PROTOCOL TITLE: Improving quality of life for adults living with chronic pain
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1) Abstract of the study

Persons living with HIV (PLWH) are at increased risk for chronic pain conditions, with prevalence rates estimated to be between 55-67%. While acute pain is a life-sustaining biological response to tissue damage or injury, chronic pain is a separate condition that often causes significant physical and psychological suffering. Causes of chronic pain among PLWH include disease progression, the impact of the virus on immune and nervous system function, and medication side-effects. PLWH, like many other chronic pain patients, may be prescribed opioid medications, which have not been found to be effective in managing non-cancer related chronic pain. Additionally, the significant risk of dependence and overdose far outweigh the potential benefit of opioid medications for chronic pain. Governing bodies in medicine have called for non-pharmacological interventions to be considered front-line treatment recommendations for chronic pain management. Mind-body interventions, such as mindfulness, yoga, and Tai Chi, have been shown to be effective at reducing pain symptoms and improving psychological outcomes for individuals with chronic pain. Unfortunately, few studies have examined the use of mind-body interventions for chronic pain management for PWLH, with even fewer using formative research to modify interventions to meet the unique needs of this vulnerable population. The research plan proposed in this application will address these gaps in the literature. This study will examine the feasibility and acceptability of a mind-body intervention, Qigong/Tai Chi Easy, for chronic pain management among PLWH. We will recruit 40 individuals from the Comprehensive HIV Program at Temple Health. Following informed consent, participants will be randomized to mind-body arm or health education control arm. Participants in both arms will complete baseline assessment followed by a 10-week intervention. The mind-body intervention group will meet weekly for 60-minute sessions and be provided with a video for at-home practice. The health education group will also meet weekly for 60 minutes and be assigned weekly homework related to the topics discussed in session. At the conclusion of the 10 weeks, participants will complete at post-intervention assessment. A 3-month follow up assessment will also be completed. In addition to feasibility (i.e., recruitment rates, retention) and acceptability (i.e., satisfaction ratings), we will assess pain symptoms (general and specific), perceived stress, depression, quality of life, and HIV medication adherence. We anticipate that

the study will demonstrate feasibility and acceptability as evidenced by adequate enrollment, retention, and satisfaction. Findings from the proposed study will be used to inform a future research grant with power to detect efficacy of the mind-body intervention for chronic pain management.

2) Protocol Title

Improving quality of life for adults living with chronic pain

3) Sponsor / Funding

This study is funded by the National Center for Complementary and Integrative Health (NCCIH) of the National Institutes of Health (NIH).

4) Investigator

Eugene M. Dunne, PhD

Assistant Professor, Oral Health Sciences, Kornberg School of Public Health, Temple University

5) Objectives

The primary objective is to examine the feasibility and acceptability of Qigong/Tai Chi Easy for chronic pain management for people living with HIV. A small randomized pilot study (*N* = 40) will assess feasibility and acceptability of a 10-week Tai Chi intervention plus a video recording for at-home practice and a health education control group. This study will examine recruitment and retention, number of sessions attended, self-reported at-home practice of Tai Chi, and patient acceptability of the intervention and control conditions.

6) Background

Chronic pain is a significant public health concern in the United States, and it is the most common reason patients seek medical care in the United States, with more than 100 million pain cases per year[1]. Patients experiencing chronic pain often present to emergency departments[2], which significantly increases costs to the individual and the healthcare system. Estimates of the healthcare costs of chronic pain range from $560 to $635 billion per year[3]. Chronic pain is a condition that lasts beyond an expected healing time, typically defined as 3-6 months[4,5]. Acute pain is a life-sustaining biological response to tissue damage or injury and can often be treated effectively with medications and physical therapies. Conversely, chronic pain is a condition that is often accompanied by physical and psychological suffering, helplessness, and maladaptive coping responses[3,6]. Chronic pain takes an emotional toll on the patient as they try to manage the long-term interference in

functioning. Patients with chronic pain often experience depressive symptoms and report decreased quality of life[7,8]. Similarly, stress processes and coping can alter the experience of pain, such that negative emotions may increase the severity of pain, while positive affect can reduce the experience of pain[9]. Approaches to address chronic pain management require both physical and mental components.

