Physical Therapy Versus Internet-Based Exercise Training for Patients With Knee Osteoarthritis (PATH-IN)

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RESEARCH STRATEGY

A. Demonstrate that the condition imposes a significant burden on the health of individuals and/or populations (*Criterion 1*)

A.1.0 Knee Osteoarthritis (OA) is Highly Prevalent. Knee OA is one of the most common chronic health conditions in the U.S., affecting about 9.3 million adults [1]. Recent data show that 45% of people will develop symptomatic OA in their lifetime [2]. Knee OA disproportionately affects racial and ethnic minorities (particularly African Americans), women and individuals with lower socioeconomic status [2,3]. Because of the forecasted growth in the U.S. older adult population, the prevalence of knee OA is expected to rise dramatically over the next several decades [4]. In addition, studies show knee OA is occurring earlier in the life course, affecting younger adults more often than in previous years [5,6]. This is likely due to the increased incidence of traumatic knee injuries and obesity, two main risk factors for knee OA. The rising prevalence and earlier occurrence of knee OA highlight the need for effective disease management strategies.

A.2.0 Knee OA Has A Significant Negative Impact on Many Patient-Centered Outcomes. Pain is the leading concern for patients living with knee OA and the most common reason for seeking health care for this condition [7]. However, pain is only one of many patient-centered outcomes negatively affected by knee OA. Disability and functional limitations are also very common. In fact, OA is the most frequently reported cause of disability in the U.S. [8], commonly affecting walking, stair-climbing, and other daily tasks [9]. Among older adults, disability from knee OA is as great as that due to cardiovascular disease and greater than any other medical condition [9]. Data from the National Health Interview Survey show that people with arthritis-related disability (including knee OA) have more numerous, longer, and more bothersome disabilities than people with heart disease-related disability [10]. Many studies have also shown that OA negatively impacts a wide range of other outcomes including sleep difficulties [11,12], fatigue [13], depressive symptoms and other aspects of psychological health [14], work limitations [15], social participation [16], and overall quality of life [17,18].

The following quotes from patients in our recent focus groups illustrate the impact of knee OA from the patient perspective: *"Getting up your normal daily movement is what you might say restricted…because it's an enormous amount of pain." "I take a lot of (work) leave. And it bothers me so bad that I have to take a lot of leave just to sit at home and lay at home. I just can't sand the pain." "When I go through it (OA pain), it's like it turns my whole day around. Because it's like you're thinking that 'cause you've already promised people you're going to be somewhere…so you really have to fight through that pain."*

B. Explain how the results of the study would likely improve health care and outcomes (*Criterion 2*)

B.1.0 Overview of the Project's Impact on Health Care and Outcomes. This project has great potential to impact health care performance and outcomes by evaluating strategies to improve pain, function, and other patient-centered outcomes among the large number of patients with knee OA. As described below, physical activity is a key component of managing knee OA symptoms and minimizing functional limitations. However, the majority of adults with knee OA are physically inactive, and additional evidence-based strategies are needed to help these patients to adopt and maintain regular activity [19-21]. Physical therapy (PT) is one resource for instructing patients with knee OA in an appropriate exercise program. However, as described below, there are limitations to PT services that may particularly impact medically underserved patient groups. This study will compare the effectiveness of standard PT and a novel, tailored internet-based exercise training (IBET) program that could be disseminated widely and therefore improve physical activity levels and associated patient-centered outcomes among many patients with knee OA.

B.2.0 Physical Activity is a Key Component of Managing Knee OA but Highly Underutilized. Many studies have confirmed that both aerobic and strengthening exercises improve pain, function, and other key outcomes among patients with knee OA [22,23]. A meta-analysis of clinical trials of exercise for knee OA found that pooled effect sizes (e.g., magnitude of treatment response) for aerobic exercise were 0.52 and 0.46 for pain and disability, respectively; for strengthening exercises, pooled effect sizes were 0.39 and 0.32, respectively [24]. These are medium-to-large effect sizes are comparable to those observed for pharmacological treatment of OA [25]. Based on this evidence, *exercise is considered a cornerstone of managing knee OA* [26,27].

