necessarily different at IFH, we think this presents an opportunity to better support and understand the patient/provider shared decision-making about acupuncture as an option. Further, FQHCs are generally lower resourced settings utilized by an often vulnerable and underserved population making the inclusion of participants from such sites particularly important for broader representativeness even with a smaller sample. That it requires enrolling 20% of the number of eligible patients at that site is well within the bounds of what

Table 1. Summary of Health Care Systems

Health Care System	Investigator(s)	Location(s)	# eligible Patients*	Target Trial Enrollment
Kaiser Permanente Washington	Lynn DeBar, PhD Karen Sherman, PhD	Washington State	9865	180
Kaiser Permanente Northern California	Andrew Avins, MD, MPH	Northern California	36,418	300
Institute for Family Health (IFH)	Ray Teets, MD	New York	686	129
Sutter Health	Alice Pressman, PhD	Northern California	8000	219

over 65, visit for low back pain, no dementia, data from 2017

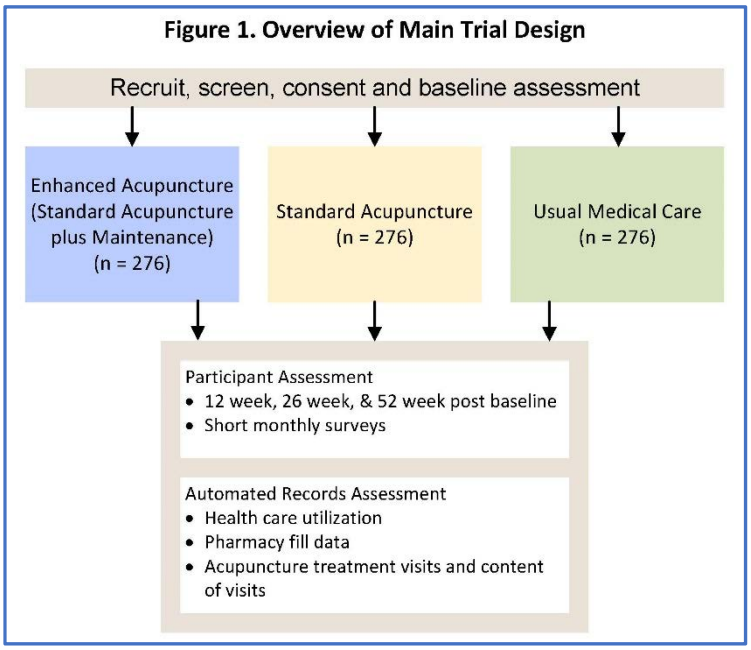
we've been able to recruit through some of our other pain-related studies that have included older adults. Finally, KPWA, KPNC, and SH are all part of the Health Care Systems Research Network (HCSRN) which includes many other HCSs across the country that many of us work with closely and that we could potentially add as performance sites if there were recommendations to do so during the UG3 preparatory year.

Establishing Acupuncture advisory panel and finalizing clinical workflow, treatment parameters, and related data collection forms for acupuncturists. One critical activity in the UG3 preparatory year is to ensure that the many details associated with the provision of acupuncture services and related data collection are fully refined during this time. Although our team has considerable experience with acupuncture protocols in past studies we believe this project will be strengthened by including an advisory group of acupuncturists who can help refine the important details of our approach by advising on: (1) breadth of treatment protocol (allowed treatments) and optimal dose (number and frequency of treatment sessions for both standard and maintenance acupuncture), (2) recruitment and qualifications of acupuncturists serving as treatment providers for the main trial, and (3) finalization of data collection forms to be completed by acupuncturists at each session so that we can fully characterize needling (e.g., number of needles, specific point locations, needle retention time, position of patient during the treatment) as well as use of lifestyle management advice. Our Acupuncture Advisory Panel consists of 8 acupuncturists collectively bring deep experience with provision of acupuncture in their respective communities and within HCSs, research implementation, and acupuncture policy-related work.

Optimizing patient recruitment and retention: formative research to refine approach, materials, and conducting a limited pilot. We plan to use formative research to refine our patient recruitment processes and materials during the UG3 year and conduct a small pilot of the intervention (with four participants) to ensure our readiness to conduct the full trial in the UH3 period. We will conduct focus groups and follow-up usability testing to have patients from our target population review and advise on recruitment materials and processes. From among those participants in this formative research at KPWA and IFH, we will invite four participants to receive up to six sessions of acupuncture with two study-identified community acupuncturists so that we can pilot the intervention process and study assessments. Debrief interviews with these patient participants and acupuncturists will further help us to refine our study processes and materials for the main trial.

Other UG3 activities. Other critical activities to be carried out in the UG3 year include working in partnership with the HCS CCC and associated work groups to: (1) address any relevant regulatory & ethical issues including finalization of participant consenting processes and establishing a single IRB for the study (Ethics/Regulatory working group), (2) ensure standardized electronic data collection when possible, refining quality control methods, and finalizing data sharing plans (Electronic Health Records working group); (3) refine our analytic approach to optimize the rigor and comprehensiveness of our approach (Biostatistics and Study Design working group); (4) refine patient reported outcome measures and acupuncturist treatment process measures and harmonizing as able with assessment tools used by other Collaboratory awardees (Patient-reported Outcomes working group); and (5) identify potential HCS factors important to address to ensure that the trial can be carried out as planned and, if the trial has positive findings, to support referral and acupuncture treatment for older adults with cLBP in diverse HCSs including those using a fee for service model. Our collective investigative team has expressed interest and willingness to serve on the HCS-CCC working groups and we expect will bring pertinent experience to these forums.

UH3 Phase: Implementation of AcuOA Trial



Overview

We propose a 3-arm multisite pragmatic trial to evaluate two types of acupuncture. Our trial of 828 older adults (≥65 years) with cLBP will compare standard acupuncture (SA; 12 weeks of acupuncture) and Enhanced Acupuncture (EA; 12 weeks of SA, 12 weeks maintenance) to usual care (UC) (each group, N=276). Participants will be recruited from four HCSs (KPWA and KPNC, which have Kaiser Permanente health plans; Sutter Health; and Institute for Family Health, a system of federally qualified health centers). Figure 1 provides an overview of our planned activities.

Participant Identification and Eligibility

Source: All participants will receive their primary care services from one of the four participating HCSs and have EHRs available for them. In 2017, over 55,000 individuals who were 65 years of age or older made visits to health care providers in these systems, so we anticipate an ample sample pool from which to recruit.

Inclusion and Exclusion Criteria: While inclusion and exclusion criteria will be finalized during the UG3 planning year, we anticipate a broad spectrum of older adults will be eligible.

Proposed inclusion criteria:

- Is at least 65 years of age
- Recently visited a health care provider for low back pain (may allow a visit within the last 12 months)
- Received primary care at one of the participating health care systems.
- Has back pain that is uncomplicated with or without radiculopathy.
- Ability to understand study procedures and to comply with them.

Proposed exclusion criteria:

- Back pain < 3 months
- Mild symptoms (currently discussing criteria, probably PEG <3 or PEG general function <3)
- Specific types of back pain (cancer, vertebral fractures, spinal infection, active inflammatory disease)
- Receiving workers compensation or involved in litigation

- Does not speak and write English or Spanish
- Medical conditions that will make treatment difficult or inappropriate (currently under discussion)
- Acupuncture within the last 6 months
- Living in a nursing home, on Hospice, or palliative care
- Inability or unwillingness to give informed consent
- Dementia
- Inability or unwillingness of individual to give written informed consent.

Study Interventions

Standard Acupuncture: Refinements to the allowed intervention protocol are being determined in collaboration with our acupuncture advisory panel during the UG3 year. We anticipate a broad treatment protocol that recommends local and distal acupoints, with options for patient customization (e.g., range of number of needles, specific point locations, range of needle retention times, intent to get de qi, recommendation on acupuncture needles). This approach reflects the reality of US acupuncture practice with practitioners enabled to tailor treatment to the needs of participating patients. Acupuncturists will need to ensure that all patients are comfortable with treatments proposed for them. We will probably allow acupuncturists to work with patients to determine the appropriate number of treatments for each person.

Because the optimal dose of acupuncture is unknown, we used several strategies to determine our proposed maximum treatment number. Discussions with long-time acupuncturists with experience treating older adults suggest that up to 15 visits during the 12-week treatment period would be appropriate. This is consistent with the greatest number of allowed treatments in some of the largest acupuncture trials to date,[32-34] though some used 10[27-29] to 12 treatments.[30,31] Acupuncturists may not need all these visits for every patient.

