The University of Arizona

Combination Therapy of Home-based Transcranial Direct Current Stimulation and Mindfulness-based Meditation for Self-management of Clinical Pain and Symptoms in Older Adults with Knee Osteoarthritis

NCT04375072

July 24, 2024

IRB Protocol for Human Subjects Research

Basic Information	
Title of Study:	Combination Therapy of Home-based Transcranial Direct Current Stimulation and Mindfulness-based Meditation for Self-management of Clinical Pain and Symptoms in Older Adults with Knee Osteoarthritis
Short Title:	Home-based tDCS and Mindfulness-based Meditation for Self-management of Clinical Pain and Symptoms
Principal Investigator Name:	Hyochol Ahn
Principal Investigator's Department/Unit:	College of Nursing

1.0 Background (Limit 1,000 words):

Provide the scientific or scholarly background for the proposed Human Research. Discuss relevant prior experience or preliminary data (e.g., existing literature).

Arthritis is one of the leading causes of pain, impairments of activities in daily life, and disability in people aged 45 and above. Of the 53 million adults diagnosed with arthritis, more than 22 million (42%) reported trouble with their activities of daily living due to arthritis. Osteoarthritis (OA) is the most common of the arthritic conditions, with the knee being the most commonly affected joint. Patients with chronic pain, such as knee OA pain, do not have sufficient pain relief, and this leads to decreased physical functioning and mobility disability. OA pain is characterized by altered pain and sensory processing in the central nervous system similar to other chronic pain syndromes. Because pharmacologic treatments can increase adverse events among older adults, there is a growing interest in non-pharmacological interventions targeting central nervous system pain processing for this population. Specifically, noninvasive brain stimulation, such as Transcranial Direct Current Stimulation (tDCS), has received significant attention for the treatment of pain in chronic conditions due to its neuromodulatory effect. tDCS involves the application of weak direct electric current to the head in a noninvasive and painless manner, leading to the modulation of the resting membrane potentials of neurons and alteration of the endogenous excitability of the targeted cortical area. This stimulation is believed to mediate analgesic effects by modulating pain processing pathways. Also, mindfulness-based meditation (MBM) has been shown to improve pain-related brain function and alleviate pain in multiple chronic pain conditions. Since tDCS is a noninvasive and safe approach to facilitate neuroplasticity, it may enhance the brain's ability to adaptively reorganize in response to other clinical interventions, including mindfulness-based interventions. Therefore, we will examine the effect of tDCS paired with MBM in older adults with knee OA pain. Our hypothesis is that remotely supervised tDCS paired with MBM at home will decrease clinical pain and OA-related clinical symptoms, improve physiopsychological pain processing, and increase participant satisfaction with treatment.

2.0 Lay Summary:

Provide a brief description of the proposed research using terms that someone who is not familiar with the science or discipline can understand.

Knee osteoarthritis pain is one of the most common pain conditions among people over 45 and pharmacological interventions do not adequately address this common comorbid condition. The proposed study examines an evidence-based nonpharmacological intervention targeting pain-related brain function: self-administered, remotely supervised transcranial direct current stimulation at home combined with mindful-based meditation. This study has the potential to significantly improve the self-management of pain, decrease public health expenditures, and improve the quality of life for older adults.

3.0 Purpose:

Describe the purpose, specific aims, objectives, questions to be answered, hypotheses, and/or primary and secondary study endpoints of this Human Research protocol.

The purpose of this project is to assess the effect of the self-administered tDCS paired with MBM in 200 older adults with knee OA. The specific aims are the following: determine the effects of active tDCS paired with active MBM on clinical pain and OA-related clinical symptoms (specific aim 1); determine the effects of active tDCS paired with active MBM on physiopsychological pain processing (specific aim 2); determine the effects of active tDCS paired with active MBM on participant satisfaction with treatment (specific aim 3). evaluate the effect of MBM paired with tDCS on pain-related brain function (specific aim 4); and evaluate the relationship between pain-related brain function and pain catastrophizing behavior and OA-related clinical pain (specific aim 5).The central hypothesis is that remotely supervised tDCS paired with MBM at home will decrease clinical pain and OA-related clinical symptoms, improve physiopsychological pain processing, increase participant satisfaction with treatment, and decrease maladaptive changes in pain-related brain function. The study endpoint is 4 months, including monthly follow-up telephone assessments for 3 months after the completion of intervention.

4.0 Funding Information:

Indicate all sources of funding for the project, including gift funds, departmental funds, or other internal funding. For each funder, list the name of the funder, and the institutional proposal number or award number you received from Sponsored Projects. eIRB tip: For externally funded projects, the institutional proposal or award number provided must be linked in the "Study Funding Sources" section in eIRB.

☐ **No Funding**	
	Name of funding source: National Institute of Health (NIH)

☒ **Federal Funding**, including flow-through federal funding (i.e., NIH, NSF, DoD, etc.)	Institutional Proposal or Award Number: **5R01NR019051-04**
	eDoc # (for multi-site projects): **NCT04375072**
☐ **Industry Funding**	Name of funding source:
	Institutional Proposal or Award Number:
	eDoc #:
☐ **Foundation Funding**	Name of funding source:
	Institutional Proposal or Award Number:
☐ **Department Funding**	Name of funding source:
☐ **Gift Funding**	Name of funding source:
☐ **Other**	Name of funding source:

5.0 Resources Available to Conduct the Human Research:

Describe the resources (facilities, time, emergency resources, etc.) available to recruit, consent, conduct study procedures, and analyze data.

This study, funded by NIH, was approved by the IRB at the University of Texas Health Science Center at Houston and the IRB at the Florida State University at Tallahassee. On this R01 project, all the data will be collected at Dr. Ahn's laboratory in the UA College of Nursing building at a single site and continued from where the study has left off. Previous participant data will be compiled from the other previous sites and be used in UA. Adequate equipment and resources are available in the Ahn laboratory to carry out the procedures and accommodate the personnel described in this proposal.

<u>Processing and Analysis of Imaging Data</u>

Processing and analysis software will be used to analyze the image data collected within this project. This software will not be used for any of the medical purposes listed in the International Medical Device Regulators Forum, *Software as a Medical Device (SaMD): Key Definitions* document. In other words, the software will not be used for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury,
- investigation, replacement, modification, or support of the anatomy or of a physiological process,
- supporting or sustaining life,
- control of conception,

- disinfection of medical devices,
- provide information by means of in vitro examination of specimens derived from the human body.
- provide means and suggestions for mitigation of a disease,
- provide information for determining compatibility, detecting, diagnosing, monitoring or treating physiological conditions, states of health, illnesses or congenital deformities,
- be an aid to diagnosis, screening, monitoring, determination of predisposition; prognosis, prediction, determination of physiological status.