However, despite the strong evidence for exercise in managing OA symptoms, the majority of adults with OA are physically inactive [28,29]. In a recent study of adults who had or were at risk for knee OA, only 2% of African Americans and 13% of whites were currently meeting guidelines for physical activity [29]. Recent data from the Centers for Disease Control and Prevention (CDC) show that among US adults with arthritis (primarily OA), over half report doing 0 minutes of walking per week, and 66% reported <90 minutes of walking per week (which is the minimum amount of weekly walking shown in a randomized clinical trial to lower pain and improve function) [30,31]. In addition, health care providers often do not incorporate recommendations to exercise for patients with OA and other musculoskeletal conditions [32,33]. Primary reasons for low rates of exercise recommendations include: limited contact time with patients, lack of knowledge of clinical guidelines and appropriate exercises, and lack of support materials [34,35]. These barriers can all be addressed by the proposed internet-based exercise training program.

B.3.0 Physical Therapy is a Resource for Helping Patients with OA to Increase Exercise, but There are Access Limitations. PT is a recommended component of treatment for patients with knee OA [26,27,36], typically focusing on evaluation of patients' functional limitations and prescription of a home exercise program. Although PT is clearly an important resource for helping patients with knee OA to increase physical activity, there are limitations in multiple dimensions of access to PT for patients with knee OA. First, there is a nationwide shortage of physical therapists to meet this demand. 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 [37]. Second, in addition to a general shortage of physical therapists, there are medically underserved areas in which therapists are even rarer or lacking entirely. This is particularly important because patients who are more likely to reside in medically underserved areas (e.g., racial and ethnic minorities, individuals with lower socioeconomic status) are also those who bear a greater burden of knee OA [3,38,39]. Third, patients without health insurance have little or no affordable access to PT services. Even for insured patients, copayments often make this service cost-prohibitive, and this challenge is likely to continue for low income patients despite the implementation of the Affordable Care Act. Fourth, even for patients with adequate health insurance, the number of covered PT visits for knee OA has been declining, and the number of allowed visits is not sufficient to provide patients with the instruction, and support needed to adopt and maintain an exercise program, particularly in the context of a chronic pain condition [40]. Fifth, some patients opt not to seek PT for knee OA because of time and schedule constraints, even when insurance and copayments are not a barrier. All of these access-related issues highlight a need for novel, alternative methods to provide patients with knee OA with instruction and support physical activity. In fact, there is widespread consensus that evidence-based interventions are needed to help adults with OA to adopt and maintain adequate levels of physical activity [19-21]. In the 2010 National Public Health Agenda for Osteoarthritis, the second overall recommendation (out of 10) for reducing the burden of OA in the US is to "*widely promote programs of low impact, moderate intensity aerobic activity and muscle strengthening exercise for adults with knee and hip OA*." A specific priority is to "*increase access and continue to identify additional effective packaged programs for physical activity that can be delivered safely in a variety of acceptable and accessible formats and settings*." These points have all been echoed by the patient stakeholders involved in this project, who voiced a need for instruction, support, and accountability to help them in being physically active.

B.4.0 Internet-Based Physical Activity Programs Can be Widely Disseminated, but Evidence is Needed in Knee OA. There has been increasing use of the internet to deliver physical activity and other behavioral programs [41]. While face-to-face PT visits and other physical activity programs clearly have value, there are several important opportunities associated with internet-based delivery. First, internet-based programs can be delivered widely at relatively low cost. Second, these programs remove transportation related barriers and offer flexibility in terms of the times in which patients can access the program. Third, internet-based programs can allow tailoring of physical activities to individuals' preferences and abilities; this is important because research has supported the utility of a tailored approach to physical activity [42].

A number have studies support the effectiveness of internet-based physical activity programs [41]. However, the majority of studies have focused on young and middle-aged adults, with very little research targeting individuals ≥65 [43]. This is an important limitation when considering patients with knee OA. A recent study evaluated a 12-week internet-based physical activity program among sedentary older adults [43]. The program involved both video-based and text format guidance and offered an individually tailored approach to physical

activity recommendations. This program resulted in significant increases in all types of physical activity, as well as significant improvements in physical function and mental health. Another recent small study of an internet-based program was also effective in improving physical activity levels among sedentary older adults [44].

