Introduction Page

1 * Abbreviated Title:
Duloxetine plus Exercise for Knee Osteoarthritis (DEKO)

2 * Full Title:
A Feasibility and Pilot Study of Combined Treatment Protocol using Aerobic Exercise and Duloxetine in Older Adults with Symptomatic Knee Osteoarthritis and Comorbid Depression

3

* Select Type of Submission:

- [ ] **IRB Application**
- [ ] Humanitarian Use Device (for FDA approved Indication & non-research purposes ONLY)
- [ ] Single Patient Expanded Access (pre-use)
- [ ] Single Patient Emergency Use (post-use)
- [ ] Unsure if this proposal requires IRB review (Not Human Subject Research)

Note: The Type of Submission cannot be changed after this application has been submitted for review.

4 Original Version #:
HP-00089160

Research Team Information

1 * Principal Investigator - Who is the PI for this study (person must have faculty status)? ***Faculty status is defined as being a full-time (>51% effort) faculty member holding one of the following titles at UM: Professor; Associate Professor; Assistant Professor.***
Alan Rathbun

CITI Training:ID00000030

1.1 * Does the Principal Investigator have a potential conflict of interest, financial or otherwise, related to this research?
☐ Yes ☐ **No**

2 Point of Contact - Who is the alternative point of contact for the PI? This person can be a study coordinator or any other study team member. In case the IRB cannot contact the PI, this person is a secondary person to contact:
Alan Rathbun

CITI Training:ID00000030

2.1 Does the Point of Contact have a potential conflict of interest, financial or otherwise, related to this research?
☐ Yes ☐ **No**

3 Other Team Members - list all additional members of the research team for this study. DO NOT include the PI or POC in this list:

	Name	Edit Submission	cc on Email	Research Role	Has SFI?	CITI Training
View	Lexie Shaffer	no	yes	Research Team Member	no	
View	Rhea Mehta	no	no	Technician or Assistant	no	ID00012789
View	Jason Peer	no	no	Research Team Member	no	ID00006173
View	Alice Ryan	yes	no	Research Team Member	no	ID00012869
View	Yu Dong	no	no	Research Team Member	no	ID00012591
View	Marc Hochberg	yes	no	Research Team Member	no	ID00000018
View	Justine Golden	no	no	Research Team Member	no	ID00007366
View	Denise Orwig	yes	no	Research Team Member	no	ID00001309
View	Lynda Robey	yes	no	Research Team Member	no	ID00005538
View	Brock Beamer	yes	no	Research Team Member	no	ID00000006
View	CARTER DAVIS	no	no	Research Team Member	no	
View	Mark Luborsky	no	yes	Research Team Member	no	ID00019142

IMPORTANT NOTE: All research team members (including PI) must have current CITI and HIPAA training completed.

Resources

If this study is a collaborative UM/VA study, please clarify which resources are being used at each institution.

1 * Describe the time that the Principal Investigator will devote to conducting and completing the research:
This research is part of the PI's K01 Research Scientist Development Award (K01AG064041) from the National Institute on Aging; therefore, Dr. Rathbun will devote 75% of his time to conduct and complete this research study.

2 * Describe the facilities where research procedures are conducted:
Research procedures will be conducted at VAMHCS (Baltimore VAMC, Baltimore VA Annex, VA-Loch Raven), University of Maryland Baltimore (UMB) School of Medicine Division of Gerontology, and UMB General Clinical Research Center. Screening, enrollment, and testing procedures will be conducted at the Baltimore VAMC and UMB GCRC. The intervention procedures will take place at the UMMC GCRC and Baltimore VA Annex and/or Loch Raven sites.

3 * Describe the availability of medical and/or psychological resources that subjects might need as a result of anticipated consequences of the human research:
Study clinicians are available to assess acute medical/psychiatric issues. Psychiatric care will be available for participating individuals through the study psychiatrist. Research areas are equipped with lifesaving equipment (AED, etc.) and staff. As stated in the consent form, "The VA Maryland Healthcare System (VAMHCS) will provide necessary medical treatment (not just emergency care) to a research subject injured by participation in a VAMHCS research project." Thus, the necessary resources are in place to deal with unanticipated adverse events.

4 * Describe the process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions:
All research personnel maintain up-to-date training in human subjects research. All personnel are well-versed in study and unit SOPs. Delegation of authority to perform specific tasks is made by the PI only when personnel are fully-trained and demonstrate competence. There will be communication between UMB and VAMHCS personnel, and any changes to the study protocol will be communicated to all members of the research team.

Sites Where Research Activities Will Be Conducted

1 * Is this study a:

- ☐ **Multi-Site**
- ☐ Single Site

2 * Are you relying on an external IRB (not UM) to be the IRB of Record for this study?

☐ Yes ☐ **No**

3 * Are any other institutions/organizations relying on UM to be the IRB of Record for this study?

☐ Yes ☐ **No**

3.1 Attach the applicable regulatory documents here (i.e., IRB Authorization Agreement (IAA), FWA, local ethics approval, other IRB approvals, etc.). Final UM approval will be contingent upon final execution of all required regulatory approvals:

Name	Created	Modified Date

There are no items to display

4 * Is UM the Coordinating Center for this study? (Applicable for multi-site studies. A Coordinating Center is responsible for overall data management, monitoring and communication among all sites, and general oversight of conduct of the project.)

☐ **Yes** ☐ No

5 Is VA the Coordinating Center for this study? (Applicable for Collaborative studies between the VA, UM and other sites. A Coordinating Center is responsible for overall data management, monitoring and communication among all sites, and general oversight of conduct of the project)

☐ Yes ☐ **No**

6 * Institution(s) where the research activities will be performed:

- ☐ University of Maryland, Baltimore
- ☐ University of Maryland, Upper Chesapeake Kaufman Cancer Center
- ☐ **VAMHCS**
- ☐ **UMB School of Medicine**
- ☐ Marlene and Stewart Greenebaum Cancer Center
- ☐ University Physicians Inc.
- ☐ Shock Trauma Center
- ☐ **General Clinical Research Center (GCRC)**
- ☐ Maryland Psychiatric Research Center (MPRC)
- ☐ Johns Hopkins
- ☐ International Sites
- ☐ UMB Dental Clinics
- ☐ Center for Vaccine Development
- ☐ Community Mental Health Centers
- ☐ Private Practice in the State of Maryland
- ☐ Institute of Human Virology (IHV) Clinical Research Unit
- ☐ Joslin Center
- ☐ UMB Student Classrooms
- ☐ National Institute of Drug Abuse (NIDA)
- ☐ National Study Center for Trauma and EMS
- ☐ Univ of MD Cardiology Physicians at Westminster
- ☐ Nursing Homes in Maryland
- ☐ University of Maryland Biotechnology Institute
- ☐ Maryland Department of Health
- ☐ Maryland Proton Treatment Center

- [ ] Mount Washington Pediatric Hospital
- [ ] Institute of Marine and Environmental Technology (IMET)
- [ ] Other Sites
- [ ] University of Maryland Medical System (Select below)

* University of Maryland Baltimore Building(s) where the research activities will be performed:

- [ ] Howard Hall
- [ ] Harry and Jeannette Weinberg Building
- [ ] Health Sciences Research Facility I (HSF I)
- [ ] UMMC Emergency Department
- [ ] Medical School Teaching Facility (MSTF) - School of Medicine (SOM)
- [ ] School of Dentistry (SOD)
- [ ] Hilda Katz Blaustein Research Center - School of Social Work (SSW)
- [ ] Pharmacy Hall - School of Pharmacy (SOP)
- [ ] Biomedical Research Facility
- [ ] Bressler Research Building (BRB)
- [ ] School of Social Work (SSW)
- [ ] Allied Health Research Building (AHRB)
- [ ] Maryland Women's Health Center at Penn Street
- [ ] Community Engagement Center (CEC)
- [ ] University Family Medicine
- [ ] University of Maryland BioPark - Building Two (2)
- [ ] University of Maryland BioPark - Building One (1)
- [ ] Health Sciences Research Facility II (HSF II)
- [ ] Health Sciences Research Facility III (HSF III)
- [ ] James T. Frenkil Building (Faculty Physicians, Inc.)
- [ ] Maryland Institute for Emergency Medical Services Systems (MIEMSS)
- [ ] Walter P. Carter Center
- [ ] UM Professional Building (Faculty Physicians, Inc.)
- [ ] Faculty Physicians, Inc. (FPI)
- [ ] School of Nursing (SON)
- [ ] Homer Gudelsky Building
- [ ] Saratoga Building
- [ ] 100 N. Greene St
- [ ] Lexington Building
- [ ] Other
- [ ] 4MLK Building
- [ ] Francis King Carey School of Law (SOL)

UM Coordinating Center

You indicated that UM is the Coordinating Center for this multi-site study.

2.1 *Describe the processes to ensure communication among sites.

Things to consider including in the communication plan:

- all sites have the most current version of the protocol, consent document, etc.
- all required approvals have been obtained at each site (including approval by the site's IRB of record).
- all modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.
- all engaged participating sites will safeguard data as required by local information security policies.
- all local site investigators conduct the study appropriately.
- all non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

The PI has a primary appointment within the Division of Gerontology at UMB School of Medicine and WOC appointment at the VAMHCS GRECC and offices and resources at both institutions. All members of the research team are proximally located in the Baltimore Metropolitan area and have appointments at either VA or UM. The PI has regular meetings with the research team and will be responsible for securing UMB IRB approval and VA R/D approval, as well as facilitating communication between all personnel involved at both sites. Every member of the research team has been actively involved in the design and submission of the protocol and are familiar with study procedures. Additionally, the research team has a lengthy and successful track record of implementing clinical studies involving exercise interventions that have procedures conducted at both VA and UMB. The PI will be responsible for acquiring approval for protocol modifications and disseminating this information to the study team. Protocol modifications will only be implemented after thorough review and uptake by every member of the research team. The PI and research team are well-versed in VA and UMB information security policies as related to data collection, entry, and analysis and have experience conducting similarly designed studies where data is collected at VA and processed and analyzed at UM. Regular review of the study protocol, trainings, and team meetings will ensure that the study is conducted appropriately. Any issues with non-compliance or other applicable requirements will be communicated to and discussed by the research team and reported in accordance with local policy.

2.2 *Describe the method for communicating to engaged participating sites including:

- reportable new information.
- problems.
- interim results.
- the closure of a study.

All study procedures will be conducted locally at the Baltimore VA Medical Center and University of Maryland Baltimore. No aspect of the study will be completed outside of these two institutions that share resources and personnel. The PI has VA and UM appointments and offices and resources at both institutions; he regularly spends time at both institutions and interacts with all study personnel. Every member of the research team is employed by one of or both of these institutions and will have voluntary appointments as necessary for the purposes of conducting this study (e.g., WOC). Thus, matters concerning new information, problems, interim results, and study closure will be disseminated through the regularly scheduled communication channels that will include individual and team meetings, conference calls, and email as otherwise needed. The PI will be responsible for planning, implementing, and leading all communication matters related to the conduct of this study.

Funding Information

1 * Indicate who is funding the study:

- [ ] Federal
- [ ] Industry
- [ ] **Department / Division / Internal**
- [ ] Foundation
- [ ] Private
- [ ] State Agency

2 * What portion of the research is being funded? (Choose all that apply)

- [ ] Drug
- [ ] Device
- [ ] Staff
- [ ] Participant Compensation
- [ ] Procedures
- [ ] **Other**

3 Please discuss any additional information regarding funding below:
The project is no longer federally funded. The parent award (K01 AG064041) was closed out by NIH on 3/12/2025.

Research Protocol

1 * Do you have a research protocol to upload?

- [ ] Yes
- [ ] **No, I do not have a research protocol and will use the CICERO application to enter my study information**

2 If Yes, upload the research protocol:

Name	Created	Modified Date
There are no items to display		

Risk Level

What is the risk level of your study? (Ultimately, the IRB will determine the appropriate risk level and your designation is subject to change.)

* Choose One:

- [ ] Minimal - The probability & magnitude of harm/discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations/tests.
- [ ] **Greater Than Minimal - Does not meet the definition of Minimal Risk.**

ID: VIEW4E02805225800
Name: v2_Risk Level

Type of Research

1 * Indicate **ALL** of the types of research procedures involved in this study (Choose all that apply):

- ☐ **Use of unapproved drug(s)/biologic(s) or approved drug(s)/biologic(s) whose use is specified in the protocol.**
- ☐ Evaluation of food(s) or dietary supplement(s) to diagnose, cure, treat, or mitigate a disease or condition.
- ☐ Use of device(s) whose use is specified in the protocol
- ☐ **Psychological/Behavioral/Educational Method or Procedure (i.e., survey, questionnaires, interviews, focus groups, educational tests).**
- ☐ **Sample (Specimen) Collection and/or Analysis (including genetic analysis).**
- ☐ **Data Collection or Record Review (i.e., chart review, datasets, secondary data analysis).**
- ☐ None of the above.

2 * Is this study a clinical trial OR will this study be registered at ClinicalTrials.gov?
A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

☐ **Yes** ☐ No

Lay Summary

1 * Provide a summary of the background and purpose of the study in language that can be understood by a person without a medical degree.

Symptomatic knee osteoarthritis (OA) affects 10% of men and 13% of women 60 years or older, and depressive symptoms are common, occurring in at least one-fifth of these patients. The pain and functional disability associated with knee OA are risk factors for major depression, and conversely, depressive symptoms worsen knee OA disease severity and are a barrier to pain management and engagement in physical activity. Guidelines recommend strategies for depression prevention and treatment in older adults with knee OA but provide no direction on how to simultaneously manage the co-occurrence of physical and mental morbidity among patients with or at-risk for major depressive disorder. Treatment recommendations advise exercise to manage pain and disability and improve psychosocial health in knee OA patients; however, compliance to exercise programs is low in persons with chronic pain and disability and is only exacerbated by symptoms of depression. Adherence is critical to the efficacy of interventions using physical activity to prevent or treat clinically relevant depressive symptomology, and no exercise program has ever been designed in a way to enhance compliance and tested among OA patients with or at-risk for major depression. Duloxetine is the only analgesic medication indicated for pain management in knee OA patients that has demonstrated efficacy and tolerability when treating depressive symptoms among older adults and is a viable pharmacological complement to exercise. There are no medical care protocols intended for both prevention and treatment that combine different interventions that affect symptoms of both knee OA and depression. The study goals are to evaluate the feasibility of and then pilot test a protocol comprised of aerobic exercise training plus duloxetine for the prevention and treatment of symptomatic knee OA and co-occurring depressive symptoms.

Justification, Objective, & Research Design

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * Describe the purpose, specific aims, or objectives of this research. State the hypothesis to be tested:

Aim 1: To evaluate the feasibility and acceptability of a center-based intervention that combines aerobic conditioning and duloxetine to treat knee OA and comorbid depression in older adults using quantitative and qualitative research methods to elicit patients experience of the treatment protocol

Aim 2: To pilot test the modified treatment protocol and examine recruitment rates, effects of aerobic conditioning plus duloxetine on pain, disability, and depressive symptoms, intervention compliance, and logistics of project execution among older adults with knee OA and comorbid depression

2 * Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc.:

Aim 1 design: To evaluate the feasibility and acceptability of aerobic exercise plus duloxetine for the treatment of symptomatic knee symptomatic knee OA and depression in older adults (n=10) using a single group, open-label trial, and mixed-methods to assess patients' experience of the protocol from both quantitative and qualitative assessments.

Aim 2 design: To administer a modified treatment protocol in a single group, open label pilot study, and assess patients' experience of the intervention from qualitative assessments and examine effects on clinical outcomes and other design parameters in older adults (n=20) with symptomatic knee and depressive symptoms in order to design a larger randomized controlled trial.

Protocol feasibility will be assessed via patients general experience of depressive symptoms and depression treatment at study baseline and the strengths, weakness, and areas for improvement of the combined treatment protocol during follow-up.

Pilot study testing will assess patients' experience of the modified treatment protocol and examine pre-post treatment changes in pain, disability, and depressive symptoms to evaluate the impact on clinical outcomes, and logistical parameters to be evaluated will include intervention compliance and adherence, adverse events, and recruitment and retention rates.

3 * Describe the relevant prior experience and gaps in current knowledge. Describe any relevant preliminary data:

Exercise training is recommended for the treatment of symptoms of knee OA and depression among older adults, but these patients frequently encounter disease-related barriers (e.g., chronic pain, inertia, etc.) to compliance and long-term adherence. Older adults with conditions that cause musculoskeletal and psychiatric morbidity require interventions that simultaneously address both physical and psychological symptoms, and our pilot studies resulted in OA treatment guidelines that advise using combinations of interventions to address the needs of patients and the unique symptomology they experience.

Exercise training is routinely used to manage knee OA but has never been explicitly used to also prevent and treat the co-occurrence with depression, despite physical activity interventions being associated with the largest reductions in pain, disability, and depressive symptoms. Moreover, clinical research on exercise training has shifted to exploring ways to augment protocols to improve self-efficacy, initiation and maintenance of exercise behaviors, and levels of physical activity. Although exercise training has immense potential to address the co-occurrence of physical and mental morbidity in older adults with knee OA and depressive symptoms, no such program has been designed to reduce barriers to participation and increase the effects of physical activity on the primary condition and sequelae.

