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STepped Exercise Program for Knee Osteoarthritis (STEP-KOA)

March 14, 2018

Specific Aims

Osteoarthritis (OA) is one of the most prevalent chronic conditions and a leading cause of pain and disability. Knee OA is particularly common, with a lifetime risk of 45%. The risk of disability attributable to knee OA is as great as that due to cardiovascular disease and greater than any other medical condition. Veterans have a higher prevalence of OA and more pain and functional limitations than the general population; among Veterans, users of the Department of Veterans Affairs (VA) health care system are the most severely affected.

Guidelines for treating knee OA consistently include both exercise programs and physical therapy (PT) as core components, based on many studies supporting their effectiveness. However, the vast majority of patients with knee OA are physically inactive, and PT is associated with significant and increasing costs to the VA. Exercise programs and PT share common aims of improving the use of safe and effective exercises for knee OA and increasing overall physical activity, but PT provides more specialized treatment that also addresses specific functional and biomechanical impairments that may prevent successful engagement in activity. It is likely that some patients with knee OA can achieve clinically meaningful improvements in pain and function with relatively low resource exercise programs for knee OA, with a subset of patients requiring additional attention from a physical therapist. However, there are no evidence-based models for delivering these differing types of exercise-related services for knee OA efficiently and according to patient needs.

In this study we propose to evaluate a STepped Exercise Program for Knee Osteoarthritis (STEP-KOA) in Veterans. STEP-KOA begins with a low-resource exercise intervention, with increasing intensity of the intervention approach for patients who do not meet benchmarks for improvement. Specifically, Step 1 involves three months of access to an internet-based exercise program that uses patient-specific information to tailor exercise plans. Patient who do not meet criteria for clinically relevant improvement in pain and function after Step 1 will progress to a more intensive Step 2, which adds three months of biweekly telephone support that addresses symptom-related, health-related and other barriers to physical activity. Participants who do not meet response criteria after Step 2 will progress to Step 3, which involves in-person PT visits; this final Step allows evaluation of specific functional impairments, further tailoring of exercises, and assessment of the need for knee braces or other assistive devices. This stepped intervention is matched with patient needs, and it also provides the VA with a potential approach for focusing limited PT resources on patients who do not respond adequately to initial, less resource intensive and costly strategies to improve physical activity and related outcomes. We will conduct a randomized clinical trial with the following specific aims and hypotheses:

Specific Aim 1: To examine the effectiveness of STEP-KOA on key patient-centered outcomes among Veterans with symptomatic knee OA.
Hypothesis 1: Veterans who receive STEP-KOA will have clinically relevant improvements in self-reported pain, stiffness, and function, measured by the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC), immediately following the 9-month program, compared with Veterans in an Arthritis Education (AE) control group. Similarly, we expect clinically relevant improvement in secondary outcomes of objectively assessed physical function.

Specific Aim 2: To estimate maintenance effects of STEP-KOA at 15 month follow-up, six months following completion of the program.
Hypothesis 2: At 15-months, Veterans in the STEP-KOA group will maintain improvements in WOMAC scores achieved at 9 months (i.e. there will be no estimated mean difference in WOMAC scores between 9 and 15 months). We will estimate these differences in WOMAC scores for the full STEP-KOA group as well as for subgroups defined by the combination of steps received during the STEP-KOA program.

Specific Aim 3: To describe patients who are non-responders at each Step in the STEP-KOA group, and to examine patient characteristics associated with non-response.

Specific Aim 4: To examine the cost effectiveness of overall STEP-KOA intervention, compared with the AE control group.

This study will have an important impact for Veterans because it evaluates a novel, patient-centered approach to improving physical activity and related outcomes for knee OA – one of the most common and disabling health problems. The study will have an important impact for the VA because the STEP-KOA could be a practical approach for both improving access to physical activity interventions and targeting more costly and limited PT resources for knee OA in an evidence-based manner.

RESEARCH PLAN
A. BACKGROUND AND CONTEXT

1.0 Osteoarthritis (OA) is Highly Prevalent and Disabling.

Osteoarthritis is one of the most prevalent chronic conditions in the U.S. Knee OA is particularly common, with one study indicating a lifetime risk of 45%,[1,2] and the prevalence of knee OA is expected to rise dramatically over the next several decades[3]. OA is associated with significant pain, functional limitations, and reduced health-related quality of life [4]. It is the most frequently reported cause of disability in the U.S.[5]. Among older adults, the risk of disability attributable to knee OA is as great as that due to cardiovascular disease and greater than any other medical condition[6]. OA is also associated with significant costs to both patients and health care systems. Annual health care expenditures of individuals with OA are about twice as high as individuals without OA, even when adjusting for age and gender[7].

2.0 Osteoarthritis is a Particular Burden in Veterans.

Veterans are at greater risk for OA [8], likely due in part to high rates of joint injuries and loading. Data from the 2001 National Survey of Veterans showed that over 25% of all Veterans report having arthritis (of which OA is by far the most common type), making this the third most prevalent health condition [9]. Data from Centers for Disease Control and Prevention (CDC) showed that 32% of Veterans had a doctor's diagnosis of arthritis, compared with only 22% of non-Veterans[10]. Among active duty military personnel, OA incidence rates are 1.26-2.17 times higher than comparable age groups in the general population[11].

Veterans with OA often report significant and limiting symptoms [12]. For example, among Veterans Health Study participants with arthritis (primarily OA), 85% reported that pain and stiffness were present on most days, and moderate to high levels of pain and stiffness were common [13]. Veterans who receive care within the VA health care system are at particular risk for debilitating OA. Veterans with lower extremity OA in several of our prior studies[14-16] have reported greater pain and functional limitations
than samples of patients with OA in the general population. CDC data also show that VA health care users are more likely to report a diagnosis of arthritis compared to Veterans who receive care outside the VA health care system (43% vs. 30%, $p<0.001$), even when adjusting for demographic characteristics [10]. Among Veterans with arthritis, VA health care users are also more likely to report limitation in their daily activities because of joint symptoms (63% vs. 42%, $p<0.001$).

3.0 Exercise and Physical Therapy are Key Components of Managing Knee OA but are Underutilized.

Guidelines consistently recommend both exercise programs and physical therapy (PT) as core components of managing knee OA [17-19], based on strong evidence for their effectiveness. A meta-analysis of trials of exercise for knee OA found that effect sizes for aerobic exercise were 0.52 and 0.46 for pain and disability, respectively; for strengthening exercises, effect sizes were 0.39 and 0.32[20]. These are moderate to large effect sizes and are comparable to those observed for pharmacological treatment of OA [21]. Systematic reviews also support the effectiveness of PT for improving knee OA outcomes[22,23]. Although exercise programs and PT are different treatment strategies, they share common aims of improving the use of safe and appropriate exercises and addressing OA-related barriers to overall physical activity. PT is a more specialized treatment that, in addition to providing tailored exercise prescription, incorporates evaluation of needs for devices such as knee braces, shoe lifts / orthotics, and walking aids; some patients with biomechanical and functional impairments may require these before effectively engaging in increased physical activity.

Despite strong evidence for exercise programs and PT in managing OA symptoms, both are substantially under-utilized [24,25]. In a study of adults who had or were at risk for knee OA, only 2% of African Americans and 13% of whites were currently meeting physical activity recommendations [25]. In our recent study of VA health care users with knee OA [26], less than half had ever received PT, despite a relatively long average duration of disease (14 years). Although the reasons for low use of PT for knee OA have not been fully elucidated, there are two likely contributors that are particularly germane to this proposed study. First, neither treatment guidelines nor prior studies indicate which patients with knee OA have the greatest need for or may benefit most from PT visits (versus lower resource approaches to enhance physical activity) [17-19]. Although it is likely that patients with worse symptoms or overall poorer health may have the greatest need for the specialized focus of PT, the lack of evidence leaves primary care providers without guidance for making these referrals. In our ongoing OA studies[26], this has been a common question raised by primary care providers. Second,

outpatient PT visits are a limited resource in many healthcare systems, including the VA, with demand exceeding supply. A recent model projecting the supply and demand of physical therapists between 2010 and 2020 indicates a shortage between 9,000 and 41,000 therapists in the US [27]. This further emphasizes the need for an evidence base for focusing this limited resource and identifying other, lower resource strategies that help to improve physical activity and associated outcomes in a subset of patients.

There is widespread consensus that evidence-based strategies are still needed to help adults with OA to adopt and maintain adequate levels of physical activity [28]. In the VA healthcare system, the MOVE! program incorporates physical activity into a broader program for Veterans who are overweight. Although Veterans with knee OA may benefit from this program, these patients face particular barriers that hinder physical activity and require specific guidance on appropriate, graded exercise that accounts for pain and activity limitations [29]. In summary, there is a need for novel, evidence-based physical activity programs for Veterans with knee OA that complement and help to focus PT treatment for this condition.

4.0 STepped Exercise Program for Knee OsteoArthritis (STEP-KOA): A Novel Approach

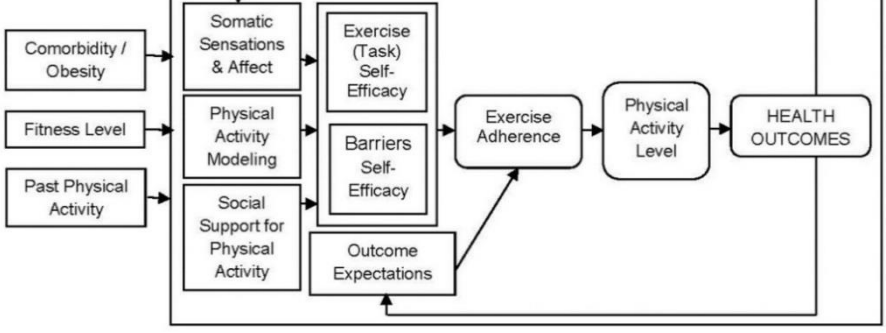
The proposed study will evaluate a stepped approach to improving physical activity and associated outcomes for Veterans with knee OA. Stepped care interventions are attractive from both patient and resource allocation perspectives [30,31]. From the patient perspective, stepped care allows the intervention to be guided by patient-centered outcomes; the intensity of the intervention approach can be increased until a clinically relevant outcome is achieved whenever possible[32]. From a resource allocation perspective, stepped care allows more costly or limited resources to be reserved for patients who do not respond adequately to other approaches. To our knowledge, no studies have previously examined a stepped approach to increasing physical activity for patients with OA. However, stepped care interventions have proven successful in other areas, including weight loss[33], comorbid pain and depression[34], and mental health treatment [35]. We believe a stepped approach is particularly appropriate in this context for several reasons. First, knee OA is highly common, and there is a need for an efficient approach to fostering physical activity in this large group of Veterans. Second, among patients with knee OA there is considerable variability in pain severity, physical function, exercise abilities, and other factors that likely influence the intensiveness of physical activity intervention needed. A stepped care approach will address this heterogeneity. Third, outpatient PT costs for knee OA are increasing for the VA, with the growing number of Veterans who suffer from this condition. A stepped intervention could guide more focused use of these visits for knee OA. Questions surrounding when to refer Veterans with OA for outpatient PT are a high priority for the VA National Physical Medicine and Rehabilitation Service, evidenced by two recent calls on this topic. Results of this project would inform those decisions by evaluating whether a stepped approach may be an effective alternative to immediate PT referral, at least for some patients.

