NIH PRAGMATIC TRIALS COLLABORATORY

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NIH Collaboratory Ethics and Regulatory Core: UG3 Consultation Call
Remote Tai Chi for Knee Osteoarthritis: An Embedded Pragmatic Trial (TAICHIKNEE)
July 24, 2023; 11:00 am-12:00 noon ET (via Zoom)

Attendees:

- Core, Coordinating Center, and NIH: Sekai Chideya (NCCIH), Beda Jean-Francois (NCCIH), David Magnus (Stanford University), Kevin McBryde (NCCIH), MariJo Mencini (Duke University), Stephanie Morain (Johns Hopkins University), Lanay Mudd (NCCIH), Pearl O'Rourke (retired), Damon Seils (Duke University), Kayte Spector-Bagdady (University of Michigan), Dave Wendler (NIH), and Qilu Yu (NCCIH)
- Demonstration Project team: Elise Coash (Tufts University), Eric Roseen (Boston University), Robert Saper (Cleveland Clinic), and Chenchen Wang (Tufts Medical Center/Tufts Medicine)

AGENDA ITEMS	DISCUSSION	ACTION ITEMS	OWNER
Brief review of Demonstration Project	Meeting attendees received the Research Strategy and Data Management and Sharing Plan for TAICHIKNEE with the meeting agenda (see supplementary material attached). Stephanie Morain facilitated the discussion. Core members, TAICHIKNEE team members, NIH representatives, and staff from the NIH Pragmatic Trials Collaboratory Coordinating Center introduced themselves. The TAICHIKNEE team members present included principal investigators Chenchen Wang, Robert Saper, and Eric Roseen and research assistant Elise Coash. **Project overview**: Chenchen Wang and Robert Saper gave an overview of the project. TAICHIKNEE will study real-world effectiveness and implementation of remotely delivered Tai Chi vs Routine Care for knee osteoarthritis pain across 4 healthcare systems in the United States with diverse patient populations. **Healthcare system partners**: Tufts Medical Center/Tufts Medicine, Boston Medical Center, UCLA Health, Cleveland Clinic Ohio, Cleveland Clinic Florida **NIH Institute Providing Oversight**: National Center for Complementary and Integrative Health (NCCIH)		

AGENDA ITEMS	DISCUSSION	ACTION ITEMS	OWNER
	Study design: The project will be a pragmatic, multisite, 2-arm randomized trial comparing the effects of a 3-month, twice-weekly, web-based Tai Chi intervention vs Routine Care for patients with knee osteoarthritis pain. **Outcomes**: The primary outcome to be measured at 3, 6, and 12 months is pain interference. Secondary outcomes include knee pain and function, use of pain medication, and quality of life. Core members had no questions about the project overview (see supplementary material attached). During the UG3 planning phase, the study team will finalize trial design, sample size calculations, and study outcomes. The study team will also conduct qualitative interviews during the planning phase with patients, clinicians, Tai Chi instructors, and healthcare system leaders. The interviews will be used to plan educational materials for the UH3 implementation phase and will explore anticipated and potential barriers to and facilitators of implementation. Both the UG3 and UH3 phases will measure implementation outcomes. Two additional rounds of stakeholder interviews in the UH3 implementation phase will explore these implementation outcomes and transferability to other healthcare systems. Kayte Spector-Bagdady asked who will conduct the qualitative analysis of the interviews. Eric Roseen replied that the interviews will be conducted locally; coding will be performed across sites with deidentified transcripts; and the study team will seek to publish the results. David Magnus encouraged the study team to use general category descriptions of interview participants (for example, “health system leadership staff” rather than “chief operating officer”) to minimize the risk of reidentification or deductive disclosure of interview participants.		
Status of IRB approval	The study will use the Tufts Health Sciences IRB as the single IRB of record. The UG3 qualitative study (consisting of the interviews described above) received an IRB determination on April 27, 2023, that the study is exempt from full IRB review in accordance with 45 CFR 46.104(d).		

AGENDA ITEMS	DISCUSSION	ACTION ITEMS	OWNER
	For the UH3 implementation phase, the IRB protocol and the informed consent document are in development.		
Risk (Does the project meet regulatory criteria for being considered minimal risk?); and consent (planned processes for relevant subjects)	For the UH3 implementation phase, the IRB protocol and the informed consent document are in development. The study team anticipates that the project will meet the regulatory criteria to be considered minimal risk. The study will use an electronic consent. Stephanie Morain encouraged the study team to recognize that use of an online meeting platform for the study will place Tai Chi instructors in participants' homes virtually, allowing them to see or hear things in the background that the participants may not have intended to share (for example, the presence of family members). Robert Saper noted that the intent is to set up the virtual meetings so that participants cannot view other participants, only the instructor, and instructors will only use participants' first names. Standard precautions will be taken with respect to protected health information in terms of any data sharing. David Magnus encouraged the study team to be aware of the potential for virtual meeting platforms and other software applications to track participants' information without their knowledge.		
Privacy (including HIPAA)	For the UG3 planning phase, HIPAA is not applicable. For the UH3 implementation phase, the IRB protocol and the informed consent document are in development.		
Monitoring and oversight	The study team intends to use a data and safety monitoring board (DSMB) and has shared the names of potential members with NIH representatives. Chenchen Wang requested advice from the Core about the typical size of a DSMB for a study like this one. Stephanie Morain encouraged the study team to view materials on the NIH Collaboratory website regarding DSMBs and recommended including people familiar with pragmatic clinical trials and the use of electronic health records for research. Pearl O'Rourke recommended using the same group for protocol review. Qilu Yu added that a single statistician is sufficient.		

AGENDA ITEMS	DISCUSSION	ACTION ITEMS	OWNER
Issues beyond this project (regulatory and ethics concerns raised by the project, if any)	Kayte Spector-Bagdady asked what the UH3 informed consent form will say about data sharing. Chenchen Wang replied that the study team is still working on the informed consent document and would appreciate advice on this matter. Robert Saper noted that most healthcare systems do not routinely collect data from pain assessments, but the study team will collect utilization data from the EHR and deidentify it. David Magnus asked if the trial will assess patients who were recruited to the Tai Chi intervention or patients who actually engaged in the intervention. Robert Saper replied that they will use an intention-to-treat approach for the analysis. Certainly they will also look at recruitment rates based on recruitment approaches. David Magnus agreed that the intention-to-treat approach is appropriate. He also encouraged the study team to consider tracking which patients are actually engaging in the intervention, such as by capturing IP addresses during intervention delivery. The study team should also ensure that the web-based tools they use do not inappropriately track or collect participant data.		
Other matters	None.		

PROJECT SUMMARY/ABSTRACT

Symptomatic Osteoarthritis (OA) affects over 32.5 million individuals in the U.S. and is a leading cause of disability and increasing medical costs. Toxicities associated with drug therapies for knee OA pain have caused the number of recommended treatments to decrease over time. There is now a critical shortage of treatment options for people with knee OA, especially because comorbidities that complicate treatment selection are highly prevalent in this older adult population.

Tai Chi, a multi-dimensional practice that integrates physical, psychosocial, and behavioral components, has exhibited clinically significant improvements in chronic knee OA pain conditions. The American College of Rheumatology clinical practice guidelines strongly recommend Tai Chi as an intervention for knee OA. Recent studies conducted during the pandemic suggest that remotely delivered Tai Chi is a promising and scalable strategy for knee OA pain. However, critical gaps remain as to the real-world effectiveness of remote Tai Chi for knee OA and its implementation across multiple Health Care Systems.

We propose an embedded, pragmatic, randomized trial that will compare the effects of a 3-month twice weekly remotely delivered web-based Tai Chi intervention versus routine care in 20-25 clinics across four Health Care Systems (Tufts Medical Center, Boston Medical Center, University of California Los Angeles Health, and Cleveland Clinic Ohio and Cleveland Clinic Florida) in four geographic regions (Eastern Massachusetts, Southern California, Northeast Ohio, Southern Florida). We will enroll 600 diverse patients with a clinical diagnosis of knee OA. Participants will be evaluated at baseline and 3 months, with additional follow-up at 6 and 12 months. We hypothesize that implementation of remotely delivered Tai Chi is feasible across four Health Care Systems and that Tai Chi, compared to Routine Care, will improve physical health (including knee-related pain and function) and mental health as well as healthcare utilization.

Our innovative study is the first rigorous multi-site, embedded, pragmatic trial of a remote Tai Chi mind-body program, in the multiple Health Care Systems outpatient practice and utilizing web-based technology, designed to improve patient centered outcomes of knee OA. The results will enable widespread adoption of mind-body approaches for knee OA across Health Care Systems and lay the groundwork for future trials comparing the effectiveness of different implementation strategies.

D. RESEARCH DESIGN AND METHODS

D.1. Overview of Study Goals and Design

Building on our combined experience acquired through a decade of Tai Chi research, the proposed study will progress in the direction of **conducting an efficient, large-scale pragmatic trial to improve health care delivery, with a particular focus on four US health care systems that have less historical involvement in research studies focused on improving pain health outcomes.**

The overall goal of this project is to conduct the "real world" assessment of health care strategies and clinical practices and procedures in health care systems that will lead to improved care for populations with Knee OA in a variety of healthcare contexts, with a strong focus on populations with health disparities. Results from the pragmatic studies will inform policy makers, payers, doctors and patients across diverse patient care settings.

In brief, this 12-month embedded, pragmatic, randomized trial will test the effectiveness of a 3-month twice weekly remotely delivered web-based Tai Chi intervention, compared to routine care, in 20-25 clinics across four Health Care Systems (Tufts Medical Center, Boston Medical Center, UCLA, and Cleveland Clinic Ohio and Cleveland Clinic Florida) in four geographic regions (Eastern Massachusetts, Southern California, Northeast Ohio, Southern Florida).

We will deploy the project in two phases: 1) a 1-year UG3 Planning Phase in which study procedures will be finalized, and 2) a 4-year UH3 Clinical Trial Phase during which an innovative, multi-site embedded Pragmatic trial will be conducted. We will work with our scientific advisory and stakeholder committees to select a final list of secondary outcomes and covariates. We will finalize the trial design, sample size calculations, and outcomes in collaboration with the NIH and Collaboratory Coordinating Center and associated Workgroups. The Data Coordinating Center at the Center for Clinical Trials at Tufts CTSI is responsible for overall study conduct, training, and site monitoring. The trial schema and conceptual framework are shown in **Figure D.1.** A PRECIS-2 diagram and table describing the trial design along the pragmatic-explanatory continuum of clinical trial design is in **Table D.1.**

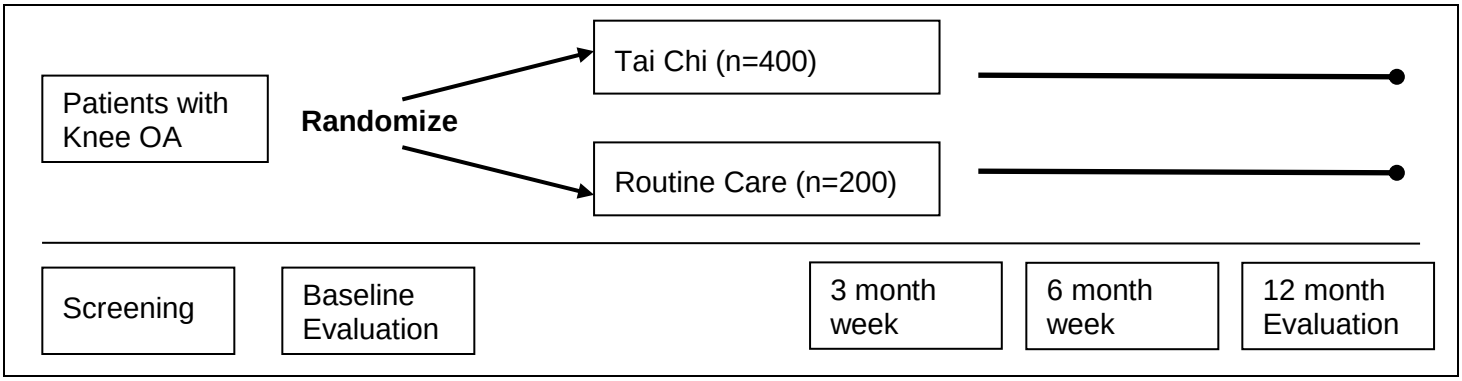
Our design examines 2 treatments: remote Tai Chi + routine care vs. routine care alone. In the Planning Phase we will work with participating clinics to systematically identify routine care processes, including pharmaceutical pain management, weight loss, and physical therapy. We will identify site differences and develop consensus for key processes. We will enroll 600 diverse patients across four Health Care Systems with a clinical diagnosis of knee OA.

The Primary Outcome will be the change in the PROMIS Pain Interference (8-item short form evaluating the extent to which pain interferes with physical, emotional and social activities) from baseline to 3 months, collected using interactive mobile technology. Change in pain will be further contextualized by additional assessment of patient-reported psychological symptom using standardized questions and secondary analyses will be adjusted for level of physical activity.[77,78] The primary time point will be at 3 months with secondary time points at 6 and 12 months. Primary and Secondary outcomes and covariates are presented in **Section D.15.**

Randomization: We will use patient-level randomization and will stratify randomization by site to reduce imbalances between intervention groups at each site. These procedures should also minimize the potential for bias based on procedures used at different participating sites or by different clinicians at these sites.

Our power calculations suggest that 600 randomized enrollees will be adequate to address our primary and secondary endpoints (see **Section D.21**). Based on our prior experience with OA and large-scale pragmatic clinical trials, we expect to be able to conduct the trial across four health care systems that provide care to pain patient populations and will become part of and work with the NIH HCS Research Collaboratory.

Figure D.1. Study Schema



D.2. The Study Sampling Framework

We will recruit and randomize 600 adults across four regions with a diverse and representative population: 20-25 clinics across four Health Care Systems in both rural and urban communities in Los Angeles, Eastern MA, Cleveland Clinic Ohio, and Cleveland Clinic Florida (see **Estimated Racial/Ethnic and Gender Enrollment Table and Figure D.2**).