4 * Provide the scientific or scholarly background, rationale, and significance of the research and how it will add to existing knowledge:

Knee OA and depression are both leading causes of disability worldwide and are responsible for significant physical and mental morbidity among older adults with multiple medical conditions. Patients with conditions that cause chronic pain and depression place a large strain on health care resources and result in increased health care expenditures, faster physical and mental decline, and greater mortality; a problem that will only continue to grow with the aging US population. There is a lack of coordinated medical care for older adults with knee OA and depressive symptoms, and if feasible and efficacious, a combined treatment strategy that could be implemented in primary care may serve as a clinical model for prevention and treatment in the context of musculoskeletal illness and psychiatric comorbidity in older adults.

Supporting Literature

1 * Provide a summary of current literature related to the research: ***If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer box below.***

Knee OA is a localized disease associated with aging that represents a failure of normal joint repair and is pathologically characterized by synovial inflammation, degradation of articular cartilage, and changes to subchondral bone (1). The condition often manifests with symptoms of pain and disability, but there is heterogeneity in its clinical presentation, reflected by diverse measures of structural severity, patient-reported measures of symptomology, and physical performance assessments (2). Previous studies have identified different groups of OA patients with unique constellations of symptoms, in particular, a depressed mood phenotype, which is associated with muscle weakness, greater pain severity, more functional disability, and slower gait speed (3, 4). Disease progression may occur faster in the 20% of OA patients with depressive symptoms and other psychosocial impairments, and receipt of clinical care for depression is an integral part of medical management (5-7).

Comorbid depression is associated with lower quality of life, greater healthcare use and cost, and increased mortality rate in OA patients (8, 9). Despite its detrimental effects, depression is under-recognized and under-treated in OA patients, likely due to the variability in expression of depressive symptoms (10-12). Physicians evaluate and treat depression based on the presence and absence of a single, clinically and etiologically heterogenous syndrome, which combines disparate symptoms together in a way that results in a loss of information that is critically relevant to intervention efficacy and effectiveness (13). This one size fits all approach may explain why single treatments focused on either the primary condition or sequelae are often ineffective in patients with chronic physical diseases (such as knee OA) and comorbid depression (14). Current interventions for knee OA patients with comorbid depression lack specificity, and an approach that targets the specific needs of this group may provide for more effective clinical care (13, 15).

Research indicates the relationship between OA disease severity and depressive symptoms is bidirectional: arthritis symptoms can affect depression onset and severity over time, and depression may cumulatively impact OA pain, disability, and disease progression (15-18). For example, evidence indicates that among OA patients increases in pain severity are associated with worsening of depression (16). Slow gait speed has also been shown to result in a two-fold increase in risk of experiencing severe depressive symptoms (19). Conversely, research has demonstrated that depressive symptoms among individuals with knee OA are independently predictive of greater pain severity and worse physical performance, which may lead to a higher likelihood of structural disease progression (15, 17, 18). These bidirectional effects may form a positive feedback loop, where each condition exacerbates the severity of the other over time, and addressing this synergism is necessary to increasing the efficacy of a treatment protocol for these patients.

Clinical care for knee OA patients emphasizes pain management using analgesic medications, and in the presence of significant functional limitations, surgical intervention (20). Whether depression influences OA disease severity through biological, psychological, or behavioral mechanisms, the distal impact on clinical outcomes may be decreased treatment efficacy, where depressive symptoms act as a treatment effect modifier (21). This hypothesis is supported by qualitive research identifying depression as a factor that interferes with self-management of pain and physical activity in knee OA patients (22, 23). In addition, studies examining analgesic treatment outcomes in OA patients found that depressive symptoms were associated with a higher probability of inadequate pain relief (24, 25). The influence of comorbid depression on clinical outcomes is not limited to pharmacological treatment but extends to surgical intervention. Depressive symptoms are associated with a greater likelihood of total knee replacement, higher post-operative pain, and more 30-day hospital readmissions for surgical complications (26-28). For successful medical management, older adults with knee OA and comorbid depression require a treatment protocol that directly addresses symptoms of both conditions in order to disrupt the positive feedback loops that form between OA disease severity and depressive symptoms.

Designing interventions for OA patients with depressive symptoms requires an understanding of the population treatment patterns and patients preferences and experiences with depression interventions. Depression treatment in OA patients not only reduces depression severity but also lessens pain and disability, and although guidelines advise considering modifiable factors when managing OA disease severity, depressive symptoms are under-treated in OA patients (10, 29-31). In those with knee OA and comorbid depression, fewer than half receive mental health care services, and this clinical care gap increases as general health declines (10). In general, patients are open to receiving non-pharmacological depression interventions and combined treatment protocols (32). Furthermore, nationally representative survey data suggests that two-thirds of depressed OA patients have taken antidepressants, which may be for the treatment of chronic neuropathic pain (30, 33). By contrast, fewer than 20% of knee OA patients with comorbid depression have used combination therapy, which is not surprising because only two protocols using more than one intervention simultaneously have ever been designed for these patients (30, 34, 35). Evidence suggests antidepressants are a feasible method for pain management in depressed OA patients that could be combined with another intervention (e.g., exercise) with demonstrated efficacy.

Research has demonstrated that exercise training reduces depressive symptoms in OA patients, but existing studies are limited to interventions designed for other purposes and were tested in general samples (36, 37). Only three clinical trials have examined depression interventions in OA patients with comorbid depression, and none utilized exercise training or a combined treatment protocol (29, 38, 39). These studies evaluated depression interventions that provided improved access to care or stepped clinical treatment using antidepressants, psychotherapy, and/or pain self-management (29, 38, 39). Unfortunately, the effects of interventions focused solely on depression in OA patients decline with greater initial pain severity and functional disability.(40) Exercise training in OA patients is associated with larger decreases in depressive symptoms, pain, and disability than other non-pharmacological interventions and may offer the greatest efficacy among available depression treatments (36, 37, 41, 42). However, adherence to exercise training protocols in OA patients is low, primarily due to the chronic pain associated with the condition, but also poor psychosocial health (23, 43). Combined treatment protocols have shown greater efficacy compared to standard care in OA patients and can be used to negate the limitations of a single intervention (34, 35). The current study proposes exercise training to treat depressive symptoms and reduce OA disease severity in knee OA patients with comorbid depression and an antidepressant complement to mitigate chronic pain and enhance psychosocial well-being and physical activity.

References

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2 If available, upload your applicable literature search:

Name	Created	Modified Date

There are no items to display

Study Procedures

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below. (If this study is a collaborative UM/VA study please list each procedure that is being conducted and the locations where it is being conducted.)

1 * Describe all procedures being performed for research purposes only (these procedures would not be done if individuals were not in the study) and when they are performed, including procedures being performed to monitor subjects for safety or to minimize risks:

Overview: Potential participants will be identified from existing data sources that include the 1) VISN5 Corporate Data Warehouse, EPIC clinical data, and ResearchMatch.org and 2) study advertisements disseminated by the research team within electronic and print mediums and other digital platforms using a private sector company (BuildClinical Inc.) specializing in online recruitment for academic research studies. Identified participants will be pre-screened by telephone (15-30 minutes) and those who satisfy pre-screening criteria will be invited to complete two in-person screening visits (4-6 hours) that will each last 2-3 hours. Eligible participants who choose to enroll into the study will experience a 12-week hybrid aerobic exercise program, during which they will be taking the study medication (duloxetine), as prescribed by the study psychiatrist. Before the exercise program starts, participants will complete two testing visits that will each last 1-2 hours and assess mental status and functional capacity as described below and third visit in which they meet with the psychiatrist to receive the medication prescription. These study visits will essentially be repeated at the conclusion of the 12-week hybrid aerobic exercise program to determine what, if any, impact our interventions (exercise and duloxetine) had on participants' physical and mental health. A more complete description of procedures is below.

Telephone Interview Pre-Screening (15-30 minutes): Potential participants who are identified from advertisements or existing data sources will be contacted by telephone to confirm initial eligibility. With oral consent, participants will be screened for English language speaking ability, age of 40 years or older, and the presence of symptomatic knee OA: 1) having been told by a doctor he/she has OA in one or both knees; 2) knee pain, aching, and stiffness, on most days for at least one month; 3) current pain of "moderate" or greater on a Likert scale; and no plans to undergo surgical intervention for knee OA in the next 3 months. Pre-screen questions will also assess current mood to determine whether individuals have or at risk for depressive symptoms and/or major depression using the 9-Item Patient Health Questionnaire ([PHQ-9] score >= 6) as well as evaluate their willingness to participant in exercise training and take a prescription medication. Additionally, we will examine current exercise habits and prescription and non-prescription medications and any over the counter supplements. Individuals' current medications will be reviewed and documented by the study psychiatrist, who will assess potential participants' suitability to take duloxetine in the context of any pharmacotherapies they may be receiving, including any other commonly prescribed medications. Participants satisfying pre-screening criteria who are determined to be eligible to receive duloxetine will be invited to in-person screening visits.

COVID-19 Precautions for In-Person Study Visits: Study procedures and staff will adhere to CDC guidance and UMB and VA policies to minimize the risk of COVID-19 infection due to study participation. Strict social distancing and COVID-19 prevention strategies will be followed for all in person visits.

Phase 1: Physical and Mental Health Screening Assessments:

Screening - Visit 1 (120-180 minutes): The first in-person screening visit will take place at private offices at the VA Maryland Health Care System (VAMHCS) Geriatric Research Education and Clinical Center (GRECC) to determine if participants meet initial inclusion and exclusion criteria. The informed consent form and HIPAA form will be reviewed with the participant in a private room. Adequate time will be allowed to answer all the prospective participant's questions and concerns, and a short five question survey will be completed by the participant to ensure an understanding of the informed consent form and research study procedures. A copy of the signed informed consent form will be provided to the participant, and the attending staff member will also complete a documentation of the informed process attesting that such procedures comply with relevant regulatory policies and pertinent aspects of the study protocol. Enrolled patients will first complete a Participant Information Form and then the PHQ-9 to re-screen for being at risk of depressive symptoms and/or major depression (PHQ-9 score >= 6), those not meeting screening criteria will be thanked for their time, while eligible patients will continue with the enrollment process. The Mini Mental State Examination (MMSE) will then be administered to evaluate for cognitive impairment (MMSE score < 20), and persons with symptoms of dementia will be thanked for participating in the study. A Structured Clinical Interview for DSM-V (SCID-5) will be performed to gather information to diagnose relevant psychiatric conditions. With participants' approval, SCID-5 interviews will be audio recorded and reviewed for staff training and quality control purposes to ensure fidelity. Participants satisfying mental health screening criteria will be invited back for a second screening visit. Individuals who are determined to be ineligible will be thanked for their time, and any excluded participants with potential psychiatric comorbid condition(s) will be provided a brochure for mental health care resources.

Screening - Visit 2 (120-180 minutes): The second screening visit will take place at the GRECC clinical offices and include a medical history and physical examination with the study geriatrician to assess their suitability for exercise and continued eligibility. This process will include a fasting blood draw (approximately two tablespoons) to measure electrolyte, hormone, lipid, and cholesterol levels and to determine an average blood sugar level over the past three months. After completing the fasting blood draw, participants will be provided a snack and the opportunity to eat before continuing with other screening procedures. Premenopausal and perimenopausal women, defined as those who have had a normal menstrual period in the previous 12 months, will provide a urine sample for a pregnancy test. Premenopausal and perimenopausal women who have a negative pregnancy test that are sexually active will also be assessed regarding their current practices regarding methods to prevent pregnancy. Individuals who do not pass the medical history and physical evaluation, which could be due to any condition deemed by the study team to endanger the health of the participant or unduly confound the results, will be restricted from study participation.

Phase 2: Pre-Exercise Program Testing Visits:

Baseline Data Collection – Visit 1 (60-90 minutes): Enrolled participants will complete structured data collection and physical performance testing at the VAMHCS GRECC prior to starting the treatment protocol. Structured data collection will consist of questionnaires evaluating joint pain, disability, stiffness, and health-related quality of life; affective symptoms and pain catastrophizing; and fatigue, sleep impact, self-efficacy, and patient activation and readiness for health behavior change. Physical performance evaluations will include timed chair stand test, 20-meter fast paced walk test, timed up and go test, and 6-minute walk test. These procedures are described in more detail below.

1. Timed Chair Stand Test: a lower extremity test to assess leg strength and endurance. Participants are instructed to sit in the middle of a chair and place their hands on the opposite shoulder, crossed at the wrists, while keeping their back straight, feet flat on floor, and arms against chest. On the word "Go," timing of participants begins, and the number of times that he/she comes to a full standing position in 30 seconds is counted.

2. Timed Up and Go Test: a physical performance evaluation designed to assess mobility. Participants wear their regular footwear and can use a walking aid, if needed. They begin by sitting back in a standard armchair and a line 10 feet away on the floor is identified. Participants then get up from the chair and walk to the line on the floor, turn around, walk back to the chair, and sit down; timing begins on the word "Go" and stops when the participants sit down again.

3. 20-meter Fast Paced Walk Test: a reliable and valid measure of physical performance among older adults with knee osteoarthritis. Participants will be directed to walk at their usual pace from a starting point to an orange cone 20-meters away. Timing with a stopwatch will begin after the first step from the starting line and end when the first step goes over the finishing line. Participants can use a walking aid, if needed, and will be recorded on the data collection form. Two trials will be conducted, and the average time was used.

4. 6-Minute Walk Test: a sub-maximal exercise test used to assess aerobic capacity and endurance. The objective is to walk as far as possible for 6 minutes back and forth in a hallway between two cones, 30 meters apart, while pivoting briskly around the cones and continuing back the other way without hesitation. Patients will be exerting themselves, and they may get out of breath or become exhausted. Participants will be permitted to slow down, stop, and rest as necessary, as well as lean against a wall while resting, but will resume walking as soon as possible. The distance covered over a time of 6 minutes is measured.

Baseline Data Collection – Visit 2 (90-120 minutes): Enrolled participants (n=20) for Aim 2 will complete semi-structured data collection in the form of a qualitative interview at the VAMCHS GRECC after structured assessments and physical performance testing. Qualitative interviews at baseline among participants will consist of open-ended questions assessing patient's perspectives on arthritis knee pain and depressive symptoms, the co-occurrence of the two conditions and salient attributes, potential treatment options, as well as patient activation and readiness for health behavior change.

A graded exercise test (GXT; described below) will also be administered, where electrodes monitor heart rhythm, and results will inform individualized training plans for each participant as defined by peak heart rate. Participants will be asked to exercise to voluntary exhaustion on a treadmill. The GXT will be performed by a VA staff clinician (MD, CRNP, PA-C) trained in this procedure and certified according to IRB approved GRECC guidelines with the assistance of CPR-trained exercise physiologists and nurses. GXTs are stopped if participants reach the end of the testing protocol, indicate they are unable to continue or they experience any of the following: chest pain, dizziness, faintness, fatigue, pallor, cyanosis, cardiac arrhythmias or decompensation, or hyper-or hypotension.

GXTs will also assess cardiovascular health and safety of exercise training. Participants walk or jog on the treadmill up a grade as long as possible (usually 6-10 minutes). Treadmill speed and grade are increased every 1-3 minutes during the test. Heart rate and electrocardiogram are monitored continuously, and blood pressure is monitored every 2-3 minutes for the duration of the test and recovery period. Results from GXTs will be documented by research staff, and individuals who exhibit symptoms of cardiac or pulmonary disease according to New York Heart Association Class 3 or higher which would preclude safe exercise participation will be excluded. Patients who cannot safely exercise will receive information on how to follow-up with their normal medical provider(s) for clinical care and/or evaluation by a cardiologist.

Phase 3: Duloxetine Medication Prescription Visit:

Clinical Psychiatry Visit (30-45 minutes): Participants will have study visits with the psychiatrist at the University of Maryland Baltimore (UMB) General Clinical Research Center (GCRC). At the initial visit, the psychiatrist will conduct a clinical interview to collect mental health history data and will evaluate patients in terms of their mental status and depressive symptom severity and provide participants with a medication prescription for duloxetine. Duloxetine is an FDA-approved selective serotonin and norepinephrine reuptake inhibitor approved for the treatment of neuropathic pain in knee OA patients, and participants will be responsible for filling their medication prescriptions with support from research staff and taking the drug regularly as indicated by the physician. Individuals who are currently taking an antidepressant will be required to taper off their existing medication, which generally takes between one to two weeks, completed under the direction of the study psychiatrist. After meeting with the study psychiatrist, participants will be provided with a prescription for the study medication, duloxetine, which they will obtain immediately following the visit at the UMMC Pharmacy at Weinberg at no cost to them. Prescriptions will be provided in a 90-day supply (160 - 30 mg pills). Everyone will have a starting dosage of 30 mg/day and be titrated up to a daily optimal dosage of 60 mg/day as tolerated. Participants taking an antidepressant other than duloxetine at enrollment will transition to the study medication after tapering off their current pharmacotherapy.