As described below, STEP-KOA begins with a low-resource intervention, involving access to an internet-based exercise program for knee OA (Step 1). Patients who do not meet response criteria for pain and function, established by the Outcome Measures in Rheumatology group and the Osteoarthritis Research Society International (OMERACT-OARSI[36]), after Step 1 will progress to a more intensive intervention approach, adding telephone counseling to address barriers to physical activity (Step 2). Patients who still do not meet response criteria after Step 2 will progress to a more intensive Step 3, involving in-person PT visits. These visits will provide evaluation of functional impairments, further tailoring of exercises, and assessment of the need for devices that may also be needed to improve overall activity, as well as pain and function.

5.0 Theoretical Model of Physical Activity Behavior.

We have based STEP-KOA on Social Cognitive Theory (SCT; Figure 1) because of its comprehensive framework and its wide use in physical activity literature and other effective behavioral interventions for OA [37]. SCT emphasizes that cognitive, behavioral, personal and environmental factors interact to influence motivation and

Figure 1: Social Cognitive Theory Applied to Physical Activity



behavior. *Self-efficacy*, a central concept of SCT, is a powerful predictor of physical activity [38]. Self-efficacy refers to one's belief in their ability to successfully complete a course of action, such as increasing physical activity. There are two types of self-efficacy that are important for physical activity behavior [39]; t*ask self-efficacy* (e.g., exercise self-efficacy) is the belief that one can actually do the behaviors in question, and *barriers self-efficacy* is the belief that one can regularly perform a behavior in the face of common barriers such as lack of time, pain, etc. Each component of STEP-KOA addresses both types of self-efficacy. A second central concept of SCT is that of *outcome expectations,* defined as the anticipated results of a given behavior such as physical activity. SCT posits that individuals are more likely to engage in if they believe it will result in positive changes to valued outcomes (e.g. pain relief) [40]. Each component of STEP-KOA also addresses outcome expectations. Overall, STEP-KOA provides augmented strategies for addressing SCT constructs for patients who do not have a clinically meaningful response to earlier steps.

6.0 Preliminary Studies

6.1 Virtual Exercise Trainer for Patients with Knee OA (VET-KOA): Step 1 Intervention. The internet-based exercise training system we will employ in Step 1 has been developed and tested by Visual Health Information (VHI), through a Small Business Innovations Research Grant from NIH[41]. VET-KOA was developed by a multidisciplinary team of patients, physicians, and physical therapists, with a goal of mirroring a rehabilitation experience that provides personalized exercise recommendations and ongoing monitoring and progression of activities. The program includes the following components:

1. Tailored Exercise Routines. VET-KOA includes five exercise levels that span a continuum of functional abilities. Initial assignment to an exercise level is based on patients' responses to a 14-item measure of pain and function (modified short form of the Western Ontario and McMaster Universities Osteoarthritis Index; mSF-WOMAC,)[42] and other items assessing exercise abilities and function. The algorithm for assigning patients exercise levels was validated against recommended assignments by physical therapists familiar with the exercise levels. Exercises within each level are based on clinical guidelines and selection by a panel of orthopedic surgeons, physiatrists, rheumatologists and physical therapists. Exercise routines, randomly generated within each level, include strengthening exercises that target multiple muscle groups (with a focus on those supporting the knee), as well as stretching exercises. Patients are also prescribed aerobic exercises appropriate for each level.

2. Animations of Strengthening and Stretching Exercises. When patients log in to VET-KOA, a static version of their strengthening and stretching exercises is displayed. Patients can click on each exercise to view the animated version. These files use vector graphics, which allow for nearly instantaneous presentation of the animations even with slow Internet connections. These video presentations are important for instructing patients in safe, appropriate ways to perform each exercise.

3. Monitoring and Progression of Exercise Routine. Participants are asked to record their exercises after each session. Patients can request at any time to move to a harder or easier exercise level; they are enabled to move to a harder exercise level as long as their mSF-WOMAC score is better than or equal to their previous score. If this score is worse than previously, they are given a new exercise routine at their current level. If patients have difficulty with any particular exercises, the system also provides an option to exchange that exercise for another within the same level.

4. Pain Monitoring. Patients are also asked to report any increases in pain as a result of their exercises. If patients record increased pain for three consecutive sessions without requesting a lower exercise level, a suggestion is given to consider trying an easier exercise level. If patients do not record increased pain for two weeks but have not requested an increase in exercise level in that interval, they are encouraged to try a more difficult level.

VET-KOA Preliminary Data.

Participants and Procedures. A pre- and post-training study was conducted to assess the acceptability, feasibility, and efficacy of the virtual exercise training website[41]. Participants were 52 patients with diagnoses of knee OA, referred by their physicians. Eligible patients were given access to VET-KOA for eight weeks. Results. Participants had an average age of 63 years (SD=10); 52% were male; 38% had less education than a 4-year college degree. Use of the website was high; on average participants logged into the website an average of 47.2 (SD=12) of the possible 56 program days. Participants recorded completing strengthening / exercises an average of 37.8 (SD=12.5) days and aerobic exercises an average of 35.1 (SD=12.8) days. The mSF-WOMAC (primary study outcome) decreased by about 7 points following the program, which is a substantial improvement and a large effect size (Table 1). We also compared changes on the mSF WOMAC between participants with <4 years vs. ≥4 years of college education. This was of interest since VA health care users tend to have lower education levels than the general population. We found comparable changes; participants with <4 years of education reduced mean mSF WOMAC scores from 19.8 to 13.8 (a highly clinically relevant 30% change)[43], and those with ≥4 years of college education reduced mean mSF WOMAC scores from 15.4 to 8.5. There were also no substantial differences in study outcomes by gender. These data provide support for a positive response among VA healthcare users. The World Health Organization Quality of Life (WHOQOL) physical subscale and knee self-efficacy scale also improved significantly in this study (Table 1). 80% of study participants indicated experiencing "some" or "a lot" of improvement after using the website, and 43% reported a reduction in the use of pain medication. Patients also indicated a high degree of satisfaction with the program; on a scale of 18 items covering a broad range of aspects of the program and website (range 0-4), the mean score was 3.1 (SD=0.5). Also confirming patient satisfaction, 78% indicated that they would like to use the site in the future.

Table 1. Results of Pilot Study of Virtual Exercise Training System

	Baseline		8-Week Follow-up		Test Statistics	
	Mean	SD	Mean	SD	*p*-value	*pr*
mSF-WOMAC	17.00	7.67	10.42	7.94	<0.001	0.70
Pain Subscale	5.67	2.60	3.60	2.91	<0.001	0.66
Function Subscale	8.10	3.99	4.87	4.10	<0.001	0.67
WHOQOL-Physical	67.28	15.87	72.21	14.44	0.015	0.33
Self-efficacy	16.94	4.77	19.59	6.06	<0.001	0.54

SD=standard deviation; pr = point-biserial partial regression coefficient as measure of effect size with .14 small, .36 medium, and .51 large effect

Veteran User Testing of VET-KOA Program. We have met with five Veterans with knee OA at the Durham VAMC, who provided us with feedback about the VET-KOA features and usability. These Veterans were very positive about the program, found it to be user-friendly, and stated that Veterans would be likely to use this. They particularly liked the animated exercises. These Veterans also recommended minor changes, including: 1.) Enhancing usability of several components so they are even simpler for veterans who have no computer experience (e.g. more instructions about website navigation), 2.) Adding a feature to track progress, 3.) Adding an option for more exercises. These changes will be incorporated into the website prior to beginning the trial.

6.2 Studies Involving Telephone-Based Physical Activity Counseling for Knee OA: Step 2 Intervention. Dr. Allen and colleagues have completed two HSR&D-funded clinical trials, *Self-Management of OA in Veterans: A Telephone-Based Intervention (HSR&D IIR 04-016)* and *Patient and Provider Interventions for Managing OA in Primary Care (HSR&D IIR 10-126),* which included telephone-based physical activity counseling [16,26]. This experience forms the basis for our Step 2 intervention. Both of these studies resulted in significant improvements in OA outcomes, and there were high rates of call completion.

6.3 Physical Therapy Intervention for Knee OA: Step 3 Intervention. Drs. Allen, Hoenig and Bongiorni recently conducted a clinical trial at the Durham VAMC to evaluate *Group Physical Therapy for Veterans with Knee OA (HSR&D IIR 09-056)*[44]. Group-based PT was compared with traditional individual PT, and our individual PT protocol forms the basis of Step 3 for the proposed work. Among 161 participants assigned to the individual PT arm of this study, 97% at least one scheduled visit and 88% completed both planned visits.

6.4 **Other** Exercise Studies at the Durham VAMC and Duke (Drs. Morey, Hall, and Huffman). Dr. Morey has directed physical activity trials and clinical exercise programs at the Durham VA for over 25 years. She directs a longstanding and award-winning facility-based exercise program for older Veterans (Gerofit), a majority of whom have OA. In the last two years, she has received in excess of 2.1 million dollars to disseminate Gerofit to VA medical centers across the country. Her research focuses on examining modes of exercise delivery and

their impact on outcomes pertinent to older Veterans (HSRD-06-252, RR&D IIR E2756 and E3386). [45] Drs. Huffman and Hall have both collaborated closely with Dr. Morey on studies of home-based physical activity. Dr. Huffman conducted secondary analyses of these data and reported that physical activity levels were consistently lower among those with arthritis, but these participants still increased physical activity and reported improved outcomes as a result of a home-based program.[46] These results support the potential for home-based and stepped care physical activity programs for Veterans with OA. Dr. Hall has led several secondary analyses of trials led by Dr. Morey, focusing on predictors of adherence [47,48]. Lessons learned from these analyses have been incorporated into the proposed study, particularly related to goal-setting in the Step 2 intervention.