Additionally, all software used to process and analyze image data collected during this project is used in "Exempted investigations" based on the Code of Federal Regulations Title 21 Section 812.2 (c)(3)(iv). In other words, the software

- is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

A Medical Device appendix will be submitted for any software used in this project that does not satisfy the above requirements.

6.0 Study Population:

6.1 Select all the categories of participants included in the research:

☐ Healthy adults	☐ Non-English-speaking subjects
☒ Non-healthy adults	☐ UA staff/faculty
☐ Children (under 18 years old) *	☐ UA students
☐ Pregnant women, neonates, and/or fetuses*	☐ Banner employees
☐ Prisoners*	☐ Refugees
☐ Native Americans, Alaskan Native, and Indigenous Populations*	☐ Other – please explain: Click or tap here to enter text.
☐ Adults unable to consent (i.e., cognitively impaired adults) *	

6.2 For each of the above selected categories, describe the inclusion and exclusion criteria. Indicate age range, gender, and ethnicity.

Similar to our previous work, participants who are 50-85 years old will be considered eligible if they (1) have symptomatic knee OA based on American College of Rheumatology clinical criteria, (2) have had knee OA pain in the past 3 months with an average of at least 30 on a 0-100 NRS for pain, (3) can speak and read English, and (4)

have no plan to change medication regimens for pain throughout the trial. The age range was selected to include a higher proportion of persons with knee OA pain. There will be no restrictions on gender or ethnicity. According to American College of Rheumatology criteria, participants should meet at least 3 of 6 criteria, including age > 50 years, experience stiffness, the physical property of being inflexible and hard to bend, < 30 minutes in a day, crepitus, bony tenderness, bony enlargement, and no palpable warmth. Participants will be excluded if they have any concurrent medical conditions that could confound the interpretation of outcome measures, pose a safety risk for any of the assessments or interventions, or preclude the successful completion of the protocol. Specific exclusion criteria are: (1) history of brain surgery, brain tumor, seizure, stroke, epilepsy, or intracranial metal implantation,(2) systemic rheumatic disorders, including rheumatoid arthritis, systemic lupus erythematosus, and fibromyalgia, (3) alcohol/substance abuse, (4) diminished cognitive function that would interfere with understanding study procedures (i.e., Mini-Mental Status Exam score ≤ 23), (5) prosthetic knee replacement or non-arthroscopic surgery to the affected knee, (6) hospitalization within the preceding year for psychiatric illness, (7) no access to a device (e.g., smartphone, computer) that can be used for secure video conferencing for real-time remote supervision, and (8) skin or scalp conditions that may be aggravated by tDCS stimulation.

Specific inclusion/exclusion criteria for Magnetic Resonance Imaging (MRI) procedures.

- Participants must be able to tolerate small, enclosed spaces and have no medical devices or implants on or in their bodies.
- On a case-by-case basis, and only if the provenance and safety of the implant can be established, individuals with certain implants may be able to undergo an MRI scan. Such implants may include, cardiac stents, carotid stents, cardiac valve replacements, bone and joint pins and screws, some IUD and birth control implants.
- Participants will be excluded from this study if they have any history of pacemakers or pacer wires, open heart surgery, artificial heart valves, aneurysm clips, cochlear implants, braces or extensive dental work, implanted electrical or mechanical devices, tissue expanders, foreign metallic objects from explosives, shrapnel or metalwork fragments, or artificial limbs. Participants will also be excluded if they are pregnant, claustrophobic, have tremors or cannot lie still for1-2 hours, or weight more than 300 pounds.

6.3 Describe the total number of subjects to be enrolled locally under this IRB approval. If obtaining specimens, specify the maximum number of specimens needed for this project.

The number of subjects who are expected to be enrolled and screened is 240, and the number of subjects needed to complete the research procedures (i.e., numbers of subjects excluding screen failures.) is 200. The number of subjects who are expected to be enrolled and screened for MRI is 80, and the number of subjects needed to complete the MRI procedures is 40. Locally, we will recruit 36 participants in UA. 28 participants will be for both the tDCS/MBM and MRI procedures combined and 8 participants will be for the tDCS/MBM procedure alone.

7.0 Recruitment Methods:

7.1 Select the methods used to recruit individuals.

☒ Email	☒ Screening of the Electronic Medical Record (EMR)
☒ Face to face	☐ Social media
☒ Flyers	☐ SONA System
☐ In person presentations	☐ TV, Radio, Print
☐ Online advertisements	☐ Other – please explain: Click or tap here to enter text.
☒ Phone calls	

7.2 Explain the recruitment process. Describe how potential subjects will be identified, where recruitment will take place, when recruitment will occur, and the methods that will be used to recruit individuals.

Participants will be recruited under the direction of the PI. PI will oversee participant screening and recruitment. The study team will hand out study flyers/brochures to potential study participants, and those patients who contact the study team for more information about the study will be approached by study investigators or trained study personnel for further determination of eligibility screening requirements and informed consent in-person at a scheduled baseline visit. Coordinators will also recruit through the collaboration with the UA Department of Orthopedic Surgery (Department Chair: Dr. John Elfar) as a study team.

Patients will be identified as potential subjects by a co-investigator on the study team during consultation for standard of care treatment of their knee pain. The study opportunity will be initiated by the treating provider. Only those patients that have expressed interest in the study and have agreed to be contacted will be approached by a study team member through phone, email, or in-person. The study team will review the EMR and confirm eligibility.

The consent process will occur during face-to-face discussions with a study team member. The informed consent form will be read and reviewed by an approved member of the study team and all questions will be answered. The subject will be given ample time to ask questions and review the consent form before deciding about participation. All subjects will provide written informed consent before beginning any study activities and all will be given a copy of the signed consent form.

8.0 Diversity, Equity, and Inclusion

8.1 Explain how the research plan (recruitment, study population, data collection, etc.) is equitable and represents the demographic makeup for the location in which the research will be conducted.

The study will not favor or exclude any group of people outside the exclusionary criteria, which are implemented to prevent adverse events within the study to protect participants. Study staff will create an open and transparent environment to make sure participants are not only well-informed but feel safe when participating in the study.