Chronic pain commonly co-occurs for many of the 1.2 million persons living with HIV (PLWH) in the United States[10-13] with a recent meta-analysis reporting rates ranging from 55% to 67%[14]; thus, between 660,000 and 804,000 PLWH are suffering with chronic pain conditions. Central or peripheral neuropathies account for nearly half of chronic pain conditions among PLWH; these neuropathies result from multiple mechanisms including disease progression, the impact of the virus on the nervous system, medication side effects, suppressed immune function, and AIDS-related opportunistic infections[14]. Neuropathic pain related to damage to the nervous system caused directly by virus progression or medication side effects in PLWH is challenging to manage with poor response to analgesic medications[12,16]. Research also suggests that pain prevalence and severity increases with HIV disease progression[17], such that patients with secondary infections related to HIV were twice as likely to report chronic pain compared to those who were effectively managing disease progression with antiretroviral medications. Additionally, PLWH are increasingly an “aging population” as highly effective antiretroviral medications allow for life expectancies similar to the general population. PLWH now face increasing rates of chronic pain conditions associated with aging, with musculoskeletal pain (e.g., chronic low back pain) being the second most common form of pain for PLWH.

PLWH also have high rates of comorbid mental health and substance use conditions[15], which are the strongest predictors of acute pain becoming chronic. Importantly, chronic pain is associated with missed clinic appointments and nonadherence to HIV antiretroviral medication (ART) among PLWH[12]. Managing chronic pain for PLWH can improve medication adherence, reduce suffering, improve quality of life, and lower healthcare costs. Chronic nonadherence to ART medications results in poorer health as indicated by biological outcomes (e.g., CD4 count and viral load) and increases the risk of transmission to uninfected individuals[18].

HIV patients with chronic pain (like many pain patients) may be prescribed opioid medications to manage their severe pain symptoms. Clinical guidelines for chronic cancer-related pain management suggest the use of opioid analgesic therapy for patients with persistent moderate to severe pain intensity[19,20]. In the late 1990s, there was a realization that pain was being undertreated for PLWH and medical organizations called on health professionals to improve the management of pain through various initiatives, including labeling pain as the “fifth vital sign”[21-23]. Effective pain management became an ethical issue for physicians consistent with the principle of nonmaleficence, or “do no harm” to patients[24]. These events resulted in a dramatic increase in opioid prescriptions for chronic non-cancer pain treatment[25]. While opioid medications can be effective at treating acute pain, there is little evidence supporting their long-term use for treating non-cancer chronic pain[26]. The opioid epidemic is of great concern, and is partly attributable to the mismanagement of chronic pain conditions. Between 1999 and 2015, nearly 200,000 overdose deaths have been attributable to prescription opioid medications[27,28]. As a result, the CDC has called on non-pharmacological interventions to be utilized as first-line treatments for chronic pain. Furthermore, the

opioid epidemic is becoming a driving force of HIV transmission, as individuals who misuse prescription drugs transition to heroin use and injection drug practices. The New England region has seen recent increases in HIV infections attributed to the opioid epidemic, following decades of progress in HIV medicine. Poor management of chronic pain and misuse of prescription opioids threaten the progress made by the HIV medical community. Access to evidenced-based, non-pharmacological interventions may improve pain control and reduce demand for prescription opioids.

Comprehensive chronic pain management approaches often include psychological and mind-body interventions, such as cognitive behavioral therapies (CBT), relaxation-based techniques, yoga, or Tai Chi, all of which have moderate efficacy based on randomized controlled trials and meta-analyses[29-33]. Tai Chi has been used to treat both neuropathic and musculoskeletal pain, the two most common pain conditions among PLWH. Physical mechanisms of pain improvements resulting from Tai Chi include improved balance and reduction in neuropathy symptoms[34, 35]. Regarding musculoskeletal pain conditions, Tai Chi has been shown effective at improving pain symptoms related to low back pain and osteoarthritis[36]. Although neuropathic and musculoskeletal pain conditions are different in their etiology, the potential mechanisms for non-pharmacological pain management approaches are hypothesized to be similar; for example, increased physical movement can reverse the muscle atrophy often associated with chronic pain conditions related to maladaptive fear of movement (i.e., kinesophobia). Further, Tai Chi activates the relaxation response, which is associated with decreased stress and improved mood[37]. These combined physical and mental benefits are hypothesized to be the mechanisms for pain amelioration. Behavioral and mind-body interventions that involve relaxation yield a “top-down” control of pain, such that observed changes in cerebral gray matter are associated with enhanced cognitive reappraisal of pain[38]. Tai Chi, as a mind-body intervention for chronic pain, is hypothesized to improve management and coping related to neuropathic and musculoskeletal pain. While there are various long forms of Tai Chi, a modified shorter form of Qigong/Tai Chi Easy has been found to be efficacious in clinical trials for improving quality of life and fatigue[39-42]. Qigong/Tai Chi Easy, a low-intensity form of meditative movement, combines gentle movement, relaxing breath, and cultivates a meditative state[40]. The Qigong/Tai Chi Easy protocol also includes instruction for shaking of the hands and feet, which may bring awareness, circulation, and blood flow to areas affected by neuropathy for PLWH.