6.5 Summary of Preliminary Work. In summary, this preliminary work shows:

1. A well-developed internet-based exercise program for knee OA, including strong pilot data for feasibility, efficacy and patient satisfaction; this forms the basis for Step 1 of STEP-KOA.
2. Established protocols for telephone-based physical activity counseling and in-person PT visits, within the context of randomized clinical trials, which form the basis of our Step 2 and 3 interventions (described in detail below).
3. Successful processes for identifying, enrolling and retaining Veterans with OA into clinical trials of behavioral interventions, including physical activity and PT.

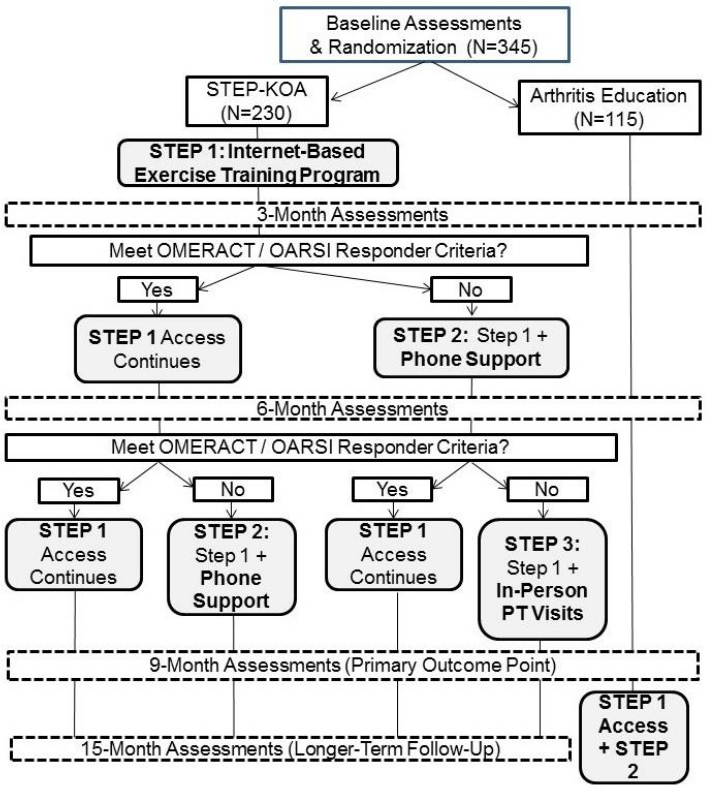
B. SIGNIFICANCE

This study will have a significant impact for Veterans and VA healthcare system, for the following reasons:

- Knee OA is one of the most common and disabling conditions among Veterans, and for many of these patients pain is not adequately controlled with pharmacotherapy and other typical clinical care.
- Although exercise programs and PT improve outcomes among patients with OA, most of these individuals are sedentary and need support to increase physical activity [25]. Further, arthritis is a key barrier to activity in patients with other conditions such as cardiovascular disease, diabetes, and obesity [49-51]; helping Veterans with OA to increase activity can therefore have an important impact managing many other health outcomes.
- STEP-KOA combines different strategies for improving physical activity, with an increase in the intensiveness of the approach for patients who do not meet benchmarks for improvement. This holds advantages over a "one-size-fits-all" approach, where individual patients may or may not achieve improvement with a given intervention. STEP-KOA modulates intervention intensity to meet patients' needs.
- Step 1 can be administered widely at relatively low cost, and Step 2 is also a less costly approach to in-person PT visits (Step 3). Implementation of Steps 1 and 2 could therefore allow the VA to focus outpatient PT costs toward Veterans who fail to achieve clinically relevant improvement with lower cost exercise-related interventions. In addition, the goal of Specific Aim #3 is to describe patient characteristics associated with success in a low-resource intervention (Steps 1 or 2) vs. a need for more intensive or in-person care. This information has the potential to ultimately guide referrals to PT or other exercise-related care for knee OA. For example, if we find that participants who are older or who have worse baseline pain, functional limitations or general self-rated health are highly likely to progress to Step 3, these individuals could be targeted by the VA for PT referrals, which are most likely to meet their needs; conversely, patients who are younger and have better health and fewer symptoms could be steered toward beginning with the Step 1 program.
- If effective, STEP-KOA could serve as a model for other chronic conditions for which exercise and PT are key treatment components (e.g., low back pain).

C. METHODS

1.0 Study Design. This will be a randomized controlled trial with participants assigned to two groups: STEP-KOA and Arthritis Education (AE) (Figure 2). We chose AE as the control condition for two primary reasons. First, this is an active condition, which will allow all participants to receive an OA-related intervention immediately. This may improve satisfaction and retention of participants, and it will help to account for any effects due to simply participating in an active intervention (e.g., attention effects). Second, AE has been utilized as an effective, feasible control condition in a number of other studies of behavioral interventions for OA [52-55]. We will use a 2:1 randomization ratio (STEP-KOA: AE Control); this design gives us ample sample size to characterize the STEP-KOA process and to explore characteristics of responders and non-responders at each evaluation time point (Specific Aim #3). Randomization will be stratified by gender and study site to ensure groups are balanced in these respects, since there is potential for treatment effects to differ based on these characteristics. Measurement time points are shown in Figure 2. Three and six-month assessments will be used to determine whether participants in STEP-KOA need to progress to more intensive steps. The primary outcome point (Aim 1) will be at nine months. In addition, Aim 2 will examine whether any effects are maintained in the STEP-KOA group in the six months following the intervention period (15 months post-randomization). A six-month follow-up period is meaningful for assessing maintenance in the context of physical activity trials among patients with OA [56,57], and it is feasible to complete within the study period. Following completion of 9-month assessments, participants assigned to the AE control group will receive access to the internet-based exercise training program, along with the Step 2 exercise counseling calls. (Therefore, the AE group will not complete 15-month assessments, as Aim 2 will now include the STEP-KOA group only.) We chose to provide treatment to the AE group after nine months because 15 months was deemed to be an overly long waiting period in the context of a symptomatic condition; this not only raises ethical concerns but scientific ones, since a long wait list period would increase the likelihood of participants seeking physical therapy outside the context of the study during that time frame. We acknowledge that this strategy means that we will not be able to test between-group differences at a longer-term, 15-month follow-up period. However, we will still gain valuable information by assessing whether any changes observed within the STEP-KOA group are maintained over time (9-months to 15-months) and whether this may differ among participants exposed to the different Steps of the program. All participants will continue other usual medical care for OA during the full study period, as recommended by their providers.



2.0 Study Sites. This study will be conducted in two sites in the VA Mid-Atlantic Health Care Network (VISN 6), Durham, NC and Greenville, NC, to enhance generalizability. The Durham VAMC is more urban, and the Greenville VAMC (also known as the Greenville Health Care Center) is located in a more rural and coastal region. Participants will be able to select a different study site from the one originally assigned if their location is closer to the other site.

3.0 Participant Eligibility Criteria. This study will involve n=345 Veterans with symptomatic knee OA. All participants must meet the following criteria: 1) Diagnosis of Knee OA (identified from VA electronic medical records and self-report) and 2) Current Joint Symptoms (based on self-report). In particular, participants must self-report having an average knee pain of 3 or greater (on a scale of 0-10) over that past two weeks. Patients meeting the following criteria will be excluded: Currently completing PT visits for knee OA; Gout (in knee),

rheumatoid arthritis, fibromyalgia, or other systemic rheumatic disease; Dementia; Psychosis; Active substance abuse disorder; meniscus or ACL tear in the past 6 months; total joint replacement, other major lower extremity surgery in the past 6 months or planned in the next 9 months (e.g., wait list or referred to non-VA care for Orthopedic surgery); Severe hearing or visual impairment; Serious / terminal illness; Other health problem that would prohibit participation in the study and/or warrant immediate PT; Current participation in another OA intervention study; Unstable angina; History of ventricular tachycardia; Unstable chronic obstructive pulmonary disease (two hospitalizations within the previous 12 months and/or on oxygen); Uncontrolled hypertension (diastolic blood pressure >110 mm/Hg or systolic > 200mm/Hg, measured at the baseline visit); Stroke with moderate to severe aphasia, recent history of three or more falls (follow-up questions by a clinician will determine whether patient is likely at risk for continued falls and would therefore not be a good candidate for a new home exercise program), resident of a long-term care facility, hospitalization for a cardiovascular condition in the past 3 months.

Based on patient populations at our planned VA sites and experience from our previous studies, there will be an ample number of patients eligible for the proposed study. In a recent data pull, there were 3,039 patients at the Durham VAMC and 882 patients at the Greenville VAMC who had ICD-9 codes indicating knee OA and no codes for our exclusion criteria. In our completed trial, *Self-Management of OA in Veterans: A Telephone-Based Intervention*, 29% of patients who met initial eligibility criteria based on ICD-9 codes were ultimately eligible and consented to participate. Based on our recent data pull, this would result in approximately 1,137 enrolled participants for the proposed study.

4.0 Enrollment Procedures.

We will recruit participants in three ways, which we have successfully employed in prior VA clinical trials: 1.) *self-referral*, 2.) *provider referral*, 3.) *direct contact* by the study team. *Self-referral* will involve placing posters and brochures in clinic waiting rooms and other common areas, as well as on the closed circuit television. VA clinicians may also give these brochures to patients who may be interested in the study. To facilitate *provider referral*, we will meet with primary care providers to inform them about the study and give study information by email and paper forms. We will set up a consult for referring patients to the study within the electronic medical record. Methods for *direct contact* of patients by the study team will begin with a data pull of patients who have ICD codes for knee OA and no exclusionary diagnoses, followed by an introductory letter. For participants recruited via all three methods, the study team may review VA medical records to verify a diagnosis of knee OA and lack of exclusionary diagnoses. The study team will also administer a screening questionnaire via telephone to further assess eligibility. If patients meet screening criteria and are interested in participating, they will be asked to come to their VA clinic for a baseline visit, which will consist of consent and baseline assessments. Study exclusion criteria (described above) that may make it unsafe to participate in regular activity will be assessed at multiple time points during the enrollment process. First, they will be identified from electronic medical records at the initial data pull (prior to sending out recruitment letters). Second, they will be included in the telephone-based screening questionnaire described above. Third, research assistants will scan participants' medical records prior to the baseline assessment to ensure these have health problems have not emerged since the phone screening. Fourth, at the baseline visit research assistants will ask participants if they have had any health changes or new symptoms since the phone screener. At the baseline visit, trained research assistants will measure participants Resting Blood Pressure using a digital sphygmomanometer after the consent process. Participants with diastolic blood pressure >110mm/Hg or systolic >200mm/Hg will be advised to be seen at the Emergency Department or Urgent Care immediately. Participant will not be able to continue until given a clearance. Elevated BP may be detected by trained research assistant at the baseline visit. Participants with signs of acute end-organ damage such as current chest pain, dyspnea (difficult or labored breathing) at rest, new onset of blurry vision, or new neurological deficits consistent with a stroke will be advised and assisted in seeking emergency medical care. We note that our total sample size goal of n=345 pertains to the number of participants who complete baseline assessments and are informed of their randomization assignment. It is possible that some patients will be determined to be ineligible between the time of consent and randomization assignment; these patients will not count toward the sample size goal. Research assistants will also be trained to assess potential symptoms of acute inflammation (swelling, warmth, pain flare); these Veterans will be evaluated by Dr. Huffman or another health care provider prior to participation.