Participants will be contacted on a biweekly basis by research staff throughout the duration of the study to complete a telephone-based interview to assess for potential drug-related adverse events as well as medication adherence. At the first Biweekly Medication Telephone Assessment, we will evaluate for any initial reactions to taking duloxetine and/or tapering from an existing prescription medication. If no problems are reported based on participant responses, they will be instructed to increase duloxetine dosage to 60 mg/day as prescribed, and/or continue the medication taper and transition as instructed by the study psychiatrist. When participants report any non-urgent possible drug side effects, they will be instructed to continue taking duloxetine at their current medication dosage, and research staff will contact the study psychiatrist for guidance and respond to participants with 24 hours. Potential medication-related adverse events will be documented, evaluated, and reported in accordance to study procedures. In the instance of an acute medical emergency related to their mental health or prescription medication, participants will be instructed to activate emergency care using 911.

Phase 4: Exercise Training Program combined with Duloxetine:

Hybrid aerobic exercise program: After starting duloxetine, patients will be participating in a walking program conducted three times per week, which will last 12 weeks. The aerobic exercise treatment plan will be a hybrid walking program that is expected to be completed 1 day per week at the Baltimore VA Medical Center's exercise facilities (VA Baltimore Annex or VA Loch Raven) and 2 days per week at home. Every participant will be given a Fitbit device for the at home portion of the exercise program to record daily step counts. The step count should reach a minimum of 7,000 steps per day, at least two days each week, which will not include the day they exercise at a VA facility. At center-based sessions, participants will be under the direct supervision of an exercise physiologist while they complete the treadmill walking program, and they will also be asked about their at-home exercise participation during this time. Furthermore, the objectively monitored physical activity data (e.g., daily step counts) recorded by participants' Fitbit devices will be downloaded regularly by study staff for data collection purposes to assess the at-home portion of the hybrid aerobic exercise program.

Training programs are individualized based on each participant's walking capacity and defined by peak heart rate (HR max) achieved during baseline GXT. Supervised exercise will be started conservatively with a goal of 15 minutes total duration at 40-50% Heart Rate Reserve (HRR) determined according to the formula of Karvonen (Training target HR = %(HRmax - HRrest) + HRrest). Individuals unable to walk continuously will exercise intermittently for several minutes as tolerated, with rest intervals, and advanced as tolerated. Treadmill training velocity and/or incline and duration are gradually increased as tolerated to reach the goal of 60-75% of HRR and 50 minutes. To assess treatment fidelity, research staff will monitor progression weekly. Heart rate, blood pressure, and blood glucose (for diabetic subjects) will be measured pre- and post-exercise sessions. Rating of perceived exertion will be measured post exercise session only. Heart rate and/or blood pressure may also be assessed periodically throughout the training session. During weekly exercise training sessions, physiologists will routinely evaluate participants overall health and well-being regarding the effects and potential adverse events of the exercise program. Any potential adverse events related to the exercise program will be documented, evaluated, and reported in accordance with general study procedures.

Phase 5: 12-Week Testing Visits (after completion of the hybrid exercise training program)

12-Week Follow-up - Assessment 1 (60-90 minutes): Approximately twelve weeks after starting the treatment protocol, participants will return for a second visit at the GCRC to complete structured data collection and meet with the study psychiatrist to assess their mental health status and depressive symptom severity and evaluate the need to modify medication dosage. Structured data collection will include the same self-administered surveys described previously for baseline in addition to an interviewer-administered assessment of expected adverse event outcomes. This final visit with the psychiatrist will be designed to create a maintenance of the pharmacologic treatment effect. Participants who complete the treatment program will receive a final 90-day prescription (90 – 60 mg pills) for duloxetine that will be filled at the UMMC Pharmacy at Weinberg and a letter with instructions for continued treatment with their regular medical care provider. They will also be provided with a brochure with local mental health care resources that are available to them.

12-Week Follow-up - Assessment 2 (60-90 minutes): The second 12-week follow-up evaluation at the VAMHCS GRECC will include a qualitative interview and physical performance tests. Semi-structured data collection during Aim 2 follow-up assessment at 12-weeks will consist of a post-treatment qualitative interview focused on the acceptability of the modified intervention in terms of its strengths, weaknesses, barriers to adherence, self-efficacy, and maintenance of the treatment protocol. At the second 12-weeks follow-up assessment, participants will also complete physical performance testing at the VAMHCS GRECC. These tasks will include the following assessments: timed chair stand test, timed up and go test, 20-meter fast paced walk test, and 6-minute walk test. Individuals who drop out and do not attend the 12-week follow-up visits will be contacted by telephone to determine the reasons for withdrawing from the study.

Data Storage and Security:

All research data will be assigned a participant number, and the only paper document that will contain both identifiable information and participant number will be the participant information form. The link file connecting the participant's name to their ID number will be kept electronically, in a password protected file behind the UMB firewall. Access to the link file will be limited to only study staff listed on this protocol. After the study project is complete, original hard copies will be kept at the VA for final storage (Geriatric Research Education and Clinical Center [GRECC], Baltimore VA Medical Center [BVAMC]). Copies will be stored in a locked cabinet in a locked office at UMB (Division of Gerontology, University of Maryland School of Medicine [UMSOM]) and associated electronic files will be secured by the Division of Gerontology (Department of Epidemiology and Public Health, UMSOM) on the I Drive of the UMB computer network.

Study documents will include:

1. Forms with identifiable information: Recruitment materials, informed consent forms, HIPPA authorization forms, evaluation of ability to complete informed consent forms, documentation of informed consent form, VA acknowledgement of notice of privacy practices, participant information form, exercise prescriptions, exercise training logs, and exercise test reports.
2. Coded data: hard copies of clinical assessment forms, qualitative interview forms and notes, surveys, physical performance assessments and coded electronic data.
3. Electronic audio recordings

1) Documents with identifiable information

Recruitment materials, informed consent form, HIPPA authorization forms, evaluation of ability to complete informed consent form, VA acknowledgement of notice of privacy practices, and documentation of informed consent form contain participants' names but not their project ID number. The only paper document that will contain both identifiable information and participant number will be the participant information form. Documents with identifiable health information will be collected at the GRECC and transported in a locked bag to be stored at the VA in a separate locked cabinet in a locked office (GRECC, BVAMC, 10 N. Greene Street, 4th floor, Room 4B-190, Baltimore, MD 21201). Documents with identifiable information that will be generated and exist outside of the VAMHCS environment for any amount of time will be secured and transported using a locked bag and secured in VA GRECC Offices.

Exercise prescriptions, exercise training logs, and exercise test reports contain participants' names but not their project ID number. Exercise prescriptions and training logs are kept in a separate locked cabinet in a locked office at the VA (VA Annex, 209 W. Fayette Street, Baltimore, MD 21201; VA Loch Raven Medical Center, 3900 Loch Raven Blvd, Baltimore, MD 21218). Exercise testing and reports to determine study eligibility will be completed and stored at the GRECC offices in the BVAMC in locked cabinets in a locked office (GRECC, BVAMC, 10 N. Greene Street, 4th floor, Room 4B-190, Baltimore, MD 21201). Completed reports will be stored in a locked cabinet in a locked office in the same location.

2A) Coded data, hard copies

Original hard copies of research assessments will be stored in a locked cabinet in a locked office (GRECC, BVAMC, 10 N. Greene Street, 4th floor, 4B-190, Baltimore, MD 21201). Research assessments completed outside of the VAMCHS will be secured in a locked bag and transported to the BVAMC to be stored in the same location. Copies will be transported in a locked bag to UMB for data entry and stored in a locked cabinet in a locked office (Division of Gerontology, UMSOM, Howard Hall, 660 W. Redwood Street, 2nd floor, Room 220, Baltimore, MD 21201). Access to coded research assessments will be limited to only research team members listed on this protocol.

2B) Coded electronic data

The data manager within the UMSOM Division of Gerontology will create a Microsoft Access database according to the PI's specifications. Paper copies of coded research data will be entered into the database and stored and managed by study staff. Finalized database information will be converted to analytic datasets for statistical analyses. Electronic data will be stored in user-restricted folders on the UMSOM computer network behind the institutional firewall and only accessible to the PI and other study staff. The UMSOM computer network backups data daily and uses industry standard security mechanisms and two-factor authentication for all users. These measures will ensure the confidentiality and security of electronic study data and other related private health information.

3) Electronic audio recordings

Audio recordings will be collected at the VAMHCS and recorded using a VA-approved (e.g., Olympus – DS7000; Philips – DPM8000; or Digitalk, Inc. – Sparky Plus USB Recorder) and encrypted, portable, digital audio recording device, and files will be directly saved to the UMB computer network. Audio files may be reviewed for supervision and research purposes by the PI, Co-Investigators, and other members of the study staff. Electronic audio recordings will be stored on the UMB and VAMHCS computer networks in user-restricted folders behind firewalls. Transcriptions of qualitative data will be conducted by study staff using Dragon Dictation Software (Professional Version) and stored in the same manner as the audio files. Transcriptions of qualitative interviews will then be processed and analyzed in the UMB Division of Gerontology (Howard Hall, University of Maryland School of Medicine, 660 W. Redwood Street, 2nd floor, Room 220, Baltimore, MD 21201). All audio recordings and transcriptions will be identified by codes only and will not contain participants' names. The link file connecting the participant's name to their ID number will be kept electronically in a password protected file behind the UMSOM firewall.

2 * Describe all procedures already being performed for diagnostic or treatment purposes (if not applicable to the study, enter "N/A"):

N/A

3 * Describe the duration of an individual participant's participation in the study:

Aim 1 and Aim 2 will involve different participants who will complete the following procedures over different time periods.

Aim 1 (N=10):

Telephone interview - 15-30 minutes
Enrollment visit 1 - 120-180 minutes
Enrollment visit 2 - 120-180 minutes
Baseline data collection visit 1 - 60-90 minutes
Baseline data collection visit 2 - 90-180 minutes
Clinical Psychiatry Visit: 30-45 minutes
Biweekly Medication Telephone Assessment: 10-15 minutes
Supervised aerobic exercise - 50 minutes per day, three times per week, for 24 weeks
12-week follow-up assessment visit 1 - 60-90 minutes
12-week follow-up assessment visit 2 - 45-90 minutes
12-week follow-up assessment visit 3 - 60-90 minutes
24-week follow-up assessment visit 1 - 60-90 minutes
24-week follow-up assessment visit 2 - 45-90 minutes
24-week follow-up assessment visit 3 - 60-90 minutes

Aim 2 (n=20):

Telephone interview - 15-30 minutes
Enrollment visit 1 - 120-180 minutes
Enrollment visit 2 - 120-180 minutes
Baseline data collection visit 1 - 60-90 minutes
Baseline data collection visit 2 - 90-120 minutes
Clinical Psychiatry Visit: 30-45 minutes
Biweekly Medication Telephone Assessment: 10-15 minutes
At-home aerobic exercise - 7,000 daily steps, two times per week, for 12 weeks
Supervised aerobic exercise - 20 to 50 minutes per day, one time per week, for 12 weeks
12-week follow-up assessment visit 1 - 60-90 minutes
12-week follow-up assessment visit 2 - 60-90 minutes

4 * Describe the amount of time it will take to complete the entire study:

Aim 1: approximately 2 years
Aim 2: approximately 3 years
Total duration: 5 years

5 * Describe any additional participant requirements:

N/A

Sample Size and Data Analysis

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * Provide the rationale and sample size calculations for the proposed target population:

For Aim 1 assessing treatment feasibility, we will use a sampling strategy driven by grounded theory framework, which is an iterative process involving the identification of thematic patterns surrounding a phenomenon of interest. The focus will not be on obtaining a generalizable (i.e., sample to population) group of participants, but rather information richness (i.e., depth and breadth) to understand the strengths and weakness of the protocol in the context of patients experience with depressive symptoms and depression treatment. Aim 1 will not have a pre-specified sample size, but methodologic research indicates that theoretical saturation on a construct of interest can be achieved with as few as twelve participants and decreases with more homogenous populations and narrower research objectives. Given the homogeneity of the target patient group and specificity of the research aim, we anticipate that 10 patients will be enough to evaluate protocol feasibility.

Recent methodologic work indicates that it is not possible to accurately estimate treatment effects in small samples, and recommendations advise assessing processes and parameters (e.g., screening rate, compliance, adverse events, etc.) that can be used for clinical trial design. With a planned overall recruitment of 30 patients during the five-year award period, which includes 10 patients for the Aim 1 feasibility assessment, the target sample size for the Aim 2 pilot test will be 20 patients to provide sufficient numbers to estimate design parameters with an adequate level of precision. To account for potential screen failures, the overall enrollment target will be 60 participants, allowing for up to 50% ineligibility at screening. The Aim 2 pilot study implementing the revised treatment protocol will also include qualitative data collection to further evaluate participants' experiences from a broader, patient-centric perspective, assessing additional construct domains relevant to intervention fidelity, as well as the strengths, weaknesses, and areas for improvement of the hybrid exercise training program. The Aim 2 target sample of 20 participants will also provide sufficient numbers to achieve theoretical saturation on the constructs of interest.

2 * Provide the plan for data analysis. Include in the description the types of comparisons that are planned (e.g., comparison of means, comparison of proportions, regressions, analysis of variance, etc.), which is the primary comparison/analysis, and how the analyses proposed will relate to the primary purposes of the study:

Aim 1 quantitative: Baseline survey data will be evaluated using descriptive statistics to assess sample characteristics of the study sample. Means and standard deviations will be reported for continuous measures, and frequencies and percentages will be calculated for categorical variables.

Aim 1 qualitative: In-person interview data from open-ended survey questions will be processed in to transcripts, coded, and subjected to an analytic theme. Verbatim transcripts will be created of all interview data so that sections of text can be analyzed in detail using a grounded theory approach. Grounded theory is a methodology that involves iterative development of theories about what is occurring in the data as they are collected, and the researcher looks for themes that emerge from the ground. Aim 1 qualitative data analyses will focus on patients' experience of depressive symptoms and depression treatment at study baseline and the strengths, weakness, and areas for improvement of the combined treatment protocol during follow-up. Quantitative characteristics will be integrated to qualitative data using thematic codes that describe the patients who are in each thematic grouping to further elucidate underlying concepts and characteristics associated with a given category.

Aim 2 quantitative: Descriptive statistics will be used to assess the baseline study sample characteristics obtained from patient-reported surveys. Means and standard deviations will be reported for continuous measures, and frequencies and percentages will be calculated for categorical variables. Clinical outcomes measured via surveys and performance tests will be examined in terms of pre to post treatment changes in pain, disability, depressive symptoms, and physical performance will be estimated, reported, and evaluated using paired t-tests. Recruitment will be assessed as the proportion of patients screened who met eligibility criteria and were consented per unit time. Attrition will be estimated as the percentage of patients dropping, and adverse events and reasons for drop out will be analyzed, categorized, and reported. Treatment compliance will be evaluated and reported separately for exercise training and duloxetine as the total number and proportion of completed exercise sessions and patient-reported medication adherence measures.

Aim 2 qualitative: In-person interview data from open-ended survey questions will be processed in to transcripts, coded, and subjected to an analytic theme. Verbatim transcripts will be created of all interview data so that sections of text can be analyzed in detail using a grounded theory approach. Grounded theory is a methodology that involves iterative development of theories about what is occurring in the data as they are collected, and the researcher looks for themes that emerge from the ground. Aim 2 qualitative data analyses will focus on patients' broader experiences in terms of their knee problems and psychological, emotional, and physical well-being in addition to the modified intervention strengths, weaknesses, and areas for improvement. Quantitative characteristics will be integrated to qualitative data using thematic codes that describe the patients who are in each thematic grouping to further elucidate underlying concepts and characteristics associated with a given category.

Sharing of Results

1 * Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared:

Results of research tests will be made available to the participant and his/her medical care provider if there is an impact on his/her clinical care or if requested by the participant. Results will only be shared with medical care providers after participants sign a release of information form.

ID: VIEW4E02808CBD800
Name: v2_Sharing of Results

Research with Drugs or Biologics

You indicated on the "Type of Research" page that your study involves use of unapproved drug(s)/biologic(s) or approved drug(s)/biologic(s) whose use is specified in the protocol AND/OR evaluation of food(s) or dietary supplement(s) to diagnose, cure, treat, or mitigate a disease or condition.

1 * List all drugs/biologics to be administered in this study. Be sure to list each drug/biologic with its generic name only.

	Drug Name	FDA Approved	IND Number	PI IND Holder
View	Duloxetine	yes		no

2 * Attach the drug package insert or investigational drug brochure for the drugs being administered in this study:

☐	Drug Package Insert(0.01)	11/23/2019 3:48 PM	11/23/2019 3:48 PM

3 If more than one drug is administered, discuss the risk implications of drug/therapy interactions:

4 * Will you be using Investigational Drug Services?

☐ Yes ☐ **No**

ID: VIEW4E0916E6E1400
Name: v2_Research with Drugs or Biologics

Drug or Biologic Storage and Handling

4.1 * Do you have a plan regarding access controls for essential and approproate research personnel?
☐ **Yes** ☐ No

4.2 * Will you have procedures for verifying physical access to the drugs(s)?
☐ **Yes** ☐ No

4.3 * Will you label the drug(s) so that it is (they are) used appropriately for the study?
☐ **Yes** ☐ No

4.4 * Will there be an establishment of a drug transfer process both into and out of the research site?
☐ **Yes** ☐ No

4.5 * Will the storage of the drug(s) be in a secure environment and include locks on doors and controlled access?
☐ **Yes** ☐ No

4.6 * Do you have a plan for only allowing trained personnel to administer the drug(s)?
☐ **Yes** ☐ No

4.7 If applicable, will the storage of the drug(s) be at the appropriate temperature, with a storage and temperature log?
☐ **Yes** ☐ No

Placebos

1

* Is this study placebo controlled?