EA: Standard Plus Maintenance Acupuncture: We are unaware of any trials of acupuncture for cLBP that used maintenance acupuncture, even though acupuncturists often recommend maintenance visits after a course of more intensive treatment. Berman and collegues[100] conducted one of the few studies that included a gradually tapering protocol as part of a knee osteoarthritis trial. In that study, treatments decreased from twice weekly to weekly to every other week to monthly. Based on discussions with experienced acupuncturists, we propose up to 6 treatments during the 12-week maintenance phase. This number may be revised during the UG3 period based on results from our acupuncture advisory panel. The advisory panel will determine whether the maintenance treatments should differ in details of the visits compared to the standard treatment.

Acupuncturists: We will work with NIH, CMS, and our acupuncture advisory panel to ensure that all acupuncturists who are part of the pool of study acupuncturists are appropriately credentialed within each site's health care system. In general, we plan to recruit acupuncturists who are already credentialed to work with some insurance through pre-existing healthcare system networks. However, other methods may also be warranted given credentialing criteria outlined in CMS's recent "Proposed decision memo for acupuncture for chronic low back pain (CAG-00452N"; https://www.cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx?NCAId=295). During the UG3 year, we expect to work closely with NCCIH and CMS personnel as well as to avail ourselves of the expertise of the Collaboratory coordinating center and

working groups to be sure we're working within CMS guidelines and that the approach is feasible and scalable for broader use should study findings be positive.

Integration of Acupuncture into Care: Each health system has a distinct way of providing general acupuncture services for **younger** adults (acupuncture is largely not a covered benefit for Medicare-insured patients in our participating HCSs). Once Medicare releases their final decision on coverage of acupuncture for chronic low back pain in the context of clinical trials, we will work with the HCSs to see how many of our patients can be treated within the Medicare reimbursement framework. We anticipate that some patients will be treated in HCS facilities. Other patients are likely to be referred to acupuncturists practicing in the community, which may not meet Medicare's reimbursement rules, but represents the most common way that acupuncturists currently practice in the US. Allowing this variability in acupuncture treatment setting best mimics real world practices.

Assessment and Outcome Measures

In clinical practice, patient-reported outcomes (PROs) are more important than objective tests for cLBP.[101] Although some health systems now include PROs in their EHRs, this practice is not sufficiently frequent or timely enough to be useful for pragmatic trials. Thus, we will collect PROs as part of our trial. These will be collected via phone or web-survey at 3, 6 and 12 months with shorter monthly surveys (Table 3). We will collect information regarding participant flow through the trial so that we are able to complete the CONSORT statement.

The NIH Research Task Force on Research Standards for Chronic Low Back Pain (RTF) made extensive recommendations for core baseline information and a set of outcome domains, including recommended measures, to use in cLBP trials.[102] We plan to include all recommendations in our PRO assessments. Baseline information will include sociodemographic characteristics (gender, age, race, ethnicity, education level, employment status, and marital status), back pain history (e.g., years since first episode of back pain, duration of current episode) and other factors that are prognostic of back pain resolution (e.g., number of pain sites and patient expectations of treatment outcome). Some information on sociodemographic characteristics is available through electronic databases (e.g., age, gender, race, ethnicity, height, weight, other pain sites), while other information will be acquired directly from the patient during the baseline interview. The core set of recommended outcomes includes physical function, low back pain intensity, pain interference, depression, sleep disturbance, and catastrophizing. **For our primary outcome, we will use the Roland Morris Disability Questionnaire** (RMDQ),[103] a legacy measure of back dysfunction used in all our prior trials. Pain intensity and pain interference will also be key measures from the Patient Reported Outcome Measurement Information System (PROMIS-29). Many other measures will come from the PROMIS -29 (Table 3).

Finally, we will ask acupuncturists seeing study participants to complete a form describing the range of services (e.g., types and location of needling and ancillary services) they have provided at each visit and the duration of the treatment. Such information will allow us to fully characterize acupuncture treatment practices and may provide important information for secondary exploratory analyses examining patient responsiveness to treatment. We have developed and used similar forms for other studies,[37,97,104] but will work with our acupuncture advisory panel during the UG3 year to refine these data collection forms and processes for collecting the information.

Table 3 Content of Baseline and Follow-up Assessments
SOURCES OF DATA FOR ACUPUNCTURE IN OLDER ADULTS

MEASURES	Baseline	Monthly	3 - month	6 - month	12 - month
BASELINE INFORMATION					
Patient characteristics (age, gender, ethnicity, race, employment status, education, height, weight, smoking status, excessive use of drugs or alcohol) (NIH Task Force Research Standards); education	x				
Back pain history (pain duration, leg pain, other pain sites, low back operation, use of selected treatments, work loss due to back pain, disability status, catastrophizing, fear avoidance)	x				
Expectations and knowledge of acupuncture	x				
CORE SET OF OUTCOMES FOR BACK PAIN STUDIES					
* Back dysfunction (24-item Roland Morris Disability Questionnaire-RMDQ)	x		x	x	x
**Low back pain intensity (0-10 numerical rating scale)	x	x	x	x	x
**Pain interference (4-items PROMIS)	x	x	x	x	x
Pain Interference and enjoyment of life (2-items PEG)	x	x	x	x	x
Physical Function (4-items PROMIS)	x	x	x	x	x
Depression (4-items PROMIS)	x		x	x	x
Anxiety Screener (GAD-2 or 4-item PROMIS)	x		x	x	x
Sleep disturbance (4-items PROMIS)	x		x	x	x
Patient Global Impression of Change (7 item scale)			x	x	x
Participant Disposition			x	x	x
Fatigue (4-item PROMIS)	x		x	x	x
Ability to Participate in Social Roles and Activities (4-item PROMIS)	x		x	x	x
Euro-QOL-5D	x				x
TREATMENT-RELATED INFORMATION					
Adverse events			x	x	x
Adherence to assigned treatment (FROM TREATMENT RECORDS)			x	x	x

POTENTIAL CONFOUNDERS					
Use of co-interventions (medications, other treatments, etc.) – ALSO HEALTH CARE UTILIZATION FROM ELECTRONIC DATA	x		x	x	x
Daily exercise and job-related activity	x		x	x	x

** Primary Outcome Measure; **Key Outcome Measure*
Blue measures are recommended by the NIH Task Force
PROMIS-29 profile V 2.0

Data Management and Quality Plan
A detailed data-quality management program including specific protocols for data collection and quality control will be developed by our team in collaboration with the NIH HCS-CCC during the UG3 phase. Data capture will use WinCati software (Sawtooth Technologies) and a web-based event tracking application that we routinely used for multisite studies. The centralized event-tracking application imports data from WinCati and enables efficient participant management from recruitment to follow-up across all study sites. Features include case management, participant event reporting, and generation of call lists to maximize WinCati capabilities.

The application has a centralized, user-friendly subject management interface for study team members. Planning for the creation of WINCati data collection forms and customization of the event-tracking application will occur in the UG3 year with systems built and finalized early in the first UH3 year. The study will collect PRO data using forms that are web-based or on paper and are administered by patients or interviewers. We will require comprehensive data management and quality procedures across all sites to ensure data provenance and integrity.

Formative and Summative research and analysis. This study includes qualitative work that incorporates both formative and summative research approaches and analyses as summarized in Table 4.[105] The formative evaluation activities will use the Exploration, Preparation, Implementation, Sustainment (EPIS) implementation framework[106,107] whereas summative work will use the RE-AIM (reach, effectiveness, adoption, implementation, maintenance) model[108,109] to document, triangulate and explain research outcomes. During the initial UG3 year, the formative research activities (patient focus groups and usability testing) will focus on developing participant recruitment materials and refining the recruitment process for maximizing study recruitment yields and demystifying acupuncture treatment for potential participants. Debriefing patients and acupuncturists participating in the pilot will provide critical feedback for any refinement necessary for the study approach and materials. After the clinical trial is well underway (UH3 year 2), we will conduct focus groups with patients and acupuncturists who have participated in the trial to get input on the implementation of the acupuncture interventions and document the experiences of participating patients and acupuncturists. Formative evaluation data will also be collected later in the project (UH3 year 3) but with the purpose of supporting the sustainment and spread of the intervention, that is to inform the broader adoption of acupuncture treatment, clinical workflow, and healthcare systems processes. The summative work to be completed in UH3 Year 2 will use the RE-AIM model[108,109] to document and help triangulate and explain the research outcomes. This model has four components: Reach, Effectiveness, Adoption, Implementation, and Maintenance. **Reach** reflects the percentage and characteristics of persons who receive the intervention. We will use EHR and assessment data to document: 1) the percentage of patients excluded from the trial and the rationale for exclusion, and 2) the percentage of patients receiving acupuncture based on the denominator of all patients approached for participation, as well as all potentially eligible patients in each health plan regardless of whether or not they were approached for study participation.