At the enrollment visit, participants who indicate they would need a tablet computer to participate in the Step 1 intervention will be oriented to basic use of an iPad. This orientation will be given regardless of group assignment, since all participants will eventually participate in the Step 1 intervention.

After the enrollment visit, at study team member will call participants to give them their randomization assignment. Participants assigned to STEP-KOA will be given orientation to the website via phone and assistance with getting set up as a new user. This may occur during the same phone call as randomization or at a separate call. Participants will be sent information on how to use the website, along with general information about physical activity and osteoarthritis. Also, participants who indicate they do not have regular internet access to participate in the study will be sent an Apple iPad Air 16GB (encrypted with FIPS 140-2) (Version 9.3.1 (13E238) with Mobile Broadband Access Calling Plan for use during the study period. We will follow procedures used by Dr. Hoenig and Mr. Caves in previous research to simplify use of these devices by patients and minimize risk of inappropriate use. This will include a set of written instructions and an agreement regarding allowed use of the Apple iPad Air 16GB (encrypted with FIPS 140-2) (Version 9.3.1 (13E238) with Mobile Broadband Access Calling Plan as part of study participation, and monitoring of monthly data use by the research team. Following the telephone orientation to the exercise website, a team member will use brief motivational interviewing strategies to encourage adoption of physical activity and use of the exercise, and explore potential barriers

5.0 STEP-KOA Intervention

5.1 Overview. We have chosen intervention Steps that are evidence-based and focus on enhancing physical activity but differ in the amount, type and mode of care provided. We have chosen three-month intervals for the Steps, based on prior research indicating this is an adequate time period to observe meaningful changes in pain and function [61]. All participants in STEP-KOA will continue to have access to the Step 1 program for the full nine-month intervention period, regardless of whether they progress to Steps 2 and 3. This is because VET-KOA may serve as a complementary resource to participants who go on to receive telephone counseling and in-person PT visits; this approach is similar to other stepped care interventions [33,35]. Further, continued access to VET-KOA is of minimal cost and would be feasible for the VA to provide to Veterans on a longer term basis. Some participants who initially meet response criteria at the three-month assessment point (and therefore remain at Step 1) may regress by six months and no longer meet benchmarks when compared to baseline pain and function. Since these patients initially met response criteria after Step 1, one likely reason for regression is encountering barriers to maintaining activity. These patients will be advanced to the Step 2 intervention at the six-month time point, since the telephone counseling intervention is aimed at addressing multiple types of barriers (Figure 2); this approach is also similar to other stepped care interventions [33,35].

We have chosen the OMERACT-OARSI responder criteria to determine which patients progress to Step 2 and Step 3 interventions [36]. These criteria were established using a combined data-driven and expert opinion approach, and they have been used in over 30 clinical trials of behavioral, pharmacological and surgical interventions for OA (e.g. [2,62]). The validity and utility of these criteria have been supported in these trials, based on expected proportions of responders to various interventions, as well as the presence of expected associations between patient characteristics and response / non-response. We purposefully selected the OMERACT / OARSI criteria for stepping, rather than physical activity based criteria, for three reasons. First, OMERACT / OARSI criteria cover domains of pain and function, which are treatment goals and outcomes of high importance to patients with OA, as well as their providers. The ultimate goal of the STEP-KOA intervention is to improve these outcomes, with physical activity enhancement being the mechanism. Second, prior studies indicate that physical activity interventions can produce meaningful change in pain and functional outcomes in the context of OA, regardless of other concurrent treatments [20]. Third, it is possible that some patients could increase physical activity but not achieve meaningful improvement in pain and functional outcomes. A likely reason for such a discrepancy is the need for more targeted physical activity to address specific deficits; this could be addressed by Step 1 and Step 2 interventions. Patients can meet OMERACT-OARSI response criteria in two ways: **1)** ≥ 50% improvement in pain OR function AND absolute change ≥ 20, **2)** Improvement in at least two of the following: pain ≥ 20% and absolute change ≥ 10; function pain ≥ 20% and absolute change ≥ 10; patient's global assessment ≥ 20% and absolute change ≥ 10. Based on prior research [2,63,64], we estimate that about 1/3 of participants will meet OMERACT-OARSI response criteria after Step 1 and an additional 1/3 (2/3 of total) will meet response criteria after Step 2. However, *the success of this study is*

not dependent on the responder rate; rather, this rate will provide important information for resource allocation if the STEP-KOA is implemented. We note that the OMERACT-OARSI response criteria include two components of our primary outcome (WOMAC). However, we have purposefully chosen alternate pain and function scales to evaluate OMERACT-OARSI response criteria, so that the primary study outcome is distinct from the scales used to determine progression to more intensive Steps. The project coordinator, not blinded to study assignment, will inform patients via telephone about whether they progress to Step 2 and 3.

5.2 Step 1: VET-KOA. Step 1 involves access to the VET-KOA program described above, with some modifications including no use of email messages. We chose an internet-based program for Step 1 for several reasons. First, there has been increasing and successful use of the internet to deliver physical activity and other behavioral programs,[65] including recent studies among older adults[66-68]; this approach also aligns with the VA's current movement toward mobile health behavioral interventions[69]. Second, internet-based programs can be delivered widely at low cost. Third, internet-based programs enhance access by removing transportation related barriers and offering flexibility in terms of the times in which patients can access the program. Fourth, internet-based programs have the capability of tailoring activities to individuals' preferences and abilities; this is important because research has supported the utility of a tailored approach to physical activity [70]. After minor changes, recommended by our Veteran "testers", are made to the VET-KOA program, we will ask an additional 10 Veterans with knee OA to use the website from home for about two weeks and provide feedback on usability. Any additional recommended changes will be incorporated prior to beginning the trial. Prior to the beginning of recruitment, the Durham VAMC Information Security Officer will review the website to determine if it meets all VA information security requirements.

Participants will be given an individualized code and instructions for accessing VET-KOA. They will also be given ankle weights and therapy bands (as in the pilot study), since these are utilized in some exercises. Participants will be given a telephone number to contact the project coordinator if they need technical support regarding the website. These telephone contacts will not involve advisement regarding physical activity and will not be handled by the exercise counselor. We will document the frequency and nature of these contacts, which will be useful in the overall evaluation of this internet-based resource. Participants will be encouraged to access the system as soon as they are randomized and throughout the study period. In accordance with guidelines for physical activity[58], we will recommend that participants complete stretching and strengthening exercises, guided by the VET-KOA website, at least three times per week. Participants will be told that it is safe and appropriate to perform aerobic exercises daily, or as often as possible, guided by the VET-KOA website. *An overall guiding principle is that participants will be encouraged to be as physically active as their abilities, health conditions, and pain allow, with an emphasis on reducing inactivity and sedentary behavior*.

When participants enter the VET-KOA website, they will be given information on principles of safe, effective physical activity, benefits for patients with knee OA (addressing *Outcome Expectations*), management of pain that may occur with physical activity (addressing *Barriers Self-Efficacy*), and dealing with general barriers to activity (addressing *Barriers Self-Efficacy*). Tailoring of the exercise program in VET-KOA is important for addressing *Exercise Self-Efficacy*; recommending exercises at appropriate levels will help to give participants confidence, especially early in the program, that they can complete these activities. If participants do not enter the website for two weeks, they will receive a telephone call from a study team member encouraging them to access the website, and most importantly to remain physically active. We may also contact the participants if we need to give them information about safety (e.g., if they are recording pain frequently in the website). Selected study team members will have access to a password-protected website that will include information on participants' use of the VET-KOA website, along with any safety-related information. There will be no PHI on this website; participants will be indicated by a unique ID only. If a study participant cannot be reached by telephone, we will leave a voicemail message asking for the participant to call the study team member. We will not leave any PHI on the voicemail message or with a family member.

5.3 Step 2 Intervention: Telephone-Based Physical Activity Counseling. Participants who progress to Step 2 will receive bi-weekly telephone calls from an exercise counselor for a three-month period. We have chosen this Step 2 intervention approach because studies indicate that personal support from an exercise counselor (or similar role) can improve physical activity [71]. Also, although this approach is more resource intensive than

an internet-based program, it is less costly than in-person PT visits and does not require Veterans to travel to a VA facility. The overall goals of Step 2 calls are to address any OA or health-related difficulties participants are having with an exercise program, provide additional *Social Support for Physical Activity*, augment *Barriers Self-Efficacy* by providing additional personalized counseling for the specific barriers, and reinforce information about the benefits of physical activity (*Outcome Expectations*). During the first phone call the exercise counselor will query participants about whether OA symptoms or other health problems have presented challenges to their engagement in exercise. The counselor will have access to participants' baseline study assessments, which include information on comorbid health conditions and other joints with arthritis; this will help the counselor to probe for potential barriers. It is also common for individuals with OA to face challenges to exercise due to their pain and functional limitations. Therefore, the counselor will work with participants to tailor the exercise types and intensity to accommodate any of these difficulties. The exercise counselor will also ask participants about any other general barriers they encountered in completing their physical activity since the last call (e.g., time demands). The exercise counselor will guide participants in a process of problem-solving any barriers, and this will be incorporated into the process of developing action plans for the following weeks. Motivational interviewing strategies, including use of open-ended questions and reflective listening, will be employed to identify any ambivalence patients experience about engaging in physical activity [72]. We have used these strategies in our studies that include telephone-based physical activity counseling[26]. During each telephone call, the exercise counselor will also engage participants in a process of goal-setting and action planning for their weekly physical activity, using "SMART" principles that emphasize that goals need to be Specific, Measurable, Action-oriented, and Time-Bound [39]. The exercise counselor will help participants to develop goals and action plans that are reasonable for them to achieve, facilitating *Exercise Self-Efficacy*.