To our knowledge, no large clinical trials evaluating internet-based physical activity programs for knee OA have been completed. One ongoing Canadian study is evaluating a physical activity website specifically for patients with early knee OA [45]. Studies have also shown significant improvements in physical activity and function following internet-based physical activity programs for patients with rheumatoid arthritis and following knee replacement surgery [46,47]. Collectively this early evidence supports the feasibility and potential for internet-based physical activity programs among patients with knee OA, but large randomized controlled trials are still needed to establish this evidence base, particularly across the spectrum of knee OA from early to late stages. The CDC maintains a list of physical activity programs (accessible on their website) that have an established evidence base for individuals with arthritis. *This list includes no internet-based interventions*. Although there are some commercially available internet-based physical activity resources, these are not geared toward patients with lower extremity OA and do not include patient-specific tailoring based on consideration of pain and functional limitations.

One limitation to an internet-based intervention is that not all patients with knee OA have regular internet access. We also recognize that this may be a particular barrier for patients who live more rurally or have lower socioeconomic status. However, the proportion of adults who use the internet regularly has been steadily rising, with about 85% of US adults reporting they are internet users; this includes 70% of adults age 50 and older and 80% of those dwelling in rural geographic regions [48]. Therefore we believe an internet-based program will be valuable to a large number of patients. In addition, the internet-based program we propose to examine in this study is currently being converted to a mobile health platform, which will further increase reach, as internet use via cell phone is growing rapidly [49].

B.5.0 Preliminary Data Support the Efficacy of an Internet-Based Exercise Training Program for Patients with Knee OA. Visual Health Information developed and pilot tested a tailored, internet-based exercise training program for knee OA, through a Small Business Innovations Research Grant from NIH (1R43HD065358). Here we describe the rigorous development process and initial testing that support the potential of this tool to improve health care and outcomes.

IBET Development Process.

This system was developed by a multidisciplinary team, including substantial input from patients, physicians, and physical therapist collaborators. Main steps in the development process included:

1. Development of a preliminary website that allowed patients with knee OA to view animated models executing prescribed exercises, followed by a small validation study.
2. Focus groups with physicians who treat patients with knee OA to obtain input on the design and features of a comprehensive IBET website.
3. Development of the IBET website, including the following activities:
   a. Creation of exercise routines at five levels across a continuum of patient functional abilities, based on clinical practice guidelines and peer-reviewed publications. A panel of orthopedic surgeons, physiatrists, rheumatologists and physical therapists contributed to selection of appropriate exercises and placed them into five levels of difficulty. There are 30 possible exercises within each of the five levels. Exercise routines, randomly generated within each level, always include strengthening exercises that target multiple muscle groups, with a focus on those that support the knee, as well as stretching exercises.
   b. Development of an algorithm for placing patients into the five exercise levels. This is based on the 14-item modified short form of the Western Ontario and McMaster Universities Osteoarthritis Index (mSF-WOMAC) [50] and several additional items that assess current physical activity, exercise ability, and use of assistive devices. The algorithm was compared to the exercise level recommended by practicing physical therapists, for eight test patients. The physical therapists were familiarized with the content of the five exercise levels, performed a live intake evaluation of the patients, and placed patients into one of the exercise levels. Each patient was independently evaluated by two physical therapists. The algorithm consistently assigned patients into slightly lower exercise levels than suggested by the physical therapists. This was considered appropriate and desirable from the standpoint of patient safety and initial adherence, particularly since patients can request a higher level of exercise at any point in the program.

c. Creation of exercise animations. Under the supervision of a physical therapist, Dr. Heiderscheit (consultant on the proposed project), each exercise was motion captured in a biomechanics laboratory. Retro reflective markers were placed on specific anatomical landmarks of the model subject and were subsequently animated. All animated exercises were then reviewed by five physical therapists to assure they represented the correct technique for performing the exercise.

IBET General Description and Features

Initial Assignment and Display of Exercises. When patients first log into the IBET site, they complete a brief set of measures, described above, to determine their initial exercise level. Next, patients may select the gender and ethnicity (Caucasian, African American, Asian or Hispanic) of the animated model that demonstrates the correct technique for performing each exercise. Each time patients log in to the system, 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 and can be made extremely small, allowing for nearly instantaneous presentation of the animations even with slow Internet connections. Patients are also prescribed aerobic exercises, corresponding in intensity to the five levels of strengthening / stretching exercises. After completing each exercise session, patients are asked to record their performance of the exercises in the website.