Complementary and mind-body interventions have been of interest to PLWH; for example, a recent survey found that complementary and integrative approaches are commonly sought and used to manage symptoms associated with HIV[43]. However, there is a lack of research examining the efficacy of mind-body approaches for PLWH. Recently released recommendations for treatment of chronic pain in PLWH indicate that behavioral interventions have moderate evidence and should be considered as first line interventions[44]. However, the authors of these recommendations acknowledge that the vast majority of evidence was derived from studies with non-HIV samples. To date, only two studies have examined CBT for chronic pain in HIV samples[45,46], yet neither study used formative research to optimize the intervention for PLWH. Interventions found to be efficacious in one chronic pain population may not translate to new populations, particularly clinical populations known to experience health disparities related to cultural or sociodemographic factors[47]. Failure to consider such differences may undermine

reproducibility and acceptability of the intervention. HIV and chronic pain are stigmatized health conditions, increasing barriers to safe and effective pain management[48]. Using formative research to modify a pain management protocol may improve acceptability by addressing HIV-specific pain experiences and disparities related to the intersecting stigmas of HIV and chronic pain.

Theoretical Framework. Mind-body interventions, including Tai Chi, are effective at improving chronic pain management[49-52], and may be particularly helpful for PLWH. Tai Chi is a practice that integrates gentle physical movements, relaxing breathing, and mindfulness meditation[53]. Randomized trials and meta-analyses examining the use of Tai Chi indicate benefits for patients with chronic conditions, including osteoarthritis, rheumatoid arthritis, low back pain, and fibromyalgia[33,50,53-56]. Tai Chi practice improves psychological outcomes and stress responses[37,58], and may enhance immune function[59,60]. Mechanisms of action for these health benefits can be explained by the relaxation response and psychoneuroimmunology (PNI) theory[61,62]. This theory postulates that stress management interventions, such as Tai Chi, may result in positive changes to stress processes, psychological changes, and behavior change. With respect to chronic pain, Tai Chi may alleviate stress associated with chronic health management and reduce kinesophobia, the fear that inhibits physical movement due to fear of exacerbating pain or re-injury[63,64]. The present study will focus on the psychological and behavioral aspects of the PNI model (highlighted by red outline in Figure 1). We expect that subsequent research will be able to explore down-stream aspects of the model if the proposed research is promising. For instance, this seminal project will allow subsequent studies to explore improvements in cortisol and catecholamine levels associated with Tai Chi. Literature on PNI suggests stress management interventions are associated with normalization of the sympathetic nervous system (SNS) and hypothalamic pituitary adrenal axis[65]. In addition to enhancing pain management, resulting improvements in physical and immune function may slow disease progression.

This program of chronic pain research is consistent with the strategic priorities of NCCIH. Further, NIH's Office of AIDS Research (OAR) has prioritized research that examines highly comorbid conditions within the context of HIV. The current application aligns with cross-cutting priorities for OAR by addressing chronic pain, which can improve medication adherence, a critical component of the Treatment as Prevention (TasP) mission. The goal of TasP is to reduce the incidence of HIV transmission by optimizing the HIV care continuum and medication adherence, such that PLWH achieve undetectable viral loads (Undetectable = Untransmittable[66]). Additionally, the Federal Pain Research Strategy (FPRS)[67] calls for the development of non-pharmacological interventions for chronic pain management. The FPRS highlights the need for tailored interventions for high-risk groups. PLWH are the ideal population to meet these priorities, as individuals with HIV are historically from low-SES and minority communities and experience significant stigmatization and health disparities[68]. While a single study has examined the use of Tai Chi to improve stress management for PLWH[69], no study has examined the use of Tai Chi as a chronic pain management intervention for PLWH.

7) Setting of the Human Research

Participants for this study will be recruited from the Comprehensive HIV Program (CHP) at Temple Health. When feasible, a member of the research team will meet

with interested participants at the CHP in a private office to describe the study in detail and obtain signed informed consent. To increase reach and access, screening of participants can also occur via telephone call with the study coordinator and eligible participants can provide electronic signature for consent. Subsequent study visits will occur at the Temple University Kornberg School of Dentistry (TUKSoD). Assessments will occur in private research assessment rooms and intervention groups will take place in a private group room on the 4th floor of the TUKSoD building. To address potential barriers to retention during the ongoing COVID-19 pandemic, participants will be offered the opportunity to attend intervention and control groups virtually through secure HIPAA-compliant Zoom meetings and can complete assessments remotely. Study staff will encourage participants to attend in-person, but recognize that the pandemic is an evolving situation that requires flexibility in intervention delivery and assessments.