We expect most calls will take about 15-20 minutes and will document the duration of each call so that we can calculate the overall effort required to complete this intervention Step. The first call will likely be longer since the counselor will take time for introductions and to explore current exercise and challenges. The exercise counselor will encourage the participants to invite a friend or family member to be involved with calls if they would like.

5.4 Step 3 Intervention: PT Visits. We have chosen this Step 3 intervention approach because physical therapists have specialized training to evaluate functional impairments and biomechanical issues and can assist patients with tailoring exercises to address these deficits. Physical therapists can also evaluate patients' needs for knee braces, shoe lifts, or other assistive devices. We posit that patients who do not experience meaningful improvement after remotely delivered physical activity interventions may have greater functional impairments or other underlying clinical issues that will benefit from in-person attention by a physical therapist.

We have based this intervention on usual PT care for knee OA within the VA healthcare system, as well as processes we have utilized in a clinical trial at the Durham VAMC [44]. Core components of PT for knee OA include: instruction in a tailored exercise program, instruction in activity pacing and joint protection, and evaluation of: mobility, stability, function, knee alignment, limb length inequalities, specific areas of weakness or inflexibility, and need for mobility aids, knee braces, and shoe orthotics. Participants will receive approximately 3-7 PT visits; the first will be about hour and the remaining visits will be about 30 minutes. Participants will be paid $10 for each physical therapy visit, plus an additional amount that varies by distance traveled (as specified in the consent form). The number of visits will be based on participants' progression and need for additional follow-up. Components of the physical therapy sessions will include:

1. Standard assessments including range of motion, strength, knee alignment, limb length equality, balance, and gait.
2. Review the participant's current exercise and provide recommendations for tailoring
3. Examine participants' affected knee(s) for edema and provide appropriate recommendations for the use of heat, cold, elevation, and / or self-massage, particularly to be used before or after exercises.

4. Observation of participants as they perform strengthening and stretching exercises to ensure proper technique.
5. Provision of recommendations for referrals to:

a. Prosthetics for assistive device (if participants experience balance or instability with walking)
b. Prosthetics for knee brace (if participants experience knee instability or significant malalignment)

c. Podiatry for shoe orthotics / lifts (if participants have a limb length inequality)

6. Instruction in activity pacing and joint protection.

PT visits can impact multiple factors associated with physical activity as outlined in the Social Cognitive Model. Specifically, these visits provide more intensive and personalized instruction in a home exercise program, which can bolster both *Exercise Self-Efficacy* and *Barriers Self-Efficacy*. Physical therapists also provide additional *Social Support for Physical Activity* and help participants to have an understanding of long-term benefits of physical activity for knee OA (*Outcome Expectations*). Finally, these visits provide additional instruction on managing pain that can occur with physical activity, addressing *Somatic Sensations*.

As of February 14, 2018, we are no longer able to provide study-specific PT at the Greenville VA Healthcare Center due to lack of an available study physical therapist. Participants may come to the Durham VA for study-provided PT, and we will compensate them additionally to account for the travel (based on mileage rates already specified in our consent form). If a participant opts not to come to the Durham VA for study PT, a clinical member of the study team may contact the participant's PCP to notify them about the participants' inability to receive physical therapy as part of study-related procedures. The PCP will also be notified that it is up to their discretion regarding whether to refer the patient to PT, as clinically appropriate. (Study-provided PT was designed to mirror routine PT for knee osteoarthritis, so the type of care that patients would receive should not differ substantially if it is provided through a typical clinical route at the VA.) If participants do not want to participate in either option, they can still remain in the study if they choose, and we will inform them that this will not have any impact on their usual care at the VA. Because some patients will not move on to Step 3 of the intervention (PT), we will inform participants of these options at the 6-month follow-up point, via phone (using a script), if the information is relevant for them.

6.0 Arthritis Education Intervention

Participants in the AE control group will receive low literacy educational materials via mail every two weeks. Because STEP-KOA is a multi-component intervention, with participants receiving different numbers of Steps, it is not possible to implement a control condition that will mirror the exact intervention "dose" received by all participants in the STEP-KOA group. However, AE will achieve the goal of providing an active, OA-related control condition. We selected a mail format because it mirrors the "remote" aspect of the Step 1 intervention that will be received by all study participants in the STEP-KOA group. We selected the two week interval for mailings because it mirrors aspects of each of the STEP-KOA interventions: Step 1 includes feedback regarding potential changes in exercise level on a two-week basis, Step 2 involves biweekly phone calls, and Step 3 involves PT visits spaced approximately 2 weeks apart. The AE intervention will include a comprehensive set of topics related to OA and its management, based on established treatment guidelines (Box 1) [17,73]. These materials will be based on those we have already developed and successfully utilized in prior HSR&D funded clinical trials among Veterans with OA[16,26].

Box 1. Topics for AE Intervention

- What is OA?
- Diagnosis of OA
- Risk Factors for OA
- Health Care Providers And OA
- Pain Medications (Oral)
- Topical Pain Medications
- Joint Injections
- Knee Braces
- Shoes and Orthotics
- Physical Activity
- Weight Management
- Joint Protection
- Pain Coping Skills
- Surgery
- Complementary and Alternative Therapies
- OA and Sleep
- OA and Mental Health
- OA and Fatigue

7.0 Measures

Study assessments will be conducted in person at baseline and 9-months (primary outcome point); interim assessments (3-months, 6-months) and longer-term follow-up (15-months) will be conducted via telephone. Assessments will be conducted by a research assistant blinded to group assignment. Participants will be paid $40 for in-person and $20 for telephone-based assessments. This measurement battery is shorter in length than those from our recent clinical trials among veterans with knee OA[26,44], and the time burden has been

acceptable to participants, with little missing data. Prior to each assessment point (either on the phone at the time of scheduling, on the phone just before assessments begin, or in-person at the time of assessment), a study team member will ask participants whether they have had any new health problems since their last assessment point. If there are new health problems, the study team will ask the nature of these problems. If these problems are related to exclusion criteria, the study team member will either: 1) Let the participant know they need to be withdrawn from the study OR 2) If it is unclear whether withdrawal is appropriate, let the participant know they will contact a clinical co-investigator and follow-up to let them know if they are eligible to continue in the study; assessments will not proceed until this is resolved. At in-person follow-up visits, research assistants will measure the participants Resting Blood Pressure; if diastolic blood pressure >110mm/Hg or systolic >200mm/Hg will be advised to be seen at the Emergency Department or Urgent Care immediately. Assessments will not proceed until these issues are resolved.

7.1 Primary Outcome: WOMAC. The primary outcome measure is the WOMAC, a measure of lower extremity pain (5 items), stiffness (2 items), and function (17 items), with items rated on a Likert scale of 0 (no symptoms) to 4 (extreme symptoms). The reliability and validity of the WOMAC total score and subscales have been confirmed [74]. The WOMAC has been widely used in trials behavioral interventions for knee OA, confirming its sensitivity to change. The WOMAC has also been validated for use via telephone [75]. To supplement the WOMAC, we will add additional measures that are part of the widely used Knee Osteoarthritis Outcome Survey (KOOS).

7.2 Secondary Outcome: Objective Physical Function. We will assess physical function using measures recommended by OARSI for clinical trials of knee OA [76]. These tests have been previously validated, with strong measurement properties and sensitivity to change in clinical trials among patients with OA. These tests will include a 30 second stair stand test, a 40m fast-paced walk, a timed get up and go test, stair climbing test, and a 6-minute walk test, following previously established procedures for each. The 30 second stair stand asks participants to rise and sit back down in a chair as many times as they can during that time period, without using hands or arms for support [77]. The 40m fast-paced walk is a timed test of walking twice back and forth (as fast as participants are able) over a 10m distance [78].The timed get up-and-go test requires the participants to stand from a standard arm chair, walk 3 meters and then return to sitting in the same chair (as quickly and safely as possible). The stair climbing test measures the time it takes to ascend and descend a flight of 12 steps (each step 18 cm high and 28 cm deep). Participants will be asked to complete the test as quickly as they felt safe and comfortable. The use of one handrail will be allowed if necessary, but patients will be encouraged to minimize their use of the handrail. The 6-minute walk test will require participants to walk as far as they can during a 6-minute periods. Walking aids are permitted as needed. Participants will be asked to walk the amount of time they are able to walk. Following these tests, we will ask participants to indicate the maximum pain they experienced, on a scale of 0-10, during the test.

7.3 Self-Efficacy for Exercise Scale. The Self-Efficacy for Exercise scale assesses individuals' confidence in engaging in exercise in nine different situations that could present barriers (including having pain when exercising) 75. For each situation, individuals are asked to rate their confidence in being able to exercise three times a week for 20 minutes each time, on a scale of 0 (not confident) to 10 (very confident). Validity of this measure was confirmed by expected associations with actual exercise, as well as physical and mental health.

7.4 Social Support for Exercise Scale. This scale includes 13 items that assess the frequency with which friends and family members (separately) engage in behaviors that may either support exercise (e.g., "Gave me encouragement to stick with my exercise program") or discourage exercise (e.g., "Complained about the time I spend exercising"). All items are measured on a scale of 1 (none) to 5 (very often). The scale has shown acceptable test-retest reliability and internal consistency reliability. In addition, the scale was correlated with exercise habits, providing evidence of concurrent criterion-related validity.

7.5 Hopkins Rehabilitation Engagement Rating Scale (HRERS), a 5-item, clinician-rated measure developed to quantify engagement in acute rehabilitation services. This will be completed by the telephone counselor at the end of the Step 2 and by physical therapists at the end of Step 3, for participants involve in those steps only.

7.6 Physical Activity, Adherence and Related Measures

Physical Activity Scale for the Elderly (PASE). The PASE is a self-report, 12-item scale that measures occupational, household, and leisure activity during a one-week period.[79] This scale was developed for use among older adults and is appropriate for patients with knee OA who typically have more limited physical activity than the general population. The PASE has been validated for use via telephone.