Changing Exercise Levels. At the end of each session patients are also given the option to move to a harder or easier workout at the next session. When patients opt for exercise progression, they are prompted to complete another web-based version of the mSF-WOMAC. If patients' mSF-WOMAC scores are higher (worse) than previously, they are not advanced to the next level yet but are instead given a new exercise routine at their current level If patients' mSF-WOMAC score is less than (better) or equal to their previous mSF-WOMAC score, they are allowed to progress within the exercise continuum. As patients progress to more difficult levels, their exercise routine may contain more difficult exercises, previously assigned exercises with increased weight, more sets or repetitions, or an increase in the number of exercises. If patients request an easier exercise routine at any point, they are first advised that slight increases in pain or discomfort are common when beginning an exercise program, and they may want to try icing and rest and then resume their current exercise program but consider reducing the frequency initially. However, participants may still choose to immediately receive a new exercise program at an easier level. In addition, if patients have difficulty with any particular exercises (e.g., it is painful or they cannot get into the required position), the system also provides an option to exchange that exercise for another within the same level.

Pain Monitoring. Patients are also asked to report any increased pain as a result of their exercises. If patients record increased pain for three consecutive settings without requesting a lower exercise level, they are sent an email suggesting they consider trying an easier exercise level. If patients do not record having increased pain for two weeks and have not requested an increase in exercise level in that interval, they are sent an email suggesting they consider trying a more difficult level.

IBET Pilot Study Data

Design. This was single group, pre- and post-training study to assess the acceptability, feasibility, and preliminary efficacy of the virtual exercise training website.

Participants and Procedures. Participants were 10 primary care physicians and 42 of their patients (approximately 4 per physician) who had been diagnosed with knee OA. Patients were identified by the primary care providers. Eligible patients were provided with an access code for the IBET site, along with written instructions for entry. Patients completed all baseline assessments within the IBET site and were assigned an exercise routine as described above. After eight weeks of access to the IBET site, patients were asked to complete an online post-intervention assessment.

Results. Participants' average age was 62 years (SD=9); half were female; 40% had less education than a 4-year college degree. Use of the website was high. On average participants logged into the website 5.87 times per week and reported completing exercises 4.7 times per week. Table 1 shows mean baseline and follow-up scores for key study measures. The mSF-WOMAC decreased by about 7 points, which is a

Table 1. Results of IBET for Knee OA Pilot Study

	Baseline	8-Week Follow-up	Test Statistics

	Mean	SD	Mean	SD	*t*-value	*p*-value	*pr*
mSF-WOMAC	18.07	7.75	11.14	8.47	6.19	<.001	.70
WHOQOL-Physical	65.55	16.53	70.52	14.53	-2.11	.041	.31
WHOQOL-Psychological	73.81	13.98	75.62	13.91	-1.09	.280	.17
Knee Self-Efficacy	16.10	4.62	18.67	5.93	-4.02	<.001	.53

SD=standard deviation; pr = point-biserial partial regression coefficient as measure of effect size with .14 small, .36 medium, and .51 large effect (Rosnow & Rosenthal, 2008).

substantial improvement and a large effect size. The World Health Organization Quality of Life (WHOQOL)[51] physical subscale and Knee Self-Efficacy Scale [52] also improved significantly. The WHOQOL psychological subscale improved, though this did not reach statistical significance. Over three-quarters of the participants indicated their knee symptoms improved "some" or "a lot" since the beginning of the study, 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 assessing satisfaction with covering a broad range of aspects of the program and website (range 0-4), the mean score was 3.0 (SD=0.5). Also confirming patient satisfaction with the website, 78% indicated that they would like to use the site in the future.