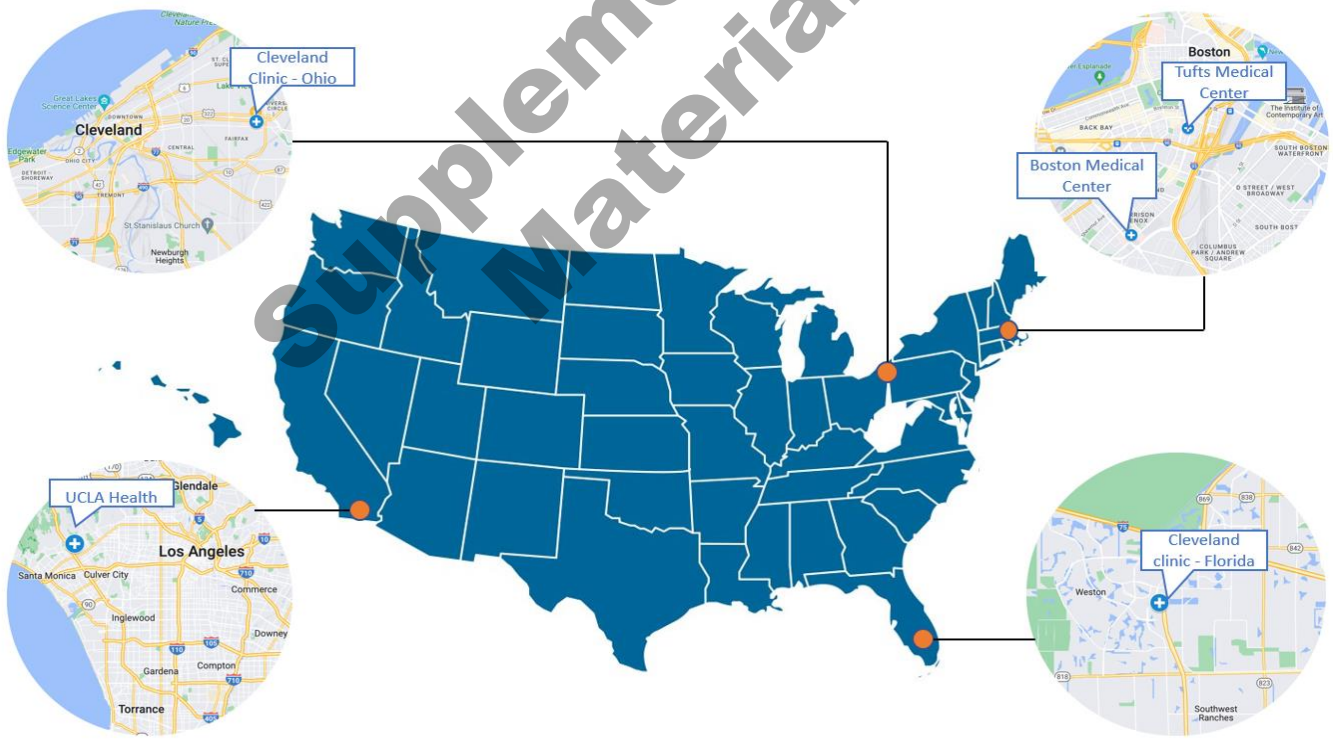


Figure D.2. Large and diverse population in four geographic regions (Eastern Massachusetts, Southern California, Northeast Ohio, Southern Florida).

D.3. Expertise of the Study Team

Our project brings together a strong multidisciplinary team with complementary expertise in all aspects necessary to complete the proposed clinical trial, including successful conduct of Tai Chi for knee OA RCTs, mind-body intervention, OA expertise, psychological health, clinical trial methodology, behavioral medicine, large pragmatic trials, and implementation science as well as Qualitative Research. The team has a full prior history of prior collaborations.[35-37,75,76,79,80] Key Personnel include:

Dr. Wang is the Director of the Center for Integrative Medicine at Tufts Medical Center and Professor of Medicine at Tufts University School of Medicine. She has extensive leadership experience in multi-site clinical trials focused on patients with Chronic Musculoskeletal pain and has been funded by VA, ACR and NIH over the last decade. Dr. Wang is an internationally-recognized rheumatology research leader in nonpharmacological pain management including Tai Chi mind-body therapies; Dr Wang will serve as MPI for the project.

Dr. Lavretsky is Professor of Psychiatry in-Residence, the Director of the Integrative Psychiatry research and clinical programs, a diplomate of the American Board of Integrative and Holistic Medicine with a track record of NIH and private funding in mind-body research (e.g., AT003480; AT009198; AT009198; AT003480). The UCLA multidisciplinary investigative team has been working together for over 20 years; Dr. Lavretsky will serve as MPI for the project.

Dr. Saper is the Nancy J. & Michael F. Roizen Chair for Wellness, Department of Wellness & Preventive Medicine, Cleveland Clinic. Dr. Saper is a clinician-investigator, former Professor of Family Medicine at Boston University School of Medicine, and past Chair of the Academic Consortium for Integrative Medicine and Health. He was recruited to Cleveland Clinic in February 2021 after a national search. He has expertise in conducting RCTs of nonpharmacologic interventions for common primary care problems such as back pain with a focus on diverse community-based primary care populations. He has published over 70 peer-reviewed papers in high impact journals, received over $20M in research funding from public and private sources, and mentored over 65 junior faculty, fellows, residents, and doctoral, masters, medical students. His research has focused on the effectiveness of yoga and PT for back pain in RCTs and pragmatic trials; Dr Saper will serve as MPI for the project.

Dr. Roseen is the Director of the Program for Integrative Medicine and Health Disparities at Boston University School of Medicine and Boston Medical Center. Dr. Roseen is an Assistant Professor of Family Medicine at Boston University School of Medicine and research associate at the Boston VA New England Geriatric Rehabilitation, Education and Clinical Center (GRECC). Dr. Roseen has received research funding from NIH (NCCIH, NICHD) and is the recipient of a NIH K23 Career Development Award focused on implementation science applied to nonpharmacologic interventions for musculoskeletal care in primary care clinics that serve low-income communities. Dr. Roseen will serve as MPI for the project and will lead evaluation of implementation across four HCS.

Dr. McAlindon, Chief of Rheumatology at Tufts Medical Center and Professor at Tufts University School of Medicine. Dr. McAlindon, is a world-renowned expert in the field of osteoarthritis and has extensive experience in clinical research and deployment of large clinical trials. He will provide methodological expertise to this proposed study.

Dr. Mittman is a world-renowned expert in the field of Implementation Science. As a senior Implementation Scientist at the Kaiser Permanente Southern California Department of Research and Evaluation, he is also a Senior Implementation Scientist at the US Department of Veterans Affairs Center for Healthcare Innovation, Implementation and Policy in Los Angeles.

Dr. Trinquart is a translational biostatistician, Director of the Center for Clinical Trials, Director of the Data and Safety Monitoring Board (DSMB) program at Tufts CTSI and the Institute for Clinical Research and Health Policy Studies of Tufts Medical Center, and Associate Professor of Medicine at Tufts University School of Medicine. Dr. Trinquart will lead the Data Coordinating Center (DCC). Dr. Trinquart has 15 years of experience as statistician for randomized controlled trials. The Center for Clinical Trials provides investigator teams' expertise on protocol development and implementation that improves efficiency and introduces innovation in all

aspects of trial design and conduct. The team has served as DCC for large multicenter trials (e.g. GEMINI) and Dr. Trinquart leads DCCs for ongoing investigator-initiated multisite trials at Tufts (e.g. PRAPELA trial). His Center also functions as part of the NCATS Trial Innovation Network JHU-Tufts Trial Innovation Center, providing statistical consultation and support for multisite trials employing innovative study designs.

Dr. Laird is a medical anthropologist specializing in the intersection of religions, cultures, and medicines. As assistant director of a graduate program in medical anthropology at Boston University School of Medicine, he has mentored dozens of students and junior faculty, including Dr. Roseen, in qualitative research methods for data collection and analysis. He has collaborated with many clinician researchers on patient-centered outcomes and integrative medicine projects. Dr. Laird will provide qualitative research expertise for this study.

Dr. Zhang, specializes in implementation science and has previous training in integrative medicine, computer science, and medical education. He has published three papers in applying implementation science methods for analyzing current research and policy for managing chronic pain. The review article which he co-authored with Dr. Wang analyzed the intervention reporting of randomized controlled trials of Tai Chi, Qigong and Yoga exercise to guide the implementation in CMP exercise programs.[79]

Dr. Siddarth is an experienced biostatistician who worked closely with Dr Lavretsky on PCORI funded pragmatic trials.

D.4. Team Experience in Recruitment and Performance of Clinical Trials

Our teams and institutions have substantial experience and resources for recruiting patients into large clinical trials. During the past decade, we have used an effective, multi-modal recruitment campaign approach to enroll large heterogeneous samples from OA populations.[13-15, 60-61] Based on our collective clinical trial experience we are confident that our proposed recruitment and retention strategies will work in this larger study (**see Human Subjects for details**).

Track Record of Successful Completion of Clinical Trials

We have considerable long-term experience in successfully recruiting patients with OA and other chronic musculoskeletal pain conditions into clinical trials.

The Tufts team has a long and successful track record of recruitment for, and performance of, clinical trials of interventions for musculoskeletal disorders, mainly knee OA.

During the period 2003 – present we performed over thirteen musculoskeletal trials, collectively recruiting over 2200 participants; all met recruitment targets and 6 of the studies over-recruited. Examples of Investigator-Initiated clinical trials in the Rheumatology Division at Tufts Medicine include:

- RCT of Vitamin D Supplementation for Knee OA Structural Progression[81] (2005-2010, 2-year duration, N=140, NIAMS R01-AR051361 Research Project Grant)
- RCT of 3-monthly intra-articular triamcinolone for Knee OA Structural Progression[82] (2010-2015, 2-year duration, N=140, NIAMS R01-AR057802 Research Project Grant)
- An RCT of Tai Chi for Knee OA Pain[36] (2005-2009, 12-week duration, N=40, NCCIH R21-AT002161 Exploratory/Developmental Grant)
- Comparative Effectiveness RCT of Tai Chi vs. Physical Therapy for Knee OA pain[37] (2010-2014, 1-year duration, N=86, NCCIH R01-AT005521, K24-AT007323, and UL1-TR001064)
- An RCT of Tai Chi for Fibromyalgia[63] (2007-2009, 12-week duration, N=66, NCCIH R21-AT003621 Exploratory/Developmental Grant)
- Comparative Effectiveness RCT of Tai Chi vs. Physical Therapy for Fibromyalgia[83] (2011-2015, 1-year duration, N=226, NCCIH R01-AT006367-01A1 Research Project Grant)
- Pilot RCT of Detecting Change in KOA Cartilage Using Enhanced MRI Imaging[84] (2011-2022, 48-week duration, N=15, sponsored by Gelita AG)

- RCT of neurobiological mechanisms of mind-body therapy for knee osteoarthritis[52] (2021-2022, 12-week duration, N=42, sponsored by American Colleague Rheumatology Research Foundation Innovative Research Award)

Over the past 10 years, Dr. Saper and his team, at Boston Medical Center and now Cleveland Clinic, have conducted five RCTs using Yoga and/or PT for low back pain.

- RCT of Yoga for chronic low back pain in a predominantly minority population[69] (2009, 12 weeks, N=30, sponsored by NCCIH K07 AT002915-04)
- RCT for comparing once- versus twice-weekly Yoga classes for chronic low back pain in predominantly low income minorities[70] (2013, 12 weeks, N=95, sponsored by NCCIH 1R01AT005956)
- RCT of Yoga, physical therapy, or education for chronic low back pain[72] (2017, 52 weeks, N=320, sponsored by NCCIH 5R01-AT005956)
- RCT of Yoga vs. education for chronic low back pain in Veterans (2018, 26 weeks, N=120, sponsored by NCCIH 5R01-AT005956S2)
- A multisite cluster pragmatic RCT "Targeted interventions to prevent chronic LBP in high-risk patients"[67] (2022, 26 weeks, N=2,300, sponsored by PCORI contract number. PCS-1402-10,867)

At UCLA, over the last five years, Dr. Lavretsky has conducted five RCTs, including a pragmatic RCT for geriatric depression.

- RCT of Yoga vs memory training in older adults with mild cognitive impairment[85] (2017, 12 weeks, N=81, sponsored by Alzheimer's Research and Prevention Foundation)
- RCT of L-Milnacipran in geriatric depression: fMRI study[86] (2020, 12 weeks, N=29, sponsored by the Forest Research Institute LVM-IT-02/Allergan Fetzima Study IIT-10018)
- RCT of brain aging and treatment responses in geriatric depression[87,88] (2020, 6 months, N=115, sponsored by NIMH R01MH097892, NCCIH K24AT009198)
- RCT of brain connectivity and response to Tai Chi in geriatric depression [53](2021, 3 months, N=220, sponsored by NIH R01AT008383, K24AT009198 and UCLA CTSI UL1TR001881)
- Pragmatic RCT of optimizing outcomes of treatment-resistant depression in older adults[89] (N=750, ongoing, sponsored by PCORI TRD-1511-33321.)

The team has experience with recruitment approaches, deployment of trial methods, development of electronic source documents; data capture technologies (e.g. REDCap), secure data sharing, preparing Manuals of Operating Procedures (MOPs), protocols, regulatory documents, FDA applications; and monitoring and audit procedures. Because of the breadth of our studies, we have accumulated experience with diverse intervention types, outcome measures and tests, including electronic pain assessments.

Approach to UG3 Planning Phase

Using our extensive experience in musculoskeletal clinical trials, we will deploy the project in two phases: 1) a 1-year UG3 Planning Phase during which we will finalize all trial procedures, and 2) a 4-year UH3 Phase

during which we will conduct the innovative, multi-site embedded pragmatic trial testing deployment of a Tai Chi among individuals with knee OA across multiple Health Care Systems.

In the UG3 Planning Phase, we will work in collaboration with the NIH and Collaboratory Coordinating Center (CCC) to finalize all trial procedures for the clinical trial. The Planning Phase aims listed below reflect the UG3 milestones outlined in the Human Subjects and Clinical Trials Information section. Subsequent sections describe the approach to achieve these aims.

UG3 Planning Phase Specific Aims:

1: Establish a collaborative and effective Project Governance and Organizational Structure among the four Health Care Systems, the NIH Collaboratory Coordinating Center and Collaborators through assembly of Working Groups, Study Teams and Panels including a Scientific Advisory Committee and Stakeholder Committees and Data and Safety Monitoring Board.

2: Identify multilevel (patient, provider, and health system leadership) barriers and facilitators of embedding a web-based Tai Chi intervention

3: Finalize the study design, recruitment and retention strategies, study materials, data capture systems, informed consent materials, and Ethical oversight structure and quality control procedures.