Additional Self-Report Physical Activity Items. We are also specifically interested in purposeful exercise behaviors. We will ask participants to report the number of times and minutes per week, on average, they are completing strengthening, stretching, and aerobic exercises

Adherence to Intervention Step Components. As described above, participants' use of the VET-KOA website will be logged within the site. For participants who advance to Step 2, we will collect information on the number of scheduled phone calls completed, and for participants who advance to Step 3, we will collect information on the number of scheduled PT visits attended.

7.7 OMERACT-OARSI Responder Criteria (for determining progression to intervention Steps)[36]. We will use single item numeric rating scales to assess average pain and function during the prior two weeks (0=no pain / no difficulties with function to 100 = pain / difficulties with function as bad as you can imagine). Similar to prior research[62], we will use the Patient Global Impression of Improvement scale for the third domain, with improvement defined as "better" or "much better." We have chosen not to use WOMAC scores in the construction of these criteria, since this is the primary study outcome. Prior clinical trials have also utilized both OMERACT-OARSI responder criteria and WOMAC scores as separate, distinct outcomes [2,63,64]. Whereas the OMERACT-OARSI criteria simply designate individuals as responders vs. non-responders, WOMAC scores describe the degree of response or change in pain and function.

7.8 Participant Characteristics Associated with Treatment Response. Specific Aim 3 will evaluate participant characteristics associated with treatment response and the need for intensification to Steps 2 and / or 3 (See Section C.8.3). We will focus on four *a priori* characteristics we believe have strong potential for predicting the need of intervention intensification: age, baseline self-reported pain and function (single items described above for the Responder Criteria), and baseline self-rated general health (excellent, very good, or good vs. fair or poor). We have selected these measures because they are single items that could be quickly and easily administered in a clinical setting to guide referral to a specific treatment most likely to meet patients' needs.

7.9 Additional Participant Characteristics. We will assess the following to describe the study sample: age, race / ethnicity, gender, household financial state, education level, work status marital status, body mass index, questions about internet and technology use, the Patient Activation Measure, , comorbid illnesses (Self-Administered Comorbidity Questionnaire)[81], joints with OA (including designation of unilateral vs. bilateral knee OA), duration of OA symptoms, and documentation of variables to verify an OA diagnosis based on American College of Rheumatology Clinical Criteria (duration of morning stiffness, presence of bony tenderness and bony enlargement, crepitus).

7.10 Knee OA and Related Care During Study Period. We will assess use of treatments for knee OA at baseline and follow-up assessments, including pain medications, topical creams, knee braces, joint injections, and assistive devices. We will assess this via self-report, as well as using VA medical records to identify receipt of physical therapy for knee OA, participation in MOVE!, and prescription pain medication use. We may also examine Fee Basis files to more comprehensively assess care received outside the VA. We will not exclude participants who have new OA treatments during the study period. However, it is important to evaluate whether there are differences in these treatments across study groups. If differences are observed, we will conduct two types of sensitivity analyses: a.) participants who received specific treatments will be excluded from analyses, b.) the specific treatment (e.g., new MOVE! participation) will be included as a covariate in statistical models. In addition, if we find that ≥20% of participants have a change in any given type of treatment, we will conduct a sensitivity analysis that removes these participants. Because of the drastic improvements typically associated with joint replacement surgery, participants having this surgery during the study period will not be included in analyses of WOMAC scores. However, since receipt of total joint replacement is also an important OA outcome, we will compare the proportions of participants in each study group who receive this surgery during the study period.

7.11 Measures for Cost-Effectiveness Analysis

Intervention Costs. We will use a micro-costing approach to derive labor and equipment costs for the STEP-KOA intervention. Labor costs for Step 1 will include programmer time to maintain the website and phone calls for technical support. Labor costs for the Step 2 intervention will include the time needed to train the exercise counselor and to conduct the telephone calls; this time will include any required pre-call preparation, post-call activities, partial call completions, call attempts and callbacks. Labor costs for Step 3 will involve the therapist's time to complete in-person visits. Hourly wage + fringe benefit rates for personnel will be applied to the labor time to derive total labor costs. The equipment costs for Step 1 include ankle weight and therapy bands, as well as the Apple iPad Air 16GB (encrypted with FIPS 140-2) (Version 9.3.1 (13E238) with Mobile Broadband Access Calling Plan costs for a subset of participants. Equipment costs for Step 3 include any devices recommended by the physical therapist. Adaptations to the existing VET-KOA website for this project will be one-time study-related costs and not included in the intervention cost estimate. Total labor and equipment costs will be divided by the number of patients in the STEP-KOA arm to derive per-patient intervention cost. We note that costs will vary across participants, participants will not all receive the same Steps. We will report this variability but are primarily interested in the average cost per participant.

Patient Resource Utilization and Costs. The intervention may affect primary care and specialist outpatient visits for OA and outpatient pain medication use. To assess VA outpatient visits and VA prescribed pain medication use and costs we will utilize the outpatient extract and pharmacy data extracts from the *DSS Outpatient National Data Extract (NDE), and the DSS NDE SAS Pharmacy Dataset.* Outpatient encounters will be categorized using clinic stop codes of interest, as well as a count of total encounters and total costs of OA-related outpatient care. We will also include fee basis OA-related outpatient care and costs of the same categories because these are of increasing importance to VAMCs.

Effectiveness Measures. We will use two effectiveness measures to calculate cost effectiveness ratios: WOMAC units (described above) and the EuroQoL EQ-5D-5L questionnaire. The EuroQol health outcome measure (EQ-5D-5L and EQ-VAS) allows us to calculate quality-adjusted life years (QALYs), and it has been used successfully in previous research among patients with arthritis [82].

7.12 Participant Feedback on STEP-KOA. We will ask open-ended questions regarding the intervention components. For example, we will ask participants about usability of the VET-KOA website, appropriateness of the number and length of telephone sessions with the exercise counselor, content of PT visits, and ways we can improve the interventions.

8.0 Data Analyses

8.1. General Considerations. Primary study analyses will be conducted on an intent-to-treat basis, with participants analyzed in the group to which they were assigned. Additional exploratory analyses focusing on more restrictive analytic cohorts (e.g., per protocol analysis) will be considered, to provide additional information about the impact of magnitude of exposure to the intervention. The main conclusions drawn from this trial will be based on the pre-specified primary and secondary hypotheses outlined below and will be tested with two-sided p-values at the standard 0.05 level unless noted otherwise. Statistical analyses will be performed using SAS for Windows (Version 9.2: SAS Institute, Cary, NC) and R (http://www.R-project.org/).

8.2. Primary Analysis (Specific Aim 1). The main study outcome, WOMAC, is a continuous measure collected at baseline, 3, 6, 9 and 15 months (STEP-KOA group only). For the primary hypothesis we will examine STEP-KOA effects at the 9-month assessment. We will use a linear mixed model (LMM) that accounts for the correlation between a participant's repeated outcome measurements over time. We will apply an unstructured covariance matrix to take into account the within-patient correlation between repeated measures. The fixed-effect portion of the model will have the form: $Y_{it} = \beta_0 + \beta_1 3month + \beta_2 6month + \beta_3 9month + \beta_4 STEP\text{-}KOA*3month + \beta_5 STEP\text{-}KOA*6month + \beta_6 STEP\text{-}KOA*9month$, where Y_{it} is the WOMAC score for subject i at t=0, 3, 6, and 9months. We will estimate the parameters in the model and set up contrasts for tests of hypotheses using the SAS procedure MIXED (Cary, NC). Specifically, for Hypothesis 1, we will test for a difference in mean WOMAC scores between the STEP-KOA and AE groups at 9-months by testing that $\beta_6=0$.

Time is coded in the model to fit a constrained longitudinal data model (cLDA), in which baseline WOMAC score is modeled as a dependent variable in conjunction with the constraint of a common baseline mean across treatment arms[83]. For improvement in precision, the model will be adjusted for stratification variables[84].

8.3. Secondary Analyses. Since the secondary outcomes, 30 second chair stand and 40 meter fast-paced walk, are continuous, longitudinally collected measures, we will use similar modeling procedures as those described above for WOMAC scores to assess between-group differences at 9-month follow-up. We will also examine Poisson or negative-binomial mixed models as a sensitivity analysis as these outcomes (particularly chair stands) can be skewed and assumption of a normal distribution may not be reasonable.

For Specific Aim 2, to examine the maintenance effects of STEP-KOA at the15-month follow-up, we will add the 15-month outcomes and the 15-month time-point to the fixed effect portion of the model. As we will only be estimating the maintenance effects for participants randomized to the STEP-KOA arm, we will drop the treatment by time variables from the fixed effects. We will set up contrasts of model parameters to estimate the difference and associated 95% confidence intervals in outcomes between the 9-month and 15-month time points. Models will also be fit to estimate these differences for subgroups defined by the combination of steps received during the STEP-KOA program by adding variables to the fixed effects indicative of the steps received as well as their interactions with time.

For Specific Aim 3, we are interested in understanding the flow of responders and non-responders through the STEP-KOA intervention. Our goal is to determine whether there are patient-level factors, already known or easily determined in routine clinic visits, which could be used by providers (individually or in combination), to guide referral of patients to a Step that is most likely to meet their needs. We will first calculate proportions of responders and non-responders at each time point and describe responder patterns longitudinally We will also calculate proportions of individuals who meet response criteria in the two-different way described in Section C.5.1. We will then examine characteristics associated with responder status at each time point, using multivariable logistic regression models. In these models, we will first focus on the four *a priori* patient characteristics: age, baseline pain and function, and baseline self-rated health, to avoid spurious statistical findings [85]. Based on clinical experience, we believe these variables have potential to predict response, and they can be assessed easily and quickly, making them practical screening tools.

8.4. Missing Data. Because the main predictors of interest, intervention arm and patient characteristics, are collected at baseline, we do not anticipate much missing data in these variables. There may be missing values in the follow-up outcome measures due to dropout, death, a missed interim assessment, or item non-response. Our main analysis technique for the primary outcomes, general linear mixed models via maximum likelihood estimation, implicitly accommodates missingness when missingness is due either to treatment, to prior outcome, or to other baseline covariates included in the model, defined as missing at random [86,87]. If the missing values are related to other measured patient factors, , then multiple imputation (MI) provides a framework for incorporating information from these variables, while still preserving a parsimonious main treatment effect model [88,89]. Depending on the type and scope of missing data, MI will be conducted via the SAS procedure PROC MI or the SAS macro IVEware (http://www.isr.umich.edu/src/smp/ive/).