B.6.0 Other OA Studies at the Duke and the Durham VA Medical Center (VAMC). Dr. Allen and colleagues have conducted other studies among patients with OA at Duke and the Durham VAMC that are part of an ongoing program of research in this patient group. One trial, *Self-Management of Osteoarthritis in Veterans: A Telephone-Based Intervention (VA HSR&D IIR 04-016),* showed that the intervention resulted in significant improvements in pain other patient-centered outcomes [53,54]. Dr. Allen is also currently Principal Investigator of two clinical trials at Duke and the Durham VAMC, *Patient and Provider Interventions for Managing Osteoarthritis in Primary Care (VA HSR&D IIR 10-126; NIAMS R01 AR059673-010) [55].* These studies are collectively enrolling n=860 patients with knee and hip OA and are examining combinations of patient (telephone-based) and provider interventions, with an emphasis on non-pharmacological treatments. Another clinical trial led by Dr. Allen at the Durham VAMC is evaluating *Group Physical Therapy for Veterans with Knee Osteoarthritis (VA HSR&D IIR 09-056) [56].* This study is comparing group-based vs. traditional individual-based PT for knee OA, hypothesizing that the group approach will result in superior outcomes (due to the overall increased number of contact hours per veteran and the group support), while requiring fewer resources to deliver. The proposed study is substantially different from our other work, evaluating a different modality, internet-based physical activity programming, for improving outcomes among patients with knee OA. However, these studies demonstrate our research teams experience with conducting large randomized clinical trials of behavioral interventions for patients with knee OA at our two proposed enrollment sites.

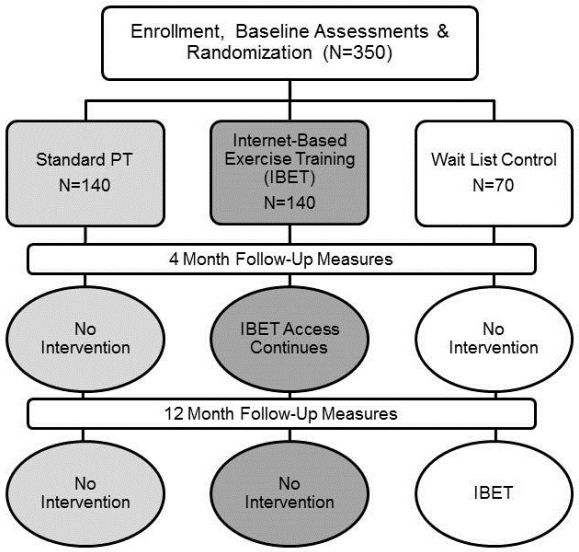
C. Demonstrate the technical merit of the application (*Criterion 3*)

C.1.0 Study Design. This will be a randomized controlled trial with participants assigned to three groups: Standard PT for knee OA, IBET for knee OA, and wait list (WL) control, with allocation of 2:2:1, respectively. Participants will be stratified by enrollment source (described below) to ensure groups are balanced in this respect. The three measurement time points will be at baseline, four months, and 12 months (Figure 1 below). The duration of physical activity and PT interventions for individuals with knee OA have varied widely. Although some positive effects were observed after eight weeks in the pilot study of the IBET program, we have chosen a four month duration for the initial intervention period in this larger trial because, based on prior research, this is an adequate time period to observe meaningful changes in pain and function [57]. The 12-month assessment will evaluate whether there are sustained effects beyond the initial intervention period. The IBET group will continue to have access to the website between the 4-month and 12-month assessment points. We have chosen to continue website access during this period to simulate the manner in which the IBET could feasibly be delivered in the healthcare and other settings. Specifically, organizations could continue access to this website for a more extended period of time at little or no additional resources expended per patient. Following completion of the 12-month assessments, participants assigned to the WL control group will receive two PT visits plus access to the IBET intervention. (Participants in this group will have no other

assessments after their exposure to these interventions.) Participants in all study groups will continue with their usual medical care they receive for OA during the full study period.

C.2.0 Enrollment Sites. We will enroll patients from two geographic regions and settings, to enhance generalizability. First, we will enroll patients who have sought care for knee osteoarthritis from the University of North Carolina at Chapel Hill (UNC), a large not-for-profit healthcare system that provides both primary and specialty care. Over 800,000 people receive outpatient care at UNC clinics annually. Second, we will enroll participants with symptomatic knee OA from the Johnston County Osteoarthritis Project (JoCo OA), an ongoing study in rural North Carolina [58]. African Americans and individuals age 60 years of age and older comprise about 20% and 17% of the county's population, respectively. Households with limited education and lower income are common; 35% of individuals over age 25 have less than a high school diploma and 30% of jobs involve manufacturing, service or farming. Therefore this county and the JoCo OA study have a high prevalence of sociodemographic groups at high risk for OA, greater OA severity, and limited healthcare access.