D.5. Assembling Study Teams and Panels

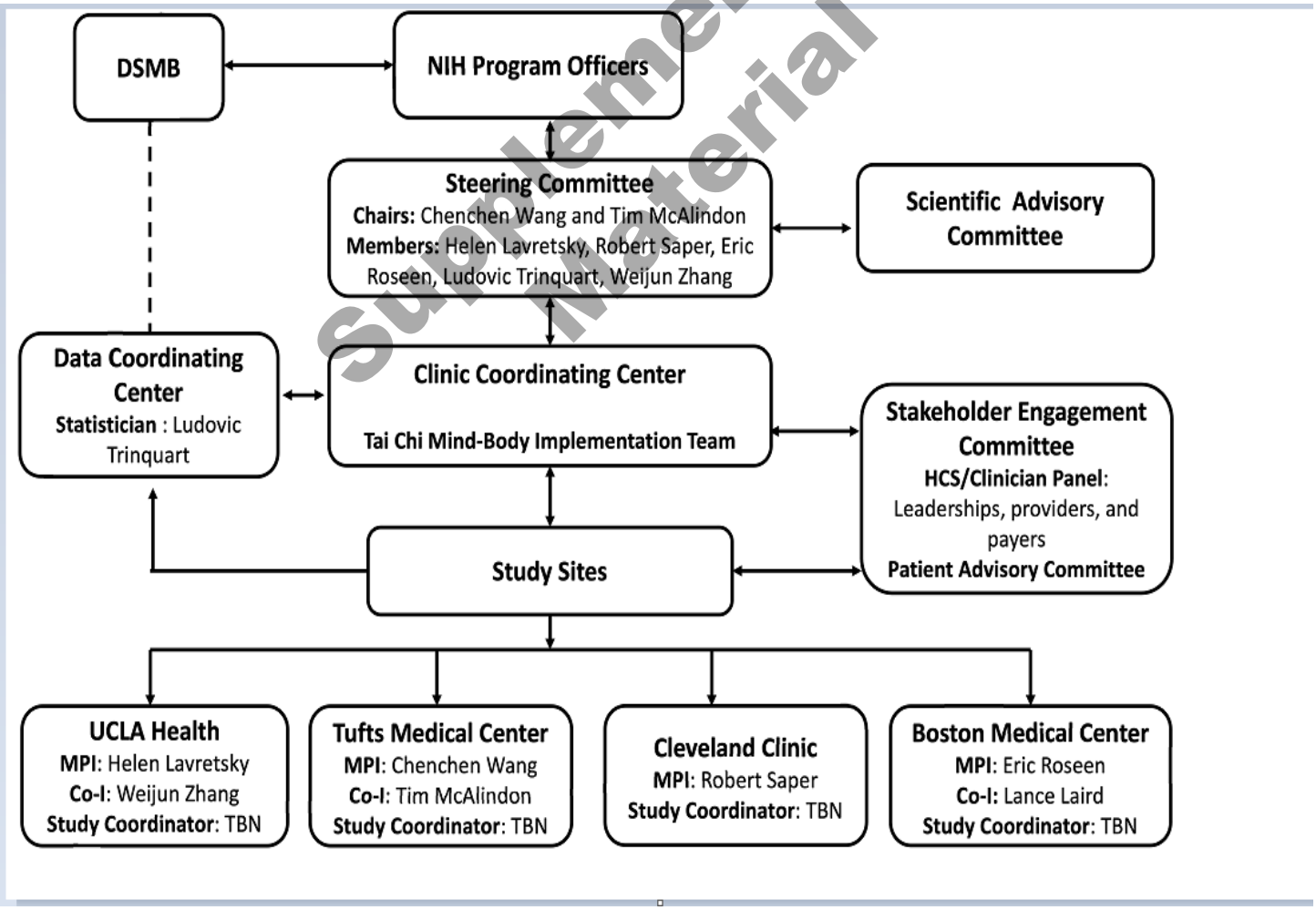


Figure D.3. Overall Structure of Study Team

Our first task will be to formalize the proposed organizational structure and membership of each of the logistical planning teams and advisory panels as described in **Figure D.3**. We will schedule meetings of each group, prioritized proportionately to the ranking of tasks on the timeline. We anticipate at least bi-weekly meetings for the higher-level tasks as planning commences.

D.5.1. Scientific Advisory Committee:

We will develop the scientific advisory committee with a mission to offer valued insights from investigators with relevant experience related to this population e.g., nociceptive pain, pragmatic trial methods, implementation science. The composition of the committee is provided in **Figure D.3**. The MPIs (Drs. Wang, Saper, Lavretsky and Roseen) will contact potential committee members to explore their interest and availability. The Committee will initially meet to learn about the proposed study and offer feedback on the relative merits and feasibility of the candidate RCT designs, plan for the study interventions (including the control condition), appropriate outcome measures and targets, and sample size projections and analytic plan, and implementation strategy. At 10 months, the Committee will meet to review the clinical study protocol, manual of operations (MOP), and Data and Safety Monitoring plan. At 12 months, the Committee will meet to review a final draft and provide feedback. When needed, the study team will contact a specific committee member for input on their area of expertise.

D.5.2. Stakeholder Committee:

We will develop a stakeholder committee to participate in shared decision making to offer feedback from patients, providers, and payers. This will lead to a trial that yields outcomes relevant to these stakeholders. This group will be to also provide feedback on tai chi intervention to allow for optimize its design for future dissemination and implementation efforts. The MPIs will work with the Tufts CTSI Stakeholder and Community Engagement team to recruit the committee. The Committee will initially meet to learn about the proposed study and offer feedback on key study design features (e.g., study design, intervention protocol, outcome measures and implementation strategy). At 10 months, the Committee will meet to review key features of the study protocol and MOP. At 12 months, the Committee will meet to review a final overview of key study design features and provide feedback.

D.6. Overall Planning Activities

We will develop the full clinical trial protocol and MOP with input from the NIH CCC and associated Work Groups, Stakeholder and Scientific Advisory committees. The meeting schedules and the synthesis of the conclusions of each meeting will be coordinated by the study coordinator. We will accomplish the following tasks according to the Timeline (see **Timeline Table**).

D.6.1. Writing the Protocol and MOP

We will develop these based on the conclusions of the respective Logistical Planning Groups and input from the scientific advisory and stakeholder committees. The overall process for this will commence with construction of a draft protocol. We will systematically task Logistical Planning Groups to scrutinize the sections of the protocol pertinent to their domains. Where appropriate, or requested, we seek input from members of the CCC and scientific advisory committee. Once a near-final draft is reached, we will request review and feedback from the CCC, scientific advisory and stakeholder committees. We will revise the draft according to critiques and feedback received.

The *protocol* demonstrates the guidelines for the proposed investigation by outlining the study objectives, scientific rationale, and procedures, while the *MOP* describes the study's organization and operations to facilitate consistent protocol implementation and data collection across study subjects. Once the Protocol is complete, the study team will determine more granular workflow including study visits, schedule of events and all study procedures. We will ensure that the clinical study protocol adheres to International Conference on Harmonisation (ICH) E6 Good Clinical Practice Consolidated Guidance and the manual of operating procedures using the NIH guidelines. The Tai Chi Mind-body implementation team and Key Stakeholder Panel will review the protocol and MOP to ensure they minimize burden on the physicians and patients. The MPIs and study staff will ensure the protocol and manual of operations documents are approved by Tufts IRB and by the DSMB.

D.6.2. Study Materials

The study team will also develop study materials to accompany the protocol and MOP. These study materials include source documents used to record study data and administrative forms for tracking subjects and their progress. In addition, guidelines and instructions for completing and retaining the forms will be developed to ensure adequate data collection, consistency, and adherence to the NIH and IRB requirements. Tai Chi instructor manuals and participant materials will also be created.

D.6.3. Data Capture Systems

During the feasibility phase, the DCC will collaborate with the MPIs to finalize the trial Design, Protocol, and Manual of Procedures. The DCC will lead the development of the Data Management Plan and of the Statistical Analysis Plan. The DCC also will develop Case Report Forms and the multiple components of the electronic data capture system (EDC) in REDCap accessed through Tufts CTSI. The EDC system will include randomization modules, instruments to collect data from site investigators and from participants. Regarding patient-reported outcome measures (PROMs), we will use HIPAA-compliant surveys sent by email via REDCap. We also will use MyCap for PROMs, an external module for REDCap. MyCap enables participants to download an app to complete clinical data collection from any mobile iOS or Android device. In REDCap and MyCap, users can create custom questionnaires or download existing EPROMs from a shared online library. Data transfer protocols and data use agreements between the DCC and the individual sites will be formalized. Data from all sites will be collected by site coordinators through the trial EDC system. As much as possible, the DCC will inform the development of the EDC system by a Common Data Model such as OMOP.
We will ensure that source data collected remains confidential. Hard-copy source data and related documents will be retained and maintained in a secure location. Electronic source data will be stored securely with password protection and system backups.

D.6.4. Training Materials

The study team will develop training materials for this study. We will also develop a plan to ensure the study-related and formal training requirements are completed in accordance to the ethical committee, such as Human Subjects Research Protection Education and Good Clinical Practice (GCP). We will develop **quality control procedures and a data management plan** to ensure that the study is conducted and the data will be generated, recorded, and reported in compliance with the protocol, and any applicable regulatory requirements. We will describe the training and certification plan to include timelines and meeting schedules to ensure all research staff involved in the study are trained and certified.

D.6.5. Maintaining Quality

The research team will develop training materials for study-specific procedures and data management specifying all relevant aspects of data collection and processing for the study (including data validation, cleaning, correcting, and releasing). We will plan to ensure and document staff completion of study-related training and formal training requirements in accordance to the ethical committee, such as Human Subjects Research Protection Education and Good Clinical Practice (GCP). We will develop quality control procedures and a data management plan to ensure that the study is conducted and the data will be generated, recorded, and reported in compliance with the protocol, and any applicable regulatory requirements. We will describe the training and certification plan to include timelines and meeting schedules to ensure all research staff involved in the study are trained and certified.

D.6.6. Ethical and Regulatory Oversight

For this proposed investigation, **Commercial Institutional Review Board (IRB)** is selected as independent pay-for-service IRB that provide regulatory and ethical review services for academic and non-academic institutions to conduct reviews of research involving human subjects. Tufts IRB Informed Consent Form (ICF) template language to develop the study-specific ICF for subjects to consent to participate in research. The study team will draft the ICF to include important elements of informed consent and HIPAA research authorization language. Necessary regulatory documents, such as the Informed Consent Form, protocol, MOP, subject-facing study materials, advertisements, and administrative forms, will be reviewed and finalized by the MPI prior to IRB submission. These documents will be submitted by the submission deadlines and IRB review and approval is estimated to take approximately 4 to 6 weeks after the IRB Meeting Date.

The Institutional Review Board is charged with the protection of human subjects through the oversight of all investigators and their research projects. Study personnel will be trained in Ethical Conduct for Human Subjects Research, Good Research Practices, HIPAA protections and computer security using resources from NIH and the Commercial IRB. The Commercial IRB will serve as the central IRB for the project. We will work with the NIH and CCC to onboard any additional sites through a structured process for regulatory compliance. Research personnel will be uniformly trained in data collection and management and will participate in regular conference calls to evaluate recruitment and enrollment activities and address issues surrounding IRB regulatory compliance and data monitoring. We will work with the NIH and CCC infrastructure to develop the informed consent process and documents. Clinical trial data will be stored at Tufts datasets will not include patient identifying information. Patients will instead be assigned a unique study identification number. At the end of the trial, de-identified study datasets will be archived. We will work with the NIH and CCC consortium to comply with data sharing procedures.

D.6.7. Assembling a DSMB

The Center for Clinical Trials at Tufts CTSI runs a DSMB program for investigator-initiated trials. Since 2017, the Center has provided full-service DSMB for 17 trials. We provide DSMB setup activities (member selection, development of charter and Data and Safety Monitoring Plan) and per meeting activities (planning & coordination of meetings; development of open and closed reports; post-meeting review & meeting minutes). By leveraging this experise, the DCC will convene a DSMB and develop a Data Safety Monitoring Plan by using the NIH guidelines to address the potential risks to subjects and determine the process for collecting and reporting of adverse events to IRB, NIH, and Advisory Committees. Members of the DSMB, including a patient representative, will be independent of the study investigators. The DCC will develop a DSMB Charter that will be approved by the DSMB members.

D.7. Selection of Participants

We will finalize eligibility criteria during the Planning Phase based on the framework below.

Inclusion Criteria:

- Age 45 years or older
- Fulfills the American College of Rheumatology criteria for symptomatic OA.[110]
- Patient PROMIS Pain Interference score ≥ 40 (100 mm visual analog version score)
- Able to provide informed consent
- Willing to complete the 12-month study, including twice- a-week remote Tai Chi sessions if randomly allocated to the experimental group
- Has access to a home computer or device that will allow telehealth delivery of the intervention

Exclusion Criteria:

- Currently practicing Tai Chi
- Serious medical conditions in the opinion of the MPIs limiting the ability to participate in the study
- Unable to walk without a cane or other assistive device

D.8. Identify multilevel barriers and facilitators of embedding a remote Tai Chi intervention in multiple healthcare systems (AIM 2)

Through engaging local stakeholders associated with participating clinics we will identify multilevel barriers and facilitators of embedding web-based Tai Chi intervention in primary care clinics of four HCS. We will utilize the integrated-Promoting Action on Research Implementation in Health Services (**i-PARIHS**) implementation framework, the most commonly used framework for understanding the role of facilitation, as a guide to design facilitation.

Our investigative team encompasses experts in integrative medicine programs within each of the included health care systems. They are well-suited to address broad sets of implementation challenges in promoting the Tai Chi mind body intervention, e.g., lack of awareness among patients and staff, resistance to change at all levels of the health care system, constrained resources and limited implementation expertise. To ensure

successful design of this implementation facilitation, we will recruit a combination of experts and community stakeholders to form an Advisory Committee. The committee will represent expertise in knee OA, chronic pain, Tai Chi, and implementation strategies in primary care and specialty settings. This Advisory Committee will review and provide input to the initial implementation strategy design in Year 1 and iteratively as needed throughout the study period. They will participate in developing and supporting activities to increase knowledge and skills of patients and providers, build interdepartmental relationships among integrative medicine, primary care, and rheumatology.

D.8.1. Patient strategies

We anticipate that some of the recruitment strategies described above would be pragmatic and feasible in real world settings. For example, developing and disseminating Patient strategies include printed and electronic educational materials that present remote Tai Chi as a safe and effective evidence-based treatment for knee OA. These will be written, reviewed, and revised by the researchers with patient input. Content will be written at a sixth-grade reading level. Patients with a new episode of knee pain will be mailed a brochure *to their home address on file* and sent the electronic copy via the patient portal.

D.8.2. Provider Strategies

Provider strategies include one-hour **interactive grand rounds/lunch seminars** that allow for shared learning between clinicians and Tai Chi instructors. These grand rounds will be facilitated by local members of the facilitation team. Food will be provided, and clinicians can earn continuing education credits. These meetings will take the place of mandatory administrative meeting per month ensuring providers have time protected to attend. Attendance will be tracked. We will compile email lists and send reminders to PCPs to encourage referrals to the study.