8.2 Describe whether non-English speaking subjects will be included in the study. If yes, please explain how your research team is prepared to meet the needs of the population. If not, please explain why non-English speakers will be excluded from the study population.

Non-English-speaking subjects will not be included in the study. The study requires patient feedback on levels of pain through various paper surveys and verbal communication with tests in the lab. In order to maintain data clarity, subjects will be required to speak English as the current staff are not multi-lingual or have translators available.

8.3 What methods will you use to collect demographic information from participants? If you will not collect demographic information, please explain why not.

Demographic information will be obtained through a paper Medical History Questionnaire. All participants will complete a thorough questionnaire to collect demographic and medical history details, including age, sex, height, weight, duration of knee OA, current and past treatments for knee OA, comorbid conditions, and current medications.

9.0 Consenting Process:

9.1 Indicate the informed consent process(es) and/or document(s) for the study. Check all that apply.

Written Consent
☒ Informed Consent (ICF) – written or electronically signed form
☐ Parental Permission – written or electronically signed form
☐ Assent (participants under 18) – written or electronically signed form
☒ Combined ICF/PHI Authorization – written or electronically signed form
☐ Protected Health Information (PHI) Authorization – written or electronically signed
☐ Translated Consent/Assent – written or electronically signed form(s)
☐ Short Consent Form – written or electronically signed form (see guidance on Short Form process)
☐ Debriefing Script or Form – document used to properly inform subjects of the study's purpose when intentionally deceived

Oral/Online/Unsigned Consent
☐ Informed Consent – oral script/online/unsigned
☐ Parental Permission – oral script/online/unsigned
☐ Assent – oral script/online/unsigned
☐ Translated Consent/Assent – oral script/online/unsigned

Waivers of Informed Consent and/or PHI Authorization
☐ Waiver of Consent
☐ Full Waiver of PHI Authorization
☒ Partial Waiver of PHI for Screening Purposes

9.2 Describe in detail the consent processes checked above, including any waiting period for subjects to sign the consent, steps to minimize the possibility of coercion or undue influence, and the language used by those obtaining consent.

Subjects will have the option to participate in either the tDCS/MBM portion of the study alone or combined with the MRI scan portion at the start of the recruitment process. If the subject decides to participate in tDCS/MBM, an informed consent form will be given. There will be additional check box for the subject who decides to participate in MRI scan and additional signature will be collected.

Subjects will participate in the study only after they provide signed consent. Participation in this study is completely voluntary. All participants will be informed of the nature of the procedures and associated risks.

The consented subject will be screened for any contraindications to MRI and magnetic materials. The investigator or MRI Technologist will explain the MRI system and the scan that the subject will take part in. The subject will be asked to lie down on the scanner bed. Some part of the subjects' body may be covered or enclosed within an FDA or UA

HSPP approved MRI coil. The subject may be asked to interact with a peripheral system such as a button, joystick, or TV system before, during, or after the scan.

Where will the original signed consent and PHI authorization documents be stored?

The original signed consent and PHI authorization documents will be stored in a locked office within a locked cabinet with the keys accessible only to the staff and PI.

9.3 Acknowledgement of consent form storage.

☒ I will store original signed consent and/or PHI authorization documents for at least 6 years past the time the study is concluded.
☐ For studies involving minors, I will store original signed consent and/or PHI authorization documents for at least 6 years after the youngest participant turns 18.
☐ Not applicable – I am not collecting signed documents.

10.0 Research and Data Collection Procedures:

10.1 Select the methods of data collection that will be used in this study (select all that apply):

☒ Anthropometric measures (e.g., height, weight, waist circumference, etc.)	☐ Participant observation
☐ Audio/video recording	☐ Screening data
☐ Benign interventions	☐ Self-health monitoring (e.g., pedometers, food diaries, etc.)
☐ Biological specimens – blood draws	☒ Surveys – paper
☐ Biological specimens – clinically discarded blood or specimens	☐ Surveys – internet (including online and email-based data collection)
☐ Biological specimens (urine/feces, tissue, saliva, skin, hair, nails, nasal swab)	☐ Surveys – telephone
☐ Clinical Data Warehouse (CDW)	☒ Randomization with control and experimental groups
☐ Cognitive or behavioral measures, including daily diaries	☐ Records – billing
☒ Data collected using other communication/electronic devices (e.g., cell phones, pagers, and texting devices)	☐ Records – educational
☐ Data previously collected for research purposes	☐ Records – employee
☐ Deception	☐ Records – lab, pathology and/or radiology results
☒ Instrumentation, equipment, or software not approved by the FDA	☐ Records – mental health
☐ Interviews – focus groups	☐ Records – substance abuse
☐ Interviews – in person	☐ Research imaging protocols
☐ Interviews – virtual/online	☐ Recombinant DNA
☐ Medical records review	☐ Social networking sites
☐ MRI/ultrasound with contrast	☐ Stem cells
☒ MRI/ultrasound without contrast	☐ Radiation Scans (X-Ray, CT Scans, etc.)
☒ Non-invasive instruments (e.g., external sensors applied to the body)	☐ Other activities or interventions – describe: Click or tap here to enter text.