Figure 1. Overview of Trial Design



C.3.0 Participant Eligibility Criteria. This study will involve n=350 patients with symptomatic knee OA who meet the following criteria for at least one knee:

- Physician Diagnosis of Knee OA. For participants enrolled from the UNC healthcare system, this will be identified from electronic medical records and based on prior radiographic or MRI findings. For participants enrolled from JoCo OA, this will be identified from previous study-based radiographs and report of knee symptoms.

Current Joint Symptoms. We will use the following validated item: Do you have pain, aching or stiffness in one or both of your knees on most days of the week? Exclusion criteria will be assessed from electronic medical records (UNC participants), study records (JoCo OA participants) and telephone screening. A detailed list of exclusion criteria is shown in the Human Subjects Protection section. Briefly, main exclusion criteria include: no regular internet access, currently meeting physical activity guidelines, currently receiving PT for knee OA, health conditions that may make participation in mild to moderate physical activity unsafe, and pain-related conditions that could confound study outcomes. Based on the patient populations in our enrollment sites and experience from our previous studies, there will be an ample number of patients eligible for the proposed study. Our estimate of potentially eligible patients at UNC is based on the number of outpatients age 55, n=119,517, and the prevalence of symptomatic knee OA in this age group (about 12%) [59,60]. Based on these numbers, we estimate there will be a total of over 14,000 patients with knee OA at UNC. Given this large number, we will be able to focus recruitment on patients who live within reasonable driving distance to study enrollment sites and physical therapy clinics (which still encompasses a range of geographic regions in terms of urban / rural status). In JoCo OA, there are approximately 330 participants with radiographic, symptomatic knee OA. In our recent trial of telephone-based osteoarthritis self-management [54], which also enrolled patients with hip and / or knee OA, 29% of patients who met initial eligibility criteria were ultimately eligible and consented to participate. We acknowledge that the enrollment rate for this study may be lower because of the requirement of regular internet access. However, even if the enrollment rate was as low as 15%, this would translate into 50 patients from JoCo OA and over 2,000 from UNC. This exceeds our sample size goal, and we will enroll as many patients as possible from JoCo, since this is the smaller of the two enrollment sites.

C.4.0 Enrollment Procedures. We will include three methods of recruitment, which we have successfully utilized in prior studies at Duke and the Durham VAMC. First, we will use a variety of methods to advertise the study to potential participants. These may include: posting flyers and brochures in UNC clinics and other locations in the community; advertisements on a UNC website, physical therapy clinic websites, and other websites appropriate for reaching our target patient group; advertisements in newsletters, magazines and other appropriate print media; email blasts to UNC employees; advertisement on the UNC closed circuit television.

Second, UNC providers will be given flyers and brochures that they may distribute to patients. These self-and provider-referral activities will be conducted in a variety of UNC clinics and community locations that serve diverse groups of patients, particularly with respect to insurance and socioeconomic status. For example, we will include the UNC Ambulatory Care Center, a large "safety net" clinic. Third, we will use UNC medical records to identify patients with diagnoses of knee OA and no exclusionary diagnoses, based on ICD-9 codes. Similarly, we will use data from JoCo OA to identify participants with verified knee OA or chronic knee symptoms that may be a sign of knee OA and no known exclusionary diagnoses. We will mail and or e-mail introductory letters to these individuals on behalf of the study team. Inclusion of this "direct contact" recruitment method is important for reaching eligible, interested patients who are not reached by self- or provider-referral methods; this enhances both the "accessibility" of the study to patients and the generalizability of the participant sample. For all potential participants we will conduct a brief telephone screening questionnaire to verify for eligibility. This will include questions that pertain to the American College of Rheumatology clinical criteria for knee OA. . We will obtain participants' permission to ask a limited number of questions. If patients meet telephone screening criteria and are interested in participating, they will be asked to meet a study team member to complete consent, HIPAA authorization, and baseline assessments. Following baseline assessments, participants will be given their randomization assignment by the project coordinator via telephone (since the research assistant who conducts baseline and follow-up assessments will be blinded to participants' group assignment). Randomization will be based on a computer generated sequence maintained by the project statistician or programmer. Participants assigned to the standard PT group will then be scheduled for their initial visit. Participants assigned to the IBET group will be given instructions and an individual code to access the website, as well as ankle weights and resistance bands. Participants randomized to the WL group will be informed they will be provided with two PT visits and access to the IBET website after their follow-up assessments are complete.