8.5. Sample Size. The sample size estimate of n=345 patients is based on a 2:1 randomization and the comparison of the primary outcome between the STEP-KOA and AE control arms at 9 and 15 months. Since AIM 3 is to describe the responder patterns for the Step progression in STEP-KOA we are using a 2:1 randomization to facilitate our ability to evaluate these patterns[90]. For sample size calculations we used methods appropriate for ANCOVA type analyses [91], which are equivalent in terms of efficiency to our linear model in randomized trials [83]. This method is based on performing a two-sample t-test sample size calculation for the between group difference, multiplied by a factor 1-(rho)^2, where rho represents the Pearson correlation between baseline and follow-up time point outcome measures. This sample size is then inflated to compensate for potential missing observations due to attrition. We estimate a 20% attrition rate at the 9-month time point, which is conservative based on our other clinical trials among Veterans with OA, all of which have had attrition rates <20%, including one that required two or more in-person visits from participants [16,26,44]. Also, based on our previous data, we assume a correlation of 0.4 between baseline and follow-up WOMAC scores, and an SD of 17.5. With 80% power, alpha=0.05, SD= 17.5, rho=.4, and approximately 20% attrition rate by 15-months, 230 and 115 participants are needed in the STEP-KOA and AE groups, respectively, for an effect

size of 0.33. This corresponds to a 5.8 point difference in mean total WOMAC scores at 9-months between STEP-KOA and AE, which is a clinically relevant improvement [43]. We will also be powered to detect medium effect size differences in secondary study outcomes. For Aim 3, based on an assumption of 1/3 responders after Step 1, we would have about 154 participants that progress to Step 2; additional participants who initially meet response criteria at three months may regress at six-months and enter Step 2 at that time point. We also expect that about 1/3 of the total STEP-KOA group (about n=76) will progress to Step 3.

9.0 Economic Evaluation. The overall goal of Specific Aim #4 is to provide the VA with information about the value of the STEP-KOA program, from a cost effectiveness perspective. In addition to informing the VA regarding the overall average cost of STEP-KOA per patient, this evaluation will provide information on how much improvement in outcomes can be achieved for that cost. This information is important for evaluating the potential for downstream implementation of STEP-KOA under various assumptions about scale and scope. We will not evaluate differences in costs or cost effectiveness according to the number of Steps each participant received; rather this will be a simple approach that is consistent with using the VHA perspective and comparing total aggregated costs across the two study arms (STEP-KOA vs. AE) at the 9-month follow-up point. The analysis will begin with descriptive statistics of the cost and effectiveness (utility) data. We will examine each measure of effectiveness, WOMAC and mean QALY (and the scores on the different EQ-5D-5L attributes, such as pain/discomfort), using the general analytic procedures and time points described above for primary and secondary outcomes. We will calculate the incremental cost effectiveness ratio (ICER) of STEP-KOA compared to the AE control group, separately for WOMAC and QALYs. The ICER will be calculated as the difference in the average total cost per participant STEP-KOA and AE, divided by the difference in the average effectiveness per participant between STEP-KOA and AE. Bootstrapping of estimates, multiple imputation for missing EuroQoL values, and sensitivity analyses will all be conducted to ensure robustness of our results.

10.0 Data Management and Quality Control. Study tracking and randomization functions will be completed with a database previously created in our Center with Microsoft .NET. Screening and outcome measures, as well as content and results of Step 2 physical activity counseling calls, will be recorded using DatStat Illume™, a web-based survey tool. The VET-KOA website is hosted by Visual Health Information. The study team will give each participant a unique code. They will use this code to initially log in. The link between participants' unique codes to access the website and other participant information will be kept on a computer server at the Durham VA, accessible only to IRB-approved study team members. So when the website vendor sends information to the VA team at the end of the study (e.g. on participants' website usage), the VA study team will be able to link this to each participant. When this information on website usage is conveyed to VA at the end of the study, it will be done so using a VA approved method (e.g., encrypted CD). The information that the vendor will supply to VA by the end of the study includes: self-reported pain, physical function, and physical activity, as well as whether they reported an increase in pain after completing their exercises.

11.0 Privacy, Confidentiality, and Information Security

11.1 Lists of Data Reviewed and/or Collected for Screening/Recruitment and Conduction of Study:

The Personal Health Information that will be used and/or shared for this study includes:

Identifier(s)	Source(s) of Health Information
☒ Names	☒ Medical history & physical exam information
☒ All geographic subdivisions smaller than a State, including street address, city, county, precinct, and zip code	☐ Photographs, videotapes, audiotapes, or digital or other images
☒ All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, visit or treatment dates, etc.; and all ages over 89	☐ Biologic specimens (e.g., blood, tissue, urine, saliva)
☒ Telephone numbers	☒ Progress notes
☐ Fax numbers	☐ Diagnostic / Laboratory test results
☐ Electronic mail addresses	☐ Operative reports

Identifier(s)	Source(s) of Health Information
☒ Social Security Numbers	☒ Imaging (x-ray, CT, MRI, etc.)
☒ Medical record numbers	☒ Discharge summaries
☐ Health plan beneficiary numbers	☒ Survey / Questionnaire responses as described in section 7 above
☒ Account numbers	☐ Billing records
☐ Certificate and/or license numbers	☐ HIV testing or infection records
☐ Vehicle identifiers and serial numbers, including license plate numbers	☐ Sickle cell anemia information
☐ Device identifiers and serial numbers	☐ Alcoholism or alcohol use information
☐ Web Universal Resource Locators (URLs)	☐ Drug abuse information
☐ Internet Protocol (IP) address numbers	☐ Mental health (not psychotherapy) notes
☐ Biometric identifiers, including finger & voice prints	☐ Psychological test results
☐ Full-face photographic images and any comparable images	☐ Genetic testing
☒ Any other unique identifying number, characteristic, or code, describe: unique Study ID number	☐ Other, describe:

11.2 Data and/or Specimen Acquisition: Data for this study will be collected through (*check all that apply*):

☒ Prospective data and/or specimen collection obtained from participants. Provide description of processes: No specimens will be obtained during the study period. Prospective data will be collected as follows:

- The study requires use of some individually identifiable data, including participant names, street address, city, county, zip code, telephone number, and Social Security number to complete telephone screening, send recruitment letters, and appointment reminder letters. We will collect the minimum amount of study data required to complete study aims involving recruitment, outcome assessment and reimbursement. These data will we stored in the study tracking. This database will also be used to keep track of study related telephone calls to participants, opt-out calls, study payment dates, and study appointments.
- Some data will be collected prior to consent, as outlined in our HIPAA waiver request, and on page 7 "Enrollment Procedures" above. We will collect the minimum amount of data to be able to identify potentially eligible patients and contact them about the study. These data will come from VA medical records (see sections above on "Participant Eligibility Criteria" and "Enrollment Procedures"), as well as a brief telephone-based screening questionnaire to capture information not reliably included in the medical record.
- For patients who enroll in the study, other data will be collected via questionnaires (and results of functional tests), completed in person at the VA.
- Screening and outcome measures will be recorded using DatStat Illume™, provided per VA enterprise license and funded by HSR&D. Illume is a web-based survey tool. Data will be stored on a secure VA server. However, we will have consent forms and a form on which we will record results of functional assessments. All hard copies of data will be stored in a locked filing cabinet in the office of a study team member located in suite 600 of the NC Mutual Building or at the Greenville Health Care Center room 1C214. All electronic data will be stored on a secure VA server managed by Durham VA HSR&D personnel, in a folder (\\vhadurshrdfile1\$projects\STEP_KOA) accessible only to study team members on the IRB approved staff listing.
- No -data will be transported outside the VA. Consent forms with patient names will be transported from the VA interview rooms to the study team's offices in Legacy Tower by an approved study team member; these documents will remain in direct possession of the study team member in a courier bag throughout transport. VA clinicians may refer patients to the study team, with patients' permission; this will be via a consult option within the medical record.
- Apple iPad Air 16GB (Version 9.3.1 (13E238) with Mobile Broadband Access Calling Plan issued to participants will be encrypted and FIPS 140-2 validated.

☒ Retrospective data collection and/or specimens obtained from medical chart review/data access. Describe how data will be obtained (e.g., fileman, CDW, etc.): We will use a data pull as one recruitment method, as described in sections 3 and 4 above. The study programmer will comply with instructions in the VINCI File Transfer Guide for electronic download of data from the project VINCI workspace to our local file server, and the VINCI Database User guide for export of CDW data to the local study tracking database hosted on SQL server instance in the Durham VAMC Data Center. Data will be pulled for patients who have ICD-9 codes for knee OA and no exclusionary diagnoses

☐ Retrospective data collection and/or specimens obtained from an IRB-approved data and/or specimen repository. Indicate the repository source including name, VA location, and IRB number .

11.3 Level of Data: the following level(s) of data will be acquired/maintained for this study (*check all that apply*):

☒ Identified (e.g., names, addresses or other identifiers included)
☒ Coded (direct and/or all identifiers removed, study code/ID included)
☐ De-Identified (all HIPAA 18 and study ID/code removed):
  ☐ Verified Statistically
  OR
  ☐ Verified by Absence or Removal of HIPAA 18 and study ID
☐ Limited Data Set
☐ Other: Describe

11.4 Location of Data and/or Specimens, and Data Retention Plan:

- A. Data and/or Specimen Location*:* Data will be stored electronically in the study tracking database (\\vhadurhsrdfile1\$research\Distributed Apps\HSRDTrackingApp) and in a folder accessible only to study team members on the IRB approved staff listing (\\vhadurshrdfile1\$projects\STEP_KOA), managed by Durham VA HSR&D personnel. Data that will be stored electronically include identifiers such as participant names, street address, city, county, zip code, telephone number, and social security number, and may include data noted above in section 11.1. We will also keep track of study related telephone calls to participants, opt-out calls, study payment dates, and study appointments.
- Paper records of data include informed consent forms, HIPAA forms, and data collection forms and will be stored in locked cabinets either at the Durham VAMC, Legacy Towers, Suite 600 or in room 1C214 at the Greenville Health Center.

☒ Data will be also be placed at the VA Informatics and Computing Interface (VINCI; http://vaww.vinci.med.va.gov/vincicentral/VINCIWorkspace.aspx). The VA Informatics and Computing Infrastructure is a partnership between the VA Office of Information Technology and the Veterans' Health Administration Office of Research and Development. Researchers and operations staff can use VINCI to access data and statistical analysis tools in a virtual working environment through a certified VHA network computer using the VA Intranet or Virtual Private Network (VPN).