☐ Yes ☐ **No**

Psychological/Behavioral/Educational Methods & Procedures

You indicated on the "Type of Research" page that your study involves a psychological/behavioral/educational method or procedure such as a survey, questionnaire, interview, or focus group.

1 * Select all behavioral methods and procedures which apply to this study:

- ☐ **Surveys/questionnaires**
- ☐ **Key informant or semi-structured individual interviews**
- ☐ Focus groups or semi-structured group discussions
- ☐ **Audio or video recording/photographing**
- ☐ Educational tests or normal educational practices (education instructional strategies, techniques, curricula, or classroom management methods)
- ☐ Individual or group behavioral observations
- ☐ Psychosocial or behavioral interventions
- ☐ Neuropsychological or psychophysiological testing
- ☐ Deception
- ☐ Other psychosocial or behavioral procedures

Surveys/Questionnaires

You indicated that this study involves surveys and/or questionnaires.

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * List all questionnaires/surveys to be used in the study, including both standardized and non-standardized assessments:

Self-reported measures:

Patient Health Questionnaire 9-Item (PHQ-9) Scale
Knee Osteoarthritis Outcomes Scale (KOOS)
Generalized Anxiety Disorder 7-Item (GAD-7) Scale
PROMIS Item Bank v1.0 Fatigue Short Form 8a
ASCQ-Me v2.0 Sleep Impact - Short Form
PROMIS Item Bank v1.0 Self-Efficacy for Managing Symptoms Short Form 8a
Pain Catastrophizing Scale (PCS)
Pain Stages of Change Questionnaire
Home Exercise Log

Interviewer-administered measures:

Participant Information Form
Mini-Mental Status Examination (MMSE)
Hamilton Depression Rating Scale (HAM-D)
Mental Status Exam
Biweekly Medication Telephone Assessment
Expected Adverse Event Outcome Assessment

2 * Upload a copy of all questionnaires/surveys:

Name	Created	Modified Date
Home Exercise Log(0.01)	6/12/2023 9:39 PM	6/12/2023 9:39 PM
Pain Stages of Change Questionnaire(0.01)	6/12/2023 8:52 PM	6/12/2023 8:52 PM
Participant Information Form(0.03)	2/3/2021 3:43 PM	2/11/2023 5:00 PM
MMSE(0.04)	11/23/2019 4:02 PM	2/11/2023 4:56 PM
PHQ-9(0.04)	11/23/2019 4:03 PM	2/7/2023 6:22 AM
Biweekly Medication Telephone Assessment(0.04)	1/25/2021 4:13 PM	2/7/2023 6:20 AM
Expected Adverse Event Outcome Assessment(0.03)	1/25/2021 3:59 PM	2/7/2023 6:09 AM
PCS(0.02)	11/23/2019 4:03 PM	2/3/2021 8:27 PM
KOOS(0.02)	11/23/2019 4:10 PM	2/3/2021 8:25 PM
HAM-D(0.02)	11/23/2019 4:10 PM	1/25/2021 6:00 PM
Mental Status Exam(0.01)	1/25/2021 4:08 PM	1/25/2021 4:08 PM
GAD-7(0.01)	11/23/2019 4:09 PM	11/23/2019 4:09 PM
PROMIS Item Bank v1.0 Fatigue Short Form 8a(0.01)	11/23/2019 4:09 PM	11/23/2019 4:09 PM
ASCQ-Me v2.0 Sleep Impact - Short Form(0.01)	11/23/2019 4:08 PM	11/23/2019 4:08 PM
PROMIS Item Bank v1.0 Self-Efficacy for Managing Symptoms Short Form 8a(0.01)	11/23/2019 4:06 PM	11/23/2019 4:06 PM

3 * What is the total length of time that each survey is expected to take?

Self-reported measures:

Patient Health Questionnaire 9-Item Scale: 5 minutes
Knee Osteoarthritis Outcomes Scale: 10 minutes
Generalized Anxiety Disorder 7-Item Scale: 5 minutes
PROMIS Item Bank v1.0 Fatigue Short Form 8a: 5 minutes
ASCQ-Me v2.0 Sleep Impact - Short Form: 5 minutes
PROMIS Item Bank v1.0 Self-Efficacy for Managing Symptoms Short Form 8a: 5 minutes
Pain Catastrophizing Scale: 10 minutes
Pain Stages of Change Questionnaire: 5 minutes
Home Exercise Log: 1 minute

Interviewer-administered assessments:

Participant Information Form: 10 minutes
Mini-Mental Status Examination (MMSE): 10 minutes
Hamilton Depression Rating Scale: 10 minutes
Mental Status Exam: 5 minutes
Biweekly Medication Telephone Assessment: 10 minutes
Expected Adverse Event Outcome Assessment:10 minutes

4 * Are any of the questions likely to cause discomfort in participants or cause harm if their confidentiality were breached? (i.e., Illegal activities)

☐ **Yes** ☐ No

5 * Do any questions elicit information related to the potential for harm to self or others?

☐ **Yes** ☐ No

5.1 If Yes, what procedures are in place to assure safety?

The GRECC and GCRC have established good clinical practice guideline SOPs on how, when, and what to communicate around safety issues. Should a mental health crisis arise, several procedures will be followed. First, the research staff will notify one of the study investigators. Second, a study investigator or trained research staff will assess the participant further to determine the presence of an intent or plan to harm self. Third, the study psychiatrist or clinical psychologist will be contacted, if possible, and will help determine whether further action is needed. Fourth, if determined to be necessary, a study investigator or a member of the research team will escort the participant to the VA Maryland Health Care System or University of Maryland Medical Center ER for further assessment.

ID: VIEW4E09460F5EC00
Name: v2_Surveys/Questionnaires

Interviews

You indicated that this study involves key informant or semi-structured individual interviews.

1 * Are any of the questions likely to cause discomfort in participants or cause harm if their confidentiality were breached? (i.e., Illegal activities)

☐ **Yes** ☐ No

2 * Upload a copy of the interview script or guide that will be used to guide the interviews:

Name	Created	Modified Date
Aim 2 Baseline Interview Guide(0.02)	2/5/2023 10:30 AM	6/12/2023 9:58 PM
Modified SCID-5-RV(0.03)	1/3/2021 10:47 AM	2/11/2023 4:50 PM
Aim 2 12-Weeks Follow-up Interview Guide(0.01)	2/5/2023 10:30 AM	2/5/2023 10:30 AM

3 * What is the individual duration of each interview and what is the entire duration of the interviews?

Modified SCID-5-RV: 60-90 minutes
Aim 2 Baseline In-depth Interview: 60-90 minutes
Aim 2 12-weeks Follow-up Interview: 30-60 minutes

4 * How will the interview responses be recorded and by whom?

SCID-5-RV and qualitative interviews will be recorded by research staff conducting the assessments. Participants will be recorded using an encrypted and VA-approved digital audio recording device (e.g., Olympus – DS7000; Philips – DPM8000; or Digitalk, Inc. – Sparky Plus USB Recorder) that will capture the entire conversation between the participant and staff member. Digital audio files will then be transferred and saved directly to the UMB and VA computer networks in a user-restricted folders. Transcriptions of qualitative data will be conducted by study staff using the VA-approved Dragon Dictation Software (Professional Version) and stored in the same manner as the audio files.

5 * Do any questions elicit information related to the potential for harm to self or others?

☐ **Yes** ☐ No

5.1 If Yes, what procedures are in place to assure safety?

The GRECC and GCRC have established good clinical practice guideline SOPs on how, when, and what to communicate around safety issues. Should a mental health crisis arise, several procedures will be followed. First, the research staff will notify one of the study investigators. Second, a study investigator or trained research staff will assess the participant further to determine the presence of an intent or plan to harm self. Third, the study psychiatrist or clinical psychologist will be contacted, if possible, and will help determine whether further action is needed. Fourth, if determined to be necessary, a study investigator or a member of the research team will escort the participant to the VA Maryland Health Care System or University of Maryland Medical Center ER for further assessment.

Audio or Video Recording/Photographs

You indicated that this study involves audio or video recording/photographing.

1

* Indicate the type of recording (check all that apply):

- ☐ Video
- ☐ **Audio**
- ☐ Still Photo
- ☐ Other

1.1

If Other, specify:

2

* What is the purpose of the recording? (i.e., for therapeutic purposes, to establish treatment fidelity, or to establish reliability of assessments)

Audio recordings of qualitative interviews conducted in Aim 1 will be used to capture and identify themes related to patients' personal perspectives.

Audio recordings will be used at baseline in Aim 1 to capture patients' experiences on how they perceive arthritis knee pain and depressive symptoms, the co-occurrence of the two conditions, and potential treatment options

Audio recordings will be used at 12-weeks and 24-weeks follow-up in Aim 1 to elicit feedback about the protocols strengths, weaknesses, and barriers to adherence as well as factors that facilitate the maintenance of the intervention, respectively.

3

* Could the recording be likely to cause discomfort in participants or cause harm if their confidentiality were breached?

☐ **Yes** ☐ No

4

* How will individuals' identities be protected?

Audio recordings will be recorded using a VA-approved (e.g., Olympus – DS7000; Philips – DPM8000; or Digitalk, Inc. – Sparky Plus USB Recorder) and encrypted, portable, digital audio recording device, and files will be transferred and directly saved to the UMB and VA computer networks. Transcriptions of audio recordings will be conducted by study staff using the VA-approved Dragon Dictation Software (Professional Version) and will be stored in a similar manner. Transcriptions for qualitative data analysis will be stored electronically and secured behind the UMSOM computer network firewall in a restricted access folder.

Sample Collection/Analysis

You indicated on the "Type of Research" page that your study involves a sample (specimen) collection and/or analysis.

1 * What type of samples will be involved in this study? (Check all that apply)

- ☐ **Prospective (will be collected)**
- ☐ Existing (previously collected at the time of initial IRB submission)

2 * Will genetic analysis/testing be done on any of the samples?

☐ Yes ☐ **No**

3 * Will this study involve banking of samples (storing for future research use)?

☐ Yes ☐ **No**

4 * What is the purpose of the sample collection and/or analysis?

Verification of eligibility criteria in the context of comorbidity exclusion parameters.

5 * Is there the possibility that cell lines will be developed with any of the samples?

☐ Yes ☐ **No**

6 * Will the samples be released to anyone not listed as an investigator on the protocol?

☐ Yes ☐ **No**

6.1 If Yes, give name(s) and affiliation(s):

7 * Will the sample material be sold or given to any third parties?

☐ Yes ☐ **No**

7.1 If Yes, give name(s) and address(es):

Prospective Samples

You indicated that the study involves collection of prospective samples (specimens).

1 * What type of sample will be collected? (Check all that apply)

- ☐ **Blood**
- ☐ Bone Marrow Aspirate/Biopsy
- ☐ Cerebrospinal Fluid
- ☐ Saliva
- ☐ Skin
- ☐ Sputum
- ☐ Stool
- ☐ Tissue
- ☐ Tumor
- ☐ **Urine**
- ☐ Other

1.1 If Other, specify:

2 For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subject's entire participation time:
A one time sample of approximately 2 tablespoons at the medical second screening visit.

3 * What type of samples will be collected? (Check all that apply)

- ☐ **Samples obtained specifically for research purposes-obtained via a separate collection procedure done solely for the purposes of the study**
- ☐ Samples obtained specifically for research purposes-additional taken during a clinical procedure
- ☐ Leftover samples that were obtained for clinical purposes (no additional research procedures required)
- ☐ Commercial (for profit) samples
- ☐ Other

3.1 If Other, specify:

4 * How are these samples labeled? For example, do they contain name, initials, dates, Social Security number, medical record number, or other unique code?
Samples will be labeled with full name, full social security number, date, and lab order number.

5 * Will sample(s) be made available to the research subject (or his/her medical doctor) for other testing?
☐ Yes ☐ **No**

6 * If a participant withdraws from the study, will that participant have the option to get the remaining portion of their sample(s) back?
☐ Yes ☐ **No**

7 * If the participant withdraws, explain how their sample(s) will be handled (For example, will sample(s) be destroyed, anonymized, etc.):
Samples will be destroyed after clinical tests are run.

8 * Will the samples be destroyed after the study is over?
☐ **Yes** ☐ No

8.1 If No, describe how the samples will be stored, where they will be stored, and for how long.

Data Collection/Record Review

You indicated on the "Type of Research" page that your study involves data collection or record review (i.e., chart review, not self-report).

1 * What type of data will be collected/analyzed in this study? (Check all that apply)

- ☐ Retrospective/Secondary Analysis (data has already been collected at the time of initial IRB submission)
- ☐ **Prospective (data is not yet in existence and/or collected)**

2 * Will this study involve adding data to a registry or database for future use?

☐ Yes ☐ **No**

3 * Will the data be released to anyone not listed as an investigator on the protocol?

☐ Yes ☐ **No**

3.1 If Yes, give name(s) & affiliation(s):

Prospective Data

You indicated that the study involves the collection of prospective data.

1 * Where is the data being collected from? (Check all that apply)

- [ ] Medical records
- [ ] Medical images
- [ ] Commercial (for profit) entity
- [ ] Publicly available records
- [ ] Schools
- [ ] **Other**

1.1 If Other, please specify:
Data is collected directly from the research participant.

2 * What data fields will you have access to/collect for the study? For example, name, initials, date of birth, Social Security number, income, demographic information, family units, housing, etc.
Prospective data fields that are being collected include self- and interview-administered survey measures, physical performance assessments, and physical activity information from Fitbit devices.

You can also upload a copy of the data fields/variables to be collected for the study:

Name	Created	Modified Date
There are no items to display		

Clinical Trial Registration

You indicated on the "Type of Research" page that your study is a clinical trial.

1 * Does the UM Clinical Trials Registry policy require registration of this trial?

☐ **Yes** ☐ No

2 * Has this trial been registered?

☐ **Yes** ☐ No

ID: VIEW4E093BF078C00
Name: v2_Clinical Trial Registration

Clinical Trial Registration Information

You indicated that this clinical trial has been registered.

1 * Was this trial registered at www.clinicaltrials.gov?

☐ **Yes** ☐ No

2 If no, was this trial registered on a site other than clinicaltrials.gov?

☐ Yes ☐ No

2.1 If Yes, specify the name of the other site:

2.2 Provide justification for registering this trial on this site:

3 * Registration Number

NCT04111627

ID: VIEW4E093BF1D0800
Name: v2_Clinical Trial Registration Information

Participant Selection

1 * How many local potential participants (or specimens/charts) do you anticipate will be screened for this study? ***Screening includes determining potential participants' initial eligibility for and/or interest in a study.***

750

2 * How many participants (or specimens, or charts) will be enrolled/used for this study? ***A local prospective participant is considered enrolled in the study when a UM-approved Informed Consent Document (not including separate screening consent forms) is signed.***

Local - the number being enrolled at this site:
60

Worldwide - the number being enrolled total at all sites (including local enrollment):
60

3 * Gender:

- ☐ **Male**
- ☐ **Female**

4 * Age(s):

- ☐ 0 to 27 days (newborn infants)
- ☐ 28 days to 12 months (Infant)
- ☐ 13 months to 23 months (Toddler)
- ☐ 2 to 5 years (Preschool)
- ☐ 6 to 11 years (Child)
- ☐ 12 to 17 (Adolescents)
- ☐ **18 to 88 years (Adult)**
- ☐ 89 years and older

5 * Race/Ethnicity:

- ☐ **All Races Included**
- ☐ American Indian or Alaskan Native
- ☐ Asian/Other Asian
- ☐ Asian/Vietnamese
- ☐ Black or African American
- ☐ Hispanic or Latino
- ☐ Mixed Race or Ethnicity
- ☐ Native Hawaiian or Pacific Islander
- ☐ White or Caucasian

6

* Language(s):

- ☐ **English**
- ☐ Chinese
- ☐ French
- ☐ Italian
- ☐ Japanese
- ☐ Korean
- ☐ Local Dialect
- ☐ Spanish
- ☐ Vietnamese
- ☐ Other

6.1 Specify Other:

7

* Are you excluding a specific population, sub-group, or class?

☐ **Yes** ☐ No

7.1

If Yes, indicate your justification for excluding a specific population, sub-group, class, etc.:

Pregnant and lactating women are excluded from the study because taking duloxetine could be dangerous for a baby. Women of child-bearing potential must have a negative pregnancy test during the history and physical evaluation prior to enrolling in the study.

Vulnerable Populations

1 * Will you be targeting ANY of the following Vulnerable Populations for enrollment? (Select all that apply)

- [ ] Employees or Lab Personnel
- [ ] Children (Minors)
- [ ] Cognitively Impaired/ Impaired Decision Making Capacity
- [ ] Pregnant Women/Fetuses
- [ ] Wards of the State
- [ ] Students
- [ ] Prisoners
- [ ] Nonviable Neonates or Neonates of Uncertain Viability
- [ ] Economically/Educationally Disadvantaged
- [ ] **None of the above**

Only select populations which you will be targeting for enrollment. Do not include populations that may be enrolled incidentally. Enrollment of a vulnerable population is considered to be "targeted" if the study team will be aware that a subject is from a vulnerable group as a result of interaction with the subject or collection of specific information about the subject, and the research team does not wish to exclude them. "Incidental" enrollment is limited to situations where a study team is unaware that a subject is from a vulnerable group.