Effectiveness measures the impact of the intervention on important study outcomes (see Table 3). Qualitative data can be critical for a richer understanding of quantitative study findings (reach, recruitment and effectiveness). HCS **Adoption** is less relevant for this study as most acupuncture services will be provided outside the HCS (as is standard in these settings). However, there may be valuable lessons to be learned from those sites that choose to offer acupuncture within the HCS (IFH and in some instances potentially KPNC) and by tracking relevant organizational and policy changes. Furthermore, adoption may be influenced by patient and health care provider experiences which will be ascertained through focus groups conducted with patients, primary care providers and acupuncturists. Finally, **Maintenance** (the ability to sustain acupuncture services in these and broader health care settings, will be assessed through summative focus groups and stakeholder interviews. PCP focus groups will explore the conditions under which they would consider referring their older adult patients with cLBP to acupuncture. Although developing clinical decision support tools for introduction of acupuncture for treatment of cLBP in HCS would require an intensive and systematic process that exceeds what resources and time for this trial would allow,[110] focus group questions will include those designed to understand the needs of patients and clinicians regarding shared decision making for acupuncture treatment for cLBP in older adults, an important first step towards developing such decision aids. Stakeholder interview will focus on understanding factors important for clinical and operational leaders in including provisions for acupuncture treatment in their settings. Further, our acupuncture advisory panel will provide input into important factors for offering acupuncture treatment in a variety of settings (including fee for service).

Interviews will be conducted by telephone; patient focus groups will be conducted face-to-face whereas focus groups with acupuncturists and PCPs will be conducted online. The online platform being considered allows participants can engage at any time within a participation window, allowing for flexibility in terms of location and timing of participation. Multiple studies have validated the use of online focus groups to collect qualitative data from healthcare and other individuals whose busy schedules may make participation difficult otherwise.[111,112]

All audio-recorded interviews will be transcribed. In-person focus groups will be transcribed in real time by a court reporter. Online focus groups are text based and do not need transcription. Coding will be completed by trained coders using ATLAS.ti, a qualitative analysis software program that aids management and interpretation of text-based and other non-quantitative data. Coder reliability will be ensured through using an iterative process of coding the same text and comparing codes and discussing discrepancies. Code definitions will be updated as needed to ensure clarity. Once the interviews are coded for a particular phase of the study (see table 4), we will use ATLAS.ti queries to produce reports of text associated with primary codes and begin synthesizing themes from this text. ATLAS.ti allows retrieval of coded information in multiple ways, including by participant features (e.g., gender, pain diagnoses) by a code alone, or by combinations of co-occurring codes. We will also create reports of text related to key codes, using a cross-tabulation like procedure to explore how they relate to one another. We will compare themes and responses across participants and within categories of participants to examine common patterns and differences in beliefs, attitudes, behaviors and experiences. Additionally, to ensure validity, we will search for areas of contradiction across participants[113-115] and across groups. This approach to coding and data reduction will allow us to examine issues from a number of perspectives and ensures a thorough review of the data increase the breadth and depth of insights generate from the qualitative data gathered.

Table 4. Overview of Qualitative Evaluation Approach using EPIS and RE-AIM Frameworks

Trial Year / Phase	Evaluation Focus	Goals	Data / Methods
UG3 / Planning	Formative: Exploration and Preparation	Identify potential barriers and facilitators for participation/use of intervention for patients Finalize materials and procedures with patients and acupuncturists	Focus groups and user-centered design interviews with patients Acupuncturists advisory panel meetings Debrief with pilot participants and acupuncturists Provide expert consultation for IFH team
UH3 / Yr 1 Implementation	Formative: Implementation	Identify • Local adaptations to stud protocols • Changes in context (inner and outer) • Emerging barriers	Meeting observation Review of exploratory data and planning for UH3 year 2 qualitative activities
UH3 / Yr 2	Summative: RE-AIM	Document reach, effectiveness, adoption, implementation and sustainment from perspectives of key stakeholders Clarify and further explain final results of the study (4th quarter) Explore intersections and divergences between quantitative and qualitative data (4th quarter)	Focus groups with patients and acupuncturists who have participated in the trial Interviews with low engagement acupuncture patients
UH3 / Yr 3 Final Data Collection, Analysis and Dissemination	Sustainment and Spread	Integrate patient, acupuncturist, and primary care provider perspectives into recommendations for sustainment and spread of intervention. Identify health care administration and clinical work flow factors important for integrating acupuncture referral and treatment into broad array of health care systems including fee for service environments.	Focus groups with primary care providers Stakeholder interviews: internal and external to participating healthcare systems.

Power analyses, statistical, and economic analysis plan

UH3 AIM 1 Analysis Plan

Aim 1 will evaluate the effectiveness of acupuncture and acupuncture plus maintenance relative to Usual Care (UC) at 12, 26 (primary time-point), and 52 weeks after randomization. We hypothesize that both SA and EA will have longer term benefit compared to usual care. We will conduct a longitudinal analysis including the continuous outcome change in Roland Morris Disability Questionnaire (RMDQ) from baseline (primary outcome) measured at all follow-up times in one model estimated using generalized estimating equations (GEE). We chose GEE because our primary outcome, the Roland Morris Disability Questionnaire, is not expected to be normally distributed and GEE allows us to relax this assumption. We will use a working independence correlation matrix and will calculate standard errors using the robust sandwich estimator to account for within-person correlation.[116] We will include interactions between intervention groups and time (12, 26, 52 weeks) to estimate time-specific intervention effects. To gain power, since acupuncture and acupuncture plus maintenance at 12 weeks are the same intervention (maintenance period occurs 12 to 24 weeks post randomization), we will combine acupuncture groups at 12 weeks unless there is some indication of differences between groups (e.g. differing number of acupuncture treatments received up to 12 weeks by group).

For the 26-week time point we will conduct a sequential series of analyses. We will first run a regression model with three groups (acupuncture, acupuncture plus maintenance and UC) for 26 weeks. We will then assess differences in change in RMDQ at 26 weeks between the two acupuncture groups: with and without maintenance. If a statistically significant and meaningful difference (>1 pt difference) is found between the maintenance versus no maintenance groups (Scenario 1), we will

further compare each of the acupuncture groups separately to UC. Scenario 1 assessments will determine if acupuncture with maintenance is better than acupuncture without maintenance at 26 weeks and if either or both acupuncture groups are better than UC. If acupuncture groups do not differ at 26 weeks (Scenario 2), we will combine acupuncture groups for this time point and run a second regression model including only UC and the combined acupuncture group. If this regression model shows that acupuncture is better than UC, we will conclude that acupuncture improved RMDQ at 26 weeks, but maintenance was not shown to be efficacious.

To control for multiple comparisons when testing between the three groups at 26 weeks we will use Fisher's least significant (LSD) difference procedure.[122] Fisher's LSD has been shown to strongly hold the family-wise error rate at α-level for studies with three treatment groups.[123] Fisher's LSD is a simple procedure where the global Wald-test of the null hypothesis of equal means for all groups is performed first. If this overall test is statistically significant then the sequential series of pairwise comparisons will be performed as outlined previously; otherwise the procedure stops, failing to reject the over null hypothesis that at least one mean is different from the others.

We will follow the same general framework for 52 weeks as we have specified for 26 weeks. Note that we include all times points in a single model within this general modeling framework to handle correlation due to multiple outcomes on a given person.

We will conduct a similar analysis for secondary outcomes including key outcomes such as pain intensity and pain interference and will use appropriate link functions for non-continuous outcomes. All models will adjust for baseline outcome value, age, sex, and health care system as well as any baseline variables that are predictive of loss to follow-up. All analyses will be conducted following an intent-to-treat approach, including all individuals randomized regardless of their engagement with, or exposure, to the intervention. If loss to follow-up is above 15%, we will employ imputation techniques to address missing data issues.[124] The imputation method we propose uses a pattern mixture approach that relaxes the missing at random assumption. It is derived for GEE and is sensitive to potential non-ignorable missingness. However, our focus will be on minimizing loss to follow-up.

Exploratory analyses will further use secondary outcome data collected monthly including the outcomes low back pain intensity, pain interference, and physical function. We will use these measures to assess the trajectory of how long it takes until patients improve and to address questions such as "What proportion of people improve at three months if they don't improve after one or two months of acupuncture?" These exploratory analyses will help address how much acupuncture is needed to improve and at what time, given a patient's outcome trajectory, should acupuncture treatment stop if improvement has not been shown up to that time.

We will look at the role of patient expectations in improving outcomes, using a similar analysis. Should we identify key clinically meaningful groups in the UG3 year with sufficient numbers (e.g., gender, frail elderly, co-morbid pain conditions), we will conduct pre-specified moderator analyses.