Approach to UH3 Trial Phase

D.9. Overview:

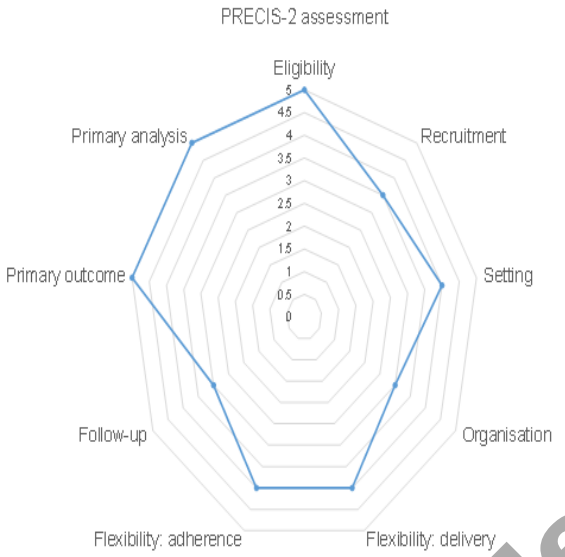
The UG3 phase will provide development of all methods, tools, and software needed to conduct the pragmatic trial by the start of the UH3 phase. We will work closely with the **NIH-CCC resource** center environment and infrastructure in deploying and running our embedded, pragmatic randomized controlled trial.

During the planning (UG3) year, we will train the Tai Chi instructors in delivery of the web-based mind-body intervention. We will design a recruitment strategy to represent diverse participant populations including Blacks/African Americans, Hispanics/Latinos, American Indians/Alaska Natives, Asian Americans, Native Hawaiians and other Pacific Islanders, as well as socioeconomically disadvantaged populations, and gender minorities.

***Rationale for Trial Design*.** Although Tai Chi has demonstrated health benefits in a variety of patient populations and clinical practice guidelines strongly recommend Tai Chi as an intervention for knee OA, no study has rigorously investigated its effectiveness when implemented in "real world" settings across multiple healthcare systems. By examining a group of heterogeneous patients with knee OA, we will examine if and how the multifaceted elements of mind-body therapy can reduce pain interference and provide important information about treatment options for clinicians and patients. The Trial is characterized as “mostly” to “highly pragmatic” across Pragmatic Explanatory Continuum Indicator Summary-2 (PRECIS-2)[90] domains (see **Table**

D.1)

Table D.1: PRECIS-2 assessment
Using the PRECIS-2 criteria, eight raters, including the PI and co-PIs, the DCC director, evaluated the trial design. The table below includes the median score across all raters for each domain. The study was judged very pragmatic across the nine domains of the PRECIS-2, except for the organization and follow-up domains.



Domain	Score	Rationale
Eligibility criteria	5	The trial population will match the population intended for the intervention. We will restrict to patients with symptomatic knee OA and a WOMAC pain subscale score of at least 40 to identify patients for whom there is equipoise
Recruitment Path	3.5	Efforts will be made for remote and in-person recruitment, using fliers, advertising, clinical visits, and informational letters with telephone follow-up.
Setting	4	Multi-HCS multisite trial with identical setting to usual care setting
Organization	3	Remote tai-chi is currently not usual practice and instructors will be recruited to deliver tai-chi. Once deployed, it does not affect the organization of usual care.
Flexibility – delivery	4	The interventions will be delivered with flexibility similar to that of usual care.
Flexibility – adherence	4	The trial is not imposing additional adherence or compliance reminders beyond usual care.
Follow-up	3	The collection of patient-reported outcomes via direct contact (survey) is not part of usual follow-up.
Outcome	5	The outcomes are direct outcomes of importance to patients or processes of care that may impact patient management and outcomes.
Analysis	5	All randomized participants will be included in the primary intention-to-treat efficacy analyses.

D.10. Study Enrollment Procedures

Participant recruitment strategy will be strongly influenced by the work of the Stakeholder Committee with an overall approach to be developed in the UG3 phase leveraging extensive patient stakeholder partnership. Participants will be approached after engaging primary care and/or specialty providers, as determined by HIPAA-waived preparation for research scans of billing diagnoses from the electronic medical records. Potential participants will be contacted through a multimodal strategy. A description of the trial, the meaning of randomization, the expectations for follow-up, and the informed consent document will all be shared with potential participants. Informed consent will include consent to transfer personal health information (PHI) to the coordinating center to facilitate outcomes ascertainment and follow-up. Informed consent may be performed via portal, videoconference, or in-person. No study procedures will be performed prior to informed consent.

We will adapt effective, multi-modal strategies that were successful in prior recruitment drives for chronic pain studies based on our experience and resources.

- Based on discussions with patients, caregivers, and primary care and specialty partners, we will devise a patient-centered approach to recruitment.
- Patients will be identified from well-established clinical networks at each of the four health care systems
- Our two mechanisms of recruitment will be through screening and referrals:

Referrals will be elicited from clinicians and through in-practice advertisements to patients and their caregivers specifically asking if the provider, patient, or caregiver experiences knee OA. Based on data provided by our

clinical partners (see **Letters of support**), we have access to a large eligible population from both primary care and specialty clinics. We expect to be able to reach (screen) over 2000 potentially eligible participants.

(1) Fliers:

IRB approved flyers will be posted throughout 25 clinical sites across four Health Care Systems, and placed on the Institutional web and social media sites, or into the myChart portions of the EMR systems.

(2) Advertising:

Tufts Medical Center is located in an urban, tertiary-care, academic hospital in downtown Boston. **Boston Medical Center,** a large safety net hospital and its affiliated health centers has a distinctly different catchment area than Tufts. Its patients include predominantly low-income diverse adults from the South End, Roxbury, Dorchester and surrounding neighborhoods. **UCLA Medical Center** is located in an urban, tertiary-care, academic hospital in west Los Angeles. **Cleveland Clinic Florida** is part of the same health system and has several hospitals and multiple outpatient primary care and specialty clinics in southeast Florida. We will use a combination of advertising strategies that we have found to be successful for clinical trials. These include advertisements in the media (radio, local television, Internet, local newspapers, public transportation, and mass mailings). Used in an overlapping fashion, these can generate a consistent stream of inquiries and applications. We will offer several modalities for interested individuals to obtain more information about the study and to self-screen. These will include an opening informative page with an interactive self-screening module using a study email address and telephone number on the dedicated research web portal.

(3) Clinical Visits and Databases:

All of our Health Care Systems have searchable clinical data warehouses that can be used for preparation for clinical research. With IRB approval, across Health Care Systems we will obtain HIPAA waivers to flag the charts of patients with a ICD-10 billing codes under M17 knee OA who have attended clinics within the last year. A direct mail-out procedure will be used to contact patients of primary care and specialty clinics. This can be done at regular intervals to identify potentially eligible participants to reach out to.

(4) Informational Letters with Telephone Follow-up:

Potential participants will be identified as above and staff will send letters/secure emails, MyChart Messages, and secure texts to these individuals with a brief description of this study. Diagnoses or other protected information will not be revealed in the letter. In addition, a pre-addressed, postage paid postcard will be enclosed with the letters. Individuals will be able to indicate on the postcard or call in to indicate whether they are interested in learning more about the study or opt-out for any future communications.
In the Planning Phase, after finalizing recruitment sites, we will develop a project leadership plan as part of the Manual of Operating Procedures (MOP). The MOP leadership plan will describe the roles and responsibilities of study personnel. In consultation with the NIH project scientists and CCC we will ensure that the project is represented on all work groups and committees (Electronic Health Records, Regulatory/Ethics, Biostatistics & Study Design, Health Care Systems Interactions, and Patient Reported Outcomes) with well-qualified team members.

D.11. Subject Screening Procedures and the Informed Consent Process

Participants will be enrolled by the following procedure: Study staff will contact potentially eligible subjects by telephone or HIPAA-compliant Zoom and describe logistical aspects of the study. Interviewers will answer any questions and obtain verbal consent for screening to inquire about the following inclusion/exclusion criteria: presence of chronic knee OA pain, currently doing Tai Chi or enrolled in clinical trial. Participants who are not screened out by these criteria will be scheduled for a baseline/screening appointment where the remaining inclusion/exclusion criteria will be evaluated. For this study, 2 questions: (1) “Has a doctor ever told you that you have knee arthritis?” (2) “Do you have pain, aching, or stiffness in one or both knees on most days?” Individuals who answer in the affirmative to both questions will be invited to attend an eligibility visit. A list of applicants who screen positive during the telephone interview will be given daily to the trial staff to schedule eligibility visits. After verifying eligibility, participants will be informed regarding study details and alternatives to participating in the study. Informed consent forms will be obtained from each participant who elects to participate. During the 3-week period prior to the start of the intervention period, we will complete the baseline assessments. Randomization will occur after the baseline evaluations, and afterwards a cohort of eligible

participants are identified. At this time, the research staff will contact eligible subjects by phone, confirm that they still wish to participate in the study, and inform them of their group assignment and the schedule for their training sessions. These procedures will be precisely described in a Manual of Operations.

Additional Screening Procedures. Potential participants will receive TUFT/UCLA//BMC/Cleveland Clinic IRB-approved telephone screening, followed by remote screening for those eligible. Prior to enrollment, the MPIs will obtain IRB-approved informed consent from subjects. Though eligibility will be assessed at baseline, participation may be terminated if the subject stops meeting entry criteria.

D.12. Study Interventions

Our design examines 2 treatment conditions; remote Tai Chi + Routine Care vs. Routine Care alone. In the Planning Phase we will work with participating clinics to systematically identify Routine Care processes including pharmaceutical pain management, weight loss, physical therapy, etc. We will identify site differences and develop consensus for key processes. We will use patient-level randomization and will stratify randomization by site to avoid imbalances across sites. These procedures should also minimize the potential for bias based on procedures used at different participating sites or by different clinicians at these sites. In the Planning Phase we will finalize the treatment protocol with detailed descriptions in the MOP to guide training and implementation.

We will encourage all participants to maintain their usual physical activities and perform no additional new exercise programs other than the exercise encouraged in the classes. Each participant will receive a web link of the dedicated research web portal with his/her unique username and password, which will lead to separate web pages of their randomized groups: remote Tai Chi intervention or Routine Care. The webpage layout and design for both remote Tai Chi group and Routine Care group will be similar. The Online Logbook section will keep exercise logs in order to track adherence to intervention and homework during the intervention period. Throughout the intervention period, we will track the reasons for and the number of missed sessions.

D.12.1. Remote Tai Chi Intervention and Instructors

The program will take full advantage of our previous Tai Chi programs' methods and strategies[35,36,61]. All program components to be used will be derived from classical Yang style Tai Chi. We will condense the 108 postures of Classical Yang style Tai Chi to 10 forms that can be learned by participants with knee OA within 3 months. The movements and postures were selected because they: (1) are easily comprehensible and can be taught via remote instruction; (2) clearly represent progressive degrees of challenge to postural stability, with weight bearing moving from bilateral to unilateral supports; (3) emphasize increasing magnitude of trunk and arm rotation with diminishing base of support and, as such, will potentially improve physical function without excessively stressing the joints; and (4) include meditative qualities that can address arousal symptoms of stress and depression. The intervention will delivered via a secure Zoom video platform. In the Workbook section of the remote Tai Chi web portal, we will include graphic illustration of sequential motions of the 10 forms with detailed description. The Video section will embed Zoom videos for live streaming.

Remote Tai Chi sessions will last 60 minutes, twice a week, for 3 months (24 sessions) based on our previous investigation.[37,91] In addition to the content of the Web portal, we will also provide the participants with printed materials on the remote Tai Chi program, including Tai Chi principles, practice techniques, and safety precautions. During the first session, the remote Tai Chi instructors will explain exercise theory and procedures of Tai Chi. In subsequent sessions, the instructor will lead the remote Tai Chi practice. Every session will include the following components: (1) warm up and a review of Tai Chi principles; (2) meditation with Tai Chi movement; (3) breathing techniques; and (4) relaxation. In the Workbook Section, we will include two pre-recorded videos to help participants to follow each session. We will instruct participants to practice at least 30 minutes a day at home throughout the intervention period. After 3-month remote Tai Chi mind body exercise training, we will also provide a booster session in month 4, 5, and 6. The 3-month remote Tai Chi mind body exercise and booster sessions will be conducted under the guidance of five certified expert Tai Chi teachers, Mr. Rami Rones (Massachusetts), Mr. Brian Muccio (Florida), Ms. Dorri Li (Kansas City), Ms. Kate Hollister (Los Angeles) and Mr. Allen Jiang (Los Angeles). They each have extensive experience conducting Tai Chi mind-body programs and have successfully completed clinical trials using both in-person and remote Tai Chi.

D.12.2 Routine Care

Information on routine care or "Guideline-Based Care" will include an educational module for primary care providers or other participating clinicians. The study team would create this educational module covering the latest guidelines for knee osteoarthritis. This module will be shared during team meetings, grand rounds, via email at start of study, and/or online CME platforms run by Health Care Systems. Watching the module will be encouraged but not required. Participants randomized to the usual care arm will receive a one page 2022 patient handout developed by JAMA on osteoarthritis.[92]

D.12.3. Concomitant Treatment of OA

We will instruct patients to maintain their regular medications and their routine visits to their doctors throughout the study. The investigators will record any changes in treatment, but will not be involved in any changes of therapy. The changes in treatment will be verified in 2 ways: (1) Patients will keep a prospective written record on a paper calendar; and (2) We will verify each participant's medication use during each study visit.

D.13. Strategies to Maintain Fidelity

D.13.1. Treatment credibility

We will evaluate treatment credibility, expectation for change, and satisfaction after the 2nd session of treatment and at post-intervention, according to procedures using a 10-point Likert scale, as we have done in our previous studies.[65,66]

D.13.2. Alternate treatments

All subjects will be medically stable prior to entry into the study protocol. However, if subjects engage in alternate treatments, they will be advised to inform the MPIs. This will be tracked, however participants will not be withdrawn from the study.

D.13.3. Follow-up Assessments

Assessments of safety will take place each study visit. Consistency and reliability of the web-based, live video Tai Chi exercise will be maintained so that each participants' intervention is delivered in the same manner. We will use the following procedures known to maintain intervention fidelity when using technology[93] and used in our previous studies [22,94] (1) All Instructors will receive project-specific trainings, including understanding of diseases (knee OA and common comorbidities), familiarity with web-based content and forum participation, standardization of Tai Chi movements and teaching style. (2) Training sessions with research teams for maintaining fidelity, including possible technical problems during session. (3) All participants will receive two testing and training sessions to ensure an adequate ZOOM set-up that allows 2-way observation between the Tai Chi instructors and participants. Instructors and research staff will also have password secured log in for the dedicated research web portal, which will lead them to their training pages.

D.14. Strategies to Maximize and Ascertain Adherence

We will use the following procedures known to enhance adherence based on established protocols from our prior intervention trials: (1) Select a population of interested and reliable individuals. (2) Discuss study logistics in detail with each participant, especially the time commitment and obtain a verbal and written commitment. (3) Schedule visits at a convenient time to minimize dropouts. (4) Fully assemble the participant group for baseline evaluation prior to randomization, so that we have a large enough pool to provide replacements. (5) Perform the randomization after the baseline evaluation. (6) Provide friendly personal contact with participants while following a protocol that is fully approved by the Institutional Review Board and ensure that adequate time is devoted to each participant to provide training and information through web portal, and answer questions, discuss concerns using the discussion forum embedded in the web portal, while always demonstrating sincere interest in the participants' physical capabilities. (7) During live video exercise and discussion on the forum, instructors will help modify movements tailored to participants' body functions and risk profiles. (8) Keep detailed intervention attendance logs**.** (9) Conduct weekly telephone calls and/or in-class announcements during the intervention period to remind participants of daily practice and solicit feedback about the home practice. (10) Provide a monthly booster session after 3-month interventions to enhance adherence. (11) Subjects will be asked to complete IRB-approved daily logs/diaries to report the amount of time spent practicing Tai Chi homework at home in the Online Logbook section of the web portals. (12) These

logs can also be collected on a weekly basis through email, and the data will be entered into a database for analysis. These data will be used to enhance the adherence.