Eligibility

1 * Do you have an existing Eligibility checklist(s) for this study?

☐ **Yes** ☐ No

1.1 If Yes, upload here. If you need a template, you can download it by clicking **HERE**. The checklists you upload will also be available under the Documents tab of this application.

Name	Created	Modified Date
Eligibility Checklist(0.03)	1/30/2021 12:35 PM	2/11/2023 9:20 PM

1.2 If No, create an eligibility checklist below:

List inclusion criteria (List each Inclusion Criteria individually, using the ADD button):

Number	Criteria
There are no items to display	

List exclusion criteria (List each Exclusion Criteria individually, using the ADD button):

Number	Criteria
There are no items to display	

After entering the inclusion and exclusion criteria above, click the Save link. CICERO will automatically generate a printable Eligibility Checklist for you to use in your research. To review the checklist, click on the resulting link below. This checklist is also available under the Documents tab of this application.

Eligibility Checklist for HP-00089160_9 v2-11-2023-1676168918007(0.01)

Recruitment

1 * Describe plans for recruitment, including the identification of potential participants (or acquisition of charts/records/samples) and initial interactions with them: (If this study involves the VA please list all sites at which recruitment will take place.):

The research team will utilize several recruitment mechanisms. First, potential participants will contact study staff directly in the University of Maryland Medical System and VA Maryland Health Care System. Interested participants that reach out to study staff or have agreed to be contacted will have their information provided to the research team through responses to advertisements and will be called by telephone and asked pre-screening questions about themselves regarding knee osteoarthritis, depressive symptoms, exercise, and medication use to assess study eligibility. They will also be asked whether their screening information can be entered into the IRB approved University of Maryland Claude D. Pepper Older Americans Independence Center (UM-OAIC) Registry (HP-00040461).

The Pepper Center registry is designed to collect and store information across research studies undertaken by investigators in the University of Maryland Baltimore (UMB) and VA. Thus, data collected in the current study will be entered into the registry and serve as a source of participants for future recruitment into new IRB approved studies carried out by UMB and VA researchers. As described in the Pepper Center Registry (HP-00040461), the only data that will be stored in the registry will be data that has previously been approved for collection by the IRB under this IRB application, and we are not requesting permission to collect new data. Only participants who approve having their data entered into the registry and agree to be re-contacted in the future for new studies will be entered in the registry. If at some time in the future participants wish to have their data removed from the registry, the data will be removed. The design and procedures related to the entry of data in the registry and their protection are detailed in HP-00040461, including the protection of PHI data by encryption and limiting access to the registry (i.e. by requiring a user name and password as well as access to the secured VA local network). If they do not wish to participate in the registry, the information will be collected on paper.

Second, we will use computer-based screening to identify potential participants with a knee OA diagnosis in the VISN 5 Corporate Database Warehouse and EPIC clinical data from the University of Maryland Medical System. A data pull of Social Security Numbers (SSNs) and/or patient contact information using the VA's Information and Computing Infrastructure (VINCI) and UMB's Clinical and Translational Research Informatics Center (CTRIC) will further enhance recruitment goals. This study already has an approved partial waiver of HIPAA Authorization for recruitment purposes. Potential participants identified from the VINCI data pull will be mailed a recruitment letter and an opt in/opt out post-card. Postage will be provided to allow for potential participants to indicate if they want to be contacted. The opt in/out post-card will not list a name and will only provide a letter number that is generated and stored in a password protected file on the VA computer network. If no response is received within two weeks, we will follow up with a phone call to gauge subject interest. Potential participants from the CTRIC data pull will first be contacted by email using REDCap, and they will have the ability to express their interest in the study using an embedded link. CTRIC electronic recruitment data in REDCap will not contain names and will have a participant contact number that is generated and stored in a user-restricted file on the University of Maryland Baltimore computer network. Individuals identified from EPIC clinical data who not have an email address will be contacted using recruitment letters, opt in/out post-cards, and eventually, a follow-up phone call to gauge interest if no responses are received.

A private sector company that specializes in online recruitment for academic research studies, BuildClinical, will assist with electronic dissemination of study advertisements. BuildClinical is a data-driven platform that helps academic researchers recruit participants for research studies more efficiently using social media, software, and machine learning. They utilize study-specific advertisements to engage participants on digital platforms such as Facebook, Google, WebMD, etc., and redirect them to a study-specific landing page should they click it. On the landing page, the person can complete an online questionnaire that gets routed into BuildClinical's platform. BuildClinical's Secure Socket Layer software, which encrypts all inputted information, keeps information private and HIPAA compliant, and the backend servers are stored in the USA at some of the most secure data centers in the world.

Lastly, ResearchMatch.org will be utilized as a recruitment tool for this protocol. ResearchMatch.org is a national electronic, web-based recruitment tool that was created through the NIH Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University as an IRB-approved data repository. A Contact Message created according to the UMB sample version will disseminated to potential participants using this electronic, web-based recruitment platform.

2 * Describe measures that will be implemented to avoid participant coercion or undue influence (if not applicable to the study, enter "N/A"):

At the time of recruitment, potential subjects are informed that the research study is voluntary. Opting not to participate will not affect their health care with their medical care provider. Potential subjects will be encouraged to take as much time as needed to decide whether they would like to participate. They will hear about the study in detail and carefully review the consent with trained staff. They will be encouraged to discuss the study and consent with family, friends, and their medical providers before signing the consent form. To ensure continued consent and understanding of the study procedures, participants may, at any time point, ask to review individual specific study procedures and any pre-procedure preparation they will need to do. Further, subjects are screened to ensure that they have an understanding of the study, adequate language and cognition to provide informed consent.

3 * Who will recruit participants (or acquire charts/records/samples) for this study? (Check all that apply)

- ☐ **PI**
- ☐ **Study Staff**
- ☐ Third Party

3.1 If you are using a third party, specify Third Party Recruiters:

4 Upload any recruitment tools such as screening/telephone scripts and introductory letters (do not upload advertisements here):

Name	Created	Modified Date
BuildClinical Screening Form(0.02)	5/10/2022 2:15 PM	3/2/2023 3:57 PM
BuildClinical Landing Page(0.02)	5/10/2022 2:15 PM	3/2/2023 3:54 PM
ResearchMatch Contact Message(0.04)	10/3/2021 9:53 AM	2/28/2023 6:05 PM
VA Recruitment Letter(0.07)	1/30/2021 2:18 PM	2/28/2023 6:03 PM
UMB Recruitment Letter(0.04)	10/3/2021 9:38 AM	2/28/2023 6:02 PM
CTRIC Email Blast Content(0.06)	10/3/2021 9:52 AM	2/28/2023 6:00 PM
UMB Opt In/Out Postcard(0.03)(0.02)	10/3/2021 9:39 AM	2/13/2023 7:23 PM
VA Opt In/Out Postcard(0.04)	2/2/2021 1:02 PM	2/13/2023 7:22 PM
Telephone Prescreening Script(0.11)	11/23/2019 5:52 PM	2/11/2023 9:55 PM

Advertising

1 * Will you be using advertisements to recruit potential participants?

☐ **Yes** ☐ No

ID: VIEW4E0BCCF811000
Name: v2_Advertising

Advertising Detail

You indicated that you will be using advertisements to recruit potential participants.

1.1 * Select the mode(s) of advertising (check all that apply):

- ☐ Radio
- ☐ **Internet**
- ☐ **Print**
- ☐ Television
- ☐ Other

1.1.1 If Other, specify:

1.2 * Provide exact text of all proposed advertisement(s):

Recruitment will involve study advertisements disseminated directly by research staff and BuildClinical through various print and online mediums and social media outlets. Recruitment materials are attached in "Advertising Details". Potential participants who respond to advertisements will be contacted by telephone about general aspects of the study. Once a potential participant responds to our advertisement, the initial interaction will consist of a pre-screening telephone call to inform the potential participant about the study and to assess initial eligibility. Obtaining information over the phone allows us to prescreen the subjects to eliminate subjects with obvious exclusions or those who do not have the disease or risk factors we are studying.

1.3 * Upload advertisement(s) here:

Name	Created	Modified Date
☐ BuildClinical Online Advertisements(0.02)	5/16/2022 10:36 PM	3/2/2023 4:01 PM

Research Related Risks

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer box below.

1 * Individually list each research-related risk, using a separate line for each. Next to each risk, delineate the likelihood/seriousness of the risk, and the provisions for minimizing the risk:

The following are risks for participants:

1. Exercise training is associated with the risk of cardiovascular complications such as chest pain, heart attack, or sudden death and complications related to stress and strains of muscles, twisted ankles, or falls. This risk is increased in patients who have heart disease. The American Heart Association estimates the risk of heart attack in these patients to be 1 in 60,000 hours of exercise. To minimize this risk, you will first undergo a medical evaluation and screening exercise treadmill test. The risk is lower in subjects with no evidence of heart disease. Exercise training programs are administered by exercise physiologists. Exercise physiologists are trained in CPR, and your heart rate and blood pressure will be assessed before and after each supervised training session or more frequently, if indicated. If blood pressure or heart rate go too high, or you develop an irregular heart rate, chest pain or leg cramps, the training will be stopped immediately. If these symptoms occur when exercising at home, you should also stop physical activity immediately, and when necessary, activate emergency medical by calling 911. There is a risk of low blood sugar with exercise. If you have diabetes, you should check your blood sugar before, during, or after exercise. If your blood sugar drops too low, sugar drinks and snacks should be consumed. If you have peripheral neuropathy (reduced feeling in your feet), there may be a risk of developing sores or ulcers on your feet. This risk is reduced by wearing proper footwear during exercise. Muscle soreness and injury can also occur during testing and aerobic exercise, but you will be taught proper stretching and exercise techniques to minimize this risk. If soreness does develop, we will work with you to reduce the soreness using stretching and ice. However, monitoring of the hybrid aerobic exercise program by trained personnel limits your risk for these occurrences. A clinical provider is on call and can be reached by phone for consult in case of any problems. Center-based training sessions will take place at a VAMHCS exercise facility. They will be supervised by exercise physiologists who are certified in exercise training and CPR. A clinical provider is on call and can be reached by phone for consult in case of any problems. Emergency medications and resuscitation equipment are available on site and should there be any unanticipated medical emergencies staff can initiate emergency care by calling 911. If 911 is activated, you would be taken to the nearest available hospital for care. We believe that it is highly unlikely that you will develop a medical emergency that would require the 911 system to be activated as in more than 25 years of training more than 1000 research subjects we have only had 1 subject who had a heart attack during aerobic training.

2. Duloxetine use is associated with the risk of potential adverse events. The most common medication side effects include nausea, upset stomach, trouble sleeping, headache, feeling dizzy, feeling confused, and excessive sweating. Uncommon adverse events are blood pressure fluctuations, severe skin rashes, sexual problems, liver disease or dysfunction, and abnormal bleeding among those taking aspirin, non-steroidal anti-inflammatory drugs, or anticoagulants. Additionally, individuals who taper off a similar medication, prior to initiating duloxetine, may experience a rebound of depression and/or anxiety, flu-like symptoms, headache, dizziness, insomnia, nightmares, nausea, vomiting, tiredness, irritability, and pins and needles. Medication tapering and transitioning to, as well as initiation and use of duloxetine, will be monitored by a medical specialist, and any adverse events that arise will be recorded and evaluated by research staff. During the instance of a medication-related event, participants will have access to a physician who will evaluate the situation and provide instructions as necessary, which may include reducing dosage or discontinuing the medication. In the unlikely scenario of a life-threatening adverse event, emergency care will need to be activated using the 911 system to address any serious medication-related side effects. Medication adherence and adverse events will be evaluated biweekly to identify and respond to any side effects and reduce the risk of more serious adverse events.

3. Pregnant, lactating women are excluded from the study. Women of child-bearing potential must have a negative pregnancy test during the history and physical evaluation prior to enrolling in the study. If you are sexually active, you could become pregnant while participating in this study, and taking duloxetine could be dangerous for the baby. You must take precautions to be sure that you do not become pregnant. The only methods that work well enough to be sure that you will not become pregnant are intrauterine devices (IUDs), diaphragms, sponges, condoms with foam, any hormone contraceptive therapy (oral contraceptives: "the pill", patches, or implants) and abstinence. If you think you might be pregnant while enrolled in this study, you will need to undergo a another pregnancy test, unless the following apply: you have had a normal menstrual period within 2.5 weeks, you are not sexually active, are not at risk for pregnancy, or you or your partner uses a permanent form of contraception.

4. The risks for exercise testing are minimal, but occasionally include fainting, dizziness, chest pain, or irregular heartbeats, and muscle soreness. A heart attack may occur, but this is extremely rare (less than 1 death in 10,000 tests) in people with no history of heart disease. Blood pressure, heart rate and rhythm, and breathing are continuously monitored by a medical doctor or Nurse Practitioner and personnel trained in CPR, exercise testing and emergency treatment. Emergency medications and resuscitation equipment are available. You may stop the exercise testing at any time if you feel distressed.

5. Assessments of physical performance involve a variety of timed walks, tests of balance, stair climbing, and getting up from a chair. There is a slight risk that participants will fall (small likelihood, moderate degree of seriousness). There is a risk that participants will experience leg claudication pain, chest pain, or become short of breath or dizzy during these tests (moderate likelihood, low degree of seriousness). Participants will be asked to inform the research staff of any symptoms they experience during these assessments and will be allowed to take breaks or stop assessment procedures as needed. Trained study personnel will be administering these tests. Study staff trained in CPR will administer these tests. Assessments will take place in a facility where emergency medications and resuscitation equipment are available.

6. Participants will provide blood samples as part of the screening process to determine eligibility. The risks for blood sampling include discomfort, bruising, swelling, fainting, and possible infection at the site of sampling. This is minimized by having skilled medical personnel perform the sampling. Participants will be told they can contact the research staff or the PI if they experience discomfort or complications at the blood draw site.

7. Distress during assessments and interviews (small likelihood, low degree of seriousness). Before consent and before and during data collection, participants are informed that they are free to decline to answer any question(s) or to discontinue at any time. If participants feel uncomfortable or fatigued, or seem so to the research staff, they are encouraged to take a break and continue again later, or to stop the interview. Research staff are trained to stop surveys/interviews if a participant becomes distressed and will have the resources needed to assist him/her in obtaining the level of support or assistance they require, including crisis intervention if needed.

8. Some participants may feel embarrassed when they have to answer questions that they may feel are personal (small likelihood, low degree of seriousness). To minimize this risk, participants are told before each assessment the nature of the questions being asked and are told to answer honestly but to feel free to not answer questions that make them feel uncomfortable. The study interviewer is trained to talk about personal material with patients and to engage in discussions in a supportive and empathic and nonjudgmental way.

9. Some participants may feel uncomfortable with being audio recorded (small likelihood, low degree of seriousness). There is also a slight risk of a breach of confidentiality regarding the identities of the participant on the recording. To minimize this risk, research staff will label all recordings with an anonymous code. Access to the file that links participant names to their project ID number will be stored behind the UMB firewall at research offices in the Department of Epidemiology and Public Health, Division of Gerontology suite (Howard Hall, 2nd Floor, Suite 200, 660 W. Redwood St., Baltimore, MD).

10. Participant may feel bored or tired due to the length of time required to complete the interviews/assessments (moderate likelihood, low degree of seriousness). To address this risk, participants will be given the option of scheduling the assessments over multiple visits. In cases in which a participant is tired or bored during an assessment/interview, he/she will be offered breaks or allowed to end the assessment and finish the remainder on another day.

11. Potential loss of confidentiality (small likelihood, moderate degree of seriousness). All project staff are thoroughly trained in issues relating to maintaining confidentiality of research data. There is a slight risk of a confidentiality breach related to data collected for research purposes from participant assessments and medical records. Study participants will be informed that information obtained through research interviews is confidential; potential risks to data security and the measures we take to protect it will be reviewed with them during the informed consent process. Numerous steps will be taken to ensure research interview data confidentiality and security. To protect confidentiality, hard copies of survey/interview data will be identified only by an anonymous code number assigned to each research participant and are kept in a locked file cabinet behind a locked office door at the VA Maryland Health Care System GRECC at the Baltimore VA Medical Center. Electronic audio recordings will be stored on the VA computer network in a user-restricted folder behind the VA firewall. Only designated research staff members have access to the password protected file that links participants' identities to their codes, which will be stored on the University of Maryland Baltimore computer network behind the firewall in user-restricted folder with multiple levels of industry standard security mechanisms. Original consent forms which contain participants' names are kept separately in locked cabinets in locked offices that are located in the VA Maryland Health Care System GRECC. Copies of paper and electronic data with identifiers will be stored within the Gerontology Division on the University of Maryland School of Medicine computer network, behind the institutional firewall, with several layers of password protection that are only known to the study team members. Electronic research data are backed up regularly. In the event of any incidents, unauthorized access of sensitive data or storage devices or noncompliance with security controls, the PI or another member of the research staff will immediately contact the appropriate personnel, including the VAMHCS Information Security Officer, Privacy Officer and the VAMHCS Research Compliance Officer and the University of Maryland IRB.