10.2 Description of research procedures.

Participants who meet eligibility criteria and give informed consent will be randomly assigned at a ratio of 1:1:1:1 to one of the four groups: (a) active tDCS paired with active MBM (n=50), (b) sham tDCS paired with active MBM (n=50), (c) active tDCS paired with sham MBM (n=50), or (d) sham tDCS paired with sham MBM (n=50) using the order of entrance in the study and previous randomization list generated via SAS software. The randomization will balance the allocation of patients to the study arms with respect to distributions of age, race, and sex. tDCS with a constant current intensity of 2 mA will be applied for 20 minutes per session daily for 2 weeks (Monday to Friday) via the Soterix 1x1 tDCS mini-CT Stimulator device (Soterix Medical Inc., NY; 6.5 inches long, 3 inches wide, 0.7 inches thick) with headgear and 5x7 cm pre-saturated, single use, individually packed sponge electrodes. The FDA has ruled that the aforementioned tDCS stimulator is a “non-significant risk” device, a requirement for Investigational Device Exceptions. The sponge electrodes snap into the custom headgear, which is secured to the participant’s head for simple and fail-safe electrode preparation. This single-position headgear with clearly labeled sponge markers eliminates room for user error and helps conserve accurate and reproducible sponge placement. Participants can only administer a stimulation session via the Soterix 1x1 tDCS mini-CT Stimulator device after being provided a single-use unlock code by the research staff once proper contact quality is achieved (only the on/off button will be adjustable by the study participants; they will not be able to adjust the device settings). After the participant enters the unlock code, the screen on the device will show a timer that counts down the minutes until the end of the session. At 20 minutes, the device will turn off automatically, and study staff will instruct the participant to remove the headset and discard the sponges and to safely store all materials for the next session. For sham stimulation, the electrodes will be placed in the same positions as for active stimulation, but the stimulator will only deliver 2 mA current for 30seconds. This sham stimulation method has been shown to be reliable and indistinguishable from active treatment. During each tDCS session, participants will practice MBM. The meditation intervention will be applied simultaneously with tDCS for 20 minutes per session daily for 2 weeks by a recorded meditation on a CD. Participants will be provided with a CD player and earphones. The recording will instruct participants to close their eyes, connect to the openness of one’s mind, and mindfully maintain and deepen the connection through breathing with more openness and awareness. The sham MBM intervention will be delivered via a CD player that will look identical in both active and sham MBM. The sham recording will instruct participants to relax and take deep breaths every 3 minutes without the specific mindfulness-based instructions (e.g., practicing mindful attention to the breath in a non-evaluative manner). All other aspects of the sham MBM intervention (e.g., body position, time spent listening to instructions, eyes closed) will match the active MBM.

Participants will perform self-administered tDCS and MBM at their home or private

room for two weeks (Mondays-Fridays) under real-time supervision by the research staff. The research staff will monitor participant for the accurate positioning of the headgear, optimized skin contact, proper usage of code to initiate the stimulation, and abide with the duration of the stimulation. Data will be collected by study staff across several points using equipment and resources available at Dr. Ahn's (PI's) laboratory at University of Arizona (see Table below). Participants will visit Dr. Ahn's lab three times, and each visit will take approximately 2 hours for tDCS/MBM study and additional 1 hour for MRI scan. Study team will not conduct a urine or blood pregnancy test.

	B		Week 1					Week 2						Monthly Follow-up		
			1	2	3	4	5†	6	7	8	9	10†		1-Mo	2-Mo	3-Mo
MRI		X											X			
MMSE	X															
Knee radiograph*	X															
Medical history questionnaire	X															
Clinical pain (NRS): primary outcome	X		X	X	X	X	X	X	X	X	X	X		X	X	X
Osteoarthritis symptoms (WOMAC): secondary outcome	X						X					X		X	X	X
Pain-related cortical response(fNIRS): secondary outcome	X						X					X				
Descending pain modulation (CPM): secondary outcome	X						X					X				
Mindfulness (FMI): secondaryoutcome	X						X					X		X	X	X
COVID-related stress: secondary outcome	X						X					X		X	X	X
CESD: secondary outcome	X						X					X		X	X	X
PCS: secondary outcome	X						X					X		X	X	X
Patient satisfaction (CSQ-8):secondary outcome												X				

Note: B, Baseline; MRI, magnetic resonance imaging; MMSE, Mini-Mental Status Exam, NRS, Numeric Rating Scale; WOMAC, Western Ontario & McMaster Universities Osteoarthritis Index; fNIRS, functional near-infrared spectroscopy; CPM, conditioned pain modulation; FMI, Freiburg Mindfulness Inventory; CESD, Center for Epidemiologic Studies Depression Scale; PCS, Pain Catastrophizing Scale; CSQ, Client Satisfaction Questionnaire. The baseline visit will occur 3 to 7 days prior to the tDCS intervention.
*Existing knee radiographs to determine OA severity using Kellgren-Lawrence scores.

†On days 5 and 10, tDCS paired with MBM will be delivered at Dr. Ahn's laboratory, followed by data collection of self-report measures (NRS, WOMAC, FMI, CSQ-8 [only day 10]), and immediately afterwards, the fNIRS and CPM will be collected.

- MRI. MRI will be completed within a week from the baseline visit and the last visit. Scans will be conducted at the Translational Bioimaging Resource (TBIR) located in UA. Only FDA-approved MRI devices will be used.
- MMSE. MMSE will be used to exclude people with diminished cognitive function (i.e., Mini-Mental Status Exam score ≤ 23).
- Kellgren-Lawrence Scores. Kellgren-Lawrence scores collected from existing patient x-rays will be conveyed from Dr. John Elfar to the research study team. If available, we will collect Kellgren-Lawrence Scores or x-rays directly from non-Banner affiliated participants. The scores will be used in the study to determine OA severity.
- Medical History Questionnaire. All participants will complete a thorough questionnaire to collect demographic and medical history details, including age, sex, height, weight, duration of knee OA, current and past treatments for knee OA, comorbid conditions, and current medications.
- Clinical pain intensity will be measured by asking participants to rate their average knee pain over the past 24 hours via NRS from 0 (no pain) to 100 (worst pain imaginable). Following the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials recommendations for clinical trials involving chronic pain, pain intensity changes assessed through an NRS will be our primary outcome measure for data analysis purposes.
- We will measure OA-related clinical symptoms using Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), which ranges from 0 to 96, with higher scores indicating worse OA pain-related symptoms.
- We will measure pain-related cortical response using a continuous-wave, multichannel fNIRS imaging system (LIGHTNIRS, Shimadzu, Kyoto, Japan). This instrument encompasses 8 light sources (each emitting laser light at 780, 805, and 830 nm) and 8 detectors connected to comfortable headgear using optical fibers. The illumination and detection optodes will be arranged in a geometrical layout that will cover the prefrontal and somatosensory cortex regions bilaterally, consistent with locations investigated in previous studies. Optical recordings will be collected during thermal and punctate pain stimulation. A temperature-controlled pain generator (Medoc TSA- II Neurosensory Analyzer) and nylon filament (Touch-Test Sensory Evaluators) will be used to produce thermal (maximum temperature of 50 Celsius degree) and punctate pain stimulation (maximum force of 300g). We will apply moderate intensity thermal and punctate stimuli for approximately 10-20 seconds, just enough time to feel the discomfort of the pain stimulation, to the most painful knee during multiple scanning runs, followed by an equivalent time period of no stimulation. In this

period of time, the fNIRS imaging system will measure the brain activity of the participant.