UH3 AIM 1 Sample Size: We determined our sample size requirements for our primary outcome RMDQ at 26 weeks that focuses on detecting differences of each acupuncture group compared to UC. Given a sample size of 630 total participants (210 per group) we have at least 90% power to detect a minimally clinically important difference (MCID) of two points on the RMDQ[29,117]between each acupuncture group

and UC assuming a SD of 6 and only testing for pairwise comparisons if the omnibus F-test was statistically significant to control for multiple comparisons. Power was calculated via simulation using R software. Therefore, we have high power to detect a MCID difference between SA and UC as well as EA and UC. If instead we assume that at 26 weeks SA attenuates to be equivalent to UC and EA has a 2 point MCID improvement relative to both SA and UC we will have 91% power to detect a difference between SA and EA or UC and EA. So we are sufficiently powered (≥90%) to detect MCID differences between all pairwise group comparisons.

For any two group comparisons, given our sample size of 210 per group and SD of 6, the minimal detectable difference is 1.15 pts (i.e. the 95% CI width around difference in means between groups is +/- 1.15 pts). Further, for secondary analysis for the binary outcome 30% improvement in RMDQ from baseline we have >90% power assuming the probability of improvement in UC was between 33%[29] and 44%[3] and the MCID was a 15% improvement above UC for each of the acupuncture groups. Assuming a conservative 20% loss-to-follow-up rate we inflated our sample size to 263 per group (789 total) to assure that we are well powered for all analyses of interest.

AMENDMENT: These power calculations were completed after the grant application was submitted at the request of NCCIH. They suggest a sample size of 789 is appropriate. We believe our sample size will vary between 789 and 840, depending on the appropriate loss to follow-up estimate.

UH3 AIM 2: We will perform an economic evaluation from the payer (Medicare) perspective alongside the randomized pragmatic trial comparing usual care (UC) to the addition of 12 weeks of acupuncture (SA) and 12 weeks of acupuncture and 12 weeks of maintenance acupuncture (EA) in older adults with chronic low back pain. Costs will include all healthcare utilization, including acupuncture visits, and costs will be the Medicare covered amounts, including the reimbursed costs of acupuncture.[118] Effectiveness will be measured using quality-adjusted life-years (QALYs) based on changes in the EQ-5D[119] over the study year. If costs of either of the acupuncture arms compared to UC are reduced and effectiveness increased it will be said to be cost saving and to dominate UC in terms of cost effectiveness.[118] If incremental costs and effectiveness are both increased then an incremental cost-effectiveness ratio will be calculated and compared to society's willingness to pay for an additional QALY ($50,000 to $100,000 per QALY[125]) to see if it can be considered cost-effective.

Acupuncture implementation costs (e.g., non-study-specific staff hours, materials, facility use) will be captured from study records and valued at typial community rates. We will then use several assumptions as to the amount of this reimbursed by Medicare in our analyses with our base case based on typical acupuncture reimbursement rates (or trial allowable costs per Medicare). We will capture healthcare utilization data and costs before and for the year after baseline from electronic records. For KPNC and KPWA, we will obtain this information directly from their records. We will also be able to get cost data from Sutter, but to ensure that it is complete, we will examine the feasibility of obtaining these data directly from CMS in a timely manner We will also examine the possibility of getting Medicare data from IFH in a time manner. Because acupuncture may influence other common CLBP comorbidities (e.g., depression and sleep) we will capture both total healthcare utilization for our base case and back-pain-related-only utilization to be included in a sensitivity analysis. We will

calculate overall cost-effectiveness as well as the cost-effectiveness by site so that we can examine differences in healthcare utilization and its changes across sites. All cost effectiveness analyses will follow intention to treat.

A bootstrap methodology will be used to estimate confidence intervals,[120,121] and one-way sensitivity analyses will be performed to determine the robustness of our estimates with different assumptions such as the reimbursement rate for acupuncture and the inclusion of back-related costs only.[118]

We will also add analyses from the health care sector perspective by estimating out-of-pocket medical costs paid by patients, which mainly consist of co-pays. During the UG3 phase we will explore the extent to which these amounts are available as part of the project's other healthcare utilization data, but we will also obtain data from each system as to the usual copay amounts charged for various health care services so that these can be used in the likely case that we will need to estimate patients' overall out-of-pocket costs.

RECRUITMENT AND RETENTION PLAN

For the UH3 trial, we plan to recruit 828 older adults, aged 65 years or older, with chronic lower back pain from four health care systems (Kaiser Permanente Washington, Kaiser Permanente Northern California, Sutter Health, Institute for Family Health) for our pragmatic effectiveness trial. The recruitment period will be roughly 12 months, with an allowance for up to 15 months within the overall study timeline. Identification of potential participants at Sutter Health, KP Washington and Northern California will be similar: A HIPAA waiver will be obtained to allow the study team to proactively identify potentially eligible participants (e.g., recent visit for unspecified low-back pain, age 65 and over, no exclusion diagnoses, etc.) from the EHR of each health system. We will contact potential participants' primary care providers (PCP) to ask if anyone should be excluded from study outreach. Those not excluded by a PCP within a protocol-specified time-period, will then be mailed an invitation letter and information sheet. Primary care providers at the Institute for Family Health (IFH) will directly refer potentially eligible patients to study staff for outreach and screening.

Overall recruitment process

For the sites in which we plan to use a population management approach to recruitment (KPWA, KPNC, SH), we will use our EHR systems for active surveillance to identify weekly members ≥ 65 years who made a visit to a PCP that week and for whom recent diagnostic information in the EHR suggests they are eligible. PCPs will be notified of their patient's eligibility and unless they ask that a potentially eligible patient not be contacted, the study will send invitation letters and study information to all potentially eligible patients. Patients will be encouraged to complete an online screener or contact the study team to complete the screener or get further information about the study. We will reach out directly to potentially eligible patients who have not completed the online screener or called (with up to 5 call attempts planned) to answer any study-related questions they may have and invite them to complete the screening. Oral consent will be obtained before the screening questions are asked. Screening questions will include ascertaining that patients LBP is of at least a three-month duration (cLBP)[18] and that their pain is of at least moderate severity (≥ 4 on a 0-10 numerical rating scale for pain). Patients screened study-eligible will be told more about the study by the study interviewer. Oral

consent for trial participation will be obtained by phone and a baseline interview completed. Following the baseline phone interview, participants will be randomized to one of three study arms. Similar procedures have worked well in all our previous large trials.[27,29,76,79,94]

AMENDMENT: There may be slight differences in the recruitment requirements for each health care system (e.g., letter signed by physician, in-person enrollment) based on their IRB requirements. Those will be incorporated into our final recruitment, even in the context of a single IRB.

Barriers to recruitment

Because cLBP is defined as pain persist for at least 3 months, *efficiently* recruiting suitable patients can be challenging. Patients who make health care visits may have acute back pain at the visit. We will use a tiered approach to identify suitable participants at the three West Coast sites. Our initial approach will be to recruit patients shortly after a medical visit for low back pain if they had at least one visit in the recent past. If we are not meeting our recruitment targets, our second approach will be to recruit patients who had multiple visits for back pain over the last 5 years. Finally, we will mail study materials to patients over 65 years regardless of visits for back pain. In addition, we will place advertisements in the clinics of our health plans where permitted. At IFH, physicians will be able to refer patients who have had their back problem for at least three months.

Contingency planning

If we are having difficulty recruiting participants at any one site, we are prepared to transfer resources to other sites as needed. We are also prepared to drop any sites that cannot appear to recruit at the appropriate rate. We have good contacts with investigators in the Health Care Systems Research Network, with the OCHIN network of federally qualified health centers, and with investigators whose healthcare systems are part of the NIMH mental health research network and NIDA's clinical trials network that would allow for quick identification of alternative performance sites should the need arise.

Retention and Adherence

We will use multiple strategies to maximize follow-up rates. We will keep surveys brief. Upon enrolling patients in the study, study staff at each performance site will collect the name and contact information of a relative or close friend who can be contacted should we be unable to reach the participant. The KPWA Survey Research Program (SRP) will centrally administer brief pain assessment check-ins which will measure physical function, pain intensity and pain interference at 4-week intervals (week 4, 8, 16, 20, 28, 32, 36, 40, 44, and 48) via phone and web. SRP will centrally administer follow-up assessments at 12-, 26- and 52-weeks for KPWA, KPNC and SH. Based on IFH's prior experience with multi-site research, local study staff will administer the main follow up assessments to their local participants to obtain higher retention and follow up completion rates. We will provide incentive payments for each follow up assessment ($25 for completing 12-week, $30 for 26-week, $35 for 52-week assessment). Participants will also receive $5 per monthly check-in completed, payable in a lump sum at the end of the 52-week period based on the number of monthly check-ins completed between the main assessments (i.e., up to an additional $45 total if all 9 check-ins are completed). Participants who complete all check-ins and main assessments will receive a total of $135 for participation. We will allow participants to complete assessments online, by telephone or using a mailed survey. We will update participant contact information at each survey. We will send a reminder letter a week before

each follow-up is due. We will send reminder emails or texts, based on preference, 24 hours before the survey is due. Retention in our prior trials of complementary therapies has been excellent (85% or better for back pain trials at KPNC and KPWA).