We have conducted several clinical trials in our health systems and have trained mind-body interventionists to follow standard protocols, document fidelity and identify off-protocol events. In the Planning Phase we will develop detailed training plans and provider fidelity monitoring procedures for these intervention components. These will include observation of 10% of classes by a research staff member who will use a checklist to record fidelity to the protocol. An aspect of this training will be instruction in Good Clinical Practice for human subjects' research, HIPAA privacy protections and procedures for adverse event reporting.

D.15. Patient Reported Outcome Measures

Outcome measures will be finalized in collaboration with NIH and the CCC in the Planning Phase. Our preliminary outcomes are the NIH-funded Patient Reported Outcomes Measurement Information System (PROMIS) which measure to quantify pain interference. We will also use the core set recommended by the Osteoarthritis Research Society International, and focus measurements on pain interference, pain intensity, physical function, and patients' overall assessment of their Knee OA severity[93]. The questionnaires used to assess chronic pain based on a comprehensive set out core outcomes specific to knee OA are listed below.[94]

D.15.1. Primary Outcome

The primary outcome will be the change in the PROMIS Pain Interference score (8-item short form evaluating the extent to which pain interferes with physical, emotional and social activities) from baseline to 3 months, collected using interactive mobile technology. Pain interference is a recommended chronic pain clinical trial outcome by IMMPACT.[77] We previously found that PROMIS Pain Interference target whole-body outcomes among participants with symptomatic knee osteoarthritis. Specifically, PROMIS Pain Interference scores correlated most strongly with measures of whole body pain (Short-Form 36 Bodily Pain, r = −0.73) and physical health (Short-Form 36 Physical-Component Summary, r = −0.73); their correlations were lower with other legacy measures, including with the WOMAC knee-specific pain (r = 0.47).[95]

D.15.2. Secondary Outcomes

Change in pain will be further contextualized, as recommended[77] by additional assessment of patient-reported acceptable symptom state; and treatment failure using standardized questions; and will be adjusted for level of physical activity[77] . Primary and Secondary Outcomes and Covariates are presented in **Table D.2** below and are based on a comprehensive set of core outcomes specific to knee OA.[96-98]

Table D.2. Patient Self-reported Outcomes

Outcomes	*Construct*	*Instrument*
Primary	Pain Interference with daily living	PROMIS Pain Interference Scale 8a
Secondary	Pain intensity	WOMAC pain
	Function	WOMAC function
	Depression	Beck Depression Inventory II
	Use of pain medications	Analgesic (Rescue Medication)
	Quality of life	PROMIS Global 10
	Self-efficacy	Arthritis Self-Efficacy Scale function subscale

Western Ontario and McMaster University Index (WOMAC)

The WOMAC is a validated, self-administered instrument specifically designed to evaluate knee and hip OA.[97,99] It has three subscales that we will analyze separately: pain (score range, 0-500), stiffness (0-200), and function (0-1700), with higher scores indicating more severe disease.

Rescue analgesics and concomitant pain treatments *(amount used and time-to-use*)
Scales have been developed that allow quantification of medication use in chronic pain patients based on dosage and medication class.[100]

Beck Depression Inventory II (BDI-II)
The BDI-II is one of the most widely used instruments for measuring depressive symptom severity. It consists of 21 self-report questions, with higher scores reflecting a greater degree of symptom severity. It has been validated and shown to be highly reliable.[101]

The PROMIS Global-10 (HRQoL)
The PROMIS Global-10 is a publically available global health assessment tool that allows measurements of symptoms, functioning, and healthcare-related quality of life (HRQoL) for a wide variety of chronic diseases and conditions.[102]

The Self-efficacy
This will be assessed using the lower extremity questions of the Arthritis Self-Efficacy Scale function subscale Construct and concurrent validity and test-retest reliability for the subscales have been demonstrated in patients with arthritis.[103]

D.16. Schedule of Visits and Participant Flow

The study procedures that will occur at each visit are summarized in **Table D.3.** We will collect uniform baseline and follow-up date elements. Applicants who pass the preliminary screening procedures will attend an in-person zoom screening visit where they will first complete the informed consent process. Once a subject's inclusion qualification is determined, they will be notified and subsequently the baseline evaluation will be conducted. All subjects will receive a full education about the study procedures before randomization, including how to keep study calendars, how to report other interventions, medication, adverse events, and contact information for the study team.

Table D.3. Questionnaires and Examination Measures and Frequency

Visit Sequence	Screen	Baseline	Intervention (Weekly)	Month 3, 6 &12
Consent	X			
Joint X-ray (OA patients) and eligibility	X			
PROMIS Pain Interference	X	X		X
WOMAC Pain and Function		X		X
Beck Depression Inventory II (BDI-II)	X	X		X
Quality of life (PROMIS Global 10)		X		X
Analgesic (Rescue Medication) Use		X	X	X
Arthritis Self-Efficacy Scale function subscale		X		X
Adverse events and Adherence (Diary of home practice)			X	X
Randomization* (will occur after the baseline evaluation)		X*		

D.17. Data on healthcare utilization from electronic health record

Musculoskeletal pain-related medical utilization as documented in the EMR (e.g., opioid prescriptions, referral to specialty consults and diagnostic imaging, epidural steroid injections, surgery and referral to other nonpharmacological treatments such as PT) during the 12-month study period.

D.18. Fidelity from attendance data

The primary analysis will be intention-to-treat. However, participants who attend ≥50% of Tai Chi classes over the first three months will be designated as adherent and be analyzed in a secondary per-protocol analysis.

D.19. Data management

During the trial phase, and in collaboration with the **NIH and CCC consortium**, the DCC at the Center for Clinical Trials at Tufts CTSI will monitor data quality and completeness through regular data queries, generate operational reports to support enrollment and retention, identify and address protocol violations, and manage Adverse Events data. The DCC will perform interim data analyses at regular intervals and report them to the independent DSMB. Closed reports for analyses by randomization group will be provided to DSMB members in encrypted and password protected files. Finally, the DCC will carry out the primary, secondary, and exploratory analyses, and ensure secure and protected data storage, and data sharing.

D.20. Data monitoring and quality control

We will develop a comprehensive data dictionary including which coding systems are used. Univariate and bivariate graphical plots, univariate and bivariate frequency distributions, and summary statistics on the whole sample will be used to screen data for errors and missing data that may have been missed on routine edits (performed monthly). Since these procedures will be repeated monthly and for each DSMB report, we expect that by the end of the study the database will be of the highest quality. Although we expect randomization and the large sample size to result in balanced distributions of baseline characteristics between groups, we will perform descriptive and inferential analyses to identify chance imbalances in the distribution of participant characteristics at baseline between intervention groups. These analyses will be part of the routine data monitoring and quality control of the trial. They will also be reported to the DSMB. The DCC will generate monitoring reports regarding recruitment and retention that will inform changes to the protocol and statistical analysis plan. We will monitor recruitment rates by site, patient demographics, and adverse effect and outcome data pooled across groups.

D.21. Statistical Considerations

D.21.1. Sample Size Calculation

Table D.4. Power calculations for the primary endpoint

Sample size	Effective sample size	Mean T-score at 3 months		Mean between-group difference	Correlation between baseline and 3-month T score	Power
		Tai Chi+ routine care	Routine care alone			
300/300	240/240	62±6	63±6	1	0.5	73.1%
		62±6	63±6	1	0.75	95.4%
		61±6	63±6	2	0.5	99.9%
		61±6	63±6	2	0.75	100.0%
400/200	320/160	62±6	63±6	1	0.5	68.1%
		62±6	63±6	1	0.75	93.0%
		61±6	63±6	2	0.5	99.8%
		61±6	63±6	2	0.75	100.0%

We performed statistical power calculations for the primary analysis based on the change in PROMIS pain interference score from baseline to 3 months after randomization. The PROMIS pain interference score is measured from an 8-item questionnaire with responses on a 5-point ordinal rating scale, yielding raw scores from 8 to 40. Raw scores are converted to T-scores by using the PROMIS scoring manual and by standardization to the US general population with mean ± SD scores of 50±10. A higher T-score represents higher pain interference. The minimal important change, i.e., the minimal within-person change over time above which patients perceive themselves as importantly changed, is a 3-point decrease in general (see **Table D.4).**

Kravitz et al[104] enrolled 215 patients in a randomized trial that compared the mean change in PROMIS-PI 8-item T-score from baseline to 6 months between a group randomized to a mobile device–supported n-of-1 trial for chronic musculoskeletal pain and a group randomized to usual care. The mean ±SD T-score at baseline was 64.0±5.9 vs 64.7±5.8. The mean change in T-score from baseline to 6 months was −3.22 (95%CI −4.31 to −2.13) vs −1.85 (95 CI −2.96 to −0.75), for a mean between-group difference of −1.36 (95%CI −2.91 to 0.19).

We calculated power for an ANCOVA, which is more powerful than an ANOVA of change from baseline. We considered a two-sided alpha level of 0.05. We considered an unequal allocation of 2:1 to remote Tai Chi + routine care vs. routine care alone (justification in section **D.21.2**). We further assumed a proportion of dropout of 20% at 3 months, based on our previous experience with similar populations. With 400 and 200 participants randomly allocated to the remote Tai Chi + Routine care and Routine care alone groups, we would have 320 and 160 participants after accounting for a 20% drop-out. Assuming a SD equal to 6 in both groups, based on the data from Kravitz, and assuming that within-participant correlation between the baseline and 3-month T-score is as little as 0.10, this sample size yields more than 95% power to detect a between-group difference of 2 or more (mean T-score at 3 months of 61 and 63 in the Tai Chi +routine care group and routine care alone group) with an ANCOVA with a two-sided alpha of 0.05.

In all, we estimated that enrolling 600 participants (400 and 200) over a period of 36 months, would yield the required effective sample size, after accounting for 20% loss to follow up and drop-out, to detect clinically meaningful effects on our primary endpoint.

Refinement of assumptions and calculations in the feasibility phase.
During the **UG1** phase, we will conduct additional power calculations with refined information about the correlation between within-participant PROMIS-PI baseline and 3-month scores. So far we have used a very conservative estimate of 0.1, but we anticipate larger within-patient correlation, which will lead to increased power. We also will define a serial gatekeeping testing procedure between the primary and secondary endpoints, in which secondary endpoints with a total alpha of 0.05 that it passed along if the primary endpoint is significant. We will further define a hierarchical Holm procedure for the secondary endpoints and we will explore calculations of r-power with various types of structure of correlations between endpoints.

D.21.2. Randomization

After all screening and baseline test results are reviewed and eligibility criteria are confirmed, subjects will be randomized to one of two groups if patients continue to meet eligibility criteria and sign the informed consent

form. All eligible subjects will be randomized to the remote Tai Chi or Routine Care group using a computer-generated random assignment scheme.

We will use an unequal randomization with a 2:1 ratio to remote Tai Chi + Routine Care vs. Routine Care only. This unbalanced randomization ratio offers several advantages as the larger number of participants allocated to the tai chi group will: a) give better opportunities to assess barriers and facilitators to implementation and to identify predictors of adherence; b) devote more power to clinically meaningful comparisons. In addition, the unequal allocation decreases only negligibly statistical power as compared to a 1:1 ratio (**Table D.4**).

We will stratify randomization based on site. The allocation scheme will rely on a maximally tolerated imbalance (MTI) randomization procedure, implemented with the asymptotic maximal procedure and an MTI of 3. Compared to conventional permuted blocked randomization, this procedure lowers allocation predictability and protects against chronological bias. A study biostatistician at the DCC will generate the randomization scheme which will be incorporated into the online REDCap data management system. Once the randomization form is completed, the data management system will generate the participants' assignment. Performing randomization via the online data management system will maintain allocation concealment.

D.21.3. Analysis Plan (Aim 1 and 2)

Primary analyses will be performed according to the principle of intention to treat (ITT). Results will be reported in accordance with the CONSORT Statement, as well the relevant extensions for pragmatic trials and patient-reported outcomes, which will ensure that we provide sufficient information in reports to allow for assessments of the trial's internal and external validity.

Primary endpoint: We will use an ANCOVA GLMM of the PROMIS PI score at 3 months according to intervention group and baseline PROMIS PI score as covariates, as well as site-specific random-effect term. We will use an identity link function and we will estimate the LS means and the between-group differences in LS means, along with their 95%CI, and the associated p-value. Significance will be at 0.05.

Secondary endpoints: For each endpoint, we will estimate two separate models. First, we will examine the effect of the intervention at 3 months. Second, we will estimate a model that utilizes all timepoints, including the baseline, 3-month, 6-month and 12-month evaluation. Regarding, medical utilization, we will include opioid prescriptions, referral to specialty consultations and diagnostic imaging, epidural steroid injections, and referral to PT. Our outcome measures will be the proportions of patients that are prescribed or undergo each of these during the 12-month follow-up period. Analyses of health care utilization data will use generalized linear mixed models with the distribution determined by the type of data. We will use logit link (binary distribution) for binary outcomes. For outcomes resulting in count data over the time frame such as number of outpatient visits for back pain, hospitalizations or ER visits, we will use a negative binomial distribution with log link to compare the event rates controlling for the period of follow up. We will control for site and estimate the main effect of the intervention for each outcome together with the associated 95% confidence intervals. Testing of secondary endpoints will follow a gatekeeping strategy and a hierarchical Holm testing procedure.

A detailed description of all statistical analyses will be presented in the Statistical Analysis Plan. We will finalize the SAP ahead of the unblinding of data. The SAP will contain information on each primary and secondary endpoint; the main, supplemental, and sensitivity analysis methods of key efficacy endpoints; the multiple testing procedure for controlling the overall type I error rate; and methods for handling missing data.

D.21.4. Subgroups and Heterogeneity of Treatment Effects

We prespecified the following subgroup analyses: age (<65 vs. ≥65), sex, race/ethnicity (patient identified as Black, Hispanic, Asian, other, and white), HCS, and baseline PROMIS PI score (<70 moderate or less vs. ≥70 severe).[105] We will fully pre-specify all the hypothesis-driven subgroups in the feasibility phase. Additional subgroups will be added as identified by stakeholders during or after the feasibility phase, and we will clearly report them as post-hoc hypothesis generating. We will estimate treatment effects and 95%CI within subgroups by using the models described for the primary and secondary analyses. To test for interaction, we will use likelihood ratio tests that compare models with and without interaction terms, fitted to all patients. When applicable, we will use the continuous rather than dichotomized covariate to test for interaction. Pre-specified subgroup analyses may have low statistical power to detect treatment effect heterogeneity; we will conduct formal power calculations during the feasibility phase. We will interpret the results cautiously, considering the expected number of significant subgroup analyses. To account for multiplicity, we will use Bayesian hierarchical approaches involving shrinkage techniques.