12. There are potential risks that may not yet be known.

Potential Benefits and Alternatives

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

1 * Describe the potential direct benefit(s) to participants:

Participants may or may not benefit by taking part in this study. There is no guarantee that participants will receive direct benefit from their participation in this study. They may experience decreases in arthritis knee pain and improvements in your mood and physical functioning. Also, participants may learn tools and strategies to decrease arthritis knee pain, improve your mood and emotional health, and increase your daily exercise. In addition, study participation may help the investigators learn more about how to promote physical and psychosocial well-being in adults with knee osteoarthritis and depression.

2 * Describe the importance of the knowledge expected to result from the study:

This research will contribute to our understanding of how to enhance adherence to exercise training using medication in adults with co-occurring musculoskeletal and affective disorders.

3 * Describe how the potential risks to participants are reasonable in relationship to the potential benefits:

The major risks to participants are boredom, embarrassment, potential loss of confidentiality, and physical discomfort and distress during physical performance assessments and treadmill testing, and potential adverse events related to aerobic exercise training and antidepressant medications. These risks are outweighed by the potential benefits of better understanding of how to enhance adherence to exercise training in adults with co-occurring musculoskeletal and psychiatric disorders. This understanding could lead to targeted interventions to reduce pain and functional disability and promote psychosocial wellbeing in this population.

4 * Describe the alternatives to participation in this study. If there are no alternatives, state that participation is voluntary and the alternative is not to participate. For intervention studies, describe appropriate alternative clinical procedures or courses of treatment available to subjects.

The study is voluntary. The alternative is to ask one's medical or mental health provider for a referral to an exercise program focused on increasing physical activity and/or a medication prescription for an antidepressant approved for the treatment of neuropathic pain and symptoms of depression, respectively.

Withdrawal of Participants

If the questions below are not applicable to the research (i.e., chart review), enter "N/A".

1 * Describe anticipated circumstances under which subjects will be withdrawn from the research without their agreement:
Participants will be withdrawn without their agreement under the following circumstances:

1) They experience severe distress during the study.
2) They fail to follow instructions from research staff.
3) If the PI decides that the study is no longer in the best interest of the participant.

These circumstances have been outlined in the informed consent form.

2 * Describe procedures for orderly termination:
We will close the study after the last participant interaction occurs and all data has been collected.

3 * Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection:
If a participant decides to withdraw from the research, all data already collected will be retained in pertinent data files, but no new data will be collected from the participant. This information is included in the consent form.

Privacy of Participants

If the study does not involve interaction with participants, answer "N/A" to the questions below.

1 * Describe how you will ensure the privacy of potential participants throughout the study ***(privacy refers to persons and their interest in controlling access to themselves):***

Research staff are thoroughly trained to protect the privacy of research participants. We meet with participants in private rooms with closed doors at the Geriatric Research Education and Clinical Center within the VA Maryland Health Care System and General Clinical Research Center at the University of Maryland Medical Center.

2 * Describe the location where potential participants will receive research information and detail the specific actions the study team will take to ensure adequate privacy areas:

Potential participants will receive research information in a private room with the door closed at the Geriatric Research Education and Clinical Center within the VA Maryland Health Care System and General Clinical Research Center at the University of Maryland Medical Center.

3 * Describe potential environmental stressors that may be associated with the research:

There are no environmental stressors associated with this research.

4 * Will this study have a site based in the European Union?

☐ Yes ☐ **No**

5 * Will the study have planned recruitment or data collection from participants while they are located in the European Union?

☐ Yes ☐ **No**

Access link below for information about the EU General Data Protection Regulations to assist in answering these questions.
https://www.umaryland.edu/oac/general-data-protection-regulation/

Confidentiality of Data

1 * Will stored research data contain identifiers or be able to be linked to and identify individual participants (either directly or through a code/research ID)?

☐ **Yes**

☐ No, the data will be stored de-identified/anonymous (stripped of all identifiers, no way to identify individual participants)

2 * Where will research data be kept (address electronic and paper data as applicable)? (If this is a VA study please list specific sites that data will be kept.)

1A. The VA electronic data for the feasibility study will be stored at the following drive path location: \\oitbalfpcrsch01\Grecc_share\Shared\Divuser\GRECC\shared\all\DEKODE

1B. The VA electronic data for the pilot study will be stored at the following drive path location: \\oitbalfpcrsch01\Grecc_share\Shared\Divuser\GRECC\shared\all\DEKO

2. The VA paper data will be stored on the 4th floor, Room 4B-190, of the Geriatric Research Education and Clinical Center within the Baltimore VA Medical Center.

3A. The UMB electronic data for the feasibility study will be stored at the following drive path location: I:\EPI\GERN\Alan\ExercisePlusDuloxetine

3B. The UMB electronic data for the pilot study will be stored at the following drive path location: I:\EPI\GERN\Alan\DEKO

4. The UM paper data will be stored on the 2nd floor, Room 220, of Howard Hall within the University of Maryland Baltimore School of Medicine.

5. Electronic audio recordings and corresponding transcriptions will be stored electronically on the VA and UMB computer networks in the same locations specified for #1A-B and #3A-B.

3 * How will such data be secured?

Data Storage and Security:

All research data will be assigned a participant number, and the only paper document that will contain both identifiable information and participant number will be the participant information form. The link file connecting the participant's name to their ID number will be kept electronically, in a password protected file behind the UMB firewall. Access to the link file will be limited to only study staff listed on this protocol. After the study project is complete, original hard copies will be kept at the VA for final storage (Geriatric Research Education and Clinical Center [GRECC], Baltimore VA Medical Center [BVAMC]). Copies will be stored in a locked cabinet in a locked office at UMB (Division of Gerontology, University of Maryland School of Medicine [UMSOM]) and associated electronic files will be secured by the Division of Gerontology (Department of Epidemiology and Public Health, UMSOM) on the I Drive of the UMB computer network.

Study documents will include:

1. Forms with identifiable information: Recruitment materials, telephone prescreening form, informed consent forms, HIPPA authorization forms, evaluation of ability to complete informed consent forms, documentation of informed consent form, participant information form, exercise prescriptions, exercise training logs, and exercise test reports.

2. Coded data: hard copies of clinical assessment forms, qualitative interview forms and notes, surveys, physical performance assessments and coded electronic data.

3. Electronic audio recordings

1) Documents with identifiable information

Recruitment materials, telephone prescreening forms, informed consent form, HIPPA authorization forms, evaluation of ability to complete informed consent form, and documentation of informed consent form contain participants' names but not their project ID number. The only paper document that will contain both identifiable information and participant number will be the participant information form. Documents with identifiable health information will be collected at the GRECC and transported in a locked bag to be stored at the VA in a separate locked cabinet in a locked office (GRECC, BVAMC, 10 N. Greene Street, 4th floor, Room 4B-190, Baltimore, MD 21201). Documents with identifiable information that will be generated and exist outside of the VAMHCS environment for any amount of time will be secured and transported using a locked bag and secured in VA GRECC Offices.

Exercise prescriptions, exercise training logs, and exercise test reports contain participants' names but not their project ID number. Exercise prescriptions and training logs are kept in a separate locked cabinet in a locked office at the VA (VA Annex, 209 W. Fayette Street, Baltimore, MD 21201; VA Loch Raven Medical Center, 3900 Loch Raven Blvd, Baltimore, MD 21218). Exercise testing and reports to determine study eligibility will be completed and stored at the GRECC offices in the BVAMC in locked cabinets in a locked office (GRECC, BVAMC, 10 N. Greene Street, 4th floor, Room 4B-190, Baltimore, MD 21201). Completed reports will be stored in a locked cabinet in a locked office in the same location.

2A) Coded data, hard copies

Original hard copies of research assessments will be stored in a locked cabinet in a locked office (GRECC, BVAMC, 10 N. Greene Street, 4th floor, 4B-190, Baltimore, MD 21201). Research assessments completed outside of the VAMCHS will be secured in a locked bag and transported to the BVAMC to be stored in the same location. Copies will be transported in a locked bag to UMB for data entry and stored in a locked cabinet in a locked office (Division of Gerontology, UMSOM, Howard Hall, 660 W. Redwood Street, 2nd floor, Room 220, Baltimore, MD 21201). Access to coded research assessments will be limited to only research team members listed on this protocol.

2B) Coded electronic data

The data manager within the UMSOM Division of Gerontology will create a Microsoft Access database according to the PI's specifications. Paper copies of coded research data will be entered into the database and stored and managed by study staff. Finalized database information will be converted to analytic datasets for statistical analyses. Electronic data will be stored in user-restricted folders on the UMSOM computer network behind the institutional firewall and only accessible to the PI and other study staff. The UMSOM computer network backups data daily and uses industry standard security mechanisms and two-factor authentication for all users. These measures will ensure the confidentiality and security of electronic study data and other related private health information.

3) Electronic audio recordings

Audio recordings will be collected at the VAMHCS and recorded using a VA-approved (e.g., Olympus – DS7000; Philips – DPM8000; or Digitalk, Inc. – Sparky Plus USB Recorder) and encrypted, portable, digital audio recording device, and files will be directly saved to the UMB computer network. Audio files may be reviewed for supervision and research purposes by the PI, Co-Investigators, and other members of the study staff. Electronic audio recordings will be stored on the UMB and VAMHCS computer networks in user-restricted folders behind firewalls. Transcriptions of qualitative data will be conducted by study staff using the VA-approved Dragon Diction Software (Professional Version) and stored in the same manner as the audio files. Transcriptions of qualitative interviews will then be processed and analyzed in the UMB Division of Gerontology (Howard Hall, University of Maryland School of Medicine, 660 W. Redwood Street, 2nd floor, Room 220, Baltimore, MD 21201). All audio recordings and transcriptions will be identified by codes only and will not contain participants' names. The link file connecting the participant's name to their ID number will be kept electronically in a password protected file behind the UMSOM firewall.

4 * Who will have access to research data?

The PI, co-investigators, and authorized research study staff listed on this protocol will have access to the research data. Access to data will be terminated for study staff that are no longer part of the research study.

Audio recordings of interviews collected for this study will be sent securely to a VA-approved transcription agency. These audio recordings will not contain any identifiable information.

5 * Will study data or test results be recorded in the participant's medical records?

☐ Yes ☐ **No**

6 * Will any data be destroyed? ***(Please note that data for FDA regulated research cannot be deleted however, VA data must be destroyed according to the VHA Records Control Schedule (RCS) 10-1)***

☐ **Yes** ☐ No

6.1 If Yes, what data (e.g., all data, some recordings, interview notes), when and how?

The investigators VA research records and any VA participant identifiers will be retained until the maximum retention period is reached, as defined by the Dept. of Veterans Affairs Records Control Schedule (RCS 10-1). When the maximum retention period is reached, the VA data may be destroyed using the most current data destruction methodologies that are available at the time of data destruction.

7 Do you plan to obtain a Certificate of Confidentiality?

☐ Yes ☐ **No**

7.1 If Yes, upload your Certificate of Confidentiality. If you have not yet obtained the Certificate, please note that once it is obtained, you will need to submit an amendment to attach the document, make any needed changes to the submission and make needed changes to the Informed Consent Document.

Name	Created	Modified Date

There are no items to display

8 * Discuss any other potential confidentiality issues related to this study:

In accordance with VA policy, procedures are in place for reporting incidents, i.e. theft or loss of data or storage media, unauthorized access of sensitive data or storage devices or non-compliance with security controls. Upon learning of such an incident, study staff will immediately report the incident to the VAMHCS PO, ISSO, and R&D Service.

Monitoring Plan Selection

1 * Type of data safety monitoring plan for the study:

- [ ] Will use/defer to the external sponsor's Data Safety Monitoring Plan
- [ ] **Data Safety Monitoring by a Committee**
- [ ] Data Safety Monitoring by an Individual
- [ ] There is no data safety monitoring plan in place

ID: VIEW4E1B00E30D400
Name: v2_Monitoring Plan Selection

Monitoring Plan - Committee

You indicated that the monitoring will be done by a Committee.

1 * Will the Committee be Internal or External?

- [ ] **Internal DSMB**
- [ ] External DSMB

2 * What data will be reviewed?

- [ ] **Adverse Events**
- [ ] **Enrollment Numbers**
- [ ] Patient Charts/Clinical Summaries
- [ ] Laboratory Tests
- [ ] Medical Compliance
- [ ] Procedure Reports
- [ ] Raw Data
- [ ] Outcomes (Primary, Secondary)
- [ ] Preliminary Analyses
- [ ] **Other**

2.1 If Other, specify:
QA audit reports.

3 * What will be the frequency of the review?

- [ ] Annually
- [ ] **Bi-Annually**
- [ ] Other

3.1 If Other, specify:

4 * Safety monitoring results will be reported to:

- [ ] **IRB**
- [ ] GCRC
- [ ] Sponsor
- [ ] Other

4.1 If Other, specify:

Monitoring Plan - Internal DSMB

You indicated that the monitoring committee will be an internal DSMB.

1 * List Internal DSMB Members:

	Name
View	Anjeli Inscore, Psy.D.
View	Stephen Seliger, MD
View	Lynda Robey, MS
View	Kathy Michael, PhD, RN, CRRN
View	Odessa Addison, DPT, PhD
View	Gretchen Zietowski, MS, RN
View	Jamie Giffuni, MS
View	Leslie Katzel, MD, PhD
View	Jacob Blumenthal, MD
View	John Sorkin, MD, PhD

2 * Confirm that no financial or other conflicts of interest exists for the above individuals.

☐ **Yes** ☐ No

3 * Will there be an interim efficacy analysis?

☐ Yes ☐ **No**

3.1 If Yes, when?

4 * Briefly describe the DSM review process itself. Will it be an open or closed review to the investigator? Blinded/unblinded data? How will confidentiality of individual participant data be maintained?

The SMB meets twice a year. This is a closed meeting. Investigators and team members who are listed on the research protocol are not allowed to vote on their own protocols. No PHI will be revealed when AEs are reviewed.

5 * What are the criteria defined in the protocol to be used for decision making regarding continuation, modification, or termination of study?

Failure to follow GCP, investigator non-compliance, may be grounds for suspension or termination of a study.

Research-Related Costs

1 * Is the study's financial supporter (e.g., commercial sponsor, federal or state grant or contract, private foundation, physician-sponsor) covering any research-related costs?

- [ ] No
- [ ] **Yes**

1.1 If Yes, check all that apply:

- [ ] **Research-Related Services (personnel costs, tests, supplies, exams, x-rays, or consultations required in the study)**
- [ ] Investigational or Study Device
- [ ] **Investigational or Study Drug**
- [ ] Investigational Procedure(s)

1.2 If No, who is responsible for payment?

2 * Who is responsible for the uncovered research-related costs?

- [ ] **Participant**
- [ ] Sponsor
- [ ] UM
- [ ] Other
- [ ] There will be no uncovered research-related costs

2.1 If Other, specify:

3 If the participant is responsible for any research-related costs, identify and estimate the dollar amount:
Participants will be responsible for the cost of traveling to the VAMHCS and UMB for study visits.

Compensation for Research-Related Injury

1 * Is this study under a master agreement that includes a provision requiring the sponsor to provide compensation to participants for research-related injury?

☐ Yes ☐ **No**

1.1 If Yes, please provide the date and title of the agreement and upload the portion of the contract language relevant to compensation for research-related injury:

Name	Created	Modified Date
There are no items to display		

1.2 If No (the study is not under a master agreement), is there proposed contract language concerning payment to participants for treatment in the event of a research-related injury?

☐ Yes ☐ **No**

1.2.1 If Yes, indicate the status of the contract review/approval with the ORD and upload the proposed language relevant to compensation for research-related injury:

1.2.2

Name	Created	Modified Date
There are no items to display		

Payment/Reimbursement to Participants

1 * Will participants receive payment (money, gift certificates, coupons, etc.) or reimbursement for their participation in this research?

☐ **Yes** ☐ No

ID: VIEW4E1C52A5D7800
Name: v2_Payment to Participants

Payment/Reimbursement Detail

You indicated that participants will receive payment (money, gift certificates, coupons, etc.) or reimbursement for their participation in this research.

1 * Payment/reimbursement to participants will be for: (check all that apply)

- [ ] Travel
- [ ] **Parking**
- [ ] Meals
- [ ] Lodging
- [ ] **Time and effort**
- [ ] Other

1.1 If Other, specify:

2 * What is the total dollar value of the payments/reimbursements over the duration of the study? ***Total payment(s) for participation in research of $600 or more in a calendar year is required to be reported on an IRS Form 1099.***
$270

3 * Describe the timing and distribution plan for the payment/reimbursement (schedule, means, etc.)?
Completion of screening enrollment visits: $25
Completion of baseline data collection: $50
Completion of 12 supervised aerobic exercise training sessions: $120
Completion of 12-weeks follow-up assessments: $75
Total: $270

4 * Method(s) of payment/reimbursement to be Used:

- [ ] Cash
- [ ] Check
- [ ] Money Order
- [ ] **Gift Certificate/Gift Card**
- [ ] **Other**

4.1 If Other, specify:
Vouchers for parking at VA facilities during all study visits will be provided, and participants will keep the Fitbit activity monitors.

HIPAA (Health Insurance Portability and Accountability Act)

1 * Are you affiliated with, or will you be accessing data from a HIPAA-covered entity? A covered entity might be a hospital, a physician practice, or any other provider who transmits health information in electronic form.