Because the purpose of the trial is to find out how older adults would respond to acupuncture in the "real world", we will not make exceptional efforts to maximize adherence to treatment. We will ask the acupuncturists to encourage participants to attend treatments, especially at the beginning, so they have enough visits to see if acupuncture is likely beneficial for them.

Possible competition from other trials

We are currently tracking other studies of chronic pain in the KPWA delivery system. No trials currently underway or submitted focus exclusively on older adults or on chronic low back pain. We are unaware of trials at KPNC or Sutter health that would compete with this one. At IFH, there is an ongoing study of acupuncture and yoga for chronic pain. We believe that study participants will primarily be under 65 years because of the addition of yoga. We therefore expect only minimal competition for patients.

PROTECTIONS OF HUMAN SUBJECTS

Risks to Human Subjects

UG3 Year

Qualitative, minimal risk activities will be undertaken in the planning year to inform the design of the UH3 trial. We will conduct focus groups of patients at each of the four health care systems (KPNC, KPWA, Sutter Health, IFH). The recruitment and eligibility screening approach at each site will mirror our preliminary plans for the UH3 trial. We will recruit both Spanish and English speakers for the IFH focus groups.

These recruitment procedures have been used previously in trials at KPWA and thus, deemed HIPAA compliant and proven successful for recruiting and retaining participants. All protocols will be reviewed by the study's central IRB at KPNC (and if appropriate, IFH will review its own protocol because it will have some different features). Staff at each local site will recruit and screen patients, obtain oral consent, enroll and schedule patients for the local focus groups, and handle local logistics. A KPWA qualitative team will travel to KPNC, and Sutter Health to facilitate those groups and will consult with IFH on the planning and facilitation of the focus groups there. Focus groups will be held at health system facilities, snacks and beverages will be provided. The KPWA qualitative team will obtain written informed consent prior to the start of the 90-minute focus group. A court reporter may be present to create a word-for-word written transcript of the discussion for coding and analysis. Identifiable patient information (e.g., names) will not be recorded in the transcript, but focus groups will be taped and transcribed verbatim. Participants will complete a short demographics questionnaire, so we can describe participant characteristics. Participants will be asked if they would be willing to participate in further usability and pilot testing activities. Focus group participants will be paid $50 for their time and parking will be reimbursed.

Focus group participants who expressed interest in participating in usability testing will be contacted by phone following the focus group with more information. Oral consent will be administered by phone and semi-structured interviews will be conducted to collect feedback and opinions regarding draft study materials and processes. Participants will be mailed $25 for each completed interview.

Focus group participants interested in participating in pilot testing will be contacted by phone following

the focus group with more information. Up to 4 pilot participants will be recruited at KPWA and IFH to test the feasibility and acceptability of planned study procedures, including referral of patients to pilot acupuncturists, and the completion of clinical acupuncture treatment forms by treating acupuncturists. Patients who participate in the pilot will complete a draft of the baseline assessment by phone, complete 1 to 2 check-in surveys, and may receive up to 6 acupuncture treatments. Randomization will not be used since the pilot is focused on feasibility and acceptability.

UH3 Period

We will conduct a 3-arm, randomized controlled trial of acupuncture (standard dose only), enhanced acupuncture (standard plus maintenance dose) and usual medical care for older adults (65+ years). Adults will be recruited from four health care systems (KPNC, KPWA, Sutter Health and the Institute for Family Health (IFH)). We will use standard procedures for recruitment and acupuncture delivery from KPNC, KPWA and Sutter Health and a slight modification for IFH. Follow-up of all patients will be the same. These procedures have been used previously in trials at KPWA and thus, deemed HIPAA compliant and proven successful for recruiting and retaining participants. All protocols will be reviewed by our study central IRB at KPNC (and if appropriate, IFH will review its own protocol because it will have some different features).

Randomization: Eligible and consented participants will then be randomized to one of 3 study arms: (1) usual care control, (2) standard acupuncture of up to 15 sessions over 12 weeks, or (3) enhanced acupuncture (standard plus maintenance acupuncture) of up to 21 sessions (up to 15 sessions over 12 weeks plus up to an additional 6 sessions over the next 12 weeks). The randomization scheme will be created separately for each site and cannot be changed after randomization is performed.

Referral to acupuncture: Those randomized to acupuncture will be provided with the name(s) of up to three acupuncture providers paneled to the health system who have experience treating chronic low back pain and working with older adults, have agreed to see study patients, and who are conveniently located for patients. Patients will then select a provider from those provided and the study will fax a study referral to the acupuncturist with the patient information. If the provider is at a health system owned-and-operated clinic (extremely rare), referrals may be submitted via the electronic health system chart (Epic). This mirrors how referrals to specialty services are made in some departments of the participating health systems now. At the IFH, acupuncture is provided onsite in group format and patients will be scheduled on site. The exact procedures will be detailed in the UG3 year and may be modified based on input received from patients, key stakeholders and acupuncture advisors.

As a pragmatic trial, patients are not required to complete all acupuncture visits to stay in the study. An intent to treat approach will be used. Data for each visit will be collected from the treating acupuncturist, which in turn will trigger an incentive payment to the acupuncturist for their study participation. Data will be securely submitted following each session with the following information (subject to refinement in the UG3 year): Visit disposition (e.g., completed, cancelled, no show), selected details of treatment (e.g., needle type and placement, ancillary services provided), and patient reported adverse events.

As a research-related activity, study acupuncture visits and information collected during study visits will not be entered into the patient electronic health record but will be maintained only in separate study records, which will be part of a secure database. Any acupuncture care participants may seek independent of the study would be subject to usual care billing and documentation. However, no patients nor patient insurance policies will be billed for study-related visits, as consistent with other pragmatic trials conducted in the participating health systems.

Patient follow-up assessments: Each participant will be followed for 12-months post-randomization. Participants will be invited to complete monthly check-ins per their preferred mode (phone or web)

between main assessments at 12-, 26- and 52-weeks. Check-ins will take less than 5-minutes to complete. Participants will receive a $5 incentive for each check-in completed payable as a lump sum at the end of the study (up to $45 total for the 9 monthly check-ins). Patients will be contacted via their preferred mode (phone or web) for the 12-, 26, and 52-week follow up surveys. Advance letters will be mailed as reminders to those preferring phone follow-up. Emails with the reminder and a live hyperlink will be sent to those preferring to complete follow-ups online. Participants may opt to change their preferred mode at any time. Incentive payments of $25, $30 and $35 will be sent for completing 12-, 26- and 52-week follow-ups, respectively.

Interviews with low-engagement acupuncture patients: We will recruit up to 20 subjects (5 per site) for semi-structured qualitative interviews. These will be individuals randomized to receive 15 or 21 treatments who dropped out of acupuncture early on. Oral consent will be obtained for the phone interviews, which the KPWA qualitative team will conduct. Interviews will be audio-recorded, transcribed and coded for analysis. We will mail $50 to interview participants as a thank you for their time.

In-person focus groups with patients: During UH3 Year 2, up to 10 trial participants per site will be recruited to participate in a local focus group. Interest will be ascertained at the completion of the 26-week assessment. The KPWA qualitative team will travel to KPNC, KPWA, Sutter Health and IFH to facilitate the groups; snacks and beverages will be provided. KPWA qualitative team will obtain written informed consent prior to the start of the 90-minute focus group. A court reporter will be present to create a word-for-word written transcript of the discussion for coding and analysis. Identifiable patient information (e.g., names) will not be recorded in the transcript. Following each focus groups. participants will be paid $50 for their time and parking will be reimbursed.

Online focus-groups: Up to 10 acupuncturists who have participated in the trial and up to 10 primary care providers at each clinical site will be recruited for separate online focus group discussions. These activities are expected to be IRB exempt (category 2). We will use an online platform that allows participants to participate at any time of day during a stated fielding window. This allows for flexibility in terms of location and timing of participation. The online platform generates a written transcript for coding and analysis.

Internal and external stakeholder interviews: Study team members affiliated with each participating health system will identify appropriate individuals for targeted recruitment to (IRB exempt) semi-structured phone interviews. Discussions will be recorded and transcribed for coding and analysis. We will interview up to 7 external stakeholders and 3 internal stakeholders from each site.