8) Resources Available to Conduct the Human Research

The present study aims to recruit 40 patients from the Comprehensive HIV Program. The CHP provides treatment to 1,100 adults living with HIV in the Philadelphia area. Based on conservative estimates of pain conditions in this group (~50%), there are approximately 550 patients at the CHP who may meet inclusion criteria for this study. Given these estimates, we anticipate a successful recruitment for this pilot trial.

This research is supported by an NIH K23 Career Development Award, which provides 75% effort through April 2024 for the PI (Dr. Dunne) to achieve the goals of this project.

Staff on this project will include Dr. Eugene Dunne, a research assistant, a health education interventionist, and a tai chi instructor. Dr. Dunne is a clinical psychologist (licensed in Rhode Island and Pennsylvania) and behavioral medicine researcher with over ten years of experience working on NIH-funded research studies. All study staff will complete CITI training in social/behavioral human subjects research, HIPAA trainings, and good clinical practice training. Dr. Dunne will monitor all study procedures under the guidance of his K23 mentorship team.

9) Study Design

a) Recruitment Methods

Recruitment. The recruitment strategy will be informed by patient and provider responses to in-depth qualitative interviews from Aim 1. Providers at the CHP will give prospective participants a brief overview of the study and ask for permission to introduce the patient to study staff. Study staff will review medical records for upcoming visits to determine which patients may meet study eligibility criteria (i.e., medical records indicate that patient is HIV positive and has a chronic pain condition) and inform providers in advance of their appointments. Study personnel will inform the HIV provider via email that they have a patient with an upcoming visit who meets the basic eligibility criteria (e.g., HIV and chronic pain diagnoses), and invite the provider to share basic information about the study if the provider believes

the patient would be a good candidate (e.g., physically able to participate safely). Patients will have the option to call the research team or request that the research team call them directly. A trained research assistant will reach out to patients by phone to provide more detailed study information and schedule a time to conduct the informed consent process. Recruitment material will also be available in the CHP waiting room (see attached recruitment flyer in appendix). The flyer will provide a telephone number for potential participants to call study staff and a QR code that can be scanned with a smartphone camera. The QR code will link to Qualtrics where potential participants can enter their contact information and request a callback from study stuff. Identifying information will be permanently removed from study files if patients decline screening questions or do not consent to participate. De-identified data (e.g., age, gender, race/ethnicity) will be retained for the purpose of assessing feasibility to recruit a diverse patient population.

Ryan White: As an additional recruitment strategy, we will screen patients with upcoming appointments at the dental school. It is estimated that approximately 700 adults living with HIV receive care at Temple Dental School. A query will be programmed in the dental medical record (axiUm) to identify patients with upcoming appointments. Using a similar process as described above, we will contact the dental providers, informing them that their patients may be eligible for this study. We will include a copy of the study flyer that providers can share with their patients. It is expected that many of these patients will be insured through the Ryan White program, and thus we have requested approval from the Philadelphia Department of Public Health prior to programming the query. Similar to our existing IRB-approved recruitment strategy, we will screen the medical record to confirm HIV and chronic pain diagnoses.

b) Inclusion and Exclusion Criteria

Inclusion Criteria

Participants must meet all of the following inclusion criteria to participate in this study:

1. age 45 and older;
2. HIV positive status based on clinical records;
3. chronic pain condition based on clinical records;
4. English speaking;
5. physically able to participate in a Tai Chi program;

Exclusion Criteria

Participants meeting any of the following will not be eligible to participate:

1. Inability or unwillingness to provide informed consent
2. Inability or unwillingness to engage in 10-week intervention;
3. Non-English speaking;
4. Active substance use disorder, per self-report;
5. Acutely suicidal or psychotic;
6. Self-reported participation in another research study related to chronic-pain

c) Local Number of Subjects

It is anticipated that 40 participants will be enrolled.

d) Study Timelines

It is anticipated that participants will be enrolled in the study for six months from the time of first contact to the final follow up visit. Please see Table 1 below for timeline of assessments.

1. Following consent, participants will complete a baseline assessment, which may last about 30 minutes.
2. After baseline assessment, participants will be randomized to intervention or control;
3. Next, participants will attend 10 weekly, one-hour group sessions.
4. After attending their final group, participants will return to complete the full questionnaire battery again.
5. Three months after the final group, participants will return to complete a final follow up assessment.