- A multimodal Quantitative Sensory Testing (QST) battery will be completed for Conditioned Pain Modulation (CPM). These measures will be assessed using equipment and methods available at Dr. Ahn's laboratory, including a Medoc TSA- II Neurosensory Analyzer, a temperature-controlled pain generator to produce thermal pain stimulation to the most painful knee and ipsilateral forearm and Wagner pressure algometer to produce pressure pain stimulation to the most painful knee and trapezius. We will be applying pressure stimulation combined with the participant holding their hand under cold water for one minute at most.
- Psychosocial symptoms will be measured by FMI (ranges from 14 to 56), COVID-stress scale (range from 0 to 144), CESD (ranges from 0 to 60), and PCS (ranges from 0 to 52). FMI is a 14-item instrument (range, 14 to 56), with higher scores indicating more skill with the mindfulness technique. The FMI has a reported Cronbach's alpha coefficient of 0.86. COVID-stress scale, CESD, and PCS are commonly used in clinical studies.
- We will measure participant satisfaction with treatment using the Client Satisfaction Questionnaire (CSQ-8). The CSQ-8 comprises eight items that are summed to yield an overall score of 8-32, with higher scores indicating greater satisfaction. The CSQ-8 has a reported Cronbach's alpha coefficient of 0.87-0.93. Moreover, we will evaluate the presence and severity of possible side effects of treatment at the end of each session on a 0 (not at all) to 10 (highest degree) scale. The participants will be asked in an open- ended manner whether they experienced any side effects, and they will complete a brief questionnaire assessing side effects that can occur with tDCS or MBM (e.g., itching, headache, fatigue, dizziness). This approach has been used in our previous study and frequently in other studies.

10.3 Specify the total estimated time commitment for subject participation, and the estimated time commitment for each activity.

We expect that participants will be in this research study for four months. For a two-week period, participants will perform self-administered tDCS and MBM at their home or private room for eight days (Monday – Friday) of 20-minute supervised Zoom sessions. There will also be three lab visits lasting two hours each within those two weeks: once on the first day, once in the middle of the study, and once during the last day. Should they choose to participate, there will be two visits lasting one hour in the MRI facility, once before the first lab session and once after the last lab session. Finally, we will follow up with participants once a month for three months after the two-week period through phone survey for 20 minutes each or having the participant mail their paper survey answers to the office.

10.4 If any biological specimens (blood, urine, tissue, etc.) are being collected for research, state the amount (ml/tsps./tbsp, etc.), method, frequency, and type of specimen to be collected and what the specimen will be used for.

N/A

10.5 If the study is a clinical trial, confirm registration with https://clinicaltrials.gov/ has been completed:

This study is not a clinical trial: ☐
Registration complete: ☒
Registration pending: ☐

11.0 Potential Benefits to Subjects:

11.1 Describe the anticipated benefits of this study to society, academic knowledge, or both.

The central hypothesis is that remotely supervised tDCS paired with MBM at home will decrease clinical pain and OA-related clinical symptoms, improve physiopsychological pain processing, increase participant satisfaction with treatment, and decrease maladaptive changes in pain-related function. This hypothesis will be tested by pursuing the following specific aims: determine the effects of active tDCS paired with active MBM on clinical pain and OA-related clinical symptoms (specific aim 1); determine the effects of active tDCS paired with active MBM on physiopsychological pain processing (specific aim 2); determine the effects of active tDCS paired with active MBM on participant satisfaction with treatment (specific aim 3). The proposed research is significant because it is expected to provide valuable insight into an exciting new modality of nonpharmacological pain self-management that is extremely easy, safe, and noninvasive with minimal side effects.

11.2 Describe any benefits that individuals may reasonably expect from participation (not including compensation, which cannot be considered a benefit of participation).

Brain Stimulation and meditation have been shown to reduce pain in some older adults. We cannot promise any benefits to participants in this research. However, this study will help us to understand whether self-brain stimulation and meditation will reduce pain in older adults with knee osteoarthritis, which might lead to better treatment for people with such conditions.

12.0 Risks to Subjects:

12.1 Describe all physical, psychological, social, legal, and/or economic risks that could be associated with participation in this research.

- MRI. The MRI environment is cramped and may provoke claustrophobia in some subjects. MRIs are associated with repetitive loud noises in the range of 126 – 131 dB on a 3T system. The radio frequency (RF) energy deposited in the body during an MRI scan can increase body temperature. Proximity burns may arise due to deposition of focused RF energy into the body where it touches the bore of the magnet. Known as the projectile effect, the strong magnet field can draw in MR-unsafe objects in a rapid and uncontrolled manner that can pose a serious threat to the health and life of those in the room.
  Significant risks may exist for people with:
  - Cardiac pacemakers
  - Metal clips (stents) on blood vessels
  - Artificial heart valves
  - Artificial arms, hands, legs, etc.
  - Brain stimulator devices
  - Implanted drug pumps
  - Ear implants & augmentation (e.g. cochlear implants, hearing aids)
  - Eye implants, metal fragments in eyes, colored contact lenses
  - Exposure to shrapnel or metal filings (e.g. military combat, sheet metal workers, welders)
  - Other metallic surgical hardware anywhere in the body or on the skin
  - Certain tattoos with metallic ink
  - Certain transdermal (skin) patches such as NicoDerm (for tobacco dependence), Transderm Scop (for motion sickness), or Ortho Evra (birth control)

  Significant risks can also arise if metallic or magnetic objects and materials are brought into the scanning area (e.g. jewelry, piercings, pocket knife). Such items could get pulled into the magnet at great speed and can cause serious injury.

- tDCS. The Soterix Medical 1x1 tDCS mini-CT Stimulator may cause transient minor irritation, discomfort and redness at the electrode sites. tDCS has not been shown to cause seizures nor lower the seizure threshold in animals. There are no reports of seizure induced by tDCS in human participants in the literature. However, this may not be true for epilepsy patients, whose seizure threshold rates are likely abnormal. Therefore, potential participants who have a history of seizures or epilepsy will be excluded from the study.
- MBM. The risks of MBM are minimal. Occasionally, participants report transient anxiety or mild discomfort during MBM.