Sources of materials

Participant data will be obtained from 5 sources for the pragmatic trial:

(1) Epic electronic health and administrative records used to identify potentially eligible patients for outreach
(2) Eligibility screening surveys completed by phone
(3) Baseline surveys
(4) Brief monthly check-in surveys
(5) Patient visit details and adverse events reported to the study by participating acupuncturists
(6) Main follow-up assessments at 12-, 26- and 52-week follow up points

Data for formative and summative evaluation activities will be obtained from these sources:

(1) Patient focus groups (UG3, UH3)
(2) Qualitative interviews with provider
(3) Patient usability (user centered design) testing interviews (UG3)
(4) Debriefs with acupuncturists and patients following pilot testing (UG3)

(5) Low-engagement acupuncture patient interviews (UH3)
(6) Online focus groups with acupuncturists and primary care providers (UH3)
(7) Qualitative interviews with internal and external stakeholders at the participating health care systems (UH3)

Electronic Health Record (EHR) and Administrative Data. Patient health care utilization and administrative data will be used for the identification of patients who are potentially eligible for the study and to examine pertinent health care utilization patterns among study participants (including healthcare encounters and pharmacy-related outcomes). All data will be extracted from EHR and administrative databases in each of the healthcare systems participating in the study. Prior to consent in order to identify potentially eligible patients, select variables will be extracted (to determine eligibility, as described above) and uploaded into the site's recruitment tracking system, which will be password-protected and accessible only to authorized study staff. These will be the minimum variables needed to identify and recruit patients. As part of the consenting process, participants will be informed that their EHR data will be linked to their assessment data and shared with the investigative team at KPWHRI to be included in analyses. No individual identifying data will be published or released, and data will be summarized and presented only in summary or statistical form. An important point to note is that our research staff at participating healthcare systems are employees of a department within the healthcare system. Using terms consistent with the HIPAA regulations, the research center and staff are a "business unit" of the healthcare system. Therefore, the extraction of patient health records for the purposes of research activities conducted by our research staff do not violate any confidentiality or HIPAA regulations, because HIPAA regulations permit data-sharing (including the use of the EHR) within a given business unit. All these procedures have been approved by our IRB and HIPAA compliance office and have been successfully used in many studies with no reported adverse effects.

Participant self-report data. Self-report data will be collected via online, mailed survey, or telephone-administered survey and compiled into our WinCati integrated data tracking system designed and hosted by KPWHRI which will be password-protected and accessible only to authorized study staff.

Acupuncturist treatment data: We will collect selected information to describe each treatment, including the date of treatment, number and placement of needles, use of adjunctive treatments, provision of self-care recommendations, response to last treatment, and whether the acupuncturist believes this is the last needed visit.

Data Security. All our performance sites (KPWA, KPNC, Sutter Health, and IFH) are HIPAA-covered entities and comply with all HIPAA regulations regarding data security. All study files maintained at any of our affiliated research institutes will be maintained in locked file cabinets or in a centralized location on the institute servers. Access to these data will be password protected and subject to the same security protections as other confidential health plan data. Access will be limited to staff working on this study and who require access to these files. Whenever possible, study data will be stored on our central study WinCati connected tracking system. All staff at our participating sites are trained in appropriate security protections, computer passwords are changed on a regular basis, and all staff sign annual confidentiality agreements. Data transferred from sites to KPWHRI will be done via a web-based secure file transfer (SFT) application, which uses the 128-bit Secure Sockets Layer encryption protocol and meets the 2009 HIPAA HITECH safe harbor standard. This method is commonly used in our multisite studies and has been reviewed and approved by our IRBs. No data or identifiable information will be stored on participants' phones or devices. No sensitive information will be shared in texts or emails with participants. See additional details on data security under Protection Against Risks below.

Potential risks

There are potential risks of acupuncture, of the PRO assessments, risks associated with potential loss of confidentiality and risks of increased pain or emotional distress.

Risks of acupuncture: In general, acupuncture is a very safe procedure. Because the needles are thin, they usually cause little or no pain although severe discomfort may occur on rare occasions. Occasionally, up to a week of increased pain or discomfort may occur after treatment. There have also been reports of bruising, fatigue, fainting, nausea, and infection at the insertion sites, but these also occur infrequently. Both specific and generalized side effects may occur with acupuncture therapy. Several large studies collected data on adverse events from more than 235,000 patients and studies involving more than 63,000 treatments are reported from 156 providers. Collectively, this work found that minor adverse events, for example bleeding or needle pain, are the most common, in the range of 1–10 in 100 for bleeding and hematoma and 1–10 in 1000 for strong pain during needling. In a large trial of acupuncture for cLBP, 2.3% of patients reported a moderate adverse experience that was likely due to treatment and 1 of 477 reported pain lasting one month. Serious adverse events, such as pneumothorax, persistent nerve pain, or needle breakage are very rare (typically 1 in 100,000 or less).

We plan to develop materials to train the acupuncturists for this trial, including appropriate adaptations for older adults and reminders of when to discontinue treatment and procedures for communicating with participating patients' primary care providers. In the unlikely event that an adverse effect occurs, treatment will be provided as covered by participants' existing health care coverage.

Risks associated with focus groups and qualitative interviews: The primary risk of these activities is potential loss of confidentiality (see below).

Risks associated with assessments: Research assessments consist of EHR data, survey and interview questions, and data related to the treatment visit. Collection of research data from electronic health records to identify potentially trial eligible participants could lead to accidental disclosure of protected health information. Procedures for protecting against this risk are described below. Interview and self-report survey questions focus on pain and associated impairment and functioning, comorbid conditions, and other recommended outcome measures. Participants will give voluntary responses to survey and interview questions; they will be told that they can decline to answer any questions that they want, if answering would cause them distress or concern. We have used all of these instruments in our previous research, with no known problems or distress on the part of participants.

Risks associated with potential loss of confidentiality. The confidentiality of participants could be compromised by an accidental release of name, address, or other private health information (PHI). Research staff will never see the participants' PHI or other identifiers unless necessitated by their study tasks. There is a slight risk that research records might be accessed/obtained by persons not authorized to do so. Finally, the outreach design used in this study carries the potential risk of loss of privacy and/or unwanted contacts as EHR data files are searched for eligibility for health plan patients and letters sent to these potentially eligible participants. The risk of this method is that participants would experience a loss of confidentiality and view their identification as potential research subjects as occurring without their prior consent. However, such identification and recruitment processes have been acceptable to our participants and IRBs in the many years that we have used such procedures in our trials.

Risks of worsening mental or emotional state. Some enrolled participants will have worsening pain and/or other physical or emotional problems during the study period. However, these are risks inherent in the population and would occur regardless of study enrollment. We do not believe that the risk of adverse outcomes is heightened as a function of being enrolled in the study.

Adequacy of protection against risks
All research activities will be IRB reviewed and approved to ensure participants are adequately protected against risk and all research activities are HIPAA compliant. Participants will be fully informed of the potential risks of participation, and their right to discontinue participation at any time. In addition, we will take the following specific steps to reduce known risks to participants:

Informed consent. A study interviewer will administer oral consent to prospective participants, ensure full understanding of study focus and procedures, and answer any questions. The oral consent process will describe the purpose of the study, the procedures to be followed, the risks and benefits of participation and how participants' data will be handled. This information will also have been provided in a study information sheet sent with the initial study invitation letter.

Written informed consent will be administered to all in-person focus group participants.

Minimization of Possible Adverse Events from Acupuncture Treatment: We will select acupuncturists who are already credentialed to provide acupuncture for patients with the local health system and who have experience working with older adults and chronic low back pain. We will train them on safety protocols for older adults. We will make sure that the older adults know how to prepare for their treatment (e.g., eat something in advance). Acupuncturists will focus only on techniques that are appropriate for that individual (e.g., exclude electrical stimulation for patients with pacemakers). This study will avoid infection by requiring acupuncturist to use only new, sterile (one-time use) needles that are discarded after use. This is already required of all acupuncture providers in all states where this pragmatic trial would be implemented.

Finally, patients whose symptoms significantly worsen will be referred for care within the healthcare system when clinically warranted. Medical care of patients who participate in the study will not be affected by their decision to participate or not to participate.

Protection for risks associated with research assessments. Participants will be told that they are free to not respond (on paper, web or by phone) or to terminate involvement at any time, with no adverse consequences. If a participant appears to be distressed during assessments, research staff will halt the interview and offer to call back to complete the interview. The interview will only recommence when and if the participant reports feeling capable of doing so. The interviews during the course of the study involve no specific risk or discomfort beyond those of a standard clinical interview. Interviews will be conducted by experienced and well-trained staff sensitive to these issues.

For patients involved in qualitative focus groups: if patients become upset during the focus group discussion they will be free to withdraw from the discussion. The consent process will clearly describe the voluntary nature of participation and the right to withdraw. Experienced interviewers will conduct all interviews and focus groups. These interviewers are trained to identify participant distress and to manage that distress by moving away from upsetting topics, offering breaks as needed, or providing the opportunity to reschedule a distressed focus group participant for an individual interview for a later date.