10) Study Endpoints

Endpoint. The study will end after all participants have completed the 3-month follow up.

Stopping rules. Due to the physical nature of the intervention, and the chronic pain participant population, individuals who report adverse events (AEs) related to Tai Chi will be informed about their option to withdraw from the study. Given the low risk of Tai Chi, a gentle movement, no stopping rule has been identified. If the Independent Monitoring Committee (IMC) raises any issues in the conduct or safety of the study protocol, prompt action including considering the interruption of the study will be considered. Given the low risk of this study, no interim analyses are proposed.

11) Procedures Involved in the Human Research

Pilot RCT procedures: Once enrolled, participants will complete baseline assessment and be randomized based on a random number sequence created using a research randomization program (www.randomizer.org).

Intervention. The 20 participants assigned to the experimental group will be invited to attend 10 weekly Tai Chi sessions facilitated by an expert in mind-body practice. Intervention groups will last approximately 60 minutes. They will take place at Temple Dental School, which offers private group intervention rooms and a convenient parking garage. We will utilize a Qigong/Tai Chi Easy protocol, as this is a simple form that can be easily learned and disseminated (if acceptable and efficacious). The manual is modifiable and changes can be made based on information learned in formative research. Participants will also be provided with a

DVD and web link to view at home for daily Qigong/Tai Chi Easy practice. The video will be a Qigong/Tai Chi Easy session led by our expert facilitator.

Control Condition. Participants in the time- and attention-matched control condition will be invited to participate in a 10-session health education program. The information contained in the program will be adapted from a previously developed health education control group manual created by Dr. Carey for an HIV population. Additional health education material will be based on information learned in the qualitative interviews in the formative phase of this study. The manual will not target pain or antecedents of pain (e.g., mobility, stress, mood). Examples of session material include the following: sleep hygiene, healthy diet, sun safety, and healthy homes. A Masters/Doctoral level professional with experience in health psychology will be recruited from Temple or the community to facilitate the control condition groups. Sessions will last 60 minutes.

Retention. Retention strategies will be optimized based on information learned from qualitative interviews conducted in Aim 1. In addition, we will collect patient locator information, including phone number, email address, mailing address, and contact information of up to three trusted family members or friends. Contact information will be kept separate from study data. Participants will be able to drop out of the study at any time. Those who discontinue will be asked if they are willing to provide reasons for drop out to inform future study design. Additionally, compensation plan will incentivize retention, such that baseline and post-intervention assessment will offer $30 each, while the 3-month follow-up will compensate participants $40. Participants will also receive modest compensation ($5) for attending in-person groups to offset the cost of travel, up to $50 if all 10 groups are attended.

Feasibility Measures. To assess recruitment feasibility, we will track number of participants screened, eligible, and enrolled. Intervention and retention feasibility will be calculated based on number of intervention sessions attended and number of follow-up visits completed. Rates of missing data will also be considered for feasibility.

Acceptability Measures. We will adapt the Client Satisfaction Survey to assess participant ratings of the recruitment, retention and intervention procedures. Likert-type ratings will include how helpful and enjoyable participants found the Tai Chi intervention and instructors and if they would recommend the intervention program to a friend. We will also elicit detailed responses using open-ended questions.

Fidelity Assessment. Following the formative phase of the intervention, we will develop treatment fidelity checklists based on the primary components of the Qigong/Tai Chi Easy protocol and the Health Education control group. Group sessions will be video recorded for the purpose of ensuring the instructors are delivering the interventions correctly. Video recordings will be temporarily stored on the secure Temple University servers, which will only be accessed by password-protected computers. Videos will be permanently deleted as soon as possible, after study staff ensures the instructor is covering the necessary components in each session.

A trained RA will complete the fidelity checklist immediately after each session and enter the data in a secure database. RA will review with the PI to ensure any challenges are addressed promptly.