- Demographic and clinical survey questionnaires. The potential risk of the questionnaires involves participants' feelings of discomfort or unease when reading or responding to survey questions that are personal.
- Thermal stimulation. The Medoc TSA-II Neurosensory Analyzer will be used to create thermal stimulation, which will use a heating apparatus that has a low risk of burning skin. The TSA-II is covered under FDA 510K #K922052, which has both hardware and software safety limits that will not go beyond a certain temperature limit (50 C) in order to prevent burning of the skin.
- Functional near-infrared spectroscopy. Optical fibers will be secured to the participant's scalp using the cap's grommets. Although there is no designed measure that protects the participants from the risk of discomfort due to prolonged wearing of headgear, we will assess the participants' level of discomfort through direct question immediately after wearing the headgear and periodically during the experiment. Participants will be instructed that they can discontinue the procedure if they experience any discomfort or unpleasant effects.
- Conditioned pain modulation. There are risks of bruising and lingering pain by applying gradual pressure stimuliwith the pressure algometer. The participant will tell the examiner as soon as they feel pain or discomfort as pressure gradually increases and the examiner will immediately release pressure. We will be doing the same pressure stimulation combined with the participant holding their hand under cold water for one minute at most. The participant may withdraw their hand from the cold water at any time before the minute elapses if the cold pain is too much to bear.

12.2 Discuss what steps will be taken to minimize risks to subjects/data.

- MRI. To mitigate risks, the following steps will be adopted: The protect the hearing of subjects, they will be provided with ear plugs and headphones to lower sound levels to no more than 99 dB(A). Adequate ventilation in the MRI bore and a magnet room temperature of 20°C will be maintained at all times to ensure subjects can maintain body temperature. Blankets will be provided, if necessary. To eliminate the possibility of proximity burns, pads will be used to ensure that the subject's tissues do not directly come into contact with the inner bore of the magnet during the MR imaging process. Also, for this reason, subjects' body tissues will not be permitted to form a conductive loop. Pads will be used to ensure this cannot happen. Any MR-safe or MR-conditional equipment necessary for the conduct of the scan will be introduced into the magnet room before the subject to ensure there is no risk to the health and life of those in the room due to a potential projectile effect. MR-unsafe objects are never allowed in the magnet room. To ensure that subjects can be safely scanned, they will be screened for MRI suitability at least three times: once upon prospective enrollment into the MRI arm of the study, upon enrollment, and finally on the day of the MRI scan.

- tDCS. To minimize risk associated with tDCS, participants will be asked to report any discomfort, and the examiner will monitor participants throughout the stimulation sessions. All tDCS sessions will be remotely supervised by a trained experimenter. Participants may stop at any time. tDCS has not been shown to cause seizures nor lower the seizure threshold in animals. There are no reports of seizure induced by tDCS in human participants in the literature. However, this may not be true for epilepsy patients, whose seizure threshold rates are likely abnormal. Thus, history of seizure is an exclusionary criterion for our study.
- MBM. Participants will be instructed that they can discontinue the procedure if they experience any discomfort or unpleasant effects.
- Demographic and clinical survey questionnaires. Throughout each questionnaire, participants will be reminded that participation is completely voluntary, they can refuse to answer any question, and they can stop at any time. Breaks will be given if needed. Research staff who collect data will have previous training in the conduct of all survey questionnaires.
- Functional near-infrared spectroscopy. Although there is no designed measure that protects the participants from the risk of discomfort due to prolonged wearing of headgear, we will assess the participants' level of discomfort through direct question immediately after wearing the headgear and periodically during the experiment. Participants will be instructed that they can discontinue the procedure if they experience any discomfort or unpleasant effects.
- Thermal stimulation. The following precautions will be employed in the proposed study: 1) participants will be informed that they can withdraw their arm from the stimulator at any time; 2) the experimenter will continuously monitor stimulus temperature and can manually discontinue stimulation at any point; and 3) the stimulator has a built-in shut-down system to prevent the delivery of prolonged or high-intensity stimuli. Inconvenience to participants will be minimized by delivering brief stimuli that are below the individual's thermal pain tolerance level. The thermal stimulator will start generating heat at the temperature less than human body temperature and participants will be provided with the button to stop the stimulator the moment they feel discomfort or pain. These procedures will ensure maximum patient safety and comfort while allowing successful and reliable imaging of the brain.
- Conditioned pain modulation. The risks of bruising and lingering pain will be diminished by applying slow, gradual pressure to the knee and shoulder with the pressure algometer, wherein the participant will tell the researcher to stop the moment they feel discomfort or pain and the researcher will immediately release pressure. The researcher will record the numeric reading on the pressure algometer. We will also be doing the same test while the participant's hand is in ice-cold water. We will let the participant to take their hand out of the cold water at any time it becomes too much within the one-minute time limit and the time of cold withdrawal (in seconds) will be recorded. All the

stimulation and testing sessions will be supervised by trained research staff who will monitor potential adverse effects and symptoms. At each stimulation session, participants will be asked to report any adverse events they have experienced.

13.0 Costs, Compensation, and Injury:

13.1 Describe any costs, monetary and non-monetary, that subjects may incur. This includes time.

Subjects will not incur any monetary costs. The duration of an individual subject's participation in the study is four months including follow-up phone/survey assessments. Any equipment provided will be paid for by the study.

Discuss the amount of compensation (monetary and/or non-monetary) subjects may receive. Describe if compensation will be prorated.

Subjects will receive up to $220 in gift cards for completing the main protocol, and they will receive partial payment if they do not complete the entire study. For each self-brain stimulation and meditation, subjects will receive $10 and an additional $30 for each visit to our testing center and $10 for each follow-up phone assessments. Additionally, participants who complete MRI visits will be compensated with up to $200 ($100 for each MRI data collection visit X 2 times).

14.0 Privacy of Subjects and Confidentiality of Data:

14.1 Describe steps, if any, to protect the privacy of the subjects throughout their participation (e.g., during the recruitment process, consent process, and/or research procedures).

A number of data integrity procedures will be used to ensure the validity and integrity of the data and the safety of all participants involved in the study. All procedures involving human participants will be performed at the PI's laboratory at UA College of Nursing. Relevant data and safety information obtained from each study participant will be verified against the original source documents by the study coordinator, and any identified discrepancies will be reviewed at the weekly meetings. All identifying information will be archived on a password-protected server in password-protected folders and files. Only study staff will have access to these files. We will use the double data entry module in REDCap for self-report data (e.g., questionnaires).

Computer-generated reports of variable frequencies and participant lists will be reviewed, leading to possible corrections to coding or entry. After data within a given group are checked for accuracy, the data will be stored in the password-protected

folders.

Adherence to the study protocol will be promoted throughout the trial. Of note, the research team will receive proper training using detailed manuals of procedures for all aspects of the proposed research, including treatment protocols and participant interaction, in a step-by-step fashion. All study personnel will be trained before study initiation, and the PI will carry out weekly supervision of the research team's adherence to protocols. These procedures were successfully implemented in our previous studies.