For health plan staff administrators and any health care providers involved in qualitative interviews or focus groups, they will be made aware that they are free to stop the interview or focus group participation at any time or elect not to respond to a particular question. As noted above, all transcripts will be anonymized and details of individual quotes that might make the quote identifiable will be changed to protect participants (e.g., the gender of the participant; or a detail related to the person's position in the health plan). If it is not possible to change quotes and maintain the integrity of the data, the quote will not be used in publications.

Protection for risks associated with breach of confidentiality. Multiple steps will be taken to protect participant confidentiality. Each level of data security is described below.

Data for all participants will be kept strictly confidential, except as mandated by law. All research files are kept in locked file cabinets or a locked file room or on a password-protected, study-specific file service. All electronic records are stored using multiple layers of password protection with automatic "time-outs" for terminals left unattended. Access to this system is strictly controlled with access limited according to the information a particular person needs to be able to view to carry out their job. Each time a record is accessed, it is logged and employees are monitored for evidence of inappropriate access (e.g., viewing records of family members or other employees), and inappropriate access or disclosure are grounds for disciplinary action including termination of employment. All study staff will be trained in appropriate security protections and have signed confidentiality agreements with the health system. Participants will be assigned a non-meaningful numerical code for identification in the files. Names and other identifiers will be kept in separate locked files. All computerized data will be kept on the secured computers or networks at each site. These data will be accessible only to research staff, using confidential usernames and passwords.

Digital audio recordings of focus groups are digitally encrypted files protected by a secure password and are stored on computer network drives to which access is limited by passwords and access rights granted only to a very few authorized staff. The digital recordings will be identified only by a non-meaningful research ID (001, 002, etc.) and will not have any identifying information on it.

Finally, any PHI/PII will be destroyed 5 years after the end of the study. Only datasets fully de-identified per HIPAA regulations will be publicly shared. Communications will not contain any personal health information (PHI) other than references to low back pain. No patient names or descriptors that would identify them would be used in any of the analysis or publication.

Each participating health system is a HIPAA covered entity and complies with all HIPAA regulations regarding data security. All study files will be maintained in a centralized location on a research departmental server for the study. Access to this data will be password protected and subject to the same security protections as other confidential health plan data. Access will be limited to staff working on this study that require access to these files.

Potential Benefits

Little is known about the effectiveness of acupuncture treatment for low back pain in older adults. This study will help close that evidence gap. While we cannot guarantee that all participants will benefit from the treatment they are assigned, all participants may receive some satisfaction or indirect benefit from contributing to this research.

Those randomized to an acupuncture treatment arm will qualify for more acupuncture visits than they could under any existing health insurance benefit, which may be viewed as an additional benefit. Co-payments and deductibles will not apply to study acupuncture visits.

Patients participating in the focus groups may enjoy the opportunity to provide their opinions. Further, these individuals may derive personal satisfaction from being part of a study that may have major public health implications and that will further scientific knowledge concerning the value of acupuncture.

Importance of Knowledge to be Gained

Clinical guidelines are not available for treatment of low back pain in older adults despite the need for safer and effective treatment in this population which features more disabling back pain, comorbidities and adverse effects from common treatments compared to younger patients. Although acupuncture has

been shown effective in a younger and healthier population, there's a need to get real world data on the older adult population to clarify which chronic low back pain treatments are safe and effective for older adults. The pragmatic design maximizes the likelihood of generalizable findings. This should have a direct impact on clinical practice and quite possibly, Medicare coverage decisions.

Inclusion of Women, Minorities & Children

Based on other research with older adults with low back pain, we expect 56% of participants will be female. We have selected our sites to mirror the racial and ethnic populations of the U.S. Medicare population that is 65 and older: 8% Hispanic, 9% Black, 4% Asian, <1% American Indian/Alaska Native, < 1% Native Hawaiian/Pacific Islander; 81% White, and <10% Other or mixed-race. If needed to meet these targets, we will include race/ethnicity as an inclusion criteria and oversample non-white participants. Given the large population from which we will draw, this should not be an issue. The proposed study is targeted to older adults aged 65 or older with chronic low back pain; therefore, children and adults under 65 years of age will not be included.

SINGLE IRB PLAN

We anticipate that the KP Northern California IRB will serve as the IRB of record for the UH3 period. The KP Northern California IRB will decide whether to serve as the Central IRB for the UH3 period after the study design and implementation plan have been finalized and the full protocol can be reviewed. As a contingency plan, we have budgeted for an external IRB (Advarra, formerly Quorum) to centrally review the trial; funds could be reallocated if an external IRB is not ultimately needed. A consolidated vs. centralized approach may be required if implementation differences at the IFH site (e.g., patient identification process) would be more expeditiously handled via a local IRB review.

DATA SAFETY AND MONITORING PLAN

A Data and Safety Monitoring Board (DSMB), to be established in the UG3 year, will oversee the trial and conduct reviews to evaluate the accumulated study data for participant safety, study conduct and progress. The monitoring plan will be finalized in the UG3 year by the Multiple PIs in collaboration with the Collaboratory Coordinating Center and NCCIH. The DSMB will review the study protocol and materials prior to implementation; review Adverse Events (AEs)/Serious Adverse Events (SAEs) and data on recruitment and retention efforts every six months during the conduct of the trial (or at the frequency deemed necessary by NCCIH). Outcomes from each DSMB meeting will be shared with the IRB of record and appropriate NIH program staff.

Adverse Event Monitoring

For the proposed study, we are operationally defining a serious adverse event as a death, or hospitalization during a patient's active participation in the trial and study acupuncture treatments. We will review/query active study participants' electronic health records data every six months to assess the rate of death and hospitalization. In the case of a death, a chart review will be conducted by an independent physician at the clinical site to assess whether the death was related to the study intervention (definitely, probably, possibly or unrelated to the study intervention). Because the number of hospitalizations in the study population may be high and acupuncture poses only minimal risk, we do not plan to chart-review hospitalizations as a matter of course. However, if our reports suggest a possible increased risk of hospitalizations associated with acupuncture, we will work with our monitoring groups to develop a plan to do chart reviews on all or a subset of hospitalizations. Non-serious adverse events will be collected in multiple ways: (1) during 12-week, 26- and 52-week follow up assessments; (2) via electronic acupuncturist treatment reports following each visit; and (3) from

participants who may phone the study team at any time to report AEs. A report of AEs/SAEs will be reviewed by the PIs and Co-Investigators every six months and by the DSMB annually.

Study Conduct and Progress Monitoring

The PIs and Co-Investigators will review reports related to patient recruitment, intervention adherence, retention and data completion on a weekly basis for the first six months of the study and if the study is proceeding well, decrease the reports to every other week or monthly if appropriate. However, data will be monitored continually by study programmers/analysts at Kaiser Permanente Washington Health Research Institute to identify missing observations, monitor randomization balance across arms, and tabulate drop-out rates by arm. If differential drop-out is observed, we will conduct analyses to quantify the potential impact on our estimates. Quality control will be a continuous process, maintaining thorough documentation, throughout the trial, ensuring the shortest possible turnaround time between error detection and correction. In year 4, we will initiate final cleaning and management of all our PRO and treatment record data as well as electronic records (of health service-use).

For the acupuncture interventions, treatment visits will be monitored via submission of treat visit summaries by the treating acupuncturists into a protected, HIPAA complaint database. Submission of this information will be required before payment of treatment incentives to acupuncturists. This should result in accurate information on the number of treatment visits and help us understand what proportion of patients did not need the full allotment of treatments. Detected non-compliance to the treatment protocol (number of visits or content) will be addressed immediately through more intensive supervision of the interventionist(s), consistent with how this would occur in everyday clinical care, and monitored until the adherence criterion is re-established.

The study team will create regular reports to monitor patients' progress in the trial. Participants may remain in the study even if they do not complete all the acupuncture treatments to which they are entitled per their study arm assignment.