• At UMB, this includes UMB schools designated as covered entities (School of Medicine and School of Dentistry) and entities under the University of Maryland Medical System (UMMS). The Baltimore VA Medical Center is also a covered entity.

• If you are a researcher from any school that is not a covered entity but is accessing electronic medical records from a covered entity (such as UMMC), HIPAA would be applicable. Please see a list of covered entities included under UMMS here: *executed-ace-designation-042018.pdf*

☐ **Yes** ☐ No

2 * If Yes, will the study view, access, share, collect, use, or analyze health information that is individually identifiable under HIPAA?

☐ **Yes** ☐ No

Protected Health Information (PHI)

You indicated that HIPAA applies and the study will view, access, share, collect, use, or analyze health information that is individually identifiable.

1 * Which PHI elements will be used or disclosed in this study? (Check all that apply)

- ☐ **Name**
- ☐ **Address (if more specific than Zip Code)**
- ☐ **Dates**
- ☐ Ages over age 89
- ☐ **Telephone numbers**
- ☐ Fax numbers
- ☐ **Email addresses**
- ☐ **Social Security numbers**
- ☐ Medical record numbers
- ☐ Health plan beneficiary numbers
- ☐ Account numbers
- ☐ Certificate/license numbers
- ☐ Vehicle identifiers and serial numbers, including license plate numbers
- ☐ Device identifiers and serial numbers
- ☐ Web universal resource locators (URLs)
- ☐ Internet protocol (IP) address numbers
- ☐ **Biometric identifiers, including fingerprints and voiceprints**
- ☐ Full-face photographic images and any comparable images
- ☐ **Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification**
- ☐ None

2 * Why is the PHI necessary for this research?

If SSNs are going to be used, describe the specific use and type of SSN to be used (real, scrambled, last 4 digits).

This PHI is necessary in order to identify, contact, and screen for study eligibility criteria. We will collect names, addresses and phone numbers to be able to contact participants for all aspects of their participation in the study and to be able to send them a letter if needed. Date of birth is collected in order to verify age and identify them in our study database. This study will conducted at the VA Maryland Health Care System and University of Maryland Baltimore and use resources from these institutions for the subject recruitment and enrollment. The VA requires that the last four digits of SSN of the participant be included on all consent and HIPAA forms. This is a VA requirement and not a procedure needed for this specific study. Each participant in the study is assigned an ID number that will be linked to their name, so identifying number/code has been checked for this purpose. Voice prints will be collected through our audio recordings, and these are used to collect data, and for training and supervision of staff.

3 * What is the source(s) of the PHI?

We collect this information from the participant during the course of their participation in the study.

4 * Provide written assurance that Protected Health Information will not be reused. (Note: this refers to re-use on another study or for a purpose which has not been approved, not to the re-use of screening data during the current study).

PHI collected for this study will only be used for the purposes described in this protocol. This information will not be reused or disclosed to any other entity outside this study.

5 * How will permission to allow the use/disclosure of the individual's protected health information (PHI) be obtained? (Choose all that apply:)

- ☐ **Obtain written authorization *(upload authorization form at the end of the application under "Consent and HIPAA Authorization Forms")***
- ☐ **Requesting waiver/alteration of authorization (includes waiver of authorization for recruitment only)**
- ☐ Qualifies as a limited data set (LDS)

5.1 If you are using a limited data set (LDS), please attach the Data Use Agreement (DUA):

Name	Created	Modified Date

There are no items to display

Waiver/Alteration of Authorization

You indicated that a waiver/alteration of authorization is requested.

1 * Provide rationale for how the research presents no more than minimal risk to the privacy of individuals:
We request a partial waiver of HIPAA authorization for this study for recruitment purposes only. This waiver of HIPAA authorization for recruitment purposes is justified because the use of information includes no more than minimal risk to the confidentiality of the participants information. Information collected through this waiver will only be used by study staff listed in this protocol and will not be shared with anyone outside of the project.

2 * Describe the plan to ensure the protection of PHI collected during this study from improper use and disclosure:
The information requested for use in our waiver of HIPAA Authorization will be protected by study staff from improper use and disclosure. This information will not be reused or disclosed to any other person or entity outside of this research project. This information will be stored in a secure and locked cabinet and/or on a password protected computer kept in a locked office at the VAMHCS and UMB. Only study staff will have access to this information.

3 * Describe the plan to destroy the PHI collected during this study at the earliest opportunity consistent with the conduct of the research. If there is a need to retain PHI, provide a justification:
After the sample is recruited all identifiers from potential participants who did not agree to participate or who were found to be ineligible will be destroyed/shredded within approximately 6 months of closing the study.

4 * Why could the research not practicably be done without access to and use of this PHI?
This research could not practicably be conducted without access to and use of this PHI. Access to this PHI allows research staff to screen potential participants over the telephone to determine initial eligibility prior to inviting them in for more detailed in-person assessments. Without access to this PHI, we would be placing an undue burden on participants by inviting those to enrollment visits who may not be eligible for this research study. A burden would also be placed on study staff whose time would be wasted by approaching non-eligible participants.

5 * Why could the research not practicably be done without the waiver or alteration?
This waiver allows us to screen potential participants identified from existing UMB and VA databases, or those referred to the research ream from physician-based practice referrals for study eligibility criteria, and then only approach those who appear eligible based on this screening to attend more comprehensive in-person evaluations. Without this waiver, we would be placing an undue burden on patients by conducting complex assessments on those who may not be eligible for this research study. A burden would also be placed on study staff whose time would be wasted by approaching non-eligible participants.

6 * Will the subjects' PHI be disclosed to (or shared with) any individuals or entities outside of UM?
☐ **Yes** ☐ No

6.1 If Yes, describe the individuals or entities outside of UM to whom PHI will be disclosed.
This study involves both UMB and the VA facilities and staff, and the VA study staff on the research team will also have access to PHI.

Informed Consent Process

If the study does not involve interaction with participants or a waiver of consent is being requested , answer "N/A" to the questions below.

1 * Indicate the type(s) of consent that will be involved in this study: (check all that apply)

- ☐ Not applicable (study may qualify as exempt)
- ☐ Request to Waive Consent/Parental Permission (Consent is not being obtained)
- ☐ Request to Alter Consent (Some Elements of Consent Waived)
- ☐ Request to Waive Documentation of Consent (Verbal/Oral Consent)
- ☐ **Written Consent Form**
- ☐ Electronic Consent

2 * Describe the Informed Consent process in detail:

Individuals interested in the study without evident exclusionary criterion during the initial screening are scheduled for a consent visit. They will hear about the study in detail and carefully go over the consent with trained staff in a private setting. Participants will first review the VA ICD/HIPPA form during the initial overview of the study with research staff, and then participants will review the UMB ICD/HIPPA form after reviewing the VA documentation. Family members and/or caregivers are allowed with subject approval to accompany the candidate through all processes of the informed consent. Participants will be provided adequate time to consider whether or not to participate. Informed consent will be obtained, HIPAA reviewed, and all forms signed. Research subjects will be provided with a copy of the consent form and HIPAA, and copies of the signed forms will be placed in: 1) the subjects research chart and 2) investigators files.

A custom questionnaire assessing potential participants comprehension of our consent form and study is then administered. Candidates are required to correctly answer 4 of 5 questions to indicate adequate comprehension to sign the study consent and to enter the study. The attending staff member will also complete a documentation of the informed process attesting that such procedures comply with relevant regulatory policies and pertinent aspects of the study protocol.

3 * Confirm that the consent process will explain the following:

- The activities involve research.
- The procedures to be performed.
- That participation is voluntary.
- The name and contact information for the investigator.

☐ **Yes** ☐ No

4 * Describe who will obtain Informed Consent:

PI and designated research staff.

5 * If obtaining consent from a legally authorized representative (LAR), describe how you will confirm that the individual is the LAR and can provide legally effective informed consent. *(Answer "N/A" if not obtaining consent from LARs)*

N/A

6 * Describe the setting for consent:

Consenting will take place in a private room.

7 * Describe the provisions for assessing participant understanding:

A custom questionnaire assessing participant's comprehension of our consent form and study will be administered. Candidates will be required to correctly answer 4 of 5 questions to indicate adequate comprehension of the consent form and study procedures.

8 * Describe the consideration for ongoing consent:

To ensure continued consent and understanding of the study procedures, a participant may, at any time, ask to review individual specific study procedures and any pre-procedure preparation they will need to do. The participant will also be encouraged to take as much time as needed to decide whether they want to participate and will be encouraged to discuss the study with family, friends, and their medical care providers before signing the consent form. Finally, research staff will complete a documentation of the informed process validating that procedures comply with regulatory policies and the study protocol.

Consent and HIPAA Authorization Forms - Draft

1 Upload all of your Consent Forms for approval. Use only Microsoft Word.

Name	Created	Modified Date
UMB ICD and HIPPA Marked(0.13)	1/6/2020 1:06 PM	3/13/2023 1:26 PM
VA ICD and HIPPA Marked(0.12)	1/6/2020 1:05 PM	3/13/2023 1:27 PM
VA ICD and HIPPA(0.17)	11/23/2019 7:15 PM	3/13/2023 1:26 PM
UMB ICD and HIPPA(0.16)	11/23/2019 7:15 PM	3/13/2023 1:25 PM

IMPORTANT NOTE: the above list of consent forms (if any) are DRAFT versions. Under no circumstances should copies of these be distributed to patients/study subjects. If/when this research submission is approved by the IRB, approved consent forms will be available for download and use from the "Documents" tab of the Submission's workspace (click Exit and then look for the Documents tab - approved submissions only)

1A Archived Consent Forms:

Name	Created	Modified Date
There are no items to display		

2 Upload any HIPAA authorization forms here:

There are no items to display

Please refer to HRPO's website for specific instructions for preparing informed consent documents and to access current templates:
http://hrpo.umaryland.edu/researchers/consents.html

ID: VIEW4E1C7712D3000
Name: v2_Consent Forms - Draft

Organization Review Requirements (other than IRB)

Answer the following questions to determine additional organizational review requirements:

1 **Department/Division Review** - All research submissions are required to undergo department/division/institutional review prior to IRB review. The following entity is listed as the required department/division/institutional review:

Epidemiology & Public Health

If this information is incorrect, please notify the HRPO office.

2 **RSC Review Criteria** - select 'Yes' if the answer is 'Yes' for any of the following questions. Review by the Radiation Safety Committee may be required.

* 2.1 Does the research involve the use of ionizing radiation? ☐ Yes ☐ **No**

2.2 Does the research involve the sampling of radioactive human materials for subsequent use or analysis in a laboratory?

3 **IBC Review Criteria** - select 'Yes' if the answer is 'Yes' for any of the following questions. Review by the Institutional Biosafety Committee may be required.

* 3.1 Does the research involve human gene transfer? ☐ **Yes** ☐ No
-OR-
Does the research specifically apply to human studies in which induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, and such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not expected? This type of research is often referred to as recombinant vaccine trials.

3.2 Does the research involve the exposure of human subjects to pathogenic microorganisms, or the exposure of research staff to human subjects or samples known or reasonably expected to carry infectious disease(s)?

3.3 Does the research involve the sampling of materials from persons with no known infectious disease and where the only risk to study staff is occupational exposure to bloodborne pathogens as defined by the OSHA Bloodborne Pathogen Standard?

4 **Cancer Center Criteria** - Please answer the following question to determine whether review by the University of Maryland Greenebaum Comprehensive Cancer Center (UMGCCC) is required:

* Does this protocol involve oncology patients and/or oncology data in any capacity? This includes, but is not limited to, the inclusion of cancer patients, as well as research related to prevention, treatment, or diagnosis of oncological diseases. ☐ Yes ☐ **No**

If Yes, or if you have any questions regarding Cancer Center review, please contact the UMGCCC Regulatory Office at UMGCCCRegulatory@umm.edu.

5 **General Clinical Research Center Review Criteria** - the GCRC offers free and/or cost shared resources for patient-oriented research. Click Here for more information.

Answer the following to determine if review by the GCRC may be required.

* Will the General Clinical Research Center (GCRC) facility or resources be used to conduct this activity? ☐ **Yes** ☐ No

6 **VA Review Criteria** - Answer the following questions to determine if review by the VAMHCS R&D Committee may be required.

* 6.1 - Will the research be conducted by VA Investigators including PIs, Co-PIs, and Site Investigators on VA time (serving on compensated, WOC, or IPA appointments)? ☐ **Yes** ☐ No

* 6.2 - Will the research utilize VA resources (e.g., equipment, funds, medical records, databases, tissues, etc.)? ☐ **Yes** ☐ No

* 6.3 - Will the research be conducted on VA property, including space leased to and used by VA? ☐ **Yes** ☐ No

PLEASE NOTE that the research may be funded by VA, by other sponsors, or may be unfunded.

Institutional Biosafety Committee Review Required

1 **NOTE**: based on your answers to questions on a previous page (see below) review by the Institutional Biosafety Committee (IBC) is required. This will involve extra steps on your (study team) part. Clicking the Continue button will result in the system creating a blank IBC Submission form for you. You will be required to fill out and submit this IBC form before you will be able to submit the Protocol form. The IBC Submission workspace and form can be reached by clicking the appropriate button on the left hand side of the Protocol submission's workspace (web page) after exiting the Protocol form.

2 **Question** - answered on IBC RSC review requirements page:

3.1 Does the research involve human gene transfer? - OR - Does the research specifically apply to human studies in which induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, and such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not expected? This type of research is often referred to as recombinant vaccine trials.
3.2 Does the research involve: a) the exposure of human subjects to pathogenic microorganisms, or b) the potential exposure of UMB research staff to infectious materials through the sampling or processing of materials from patients with known infectious disease or from environmental surfaces?
3.3 Does the research involve the sampling of materials from persons with no known infectious disease and where the only risk to study staff is occupational exposure to bloodborne pathogens as defined by the OSHA Bloodborne Pathogen Standard?

Yes

If the answer to this question is wrong, an IBC submission is not required, use the Jump To menu or your browser's <

3 * **Confirm** - you have read the above information and understand that in addition to the IRB Protocol form, you will fill out and submit the IBC Submission form :

☐ **Yes** ☐ No

ID: VIEW4E1AF91ED4C00
Name: v2_Institutional Biosafety Committee Review Required

GCRC Review Required

1 **NOTE**: based on answers to questions on a previous page (see below), review by the GCRC Committee is required. This will involve extra steps on your (study team) part. Clicking the Continue button will result in the system creating a blank GCRC Submission form for you. You will be required to fill out and submit this GCRC form along with the IRB Protocol form to begin the GCRC review process. The GCRC Submission workspace and form can be reached by clicking the appropriate button on the left hand side of the Protocol submission's workspace (web page) after exiting the Protocol (this) form.

2 **Question** - answered on the paged named 'Organization Review Requirements':
Will GCRC facillity, staff or resources be used to conduct this study: **Yes**

If this is incorrect, return to the 'Organization Review Requirements' and change the answer to the GCRC usage question.

3 * **Confirm** - you have read the above information and understand that in addition to the IRB Protocol form, you will fill out and submit the GCRC Submission form:

☐ **Yes** ☐ No

ID: VIEW4E1AF9143A000
Name: v2_GCRC Review Required

VA-Specific Criteria

1 * What is the relevance of this research to the mission of VA and the Veteran population that it serves*?
The co-occurrence of physical and mental morbidity in the Veteran population is one of the biggest clinical challenges facing health care providers in the VA Maryland Health Care System. This research is relevant to the mission of the VA; specifically, to develop a new treatment protocol aiming to reduce the burden of chronic pain and psychosocial impairment among persons with knee osteoarthritis and depression; two common conditions that are highly prevalent within the Veteran population and place a large strain on resources and clinical services with the Veterans Health Administration.

2 * Describe who will be enrolled in this study:

- [ ] Non-veterans will be enrolled in this study
- [ ] Only veterans will be enrolled in this study
- [ ] **Veterans and Non-veterans will be enrolled in this study**

2.1 * If non-veterans will be enrolled in this study, provide a description of non-veterans who will be enrolled (For example: community members, family members/caretakers of Veterans, clinicians/caregivers to Veterans, etc.):
Community members

2.2 If non-veterans will be enrolled in this study, provide a substantive justification** for the enrollment of non-veterans in this research:
Non-veterans will be enrolled in to this study as the findings from this research will generally benefit Veterans and their well-being.

2.3 * If this is a VA-funded study, was the use of non-veterans discussed within your merit award proposal?

- [ ] Yes
- [ ] No
- [ ] **N/A**

*
http://www.va.gov/about_va/mission.asp

VA Mission Statement
To fulfill President Lincoln's promise “To care for him who shall have borne the battle, and for his widow, and his orphan” by serving and honoring the men and women who are America’s Veterans.