Assessment. Participants in the intervention and control conditions will complete the same assessments at three time-points (baseline, post-intervention, 3-month follow-up). The RA will be present to assist with the assessment, answer questions, and provide detailed information about next steps in the study (e.g., Tai Chi or Health Education sessions). The assessment will be designed so that it can be completed in ≤ 30 minutes. Demographic information (i.e., age, race/ethnicity, education, income, marital status) will be assessed at baseline only. Additionally, participants will complete measures of pain, quality of life, stress, depression, and medication adherence at baseline, post-intervention, and 3-month follow-up. The assessment plan reflects the theoretical model, depicted in Figure 1; it will be strengthened based upon the proposed training and in response to feedback received during the qualitative phase (Aim 1). The Brief Pain Inventory – Short Form and the Pain Catastrophizing Scale (PCS) will be used to assess pain and pain-related physical and psychological outcomes. Specific pain types will be assessed using the Subjective Peripheral Neuropathy Screen Questionnaire and the Örebro Musculoskeletal Pain Screening Questionnaire. The WHO-Quality of Life-Brief (WHO-QoL-BREF) will be used to assess quality of life and has been specifically developed for use in HIV populations. Given the stress associated with managing chronic health conditions, the Perceived Stress Scale will be included to assess frequency and severity of stressful situations. Similarly, depression is highly comorbid in this population, thus the Patient Health Questionnaire will be used to assess depressive symptoms. Medication adherence will be assessed using a validated brief 3-item measure for PLWH, which assesses number of days missed, difficulty following instructions, and self-rating of medication adherence in the past 30 days. The Meditative Movement Inventory will be used to assess uptake of Tai Chi movements and potential benefits. Lastly, at the start and conclusion of each intervention session, participants will be asked to rate their pain on a visual analog scale, to assess average chronic pain rating before session and changes in pain following Tai Chi. Participants will receive a $30 gift card as compensation for completing each of the baseline and post-intervention assessment, and will receive a $40 gift card for completing the assessment at 3-month follow-up. Participants will be compensated $5 per in-person group attended to offset the cost of travel, up to $50 of all groups are attended. In sum, participants can earn up to $150.

Data Analyses. Descriptive statistics (e.g., means, standard deviations, frequencies) will be calculated to summarize participant characteristics. Between-group differences (experimental vs control) in baseline characteristics will be assessed using t-tests (for continuous variables), chi-squared tests (for categorical variables) and non-parametric tests as appropriate. Primary outcomes of interest for this pilot study will be feasibility and acceptability. Feasibility will be calculated as a percentage eligible, consented, randomized, and retained. To determine feasibility of the intervention, we will calculate the percentage of Tai Chi sessions attended. Feasibility data will be compared between intervention and control conditions using t-tests. We will consider the intervention feasible if at least 80% retention is achieved. Acceptability will be calculated as mean satisfaction ratings of the

intervention and instructors. Intervention will be considered acceptable if overall satisfaction scores are in the favorable range on Likert-type responses. This study is not powered to detect statistical differences in self-reported pain or psychosocial outcomes. Nonetheless, we will estimate effect sizes for between-group differences as a means of detecting possible effects. Using a series of longitudinal models (mixed effects models for continuous outcomes, generalized estimating equations for binary outcomes), we will estimate effects of condition on mean pain and psychosocial outcomes post-intervention and 3-month follow-up, controlling for baseline and any variables not balanced by randomization. Interest is in estimating effect sizes rather than strict statistical hypothesis testing. We will also explore possible mediators (using a product of coefficients approach to estimate path coefficients) and moderators (using longitudinal models), including sex as a biological variable. Response rates and missing data will inform subsequent trials. Analyses will be conducted using an intent-to-treat approach. Proposed longitudinal models use a likelihood based approach estimating and thus make use of observed data without directly imputing missing outcomes. Lastly, the proposed research will consider pain type as a potential confounder and/or moderator when examining outcome data, and future studies with adequate power will determine if Tai Chi results in varying levels of efficacy for management of different types of pain (e.g., neuropathic vs. musculoskeletal).

Data Management. The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All study data will be entered and stored on secure university-based servers and only accessed through password protected computers. Paper records will be stored in locked file cabinets in a locked office. Only the PI and Data Manager will have access to study files. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects. This study will use Qualtrics software for secure management of data. Participant identifiers will be kept separate from study data. The database will be secured with password protection. Electronic communication with outside collaborators will involve only unidentifiable information. We will keep an electronic audit trail to show changes to data after original entry including the date/time and user making the change. The research assistant will provide the PI with weekly reports during enrollment periods to monitor enrollment. This report will contain deidentified data and group assignment. No interim data analysis is proposed. Final data analysis will be conducted by the PI in collaboration with a consultant biostatistician. Final study data reported will be shared with the study oversight committee and NCCIH.