C.5.0 Internet-Based Exercise Training Program. Participants randomized to the IBET group will be provided with access to the website described in detail above (Section B.5.). They will be encouraged to access the system starting as soon as they are enrolled in the study and through the 12-month follow-up assessment. Participants will be able to access the website as often as they like and may log their exercise daily. If participants do not interact with the website for seven days, they will receive an email encouraging them to access the website, and most importantly to remain physically active. In accordance with current Department of Health and Human Services and other guidelines for physical activity among older adults [61], we will encourage participants to complete strengthening and stretching exercises, guided by the IBET website, at least three times per week. Because the strengthening exercises are relatively low intensity and based on experience with the pilot study, we do not believe there are safety concerns if participants choose to perform strengthening exercises more than three times per week. However, as described above, if participants do experience an increase in pain, they will be advised to rest and then reinitiate their exercise program, considering a reduced frequency initially. Also in accordance with physical activity guidelines, participants will be told that it is safe and appropriate to perform aerobic exercises daily, or as often as possible, guided by the recommendations on the IBET website for their current exercise level. *An overall guiding principle is that participants will be encouraged to be as physically active as their abilities, health conditions, and pain allow*.

Some of the strengthening exercises included in the IBET program involve ankle weights and resistance bands. Therefore we will provide participants with ankle weights that can be adjusted in 1-lb increments, up to 5 pounds, as well as two resistance bands of different tension levels. These materials were also provided to participants in the pilot testing of the IBET program.

Participants will be given a telephone number to contact a study team member if they need technical support regarding the website. These telephone contacts will not involve any advisement regarding the physical activity. Within the website, participants may contact the study team if they have questions about the program. Technical questions will be handled by a study team member familiar with the website. Any questions regarding the exercise program itself will be handled by study co-investigators who are trained as physical therapists and have expertise in this area. We will document the frequency and nature of these contacts, which will be useful in the overall evaluation of this internet-based resource.

Although the results of the IBET pilot testing were excellent, and patients were very satisfied with this program, we are planning several enhancements prior to beginning this study. These are based on feedback

from our patient advisors and other stakeholders. These changes will include: 1.) modification of the instructions regarding the recommended frequency for performing strengthening and stretching exercises, to match the proposed intervention; 2.) addition of a personalized feedback section that charts the times participants have logged into the system and completed their exercises, as well as when they have increased exercise levels; 3.) addition of a feature that will allow participants to try an entirely new exercise routine at the same level, for variety and 4.) minor modifications related to reading level of the instructions.

C.6.0 Standard PT Intervention.

C.6.1 Overview of PT Intervention. We have modeled the standard PT intervention after typical elements of care provided to patients with knee OA [62]. While there is some variability in the treatment components employed by individual therapists, common aspects of PT for knee OA include: instruction in an appropriate home exercise program (focusing on strengthening and stretching exercises), instruction in strategies for pacing daily activities and protecting joints, evaluation of specific areas of weakness or inflexibility (which can then be used to tailor an exercise program), evaluation of mobility, stability, function, knee alignment, and possible limb length inequalities, and evaluation of the need for mobility aids, knee braces, and heel lifts. We have chosen not to include physical agents and electrotherapeutic modalities (e.g., electrical stimulation, ultrasound, TENS, diathermy) in the PT intervention for this study because there is no clear evidence to date for their effectiveness in knee OA [63]; although these modalities may be utilized in some instances by physical therapists in treating knee OA, it is not common. In keeping with standard outpatient PT practices for knee OA, physical therapist assistants (PTAs) may be involved with delivering the intervention. Based on standard practice and licensure rules, physical therapists must complete the initial evaluation and develop the treatment plan. PTAs may help to follow upon the treatment plan delivery (e.g., observe and assist participants in completing assigned exercises during clinic visits), with the PT being available at all times.