VA Core Values
VA’s five core values underscore the obligations inherent in VA’s mission: Integrity, Commitment, Advocacy, Respect, and Excellence. The core values define “who we are,” our culture, and how we care for Veterans and eligible beneficiaries. Our values are more than just words – they affect outcomes in our daily interactions with Veterans and eligible beneficiaries and with each other. Taking the first letter of each word—Integrity, Commitment, Advocacy, Respect, Excellence—creates a powerful acronym, “I CARE,” that reminds each VA employee of the importance of their role in this Department. These core values come together as five promises we make as individuals and as an organization to those we serve.
Integrity: Act with high moral principle. Adhere to the highest professional standards. Maintain the trust and confidence of all with whom I engage.
Commitment: Work diligently to serve Veterans and other beneficiaries. Be driven by an earnest belief in VA’s mission. Fulfill my individual responsibilities and organizational responsibilities.
Advocacy: Be truly Veteran-centric by identifying, fully considering, and appropriately advancing the interests of Veterans and other beneficiaries.
Respect: Treat all those I serve and with whom I work with dignity and respect. Show respect to earn it.
Excellence: Strive for the highest quality and continuous improvement. Be thoughtful and decisive in leadership, accountable for my actions, willing to admit mistakes, and rigorous in correcting them.

**
a. Non-Veterans may be entered into a VA-approved research study that involves VA outpatient or VA hospital treatment (38 CFR 17.45, 17.92), but only when there are insufficient Veteran patients suitable for the study. The investigator must justify including non-Veterans and the IRB must review the justification and provide specific approval for recruitment of non-Veterans.
b. Non-Veterans may be recruited for studies that will generally benefit Veterans and their well-being but would not include Veterans as subjects. Examples include surveys of VA providers, studies involving Veterans’ family members, or studies including active duty military personnel. Although active duty military personnel are not considered Veterans, they should be included in VA studies whenever appropriate.
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e. Non-Veterans may not be entered into VA studies simply because a non-Veteran population is easily accessible to the investigator.

[VHA Handbook 1200.05 §24]

VA Prohibited Research

1 * Is the research planned emergency research in subjects from whom consent can not be prospectively obtained?
☐ Yes ☐ **No**

2 * Does the study involve children **AND** is greater than minimal risk?
☐ Yes ☐ **No**

3 * Will recruitment phone calls involve asking veterans for their Social Security numbers?
☐ Yes ☐ **No**

Additional VA

1 * For data that is combined, which site is the "Data Coordinating Center"?
UMB

2 If VA data will be combined with non-VA data, describe when and how this will occur and where the combined data will be stored.
Data will be collected at the VAMHCS GRECC and UMMC GCRC. All original research data will be stored at the VA. Copies of research data will be sent to the UMB Division of Gerontology, Department of Epidemiology and Public Health, for data entry and processing into electronic data files for analysis of study outcomes. Hard copies of coded research data will be transported in a locked bag to the Division of Gerontology for data entry and analysis and will not contain patient identifiers. Electronic qualitative research data will be transported using a VA-approved encrypted flash to the Division of Gerontology for processing and analysis. Electronic qualitative research data will not contain patient identifiers. Participant ID numbers linking research data to individuals will be stored on the UMB computer network in a user-restricted folder and file with multiple levels of password protection. Combined research data will be stored on the UMB computer network in the Division of Gerontology in a similar manner. These design aspects are iterated in more detail in the "Study Procedures."

3 If the VAMHCS is the Local Coordinating Center holding the “combined data”, how is the data collected? (This answer may overlap with Research Related Procedures. If so, please refer to that section.)
UMB is the local coordinating center that will hold combined data.

4 If the VAMHCS is the Local Coordinating Center holding the “combined data”, how is the data received and combined with the data from the other non-VA institution(s)?
UMB is the local coordinating center that will hold combined data.

VA Maryland Health Care System Review Required

1

Note: Based on the answers provided in your submission, this protocol qualifies as a VA study and therefore requires VA-specific reviews to ensure that all VA regulatory requirements are met. The VAMHCS Research & Development Committee (RDC) review is included in these VA-specific reviews and RDC approval is required prior to engaging in any research activities. **Importantly, you must submit this protocol to the VAMHCS RDC for review within 60 days of IRB approval.** Please see below for a summary of required VA-specific review steps.

****Before you initiate any of the following VA-specific review steps, please contact Kelly Lloyd (Kelly.Lloyd@va.gov), VAMHCS Research Protections Officer (RPO), to ensure full compliance with VA requirements.**

1. Ensure that you have already created a new project shell in IRBNet and that the title matches the title for this IRB application. Before drafting the IRB submission, the PI **should have completed Package 1 – ACOS New Project Review Form** found in the VAMHCS IRBNet library (log in to IRBNet first and then click on link), gotten it signed by the PI's VA Service Chief, and submitted it to the Research Service as a single document package within this project shell in IRBNet.
2. After you have received ACOS sign-off, you may submit your protocol application in CICERO. The application will be routed to designated reviewers including Kelly Lloyd, VAMHCS RPO. She will conduct a VA Administrative Pre-Review and the results will be communicated to the study team through the CICERO platform and may include suggested edits to the application and consent/HIPAA form(s). The study team will be responsible for implementing these edits in CICERO.
3. While the VA Specialty Review is being conducted in CICERO, complete the Information System Security Officer (ISSO) review form and email to Kelly so she can prepare her request for that additional, required review. You can find the form used for ISSO review in the VAMHCS IRBNet library (log in to IRBNet first and then click on link): **RDC – Information Security Officer Review Form.pdf.**
4. After all suggested edits have been made in the CICERO application and consents/HIPAA by the study team, Kelly will then send for VAMHCS ISSO and Privacy Officer (PO) review and the study team will be copied on these correspondences. (Please Note: Kelly will prepare PO review form).
5. Once you receive approval from ISSO and PO, Kelly will finalize her review and send the CICERO application on to the next UMB HRPO-required reviewing body.
6. You will then create another new package in your IRBNet project shell (i.e., the same project shell you already created for ACOS review) to submit the protocol documents for Subcommittee on Research Safety (SRS) review. You can find all applicable submission forms in the VAMHCS IRBNet library (log in to IRBNet first and then click on link). Please use this form within the library as a submission guide: **IRBNet Admin Review Checklist – Used only as a guide for submitters – Does not have to uploaded.**
7. After your protocol has been approved by the IRB, you'll create a third, new package in your IRBNet project shell (i.e., the same project shell you already created for ACOS review and used to submit documents for SRS review) to submit the protocol documents required for Research and Development Committee (RDC) review. You can find all applicable submission forms in the VAMHCS IRBNet library (log in to IRBNet first and then click on link). Please use this form within the library as a submission guide: **IRBNet Admin Review Checklist – Used only as a guide for submitters – Does not have to uploaded.**
8. Only after you have been approved by RDC, you may initiate study activities.

2 **Questions answered on 'Organizational Review Requirements' page**:

The research will be conducted by VA Investigators including PIs, Co-PIs, and Site Investigators on VA time (serving on compensated, WOC, or IPA appointments):	**Yes**
The research will utilize VA resources (e.g. equipment, funds, medical records, databases, tissues, etc.):	**Yes**
The research will be conducted on VA property, including space leased to and used by VA:	**Yes**

Questions answered on 'VA Prohibited Research' page:

The research is planned emergency research in subjects from whom consent can not be prospectively obtained:	**No**
The study involves fetuses:	
The study involves in vitro fertilization:	
The research involves work with embryonic stem cells:	
The study involves children AND is greater than minimal risk:	**No**
Recruitment phone calls involve asking veterans for their Social Security numbers:	**No**

If the answers to these questions are wrong, use the Jump To menu to return to the 'Organization Review Requirements' page to change your answers.

3 * **Confirm** - You have read the above information and understand that in addition to this IRB application form (CICERO), you are required to send a submission to the VAMHCS R&D Committee **within 60 days of receiving IRB approval**.

☐ **Yes** ☐ No

ID: VIEW4E1C8F0D7B000
Name: v2_VA Review Required

Summary of Required Reviews (other than IRB)

1 **Additional Committee Reviews** - Based on your responses to the previous questions, you have identified the following additional reviews. To complete or view these additional committees' forms, click on the links below or exit this application and click on the appropriate button on left side of this submission's webpage.

Name of Related Submission		
IBC: Exercise plus Duloxetine for Knee Osteoarthritis and Depression (HP-00089160)	Workspace	SmartForm
GCRC: Exercise plus Duloxetine for Knee Osteoarthritis and Depression (HP-00089160)	Workspace	SmartForm

2 **Required Department and Specialty Reviews** - Based on the PI's organization (department, division, etc.) affiliation and answers to previous questions (use of Cancer Center, etc.), the organizations listed below are required to review this application. These reviews are conducted online and no additional forms or steps by the study team are required.

Name of Organization	Review Status
Epidemiology & Public Health	Complete
Epidemiology & Public Health	Complete

Additional Documents

1

Upload all additional documents here:

Name	Created	Modified Date
VA Acknowledgement of Notice of Privacy Practices(0.01)	2/27/2023 5:31 PM	2/27/2023 5:31 PM
VA Notice of Privacy Practices(0.01)	2/27/2023 5:30 PM	2/27/2023 5:30 PM
Survey Packet Coversheet(0.02)	2/20/2021 8:27 PM	2/16/2023 5:46 PM
Mental Health Resources Brochure(0.02)	3/1/2021 1:44 PM	2/16/2023 5:43 PM
UMB COVID Risk Statement(0.02)	3/29/2021 8:21 AM	2/16/2023 5:18 PM
Assessment Completion Form(0.02)	8/19/2021 7:11 PM	2/16/2023 5:04 PM
Fasting Instructions(0.03)	8/19/2021 6:10 PM	2/16/2023 5:02 PM
Driving Directions(0.01)	8/19/2021 6:00 PM	8/19/2021 6:00 PM
Real SSN Access Request Form(0.02)	6/18/2021 1:11 PM	6/28/2021 2:19 PM
Evaluation of Informed Consent(0.02)	11/23/2019 7:21 PM	2/20/2021 8:23 PM
Responses to IRB - Third Review(0.01)	2/19/2020 11:08 AM	2/19/2020 11:08 AM
Responses to IRB - Second Review(0.01)	1/27/2020 8:05 PM	1/27/2020 8:05 PM
Responses to IRB review(0.02)	1/2/2020 11:21 AM	1/2/2020 11:21 AM
PO Compliance Review(0.01)	12/3/2019 12:23 PM	12/3/2019 12:23 PM
ISSO Compliance Review(0.01)	12/3/2019 12:23 PM	12/3/2019 12:23 PM

ID: VIEW4E0962513A000
Name: v2_Additional Documents

Final Page of Application

You have reached the final page of this application. It is recommended that you click on the "Hide/Show Errors" link on the upper or lower breadcrumb row of this page. The "Hide/Show Errors" will do a search of your application, and highlight areas that are required or need to be completed prior to submitting.

By submitting this application, you are electronically routing the protocol for departmental scientific review and all other necessary reviews. According to information you have provided, this application will be routed to the following Departments for review prior to being forwarded to the IRB for review. These reviews are conducted online and no additional forms or steps by the study team are required.

Name of Organization	Review Status
Epidemiology & Public Health	Complete
Epidemiology & Public Health	Complete

Required Safety Committee Reviews - In addition to the IRB, the following committees must review this submission. Each additional committee has a separate online form that the study team will be required to fill out. All committee applications (IRB plus those listed here) must be completed properly before the 'package' of applications can be submitted. The team may complete these additional forms in any order or at any time prior to submission of the IRB Application. To complete or view these additional committees' forms, click on the links below or exit this application and click on the appropriate button on left side of this submission's Workspace.

Name of Related Submission		
IBC: Exercise plus Duloxetine for Knee Osteoarthritis and Depression (HP-00089160)	Workspace	SmartForm
GCRC: Exercise plus Duloxetine for Knee Osteoarthritis and Depression (HP-00089160)	Workspace	SmartForm

You may check the progress of your application at any time by returning to the Workspace of this submission. A detailed history, including notes, dates, and times of events, is provided to you for this purpose.

If a reviewer returns the application to you, you must address their concerns and resubmit the protocol for review to all designated departments. After all departments have reviewed the application, it will automatically be sent to the IRB for review. Changes made to the submission after its approval must be submitted as modifications.

Investigator Attestation
By submitting this application, I, the Principal Investigator (PI), certify that the information provided in this application is complete and correct. Research will be conducted according to the submission as described, only by the approved principal investigator and study team members.

In addition, I agree to the responsibilities of a PI, including:

- Obtaining informed consent (if applicable) from all subjects as outlined in the submission.
- Reporting new information to the IRB per the requirements of the Investigator Manual.
- If Required, obtaining renewal of the protocol prior to the expiration of the approval period or halt all study activities upon study expiration.
- Accepting ultimate responsibility for the protection of the rights and welfare of human subjects, conduct of the study and the ethical performance of the project.
- Ensuring performance of all research activities by qualified personnel according to the IRB approved submission.
- Ensuring that research personnel have or will receive appropriate training.
- Ensuring no changes will be made in the research until approved by the IRB (except when necessary to eliminate apparent immediate hazards to subjects).

Click the "Finish" button and then click "Submit Application" in the submission Workspace.

Add a Team Member

1 * Select Team Member:
Lexie Shaffer

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.

☐ Yes ☐ **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

☐ **Yes** ☐ No

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

☐ Yes ☐ **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Ms. Lexie Shaffer is a clinical exercise physiologist at the University of Maryland Baltimore (UMB) in the Department of Medicine and Geriatric Research Education and Clinical Center in the VA Maryland Health Care System. She will work with the study team to oversee the delivery of the exercise program and will be responsible for the administration of functional tests during data collection.

Add a Team Member

1 * Select Team Member:
Rhea Mehta

2 Research Role:
Technician or Assistant

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.

☐ Yes ☐ **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

☐ Yes ☐ **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

☐ Yes ☐ **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Rhea Mehta, MHS is a student in the University of Maryland Doctoral Program in Gerontology and a Graduate Research Assistant in the Division of Gerontology, Department of Epidemiology and Public Health. Ms. Mehta has expertise in mental health and aging and will be assisting with participant screening and recruitment and data collection and entry.

Add a Team Member

1 * Select Team Member:
Jason Peer

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.

☐ Yes ☐ **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

☐ Yes ☐ **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

☐ Yes ☐ **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Jason Peer, PhD, is a practicing clinical psychologist within the VAMCHS who is licensed by the American Psychological Association. Dr. Peer has more than a decade of experience screening and treating major depressive disorder in clinical and research settings. He will be responsible for overseeing the fidelity of structured clinical interviews during the screening process for major depression and other psychiatric illnesses.

Add a Team Member

1 * Select Team Member:
Alice Ryan

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.

☐ **Yes** ☐ No

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

☐ Yes ☐ **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

☐ Yes ☐ **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Dr. Alice Ryan is a Professor of Medicine at the UMB School of Medicine and Senior Career Research Scientist in the VA Maryland Health Care System. She has almost thirty years of developing and administering clinical research in the context of exercise treatment programs.

Add a Team Member

1 * Select Team Member:
Yu Dong

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.

☐ Yes ☐ **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

☐ Yes ☐ **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

☐ Yes ☐ **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Dr. Yu Dong is an Assistant Professor of Psychiatry at the UMB School of Medicine and runs the Geriatric Psychiatry Clinic on the University of Maryland Baltimore campus. She has extensive experience in the clinical management of older adults with psychiatric conditions.

Add a Team Member

1 * Select Team Member:
Marc Hochberg

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.

☐ **Yes** ☐ No

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

☐ Yes ☐ **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

☐ Yes ☐ **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Dr. Marc Hochberg is a Professor of Medicine at the UMB School of Medicine and leads the Division of Rheumatology and Clinical Immunology as well as the Medical Clinical Care Center at the Baltimore VA Medical Center. He has more than four decades of experience conducting prospective research studies among individuals with musculoskeletal disorders.

Add a Team Member

1 * Select Team Member:
Justine Golden

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.

☐ Yes ☐ **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

☐ Yes ☐ **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

☐ Yes ☐ **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Justine Golden is the data manager within the Division of Gerontology at the UMB School of Medicine. She has been involved in data management and analysis of multiple prospective studies.

Add a Team Member

1 * Select Team Member:
Denise Orwig

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.

☐ **Yes** ☐ No

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

☐ Yes ☐ **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

☐ Yes ☐ **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Dr. Denise Orwig is an Associate Professor of Epidemiology and Public Health at the UMB School of Medicine. She has more than two decades of implementing and managing interventional studies among patients with musculoskeletal conditions.

Add a Team Member

1 * Select Team Member:
Lynda Robey

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.

☐ **Yes** ☐ No

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

☐ Yes ☐ **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

☐ Yes ☐ **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Lynda Robey is a research professional with extensive experience in regulatory policy and research administration.

Add a Team Member

1 * Select Team Member:
Brock Beamer

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.

☐ **Yes** ☐ No

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

☐ Yes ☐ **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

☐ Yes ☐ **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Dr. Brock Beamer is a Assistant Professor of Medicine and VA Staff physician. As a geriatrician, he has more than two decades of experience working on clinical research evaluating exercise interventions.

Add a Team Member

1 * Select Team Member:
CARTER DAVIS

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.

☐ Yes ☐ **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

☐ Yes ☐ **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

☐ Yes ☐ **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Mr. Carter Davis, MS, is an exercise physiologist who will coordinate with participants and the research team to schedule and implement center-based training sessions and other related aspects of the protocol as necessary.

Add a Team Member

1 * Select Team Member:
Mark Luborsky

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.

☐ Yes ☐ **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

☐ **Yes** ☐ No

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

☐ Yes ☐ **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Dr. Luborsky is a Professor of Gerontology and Anthropology at Wayne State University who will assist with the analysis and interpretation of qualitative data.