Data and Safety Monitoring. An Independent Monitoring Committee (IMC) has been formed for the purpose of clinical trial safety monitoring. The members of the IMC are not associated with this research project and work independently of the PI, Dr. Eugene Dunne, and his mentors. They are not part of the key personnel involved in this grant. No member of the Committee has collaborated or co-published with the PI within the past three years. They are qualified to review the patient safety data generated by this study because of their unique expertise. The three members selected for the IMC are Drs. Tao Liu, Christopher Schmid, and Rani Elwy. These

members have been selected for their expertise in biostatistics (Liu, Schmid), HIV and infectious disease (Liu), mind-body research (Elwy), and clinical trials evaluation (Schmid). The CVs of all members of the IMC have been submitted to NCCIH for their review and approval. De-identified progress reports, including recruitment, retention/attrition, and AEs will be provided to the IMC semi-annually. In addition, the reports will address (1) whether AE rates are consistent with pre-study assumptions; (2) reason for dropouts from the study; (3) whether all participants met entry criteria; (4) whether continuation of the study is justified on the basis that additional data are needed to accomplish the stated aims of the study; and (5) conditions whereby the study might be terminated prematurely.

12) Risks to Subjects

This is a mind-body, behavioral intervention study and should pose minimal risk to study participants. Nonetheless, untoward events may result in the following potential risks:

1. Injury or increase in pain resulting from physical movements during Tai Chi practice;
2. Emotional discomfort while participating in intervention or while responding to assessments;
3. Breach of confidentiality;
    3a. Additional risk due to virtual study activities.

To reduce the potential for risk to participants, we will actively collect information and monitor for intervention-related symptoms. We present here the measures we plan to undertake to minimize potential untoward events that may occur as a result of participation in this study.

1. **Injury or increase in pain resulting from physical movements during Tai Chi practice**: While Tai Chi consists of gentle and fluid movements, the physical nature of Tai Chi (or any exercise intervention) could increase risk of injury for participants. Further, participants will be diagnosed with a chronic pain condition, which may be exacerbated by physical movements. Special precautions will be considered to protect against this risk. First, the instructor for the proposed study is a highly recommended Tai Chi expert and former behavioral medicine researcher. Second, we will develop the intervention manual to include movements that pose the smallest risk of pain or injury. Participants will be informed that they are welcome to take breaks and skip movements as needed. Lastly, participants will be reminded that they are free to withdraw from the study for any reason. The research assistant will assess each participant's pain level at the conclusion of each Tai Chi session to ensure the safety of participants prior to leaving. If, for any reason, a participant is in need of medical attention, the participant would be escorted to Temple University Hospital located on the Health Sciences campus.
2. **Emotional discomfort while participating in intervention or responding to assessments**: Psychological distress while responding to questions related to living with chronic pain is possible, though unlikely. Participants will

be encouraged to report to the study staff any such discomfort or side effects that might occur during the intervention sessions or assessments. The principal investigator is a doctoral-level clinical psychologist with training in dealing with psychological distress and crises. In the event that a patient presents signs of severe psychological discomfort during assessments or interventions, the RA will contact that PI and the participant will be welcomed to discontinue until a later date or withdraw from the study at any time.

3. **Breach of confidentiality.** Participant confidentiality will be maintained through several strategies. Participants will be assigned a unique study identification number. The only individuals who will have access to participants' identifiers will be the PI, RA, and data manager. Data will be protected by the use of locked file cabinets in secured office space, use of password-protected computers, and storing data on internal encrypted servers. Only study personnel will have access to the secure study folders. Group interventions increase risk to participant confidentiality. Participants will be informed of the importance of group confidentiality during the informed consent process and during the first intervention group session. Research staff will instruct group members not to share the names or personal information of group members outside of the intervention environment, including with family members. Additionally, reminders will be stated at the beginning of each intervention session.
    a. **Virtual Study Activities:** we recognize that utilizing virtual platforms adds an additional layer of risk to confidentiality. Using the video-conferencing software in a non-secure environment puts the participants' privacy and confidential information at risk. We will use all possible methods to protect the privacy and confidentiality of study participants, including (but not limited to) using HIPAA-compliant video conferencing software, password protected virtual meetings and the use of waiting rooms to only allow access to known participants. Participants will be instructed to only access virtual events from a private location, to reduce unintentional risk of bystander observation. If non-participants are observed in the vicinity of virtual attendees, the participant will be moved to a waiting room for further discussion or removed from the meeting. An example of a situation where only temporary removal (e.g., use of waiting room) would be appropriate include a participant's child accidently coming into the room. In these cases, participants can resume group attendance after remedying the interruption. In addition, recorded videos will be deleted as soon as possible.
4. **COVID-19 Pandemic considerations:** when required by national/local authorities or university policy, participants will be required to wear a mask while on campus or in clinical spaces. All CDC-recommended guidance will be followed with regards to sanitizing study space and maintaining physical distancing. The rooms in TUKSoD have been assessed for safe capacity limitations.