14.2 Will data be kept for future research, including unspecified future research and genetics? Yes ☐ No☒

14.3 If yes to the above question, describe future use plans here including any storage in a repository (if applicable), and what data will be retained/reused.

N/A

14.4 Discuss how study results will be shared with subjects, families, and/or the institution, both immediately and long-term.

We will publish research results at the peer-reviewed journal and/or scientific conferences. After completion of the study, results may be shared to research subjects if they want. Subjects will be provided with copies of their MRI data upon request.

The information provided in the study will be handled confidentially. However, there may be circumstances where this information must be released or shared as required by law. The University of Arizona Institutional Review Board; other federal, state, or international regulatory agencies; or the sponsor of the study, if any, may review the research records for monitoring purposes.

We may publish the results of this research. However, we will keep participant names and other identifying information confidential to the extent allowed by law. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify participants. At most, the Web site will include a summary of the results. Participants can search this website at any time.

14.5 Indicate if the research team will be accessing any of the following records.

☐ Substance abuse records (HIPAA and 42 CFR Part 2)
☒ Medical records (HIPAA)
☐ Educational records (FERPA)*
☐ Employee records (ABOR Policy 6-912)*
☐ Other, specify: Click or tap here to enter text.

14.6 For each record source selected above, summarize the data elements to be accessed, who will access them, and how the information will be obtained.

Kellgren-Lawrence scores will be obtained from existing radiographs only accessible by the Dr. John Elfar. Kellgren-Lawrence scores will be obtained from the Dr. Elfar only after written consent has been signed. The Kellgren-Lawrence scores will be stored in REDCap for security and transmitted to Dr. Miao, our biostatistician in FSU.

14.7 Indicate where data will be stored:

☐ Box@UA	☐ OnCore
☒ Box@UA Health	☐ PACS medical imaging software
☐ Clinical Data Warehouse (CDW)	☐ Password Protected Drive
☐ Cloud Server	☒ REDCap
☐ Department Drive	☐ Transmitting/receiving subject data to/from an outside group
☒ Department Office	☐ UA Records Management & Archives
☐ Encrypted Drive	☐ Banner Server/Platform, specify:
☐ External Drive (hard drive, USB, disk)	☐Soteria
☐ Google Suite for Education	
☐HIPAA Research Computing Service	☐Other, specify: Click or tap here to enter text.

14.8 For EACH of the storage locations checked above, discuss the type of data to be stored, including if the data is identifiable, coded, or de-identified upon storage, and who may have access to the data.

Only trained research team members designated in the IRB- approved study protocol will collect data. REDCap (http://www.project-redcap.org) will be used to capture and store participant data, accessible only by research team members via an encrypted and password-protected computer. All research data will be coded using the participant's unique identifier. No name or other identifying information will be used on research data. All paper data (e.g., participant contact information, consent forms) will be placed in a locked file cabinet in a locked office within 24 hours of their acquisition. All data files will be automatically backed up daily on Box@UA Health. We will ensure data changes are documented and there is no deletion of entered data. Data will be accessible only by research team members via an encrypted and password-protected computer, and we will prevent unauthorized access to data. The code will be

maintained on Box@UA Health and will be destroyed after 3 years following closeout of a grant of contract agreement by the research team.

14.9 Storage of research records (research records should be maintained for whichever of the following time periods is the longest, select one):

☒ I will store research records for at least 6 years past the time the study is concluded.
☐ For studies involving minors, I will store research records for at least 6 years after the youngest participant turns 18.
☐ I will store research records for the length of time required by law or study sponsor, please specify: Click or tap here to enter text.

14.10 Describe what security controls (e.g., administrative, physical, technical) are in place to make sure data/specimens are secure.

A number of data integrity procedures will be used to ensure the validity and integrity of the data and the safety of all participants involved in the study. All procedures involving human participants will be performed at the PI's laboratory at UA College of Nursing. Relevant data and safety information obtained from each study participant will be verified against the original source documents by the study coordinator, and any identified discrepancies will be reviewed at the weekly meetings. All identifying information will be archived on a password-protected server in password-protected folders and files. Only study staff will have access to these files. We will use the double data entry module in REDCap for self-report data (e.g., questionnaires).

Computer-generated reports of variable frequencies and participant lists will be reviewed, leading to possible corrections to coding or entry. After data within a given group are checked for accuracy, the data will be stored in the password-protected folders.

Adherence to the study protocol will be promoted throughout the trial. Of note, the research team will receive proper training using detailed manuals of procedures for all aspects of the proposed research, including treatment protocols and participant interaction, in a step-by-step fashion. All study personnel will be trained before study initiation, and the PI will carry out weekly supervision of the research team's adherence to protocols. These procedures were successfully implemented in our previous studies.

14.11 Indicate how data/specimens will be shared with collaborating entities:

☐ Data and/or specimens will not be shared between UA and any outside group or collaborating entity.
☒ Data/or specimens will be transmitted and/or disclosed to an outside group or a collaborating entity.
☐ Data and/or specimens will be received from an outside group or a collaborating entity.
☐ PHI will be transmitted to or received from an outside group or a collaborating entity. *
☐ A Limited Data Set will be transmitted or received from an outside group or a collaborating entity. *
☐ Data/specimens will be sold to pharmaceutical companies.

Describe what information will be shared, who it will be shared with, and how it will be shared (e.g., secure file transfer, REDCap, etc.). Also include information about future use sharing and repositories Specify if the shared data will be identifiable, coded, a limited data set, or de-identified.

Dr. Hongyu Miao, the study statistician, will coordinate data management and analysis. Coded participant personal data and questionnaire data will be shared with Dr. Miao through REDCap. Dr. Miao will not have access to the code key but will have access to other personal information such as age, gender, etc. Kellgren-Lawrence scores, the numbers defining severity of osteoarthritis, will be shared with Dr. Miao once the scores, not the x-rays, are obtained from Dr. Elfar. Dr. Miao will also have access to all questionnaire results (CPM test results, MRI data, etc.) to compile into data. DUA for sending data to Dr. Miao is in progress and no PHI is being shared with external collaborators.

15.0 Additional Questions (complete as applicable):

15.1 Subject Injury: If the research involves more than minimal risk to subjects, describe the provisions for medical care and available compensation in the event of research related injury. If the Human Research has a clinical trial agreement, this language should reflect what is stated in the agreement.