D.21.5. Handling of Missing Data

All randomized participants will be included in the primary ITT efficacy analysis. We will minimize missing outcome data by our engagement and retention approaches, and by enhanced online data entry for the eCRF with mandatory fields for key variables. The primary endpoint will be collected through surveys sent by email via REDCap as well as through a mobile app via MyCap. Moreover, resource utilization (secondary outcome) will be ascertained passively through EHR interrogation in combination with patient surveys. Some patients may be missing data on patient-reported outcomes. For participants who drop out, we will systematically document the specific reason and we will perform descriptive analyses to compare participants with and without missing outcome data. For the primary endpoint, GLMM analysis handles missing data easily, under the usual assumption of missingness at random. For other sensitivity analyses, we will generally use multiple imputation approaches, including sequential multiple imputation to account for temporality of covariates across successive assessments, as we used in previous work. We will also conduct sensitivity analyses to assess robustness to the assumption of missingness at random.

D.22. Qualitative Exit Interviews and Data Analysis (Aim 3)

Qualitative testing is a key component of the engagement of patients and clinicians in this study.
For Tai Chi to have maximal potential impact on patient health, we must understand the views of key stakeholders as they experience treatment in the study; namely, our patient, HCS clinician and administrative partners. For example, we have already conducted several focus groups with patients with knee OA, in which several themes emerged: (1) risks of opioids; (2) concerns that primary care providers were insufficiently confident in treating pain; (3) worries about long-term benefits of medications, particularly reduced effectiveness over time.

We will conduct the qualitative testing in both the UG3 and UH3 phases of the project: *In the UG3 phase,* we will interview clinicians and staff in month 5-8 with focus on barriers and facilitators of embedding remote Tai Chi into health care systems. *In the UH3 phase,* qualitative exit interviews will be conducted with all stakeholder groups using semi-structured interview guides designed to probe for knowledge and impact of the remote Tai Chi intervention, barriers to remote Tai Chi use and intervention fidelity, perceived relative value, perceived impact of the implementation strategies used to promote uptake of remote Tai Chi, and perceptions and experiences related to non-pharmacological treatment.

We will conduct 100-110 semi-structured (qualitative) exit patient interviews of stakeholders from participating primary care and specialty care clinics. We will use purposive sampling[106] to capture ethnic and cultural diversity as well as a range of experience in the study—including those receiving each of the various treatments, in primary care and rheumatology clinics, and with positive and negative outcomes of treatment. The 60 patient interviews (12 at each of five sites) are expected to provide thematic saturation — when no new themes emerge from interviews.[107] If not, additional interviews will be conducted, using a theoretical sampling approach.[108] In addition, interviews with 8 clinicians and administrators at each site and HCS (0 total) should also produce thematic saturation. We will conduct these interviews when patients are in the continuation phase, after they and their clinicians have had a chance to form opinions about the long-term benefits and risks. We will also conduct interviews with a subset of 5-10 patients who exit early (i.e., drop out during the acute phase).

The patients' interview protocols will focus on their experience in the study, including the treatments, the care provided, outcome assessments, and interaction with clinicians and researchers. The audio recorded interviews will last approximately 60 minutes. Clinician/administrator interview protocols will address perceived value, attitudinal shifts, facilitators and barriers to implementation in their specific clinical settings. The clinician interviews will last 30 minutes. Interviews will be transcribed verbatim in preparation for analysis.

We will use a team-based analytical approach to conduct direct and conventional content analysis of interview transcripts.[109] *A priori* codes will be based on the Consolidated Framework for Implementation Research (CFIR), and emergent codes will be developed from the data to categorize content from the interviews. Audit trails will document the creation of codes for all codebooks. The codebooks will be modified, as needed, to incorporate new themes gained through the iterative analytical approach of coding, with new codes applied to all relevant transcripts. Using the codebooks developed, two analysts on our team will code the interviews using a qualitative data analysis software package. A manual will be developed for each code in the codebook with inclusion/exclusion criteria and examples of clear and borderline cases. In the coding process, the

analysts will meet and process any differences in the assessment of codes for each case until agreement is achieved between them. The codes determined through this agreement process will then be recorded in a master file, which will become the basis for the final analysis. This process of coding independently and then discussing each case helps to maintain inter-coder reliability.

Thematic analysis of these interviews will characterize patients' lived experience of pain and psychological well-being and its treatment; and provide a range of front-line providers' perspective of the barriers and facilitators to treatment. These analyses will capture participant perspectives on successful implementation, effective strategies were most successful, and attitudes towards scaling up delivery and uptake of remote Tai Chi interventions. This qualitative analysis will be used to (a) provide feedback to HCS leaders on the strategies that were most acceptable and impactful for promoting awareness of remote Tai Chi for musculoskeletal pain; (b) inform the development of future implementation studies to test the comparative effectiveness of different implementation strategies on remote Tai Chi uptake; and (c) disseminate findings through scholarly publications targeting the health services and implementation science communities to enhance the future implementation of remote Tai Chi in large healthcare delivery systems.

D.23. Scientific Rigor and Reproducibility

Quality control procedures will also be finalized in the Planning Phase. We will employ multiple approaches to ensure the rigor, robustness and reproducibility of findings. We use standard assessment tools for knee OA pain and related secondary outcomes, and we also collect contextual data during the study, enabling consideration of potential confounds. Study data entry in RedCap will be subject to verification checks. Missing data or data anomalies will be communicated to the investigators for clarification/resolution. All study staff must complete approved human subjects and HIPAA training programs. The PIs will hold regular meetings with study team and review documentation, the number and type of enrolled patients, reasons for exclusions and data completeness. Should excessive risk to participants be determined or data security or loss of patient confidentiality be identified the study will stop and patients notified in a manner appropriate to the risk.

D.24. Anticipated Challenges

Despite the substantial experience and resources of our teams and institutions for recruiting patients into large clinical trials, enrollment into trails and maintaining adherence can be a pragmatic challenge. In the Planning Phase we will work to develop consensus among members and be responsible for supervising and interacting with the DSMB; we will finalize our sample size and continue to assess the adequacy of our recruitment resources while developing detailed training plans and provider fidelity monitoring procedures for these intervention components; we will develop and adhere to detailed intervention protocols, following the original study protocol and Manual of Operations to ensure fidelity of the interventions; we will regularly monitor recruitment and strengthen strategies to maximize and ascertain adherence relative to our milestones for completion. These stipulations will include observation of 10% of classes by a research staff member who will use a checklist to record fidelity to the protocol. An aspect of this training will be instruction in Good Clinical Practice for human subjects' research, HIPAA privacy protections and procedures for adverse event reporting. Four MPIs will provide supervision and training to the staff during weekly Zoom meetings. Inter-rater reliability sessions will be offered every 6 months or whenever new staff joins the study team. Quality assurance assessments will be planned, scheduled, and routinely executed in a supportive team-centered environment.

D.25. Disseminating the Study Results

Four MPIs – one from each HCS will be involved in plans to disseminate study findings and ensure that findings are communicated in understandable, usable ways. Our dissemination and implementation plans are described in the ensuing D&I Potential section. We have already received helpful advice from stakeholders. The results of the project will be presented at conferences and published independently, as well as disseminated through the study website and social media, and local stakeholder organizations.

D.26. Study Timeline

The timelines align with the milestones to be achieved for both the UG3 and UH3 Phases of the project. Milestones and timeline will be refined and finalized in consultation with NIH-CCC, scientific advisory committee and program staff at the time of award of the UG3.

UG3 Phase: The chart provides a timeline by month for the 1-year UG3 Planning Phase

Task/month	1	2	3	4	5	6	7	8	9	10	11	12
Complete subcontract agreement between institutions	√	√	√	√	√	√						
Finalize roles and responsibilities of research team members		√										
Finalize assembling working groups and panels		√	√	√								
Finalize stakeholder engagement plan		√	√	√								
Finalize outcomes measures and data elements for the UG3 clinical trial		√										
Refine remotely delivered Tai Chi handout and educational materials				√	√							
Finalize sites and clinics for the UH3 clinical trial					√	√						
Completion of qualitative data collection on barriers and facilitators of embedding Tai Chi into health systems				√	√							
Completion of facilitation activities for health care systems						√	√	√				
IRB submission									√			
Finalize and test data collection methods									√	√	√	√
Finalize data management procedures							√	√	√			
Finalize clinical trial protocol										√		
Register UH3 trial with clinicaltrials.gov										√		
Finalize manual pf procedure (MOP)											√	
Final statistical analysis plan and sample size												
Approval and refinement of protocol and MOP by the steering committee											√	√
Finalize transition request for UH3 phase												√

UH3 Phase: The chart provides a timeline by quarter for the 4-year UH3 Clinical Trial Phase.

Year	1				2				3				4			
Quarter	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Finalize IRB Approval	√															
Complete Study Personnel Training	√	√														
Activate Sites and clinics and initiate enrollment			√													
Clinical Trial recruitment across sites (projected accrual target)			√	√	√	√	√	√	√	√						
Complete Clinical Trial follow-up assessments					√	√	√	√	√	√	√	√	√	√		
Written feedbacks from participants at study exit						√	√	√	√	√	√	√	√	√		
Semi-structured interviews with clinicians, staff, and leaders												√	√	√		
Conduct data analysis															√	√
Disseminate study findings (abstracts and manuscripts)													√	√	√	√
Report results in Clinicaltrials.gov																√

DATA MANAGEMENT AND SHARING PLAN

If any of the proposed research in the application involves the generation of scientific data, this application is subject to the NIH Policy for Data Management and Sharing and requires submission of a Data Management and Sharing Plan. If the proposed research in the application will generate large-scale genomic data, the Genomic Data Sharing Policy also applies and should be addressed in this Plan. Refer to the detailed instructions in the application guide for developing this plan as well as to additional guidance on sharing.nih.gov. The Plan is recommended not to exceed two pages. Text in italics should be deleted. There is no "form page" for the Data Management and Sharing Plan. The DMS Plan may be provided in the *format* shown below. Public reporting burden for this collection of information is estimated to average 2 hours per response, including the time for reviewing instructions, searching existing data sources, gathering, and maintaining the data needed, and completing and reviewing the collection of information. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to: NIH, Project Clearance Branch, 6705 Rockledge Drive, MSC 7974, Bethesda, MD 20892-7974, ATTN: PRA (0925-0001 and 0925-0002). Do not return the completed form to this address.

Element 1: Data Type

A. Types and amount of scientific data expected to be generated in the project:
The proposed research will include data from approximately **600** participants recruited from 20-25 clinics across four Health Care Systems (Tufts Medical Center, Boston Medical Center, University of California Los Angeles Health, and Cleveland Clinic Ohio and Cleveland Clinic Florida) in four geographic regions (Eastern Massachusetts, Southern California, Northeast Ohio, Southern Florida). The final dataset will include self-reported demographic information, knee-related pain and function, and behavioral data from interviews with participants.

Data will be collected using REDCap-based electronic case report forms (eCRFs). Some data will be collected through patient surveys and other data will be extracted from the Electronic Medical Records. The eCRFs will utilize REDCap's built-in data validation and data range functions to prevent entry of impossible values (e.g. negative body weight and implausible weight changes). Raw data will be exported as csv data sets and used for statistical analysis in the open statistical software R.

B. Scientific data that will be preserved and shared, and the rationale for doing so:
All study population baseline characteristics, primary and secondary outcome measures will be preserved and shared in order to make the data publicly available to the widest possible audience. With the exception of protected health information, none of the data associated with this proposal will be subject to any restrictions to data sharing.

C. Metadata, other relevant data, and associated documentation:
To facilitate interpretation of the data, data dictionaries describing each variable and all information necessary to understand the data will be developed in conjunction with the electronic data capture forms and will be maintained on the Tufts Medical Center ICRHPS Center for Clinical Trials departmental network drive. This information will be shared on the same portals that will distribute the datasets.

Element 2: Related Tools, Software and/or Code

All processed data sets entered into RedCap will be exported as csv files together with R scripts and or SAS for formatting the variables. Datasets in csv format and R scripts/SAS will not require the use of specialized tools to be accessed or manipulated.

Element 3: Standards

Monthly data quality reviews will be conducted to minimize missing data. The Data Coordinating Center (DCC) will provide training to research staff on best practices for data capture. The DCC will design the eCRF and implement data quality controls. Data will be collected using REDCap-based electronic case report forms (eCRFs) by utilizing REDCap's built-in data validation (including data completion) and data range functions to prevent entry of impossible values.

Information needed to make use of this data [e.g. the meaning of variable names, codes, information about missing data, other metadata etc] will be recorded in data dictionaries/codebooks that will be shared alongside final datasets.

Information about study protocols, including the details of our analysis pipeline will be accessible to all members of the research team and will be shared alongside our data.

Element 4: Data Preservation, Access, and Associated Timelines

A. Repository where scientific data and metadata will be archived:
Summary statistics for study population demographics, primary and secondary endpoints will be submitted to the clinicaltrials.gov record for this study.

All de-identified data as well as supporting documentation will be submitted to the Open Science Framework repository, in order to make the data publicly available to the widest possible audience. With the exception of protected health information, none of the data associated with this proposal will be subject to any restrictions to data sharing.

B. How scientific data will be findable and identifiable:
The data will be deposited with the OSF that provides services to make research data Findable, Accessible, Interoperable, and Reusable (FAIR). The OSF provides:
1. Version control, persistent URLs, and DOI registration
2. Scientific metadata creation and curation
3. Public access to data through a searchable catalog and public APIs
4. Data repository for long-term archiving

C. When and how long the scientific data will be made available:
Data will be made available at the time of associated publication or end of the performance period, whichever comes first.

Element 5: Access, Distribution, or Reuse Considerations

A. Factors affecting subsequent access, distribution, or reuse of scientific data:
With the exception of protected health information, none of the data associated with this proposal will be subject to any restrictions to data sharing.

***B.* Whether access to scientific data will be controlled:**
N/A

C. Protections for privacy, rights, and confidentiality of human research participants:
All data will be de-identified by removing the 18 protected health information: Name; Address (all geographic subdivisions smaller than state, including street address, city county, and zip code);All elements (except years) of dates related to an individual (including birthdate, admission date, discharge date, date of death, and exact age if over 75); Telephone and fax numbers; Email address; Social Security Number; Medical record number; Health plan beneficiary number; Account number; Certificate or license number; Vehicle identifiers and serial numbers, including license plate numbers; Device identifiers and serial numbers; Web URL; Internet Protocol (IP) Address; Finger or voice print; Photographic image; Any other characteristic that could uniquely identify the individual (for example detailed job description or hobbies).
Ages >75 will be indicated as > 75.