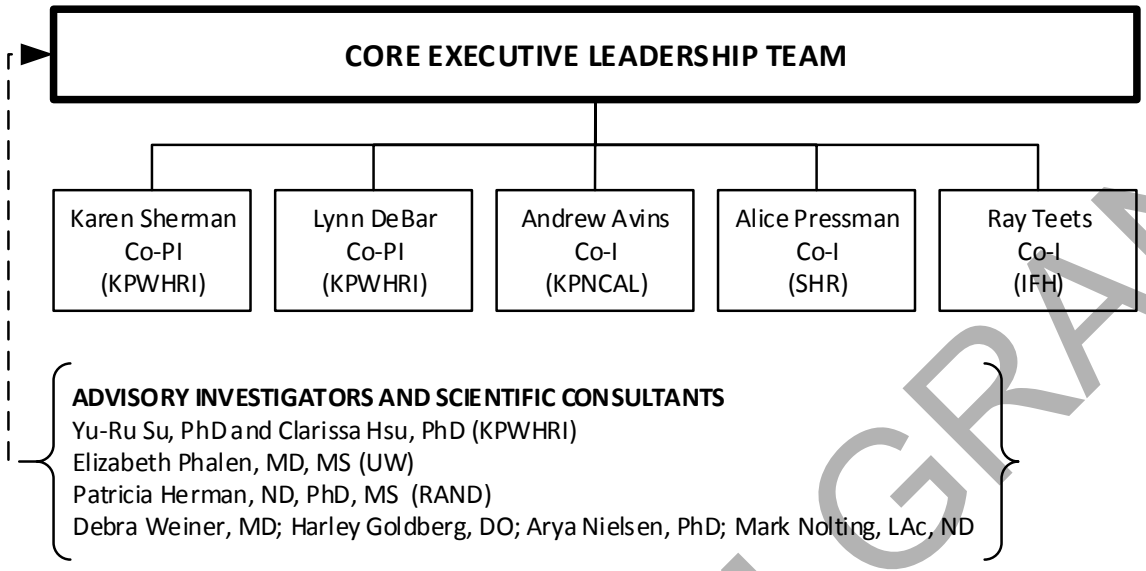
In addition to the summary of adverse events provided annually to the DSMB, the DSMB will also review reports summarizing:

1. Participant recruitment and screening (including reasons for refusal, ineligibility and exclusion)
2. Accrual of randomized participants with age, gender, race and ethnicity
3. Treatment visit distribution (by group)
4. Patient-reported outcomes data by time point (% completed)
5. Study withdrawals and reasons for withdrawal

If additional or slightly different requirements are mandated by NCCIH, we revise this plan accordingly.

OVERALL STRUCTURE OF THE STUDY TEAM

Organizational Structure, Governance, and Roles and Responsibilities



Project Principal Investigators have developed an organizational structure that will facilitate the multi-PI plan and allow for meaningful contributions by other Investigators and study consultants.

As Multiple PIs, Drs. Sherman and DeBar will jointly oversee the entire project including development and implementation of all policies, procedures and processes. They will be responsible for implementation of the Leadership Plan and the Specific Aims and will ensure that systems are in place to guarantee institutional compliance with US laws and federal policies including human research, data and facilities. In the UG3 Year, they will split leadership of the activities, with Dr. Sherman focused more on the acupuncture intervention and Dr. DeBar on the patient materials. They will collaborate closely to develop and refine all study protocols and materials. In the UH3 portion, Dr. Sherman will lead efforts to work with the other health systems to implement the trial while Dr. DeBar will lead efforts on the formative and summative evaluations. However, they will assist each other as needed. They have established a Core Executive Team consisting of Drs. Sherman, DeBar, Avins, Pressman and Teets to handle any major study decisions regarding the direction of scientific aims, allocation of resources, disputes that may arise, and other information related to the management of the proposed team-science project. Major study decisions will be made by vote of the Core Executive Team with advisory input from their team of Advisory Investigators and Scientific Consultants (see Figure). The odd number of core executive team members eliminates the chance of a tie.

Dr. Yu-Ru Su will chair the Statistical Methods Team which will interface with the NIH Collaboratory Biostatistics and Study Design core. The Statistical Methods Team will make recommendations regarding the overarching analytic strategy. Recommendations made by the Methods Committee will be seen as advisory to the Core Executive Team, and all final decisions about the scientific aims, allocation of resources for statistical investigations, and resolution of disputes will be made by the Core Executive Team

Drs. Sherman and DeBar, in collaboration with Dr. Su and the Core Executive Team, will oversee the Data Coordinating Center for the study. KPWHRI was chosen as the Data Coordinating Center because there is an existing infrastructure that has been established through the KPWHRI Survey Research Program that will support screening, baseline, monthly check in and 3, 6 and 12-month

follow up assessments. Drs. Sherman, DeBar and Su each have substantial experience in multi-site collaborations involving both primary data collection from patients and secondary data collection from electronic medical records. However, they will remain masked to treatment outcomes until the database is locked.

Choice of Contact PI: Dr. Sherman will serve as the contact PI and will be responsible for the day-to-day oversight of the study because she has conducted multiple complementary and integrative health trials in partnership with the KPWA health care system over her long tenure at KPWHRI and has long-standing relationships with other investigators on the study team. As the fiscal lead site, it will be Dr. Sherman's responsibility to manage all aspects of the NIH contract and the reporting requirements. Her team will schedule all weekly investigator meetings, record and distribute meeting minutes, oversee data use agreements, and financial contracts. Her research project manager will work with Dr. Avins's team to oversee the process of human subjects approvals and quality management reviews.

Communication Plan

Study investigators and staff will have ongoing, weekly communication by phone or e-mail to discuss study design, data analysis, and all administrative responsibilities. Weekly or bi-weekly teleconferences including the Core Executive Leadership Team and Advisory Investigators and Consultants will take place throughout the funding period. The programmer preparing data abstraction will meet weekly with the study Co-PIs. The Statistical Methods Team, chaired by Dr. Su will meet independently at least twice monthly throughout the project to work on the development of statistical methods. The two PIs and research project manager will have a separate, one-hour monthly meeting to discuss the overall progress of the study; concerns and how to manage them; review interim reports and future directions. These PI meetings will allow Drs. Sherman and DeBar to work together to discuss any changes in the direction of the research and the reprogramming of funds, if necessary.

Conflict Resolution

The Multiple PIs are committed to trust, transparency, honesty and open communication. All meetings will follow best practices to ensure fair and balanced discussions and mitigate and conflicts. If a potential conflict develops, the Core Executive Team shall meet and attempt to resolve the dispute. If they fail to resolve the dispute, the disagreement shall be referred to the NIH program staff assigned to the project for scientific issues and to the Executive Director of KPWHRI for other issues.

Change in PI Location

If a PI moves to a new institution, it may not be possible to transfer the relevant portion of the grant to the new institution. If a PI cannot carry out his/her duties, a new PI will be recruited as a replacement at one of the participating institutions.

DISSEMINATION PLAN

We conceptualize several levels of dissemination for this project. The findings on the value of acupuncture and cost-effectiveness are likely to garner national media attention because of CMS's interest in this project and the potential impact of the findings on coverage for acupuncture by Medicare. We believe that there will be widespread knowledge of the trial before findings are even available. We suspect that health plans, insurers, acupuncturists and some patients will be aware of these through secondary efforts by various professional associations and other interested organization (e.g., American Association of Retired Persons). We plan to work with these groups in a collaborative

way to initially ensure knowledge of the trial design and later findings. In addition, we will share these findings with key stakeholders as described below.

To facilitate dissemination, findings will be shared broadly with key stakeholders at participating health care systems and colleagues and stakeholders at other health care systems (e.g., federally qualified health centers within OCHIN). Results will also be published and presented to scientific colleagues interested in this field of study, including colleagues at our affiliated organizations and members of key professional societies including the American Pain Society, Academy Health, and the Health Care Systems Research Network. We will share findings with the acupuncture community, including teaching institutions and professional societies via our contacts and members of the Acupuncture advisory panel.

Findings will be presented at key scientific meetings. Target forums for this include annual scientific meetings of the American Pain Society, the American Medical Informatics Association (AMIA), the Health Care Systems Research Network and the International Research Congress on Integrative Medicine and Health (IRCIMH). They will also be presented at clinical medicine meetings as appropriate.

Findings from this study will be published, so they broadly inform the field. We anticipate publishing a protocol paper (Year 2), main outcome paper (Year 4), at least three additional secondary outcome papers, and papers relating to implementation, barriers encountered, qualitative and to evaluation activities. Target journals include general medical journals (*JAMA, JAMA Internal Medicine, Journal of General Internal Medicine, Annals of Family Medicine, Annals of Internal Medicine, Lancet*), clinical trials journals (*Contemporary Clinical Trials, BMC Trials*), pain journals (*Pain, Journal of Pain, Pain Medicine*), and CIM medicine journals (*Journal of Alternative and Complementary Therapies, Complementary Therapies in Medicine*). Given the support of CMS for this initiative and their interest in the findings of the study, as well as the structure of collaborative agreements like the UG3/UH3 mechanism supporting this study, we would expect to partner closely with our colleagues at CMS in supporting dissemination efforts including sharing the clinical findings in the public and professional media and on the CMS website as well as potentially broader dissemination efforts.

Finally, our NIH and CMS partners may have practical ideas that we have not yet considered and those would be added to our plan as well.

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