15.2 This study poses minimal risks because (1) the discomfort is transient in nature and generally subsides immediately after the procedure; (2) participants are instructed that they may stop any procedure at any time with no adverse consequences; and (3) the level of discomfort experienced by participants is below their tolerance level. Also, risks will be minimized by adhering to our exclusion criteria, and the Dr. Elfar will have full discretion to exclude participants who may be at excessive risk through thorough review of all tDCS cases prior to any procedure. A standard operating procedure has been

outlined in case of medical emergency or adverse event and the responsible physician as well as the PI will be available by phone during all cases. Only research personnel with the relevant background, training, and expertise will be able to follow the lab procedures.**Withdrawal of Subjects: Discuss how, when, and why subjects may be removed from the study. If abrupt withdrawal is necessary, discuss how subjects will be withdrawn so that they are not put at increased risk. Discuss what happens if a subject is withdrawn from one part of the study but asked to continue with other parts, such as ongoing follow-up.**

Participants will be informed that they can withdraw from the study at any time by calling study team at 520-626-6863 and that this will have no adverse impact on the study or on their own future medical treatment. A subject withdrawn from the study will not be asked to continue with other parts of the study. Data collected prior to withdrawal will be retained.

15.3 Monitoring for Subject Safety: Provide a brief lay discussion of your plan to monitor for subject safety. Describe what safety information will be collected, including serious adverse events, how safety information will be collected, and the frequency of collection including a timeline of when the data and review(s) will occur, who will review the information, and the plan for reporting findings.

If there will not be a way to monitor for subject safety, please explain.

The Safety Monitoring Committee (SMC), which was approved by NIH, will be responsible for overseeing activities related to implementing the clinical trial to ensure patient safety, conformance to the clinical protocol, overall performance of the trial components, and integrity of the data being collected. The SMC will meet prior to the start of enrollment and then annually to review study progress (e.g., recruitment, retention, and safety procedures) and participant safety concerns and as needed to adjudicate any adverse events. All meeting materials will be considered privileged by SMC members. The SMC will comprise 3 members with expertise in neuromodulation, statistics, and geriatric clinical research: Ricardo Jorge, MD, professor of psychiatry and behavioral sciences at Baylor College of Medicine; Hongyuan Cao, PhD, associate professor at the Florida State University Department of Statistics; and Jessica Lee, MD, Assistant Professor, Geriatric and Palliative Medicine, UTHealth McGovern Medical School. The SMC members are independent of the project. These members are appropriately qualified to review the scientific design and conduct of the study, to evaluate safety and risks to participants, to interpret data statistically, and to make recommendations concerning the continuation, modification, suspension, or termination of the study.

The research MRI scanner operates within FDA guidelines and is considered a non-significant risk device. This means the risks are minimal so long as appropriate precautions are taken. The Siemens MRI scanner that will be used for scans is approved by the FDA for routine clinical and research studies. This is also true for most of the

peripheral components used with the scanner as well as most of the scan types that are performed on the scanner. However, as part of the sessions we may use non-FDA-approved components, scans, and/or software. In all cases these components, scans, and software comply with all FDA guidelines with respect to MRI safety.

15.4 Data Management Plan: Please discuss the data management plan, if required by your funder. For additional resources, reference the HSPP Data Management webpage. If your sponsor/funding agency requires a Data Management Plan, please upload the approved copy in eIRB. This section and the informed consent form should contain all pertinent information including:

- **What data/metadata will be shared (imaging, survey; raw data or derived; protocol, data form; etc.)**
- **What repository will be used (if known)**
- **How will data be stored (in a de-identified or identifiable format)**

PI has substantial experience in the design and implementation of data management procedures that provide accurate recording and storage of data, participant confidentiality, and timely analysis. Based on our experience, we believe that the major data management and analysis needs for the proposed project can be met by using a high-end PC, equipped with SPSS and SAS for Windows and appropriate spreadsheet programs. All data files will be automatically backed up daily.

The data entry system will require a login identification and password to gain access to the data. Where appropriate, validation and range rules will be applied to the actual entry fields. Only the PI and designated research staff will be able to view the data in its raw state.

Participant data will be coded. Confidentiality will be protected by assigning each participant a number, which will be used in all data tabulation and subsequent publications. The list linking this number to the participant's identity will be maintained in a password-protected data file, accessible only by authorized research personnel associated with the human testing components of this project. The PI will oversee the compliance of the study, maintaining strict adherence to the requirements of the law, research protocols, and health information security. Only trained research team members designated in the IRB- approved study protocol will collect data. REDCap (http://www.project-redcap.org) will be used to capture and store participant data, accessible only by research team members via an encrypted and password-protected computer. All research data will be labeled using the participant's unique identifier. No name or other identifying information will be used on research data. All paper data (e.g., participant contact information, consent forms) will be placed in a locked file cabinet within 24 hours of their acquisition.

15.5 International Research: Describe site-specific regulations or customs affecting the research, local scientific and/or ethical review structures that differ, and if community advisory boards are involved. If so, describe their composition and involvement. For research being conducted outside of the US, please explain any local laws, regulations, or customs the IRB needs to be aware of.

N/A

Additional items needed for review:

- Word versions of applicable subject materials: Consents, PHI Authorization Form(s), Recruitment Materials, Data Collection Materials, additional Participant Materials
- Current PI CV or biosketch
- Advisor approval (if the PI is a student or medical resident)
- Department/Center/Section Review approval
- Scientific/Scholarly review approval
- Responsible physician approval and CV (if the PI is conducting medical procedures for which he/she is not clinically certified to perform)
- Additional approvals, as needed (e.g., RIA/Banner feasibility, Export Control, Radiation, COI, UA travel registry, CATS, SRC, school district approval, tribal approval, etc.)

Other items as applicable:

- HSPP Appendices
- Data Monitoring Charter and Plan
- Drug/Device information
    - Applicable drug or device appendix
    - Investigator's Brochure, drug product sheet, device manual, user's manual, instructions for use, package insert, IND/IDE documentation, FDA 1572 form, 510k indication, FDA exemption, sponsor determination of device risk, etc.
- Multi-site information (for sites engaged in research where the UA is the IRB of record)
    - Appendix for Multi-Site Research for each site
    - Documentation of reliance
    - CV and medical license (if applicable) of site PI
    - Human Subject Training Verification for site PI and site staff
- Sponsor protocol and MOPs that are used in the study (if applicable)