Element 6: Oversight of Data Management and Sharing

At Tufts Medical Center, compliance with the DMSP will be overseen by relevant local research departments/institutes and Research Administration. Compliance oversight will be performed annually at the time of submission of the RPPR, at a minimum.

Ethics and Regulatory Core Group Meeting 7/24: TAICHIKNEE Study

Facilitators: Drs. Pearl O'Rourke and Stephanie Morain

Chenchen Wang, MD, MSc – Tufts Medical Center
Eric Roseen, DC, PhD – Boston Medical Center
Robert Saper, MD, MPH – Cleveland Clinic
Helen Lavretsky, MD, MS – UCLA Health

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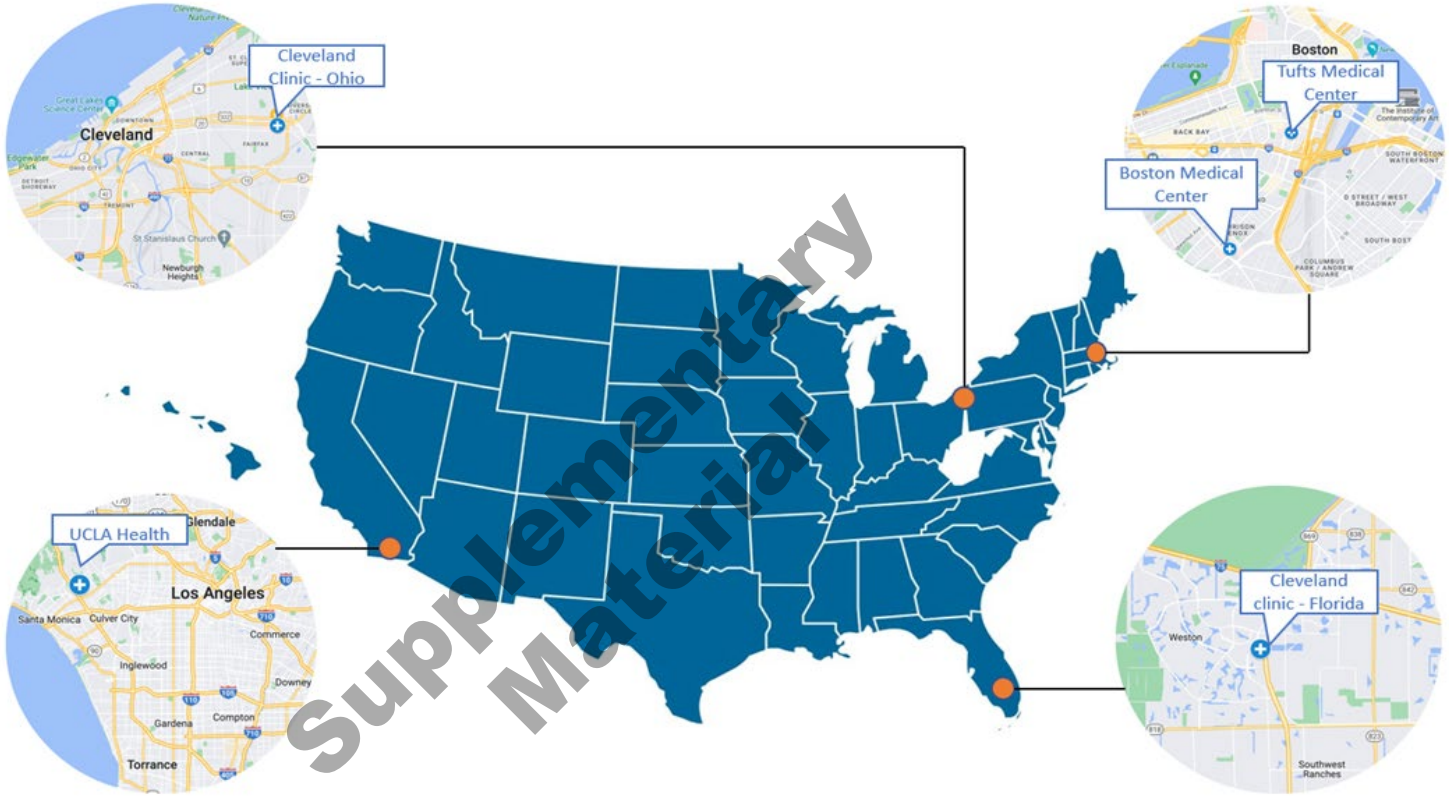
Agenda

- Brief review of Demonstration Project by the PI
- Status of IRB Approval
- Risk (Does the project meet regulatory criteria for being considered minimal risk)
- Consent (Planned processes for relevant subjects)
- Privacy (Including HIPAA)
- Monitoring and oversight
- Issues beyond this project (Regulatory and ethics concerns raised by the project, if any)
- Other

Large and diverse population in four geographic regions



Major Goal: To study "real world" effectiveness and implementation of Tai Chi versus routine care for Knee Osteoarthritis Pain across four US Health Care Systems.

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UG3 Planning Phase Aims

- **AIM 1:** Establish a collaborative and effective Project Governance and Organizational Structure among the four Health Care Systems, the NIH Collaboratory Coordinating Center and Collaborators through assembly of Working Groups, Study Teams and Panels including Stakeholder Committees and Data and Safety Monitoring Board.

- **AIM 2:** Identify multilevel (patient, provider, and health system leadership) barriers and facilitators of embedding a web-based Tai Chi intervention.

- **AIM 3:** Finalize the study design, implementation strategies, study materials, data capture systems, informed consent materials, ethical oversight structure, and quality control procedures.

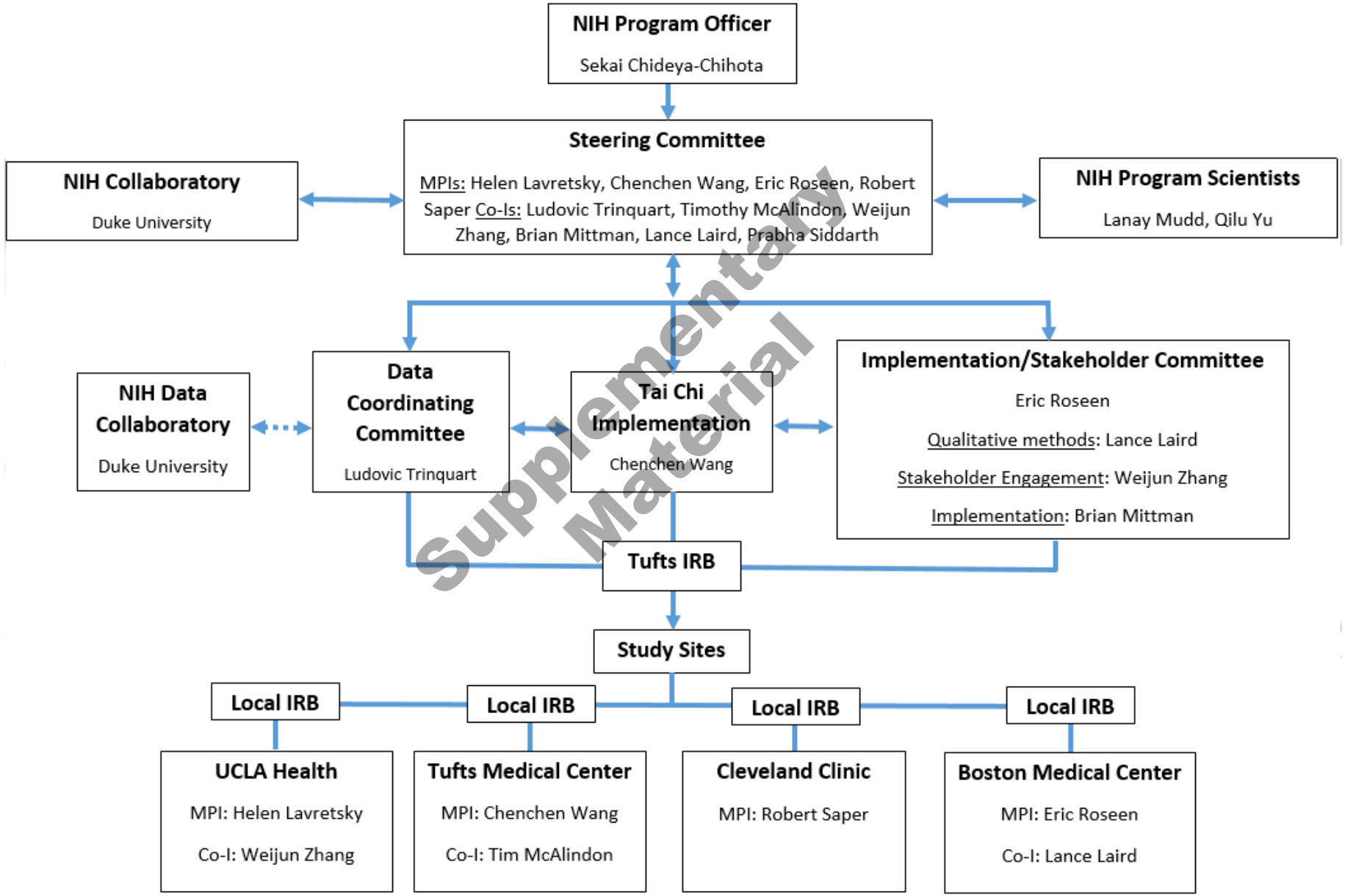
UH3 Trial Conduct Phase Aims

- **AIM 1.** Determine if the addition of remote Tai Chi to routine care improves the extent to which pain interferes with physical, mental, and social activities (PROMIS-Pain Interference at 3 months-primary outcome), knee pain and function and analgesic use (secondary outcomes) across sites.
  - ***Hypothesis 1.*** *Compared to routine care, patients receiving remote Tai Chi will exhibit greater improvement in pain interference, function, and analgesic use at 3, 6 and 12 months.*

- **AIM 2:** Determine if addition of remote Tai Chi to routine care decreases healthcare utilization identified through electronic health record and digital patient surveys.
  - ***Hypothesis 2:*** *Patients receiving remote Tai Chi compared to routine care will have fewer invasive procedures (injections, surgeries) over the one-year study period.*

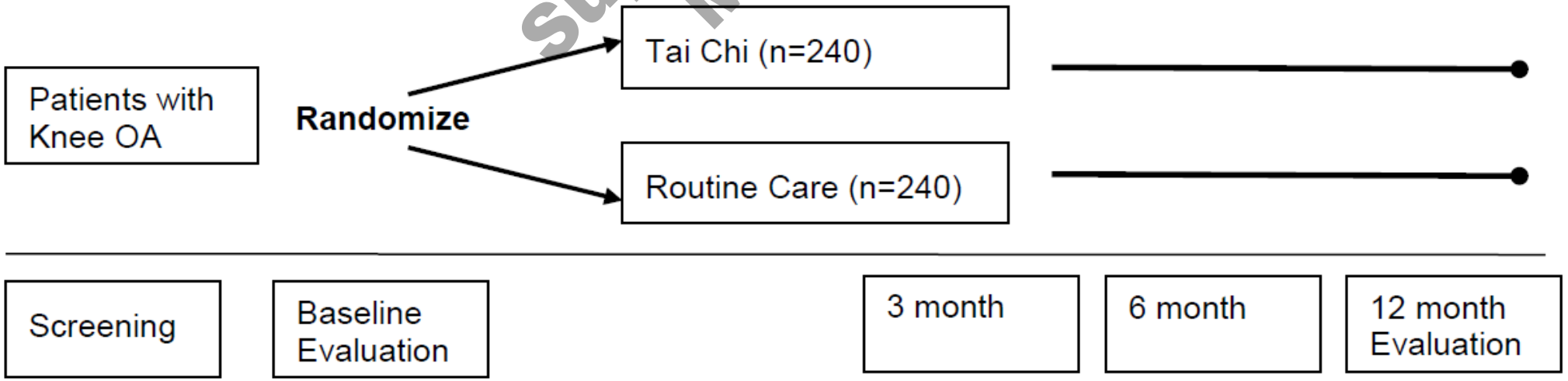
- **AIM 3:** Examine facilitators and barriers of implementing remote Tai Chi mind body therapy into the four large Health Care Systems using semi-structured exit interviews of patients, clinicians, and staff.

TAICHIKNEE Trial Organization Chart



TAICHIKNEE Trial Overview

Population	Adults over 45 years with Symptomatic knee OA (ACR Criteria)
Setting	Primary care clinics in four healthcare systems
Design	An embedded, pragmatic, randomized trial
Intervention	Remote tai chi (3-month twice weekly)
Control	Routine Care
Clinical outcomes	Pain interference (primary) Knee Pain and Function, Pain medication, Quality of life (secondary)
***Anticipated* Implementation Strategies**	Internal facilitation, educational meeting, development and distribution of educational materials
Implementation outcomes	Feasibility of implementation strategies



Milestones

1. Finalize organizational chart and regular video call meeting cadence for study team and subcommittees **(Tufts)** ***Done June 19th***
2. Finalize representatives from Study Team to join and engage with NIH Collaboratory Work Groups **(Cleveland Clinic)** ***Done June 19th***
3. Complete an overarching stakeholder engagement plan that defines specific advisory groups, their purpose, and their meeting cadence **(BMC)** ***Done June 30th***
4. Convene a Team to oversee the design and implementation of the Tai Chi intervention **(Tufts)** Convene a Team to oversee the design and implementation of the Tai Chi intervention **(Tufts)** ***Done June 30th***

Milestones (cont)

5. Convene advisory groups **(All)** ***July 31st***
6. Select and finalize with NCCIH approval Protocol Review Committee & DSMB **(UCLA)** ***August 31st***
7. Complete FWAs for all sites and reliance agreements for single IRB **(Tufts)** ***August 31st***
8. IRB approval for qualitative study using semi-structured interviews and study documents with stakeholders to understand barriers and facilitators of embedding Tai Chi exercise into routine care and health system **(BMC)** ***August 31st***

Status of IRB Approval

NIH PRAGMATIC TRIALS COLLABORATORY

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Exemption Form Approved April 27th 2023

Tel. 617.636.7512
IRBoffice@tuftsmedicalcenter.org
https://viceprovost.tufts.edu/HSIRB

Tufts | Health Sciences IRB

Tufts Health Sciences Institutional Review Board

MaryAnn Volpe, MD
Chair

EXEMPT DETERMINATION

April 27, 2023

Chenchen Wang

Tufts Medical Center/Tufts University
cwang2@tuftsmedicalcenter.org

Dear Chenchen Wang:

On 4/27/2023, the IRB reviewed the following submission:

Type of Review:	Initial Study
Title:	UG3 Preparation for Remote Tai Chi for Knee Osteoarthritis - an Embedded Pragmatic Trial
Investigator:	Chenchen Wang
IRB ID:	STUDY00003780
Funding:	Department
Grant Title:	None
Grant ID:	None
Documents Reviewed:	• consent information sheet, Category: Consent Form;• email Script.pdf, Category: Recruitment Materials;• Form 7, Category: IRB Protocol;• Tai Chi interview questions.docx, Category: Study Instruments/Participant-Facing Material;

Tufts Medical Center/Tufts University Health Sciences IRB determined that this project is exempt in accordance with 45 CFR 46.104(d).