5. **Other considerations:** Depression and Suicidality. Given the elevated rates of depression among persons living with HIV, and those with chronic pain, study staff will be vigilant of potential suicidality reported by participants. If severe depression or suicidal ideation, intent, or plan is reported during assessment or intervention sessions, the principal investigator will conduct a suicide assessment and triage appropriately. If intent and plan are stated, PI will escort participant to the emergency room, if participant is willing. Otherwise, PI will inform participant that he is required to call 911 for the participant's safety.
6. **Other considerations:** Staff Training. Research personnel, including the principal investigator, interventionists, and research assistant, will receive extensive training in the responsible conduct of clinical research. Dr. Michael Carey (Brown University), the primary mentor on this award and a licensed psychologist with 30 years of research and clinical experience in HIV and related socially sensitive topics, will oversee the training and provide supervision of the PI. Dr. Tellez will also provide local training at TUKSoD, including online NIH- and Hospital-based modules, directed readings, and team meetings. Topics will include maintaining confidentiality, safe use of protected health information, duty to warn and required reporting laws, and cultural sensitivity.

13) Potential Benefits to Subjects

There are no direct benefits to subjects for participating in this study. However, it is plausible that participants will benefit from both the Tai Chi and the Health Education groups. Participants assigned to the intervention condition will have the opportunity to participate in Tai Chi group classes with an expert instructor. Additionally, the health education classes used in this study have been well-received by participants in previous studies.

14) Privacy and Confidentiality

As this is a clinical treatment study, it will use patients' protected health information (PHI). A HIPAA Authorization Form is uploaded as part of this application.

As in any type of treatment or clinical research program, patients' privacy must be carefully guarded and respected. All written identifying information (signed recording consent forms, contact information) will be stored in locked files or digitally on a HIPAA-compliant network. Remaining data will be stored in password-protected computer files on a HIPAA-compliant network. One file will contain patient names and associated research identification numbers; at the end of the study, this file will be destroyed. All other data will reside in a file identified by subject identification numbers and from which other identifying information will have been removed, so the link between these data and subject identifiers will have been severed.

All research staff on the project will be educated about the importance of strictly respecting patients' rights to confidentiality and will have completed training concerning proper practice in accordance with HIPAA regulations.

Data files will be accessible only to the investigators and research assistants directly connected with the study. Only members of the research team will review the data. To help patients feel at ease, staff will emphasize their right to ask questions throughout the study and to abstain from any aspect of the research which makes them uncomfortable. During group sessions, all participants will be reminded of the importance of respecting the confidentiality of all group members.

No PHI data will be shared with persons unassociated with the project. When the results of this protocol are published, data are presented in aggregate and no individual identifying information is included.

15) Economic Burden to Subjects

There is no anticipated economic burden for participating in this research.

16) Subject Compensation

Participants will receive a $30 gift card as compensation for completing each of the baseline and post-intervention assessments, and will receive a $40 gift card for completing the assessment at 3-month follow-up. Participants may also be compensated $5 per in-person group attended to off-set the financial burden of traveling or parking. In sum, participants can earn up to $150.

17) Consent Process

Participants who are eligible and interested in participating will meet with the PI or RA to be provided with detailed information about the nature of the study. If an in-person meeting is not possible, the consent process can be conducted over the phone or HIPAA-compliant video conferencing and signed electronically. If remote consenting is used, study staff will remain on the phone or video conference throughout the process to ensure that the eligible participant is able to receive and open the email containing the consent form, read and understand the consent form, and have an opportunity to ask any questions prior to signing and emailing the form back to the study team. An explanation of the study will also be registered on ClinicalTrials.gov website. The PI or RA will review the Informed Consent form with eligible participants, providing details verbally and in writing. Participants will be informed that the study is voluntary, will not impact their standard clinical care, and they can withdraw at any time without penalty. The PI or RA obtaining consent will provide opportunities for participants to ask

questions at any time. Participants who are in agreement will sign the IRB-approved informed consent form and HIPAA authorization form to permit study staff to access electronic medal record information. Participants will be provided with a copy of the forms for their personal records. This copy can be provided physically or electronically (via email), depending on participant preference. Electronically signed forms will be stored in secure study folders on the Temple network. They will also be printed and stored with in-person signed consent forms in locked filing cabinets in secured office space in TUKSoD, and kept separate from study data.

18) Vulnerable Populations

Not applicable. Individuals who are vulnerable to coercion or undue influence will not be included in the human subjects activities described herein.

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