B. Data Retention Plan

☒ Research records will be maintained and destroyed according to the National Archives and Records Administration, Records Schedule Number: DAA-0015-2015-0004. Records destruction, when authorized, will be accomplished using the then current requirements for the secure disposal of paper and electronic records. Currently, destruction of research records (see DAA-0015-2015-0004, section 7.6 "Research Investigator Files" for materials included in research records) is scheduled for 6 years after the cut-off (the cut-off is the completion of the research project) and may be retained longer if required by other federal agencies. Records will not be destroyed without pre-notification to the facility records manager.
☐ Other data retention plan, describe:

11.5 Data Access and Data Recipients: Only study team members who are listed on the study staff listing will have access to identifiable data. This will be stored behind the VA firewall.
All VA research personnel who have access to VHA records are instructed, in accordance with VA policy, on the requirements of Federal privacy and information laws and regulations, VA regulations and policies, and VHA policy. All study personnel who are VA employees working within the VA system have fulfilled all required HIPAA and other VA security and privacy policy training requirements and have agreed to follow guidelines pertaining to the protection of patient data. All research staff sign VA Rules of Behavior, and all study staff are up-to-date with VHA Privacy Policy Training and the VA Office of Cyber and Information Security Awareness Training Course. The data security and privacy procedures summarized in that course include logging off or locking the computer when walking away from it; no sharing of access codes, verify codes or passwords; not allowing anyone else to use the computer under one's password; and disposing of sensitive information using VA-approved methods (e.g., shredder bins). Access to study data will be removed for all study personnel when they are no longer part of the research team.

11.6 Data and/or Specimen Transportation and/or Transmission for all data and/or specimens involved in the study:

I. ☐ Data and/or specimens will not be transported or transmitted outside of Durham VAMC environment with the exception of the subject's e-mail address as noted above.

II. ☐ Data and/or specimens will be transmitted to other VA sites using the following method(s):

A. Data
☐ Data are de-identified and thus will be sent via unencrypted e-mail or unencrypted disk (encryption is optional).
☐ Data are coded or contain identifiers and thus will be sent <chose method of transfer such as: PKI or RMS encrypted e-mail, FIPS 140-2 encrypted disk (with VA-authorized carrier and tracking), or FIPS 140-2 encrypted external drive (with VA-authorized carrier and tracking). You may identify a primary and secondary method>.
☐ Other, describe:

B. Specimens (N/A)
☐ Specimens are de-identified and thus will be sent via standard carrier (tracking is optional).
☐ Specimens are coded or contain identifiers and thus will be sent via VA-authorized carrier with tracking.
☐ Other, describe

III. ☒ Data and/or specimens will be transported to non-VA/VHA sites (e.g., academic affiliates, laboratories, etc.) using the following method(s):

A. Data
☐ Data are de-identified and thus will be sent via unencrypted e-mail or unencrypted CD.
☐ Data are coded or contain identifiers and thus will be sent via <chose method of transfer such as FIPS 140-2 encrypted CD or FIPS 140-2 encrypted hard drive/flash drive> using VA—approved carrier with tracking.
☒ Data are coded or identified and will be uploaded to sponsor website using electronic case report form (eCRF) <the VET-KOA program website http://va.helpmyknees.com will be used to access the exercise program.
☐ Other, describe:

B. **Specimens (**N/A)
☐ Specimens are de-identified and thus will be sent via standard carrier (tracking is optional) or will be hand-delivered by research study personnel. Specify method of delivery:

☐ Specimens are coded and thus will be sent via VA-approved carrier with tracking or will be hand-delivered by research study personnel. Specify method of delivery:

In accordance with the HIPAA and the Privacy Act, for any coded or identifiable data or specimens released from the Durham VAMC (with the exception of Limited Data Sets), an Accounting of Disclosure (AOD) will be maintained (e.g., in a database or spreadsheet) that includes the participant's name, date of the disclosure, description of the nature of the Individually Identifiable Information (III) disclosed, purpose of each disclosure, and the name and address of the person/agency to whom the disclosure was made.

11.7 Risk Mitigation Strategies:

☐ Data are fully de-identified (stripped of HIPAA 18 and study ID/code) before being shared outside of Durham VAMC.

☐ Specimens are fully de-identified (stripped of HIPAA 18 and study ID/code before being shared outside of Durham VAMC.

☐ Direct identifiers will be maintained separately from data and or specimens by using a code to "identify" subjects. In a separate database (i.e., a "linking" or "cross-walk" database) this code will be linked to identifying subject information.

☒ Other, specify: Information will be accounted for by regular checks and reports generated from the tracking database (e.g., information on participant stages within the study); this will be approximately biweekly. In addition the study team will maintain a check sheet associated with tasks and data collected for the baseline and follow up assessments; this will help to that all required tasks are completed (e.g., providing participant with copy of the signed consent form) and that all data collected and stored will be in accordance with the VA records control schedule. The entire study team will work collectively to oversee the privacy and security of the data.

VHI Risk Mitigation Strategies:

1. Browser Encryption - All site content, whether participant specific or generic in nature, is served using HTTPS. TLS is required, SSLv2 and SSLv3 have been disabled.

2. Firewalls - The web server is protected by both hardware and software firewalls as well as using SELinux.

3. Limited Access – Only those employees who need to maintain the server are given the server security credentials.

4. Cookies – Cookies are transmitted using encryption and protected against tampering.

5. Password Security – No clear text passwords are stored, only salted hashes of passwords. Salted passwords are SHA1 hashed. A minimum password length of 6 is enforced but there are no other requirements on the password.

6. Forgotten Passwords – Since raw passwords are not stored, we cannot provide the user with their current password. Instead, the user can reset their password by calling a study team member.

7. URLs – There is no user or session information in URLs.

8. Backups – Database backups are made nightly and are stored on durable, encrypted storage.

9. Database Segregation – The study database will run on its own web and database server. It will not be shared by other sites.

11.8 Suspected Loss of VA Information: Should any incident such as theft or loss of data, loss or theft of the VA study issued iPad, unauthorized access of sensitive data or non-compliance with security controls occur, it will be immediately reported according to VA policy. All incidents regarding information security/privacy

incidents will be reported to the ISO and PO within 1 hour of acknowledgement of issue and done so using the VHADUR Research Events Report e-mail group (VHADURResearchEventReport@va.gov).

11.9 Reporting of Results:

☒ Reporting of results, such as in scientific papers and presentations, will never identify individual subjects. Data will be presented in aggregate and individual-level data will not be published.

☐ Other results reporting plan, describe:

12.0 Study Limitations and Challenges. One limitation is that within the time permitted, we will not be able to fully evaluate long-term adherence after completion of STEP-KOA. However, we have included a 15-month assessment point that will evaluate use of the program six months after the initial intervention period. If this trial supports the effectiveness of STEP-KOA, an important next step will be evaluation of longer-term adherence. We acknowledge that all VA healthcare users have regular internet access. However about 85% of U.S. adults report being internet users, including 80% of adults of who live in rural areas [92], and these numbers are steadily rising. Therefore we believe the VET-KOA program will be accessible to a large number of Veterans, and as internet access becomes more ubiquitous, this barrier will be lessened. As the VA continues to push forward to engage Veterans in MyHealth*e*Vet, VET-KOA is the type of program that could be integrated within that platform. Additionally, VET-KOA is currently being developed for a mobile platform and could also be converted to an App format; this would further increase the reach of the program [93].

13.0 Dissemination and Implementation Activities & Roles of Clinical / Operations Partners. We will disseminate findings to the scientific community via publications in professional journals and conference presentations. We will also work with the Durham VA Press Office and colleagues at the Arthritis Foundation and Centers for Disease Control and Prevention to further disseminate these findings. If the STEP-KOA program is found to be effective, there are several VA organizations whose missions relate to the potential implementation of this program. Therefore, during development of this proposal, we have been consulting with partners in each of these areas, including the National Center for Health Promotion and Disease Prevention, and the Office of Connected Health. These partners have enthusiastically supported the project, contributed to our study design decisions, and will continue to provide input throughout the study. We plan for monthly calls with partners during the study start-up period, then at least quarterly calls and progress reports afterward. These partners will help the study team ensure that results are of high relevance to the VA, assist with dissemination of results to relevant VA partners and leadership, and provide advisement about implementation strategies.

14.0 Project Management Plan

14.1 Timeline for Study Activity Completion. We propose a 3-year study. During the first four months we will finalize study materials, databases, and processes, train personnel and work with VHI to make minor changes to the VET-KOA program. Website changes will be completed in the first four weeks, after which we will ask n=10 veterans to test the usability of the program. There will be 14 months of participant enrollment (Year 1, Month 5 - Year 2, Month 6). This will require us to enroll about 24-25 participants per month, which is very feasible based on our prior clinical for Veterans with OA [16,26,44]. Three-month follow-up assessments will be completed by Year 2 Month 9, and 15-month follow-up assessments by Year 3, Month 9. We will devote the final three months of the grant to final data cleaning, analyses, preparing manuscripts, and completing the other dissemination and implementation activities.

14.2. Training and Supervision of Study Team. Dr. Allen will train and oversee the project coordinator and research assistant. Dr.'s Allen, Morey and Hall will all contribute to training the exercise counselor regarding delivery of the telephone-based intervention. In addition, Dr. Huffman will provide the exercise counselor with training regarding clinical issues surrounding OA, particularly related to exercise prescription and response. Before starting to deliver the intervention to study participants, the exercise counselor will perform multiple practice sessions with the study team. We will also audio tape intervention calls for approximately the first 10 participants. Dr.'s Allen and Morey will listen to each of these interview sessions and provide feedback to the exercise counselor. For the remainder of the study, approximately 5% of telephone conversations will also be

reviewed by the same study team members. Drs. Allen, Bongiorni and Hodges will provide training to the physical therapists who deliver the Step 3 intervention and will attend the first 10 visits for each therapist, followed by 5% thereafter to assure fidelity to the intervention protocol.

14.3. Website Maintenance Plan. The exercise program website has been in operation by VHI, including the pilot study, for two years without problems. Planned modifications will be tested by VHI programmers, as well as veterans in our initial feasibility study. We have allocated funds for VHI for this testing, as well as programmer support for routine maintenance or unforeseen problems encountered with the website.

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