- The Health Insurance Portability and Accountability Act is not applicable; this study does not involve the use or collection of protected health information.

Reminders:

- An agreement or contract must be executed with the Tufts MC Grants and Contracts office or the Tufts University use Pre-Award Research Administration and all outside participating institutions to allow study data or material to be sent there.
- Use the current consent document with the stamped IRB validation dates to enroll subjects.
- If the HIPAA Privacy Rule applies to your research, the HIPAA Security Rule also applies. If you create, receive, store, use or disclose electronic PHI you must meet institutional Security Rule standards. Contact your HIPAA Privacy Officer for Research for more information.
- In conducting this protocol, you are required to follow the requirements listed in the Investigator Manual (HRP-103).
- The exempt status of this research will not expire. Please notify the IRB office in writing when this project is terminated.
- Any change to this project must be submitted to the IRB for review prior to implementation.

800 Washington Street, Box 817
Boston, MA 02111
Tel. 617.636.7512
IRBoffice@tuftsmedicalcenter.org
https://viceprovost.tufts.edu/HSIRB

Tufts | Health Sciences IRB

Tufts Health Sciences Institutional Review Board

MaryAnn Volpe, MD
Chair

- Any change to the stamped consent document must be submitted to the IRB for review and approval prior to use.

Sincerely,
Caitlin Farley

IRB Chair/Vice Chair/**Designee**

Association for the Accreditation of Human Research Protection Programs, Inc. — Full Accreditation

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

Form 7 Approved

Tufts
Health Sciences IRB

Form 7: Request for Exemption Protocol		
NUMBER	DATE	PAGE
HRP-210	3/27/2023	1 of 9

Upload this form with your eIRB submission. This form serves as the Protocol for applicable studies.

Complete this form in its entirety and submit to the IRB. This form must be typed.
Only the IRB may make the determination that a study is exempt; an investigator must not make this determination.
This form will serve as your protocol, so a separate protocol document is not required.

This form must be completed by or reviewed by the Principal Investigator prior to eIRB submission.

Principal Investigator (PI):	Study Title:
Chenchen Wang, MD, MSc	UG3 Preparation for Remote Tai Chi for Knee Osteoarthritis - an Embedded Pragmatic Trial

Version date: 4-27-2023

Some research qualifies for exemption from the code of federal regulations (CFR) that govern human subjects research (45 CFR 46). Research must be minimal risk and meet certain defined categories in order to qualify for exempt status per 45 CFR 46.104(d).

Research involving the following categories of subjects does not qualify for exemption:

☐ Prisoners *specifically targeted* for this research (If prisoners are not specifically targeted, incidental inclusion of prisoners can be exempt)	☐ Individuals with psychiatric, cognitive, or developmental disorders
	☐ Individuals with substance use disorder or documented misuse of substances

STOP!
*If your research involves any of the above populations and is a **chart review**, you may continue using this form.*
Otherwise, please utilize the full Protocol Template.

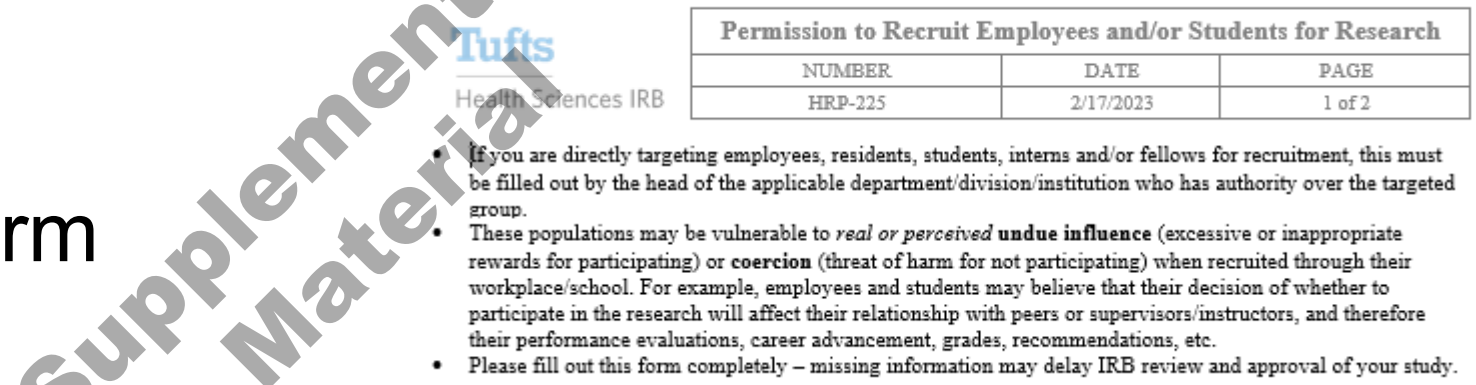
A. Exemption Categories
Check all applicable boxes below. If research falls into one or more of the following categories, it may be granted exemption.

Category		
☐	1	Research conducted in established or commonly accepted educational settings, involving normal educational practices, and not likely to adversely affect classroom instruction time or students' performance, such as:
		i) Research on regular and special education instructional strategies, OR
		ii) Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
☒	2	Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:
		i) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects; OR
		ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement or reputation; OR
		iii) Information obtained can be identifiable and sensitive but the IRB has done a limited IRB review in keeping with 46.111(a)(7), which relates to there being adequate provisions for protecting privacy and maintaining confidentiality.
		Note: Research involving survey or interview procedures or observation of public behavior does not qualify for exemption category 2 when participants are minors, except for research involving observations of public behavior when the investigator(s) do not participate in the activities being observed.
☐	3(i)	Research involving benign behavioral interventions^ in conjunction with the collection of data from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and data collection and at least one of the following criteria is met, if:
		A) The information obtained is recorded in such a manner that human subjects cannot be identified directly or through identifiers linked to the subjects;
		B) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; OR

THE PRINCIPAL INVESTIGATOR IS TO RETAIN A COPY OF THIS COMPLETED FORM IN THE STUDY FILES.

Other UG3 Approved Documents

- Consent Information Sheet
- Email Script
- Interview Questions
- Conflict of Interest Form
- Letter of Support



Tufts
Health Sciences IRB

Permission to Recruit Employees and/or Students for Research		
NUMBER	DATE	PAGE
HRP-225	2/17/2023	1 of 2

- If you are directly targeting employees, residents, students, interns and/or fellows for recruitment, this must be filled out by the head of the applicable department/division/institution who has authority over the targeted group.
- These populations may be vulnerable to *real or perceived* **undue influence** (excessive or inappropriate rewards for participating) or **coercion** (threat of harm for not participating) when recruited through their workplace/school. For example, employees and students may believe that their decision of whether to participate in the research will affect their relationship with peers or supervisors/instructors, and therefore their performance evaluations, career advancement, grades, recommendations, etc.
- Please fill out this form completely – missing information may delay IRB review and approval of your study.

Single IRB UH3 Documents

- Protocol and ICF in progress

Questions on IRB Documents

- *"IRB approval for qualitative study using semi-structured interviews and study documents with stakeholders to understand barriers and facilitators of embedding Tai Chi exercise into routine care and health system* ***(BMC)*** ***August 31st"***
  - Tufts has approval to conduct interviews, and the Tufts IRB specialist noted that any modifications could be done via updates to **Form 7**. For Tufts a modification to include patient interviews is needed.
  - The other sites have a different proposed protocol to be approved by their local IRB for interviewing stakeholders.
  - How can we adapt modifications to the Tufts protocol while remaining consistent with the protocol of the other sites?

Barriers Scorecard

Barrier	Level of Difficulty*				
	1	2	3	4	5
Enrollment and engagement of patients/subjects			x		
Engagement of clinicians and health systems			x		
Data collection and merging datasets			x		
Regulatory issues (IRBs and consent)		x			
Stability of control intervention				x	
Implementing/delivering intervention across healthcare organizations				x	

*Your best guess!
1 = little difficulty
5 = extreme difficulty

NIH PRAGMATIC TRIALS COLLABORATORY
Rethinking Clinical Trials®

Participation in working groups

Work Group	Members
Regulatory/Ethics	Chenchen Wang, Helen Lavretsky
Electronic Health Records	Robert Saper, Ludovic Trinquart
Biostatistics and Study Design	Ludovic Trinquart, Prahaba Siddarth
Health Care Systems Interactions	Weijun Zhang, Timothy McAlindon
Implementation Science	Eric J. Roseen, Brian Mittman
Health Equity	Robert Saper, Lance D. Laird
Patient-Centered Outcomes	Helen Lavretsky, Chenchen Wang
Publications Committee	Helen Lavretsky, Chenchen Wang

Embed Remote Tai Chi into Four Health Care Systems

- Convene a team to oversee the implementation of Tai Chi
- Complete implementation plan to understand barriers and facilitators of embedded remote Tai Chi in four health care systems informed by stakeholders and qualitative data
- Develop and finalize intervention training materials.
- Finalize a list of Tai Chi instructors at each site and conduct Tai Chi Instructor Training: two four-hour sessions for two weeks.
- Conduct a total of six interactive grand rounds/lunch seminars distributed across the 4 health care systems about TAICHIKNEE study.

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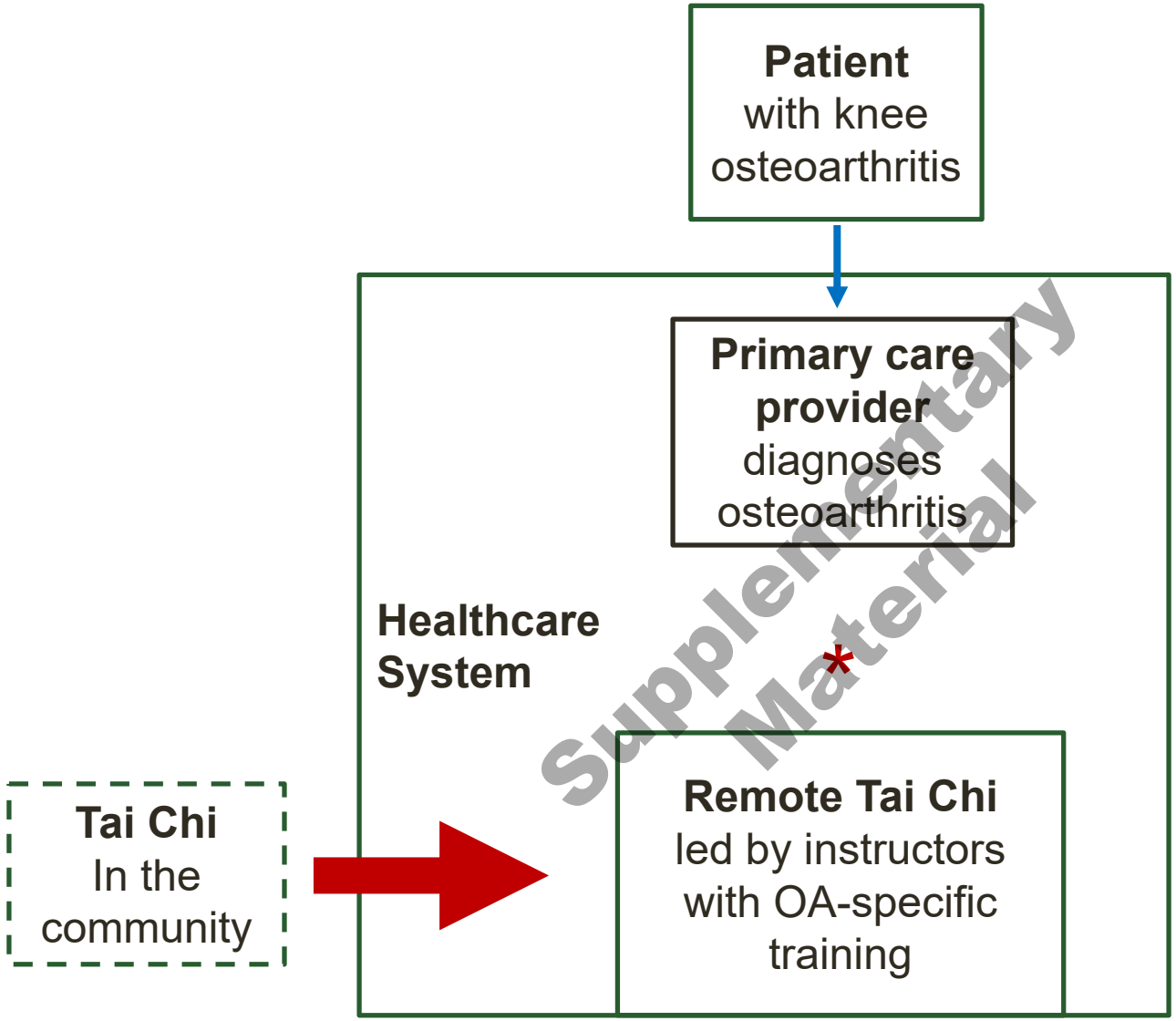
Stakeholder engagement

- **UG3 AIM 2:**
  - Identify multilevel (patient, provider, and health system leadership) barriers and facilitators of embedding a web-based Tai Chi intervention.

- **UH3 AIM 3:**
  - Examine facilitators and barriers of implementing remote Tai Chi mind body therapy into the four large Health Care Systems using semi-structured exit interviews of patients, clinicians, and staff.



*Any mechanism/strategy to recruit patients into intervention

UG3 key-informant interviews and focus groups

Category	Group
Patient	Patients with Knee Osteoarthritis
Tai Chi	Instructors
Primary care Provider	General Internal Medicine Family Medicine
Health system	Health system leaders IT/Population health staff

Biostatistics and Study Design

- Design allows for correlation in experimental group
  - Individuals receive intervention with other participants through instructors
  - Individually Randomized Group-Treatment (IRGT) trial
- ANCOVA comparing mean PROMIS PI score between groups
- 240 subjects per group gives 90% power to detect effect size of 0.333
  - Within-participant correlation between baseline and 3-month T score = 0.5
  - ICC in experimental group 0.03
  - Average cluster size of 10 individuals for tai chi classes
  - 30% drop out (missing outcome data at 3 months)
- With T score SD of 6, effect size of 0.333 corresponds to Minimal Important Clinical Difference, a between-group difference of 2 T score points

Data Sharing UG3

- Current data sharing plan: All de-identified individual-level data & supporting documentation will be made publicly available to the widest possible audience. Exception for PHI, none of the data associated with this proposal will be subject to any restrictions to data sharing
- We do not foresee any obstacles
- Waiver of informed consent NOT applicable