There is also some variability in the number of PT visits provided to patients with knee OA, based on health care setting resources, insurance reimbursement, and patient needs and availability. However, the typical range is between 3 and 8 visits. Therefore we will utilize this same range of visits for the standard PT arm in this study. All visits must be completed within the initial 4-month study period. We considered an approach where all participants would receive the same number of visits. However, we believe that allowing some degree of variability visit number, based on physical therapist assessment of patient needs, more closely reflects real-world clinical practice and will therefore be a more valid comparison to the IBET program. As part of the study we will document the number of visits for each patient in the standard PT arm.

Physical therapy in clinics proximal to UNC and within Johnston County, who have experience in treating patients with knee OA, will deliver this arm of the study. These clinics include: Comprehensive Physical Therapy Center (Chapel Hill, NC), Advanced Physical Therapy (Smithfield, NC), and UNC Physical Therapy (Hillsborough and Cary clinics). We will involve multiple therapists to enhance generalizability. Although physical therapists will be given flexibility in their treatment of these patients, there will also be some degree of standardization in the elements included (described below). This will allow comparison to a relatively standard intervention (which is important for study internal validity) while also reflecting a degree of variability that exists in actual practice. All study physical therapists will be trained in the standard PT arm elements described below. Adam Goode, DPT, PhD Yvonne M. Golightly, PT, MS, PhD, study co-investigators with clinical PT expertise, as well as experience in training physical therapists, will provide this training and oversee a subset of visits to ensure fidelity. Specifically, Drs. Goode and Golightly will observe approximately the first five study visits for each participating physical therapist and approximately 10% thereafter.

We have confirmed with PT services across multiple health systems that our planned standard PT intervention for knee OA reflects usual clinical practice. In addition we have consulted with Anita Bemis-Doherty, PT, DPT, MAS, Director of the Department of Clinical Practice for the American Physical Therapy Association. She has provided input regarding the standard PT arm of this study and supports the approach we propose. She will continue to serve on the Stakeholder Panel for this study and provide ongoing consultation to the study team in this regard.

C.6.2 Specific Activities in the Standard PT Intervention.

Evaluation: Physical therapists will gather a relevant medical history from each participant, including prior joint injuries, recent joint injections, pain level, specific functional and activity limitations, use of assistive devices, and other health problems that could affect home exercise. Some relevant information on these

topics, collected as part of the baseline study assessments, will be provided to physical therapists, within the study database, for each participant. Physical therapists will also perform standard assessments including edema, range of motion, knee alignment, limb length equality, balance, and gait. The history and evaluation will be documented in the study database on a standard form, adapted from one we have successfully used in another study of PT for knee OA [56]. Based on these evaluations, therapists will provide treatment according to standard practice for knee OA, including: prescription of therapeutic exercise, balance / neuromuscular education, manual therapy, gait / stair training and advisement about shoes / wedges. Physical therapists may provide low-cost heel lifts or exercise therapy bands for patients when indicated. However, devices such as knee braces will not be provided. This reflects standard clinical practice, where patients typically pay out-of-pocket for devices such as knee braces and acquire them separately from the actual PT visit.

Education: Physical therapists may provide participants with basic education in activity pacing and joint protection strategies, as appropriate. Activity pacing involves recognizing typical pain patterns and activities that exacerbate pain, planning for activity during typical periods of low pain, planning for rest during typical periods of high pain, and taking rest periods when pain and soreness begin to occur. Joint projection strategies include decreasing the load on the knee joints during common activities such as walking, stair ascent / descent, rising from a chair, and doing other household activities. Participants may also be instructed in the use of heat, cold, elevation, and / or self-massage, particularly with reference to use in conjunction with home exercises.

C.7.0 Patient-Centered Outcome Measures

All study assessments will be conducted in person by a trained research assistant blinded to study group assignment. Primary and secondary outcomes, as well as process measures, will be assessed at baseline, 4-months, and 12-months. Demographic and clinical characteristics will be assessed at baseline. Participants will be paid $30 for completion of assessments at each time point. We have selected our outcomes on the basis of the input from our Stakeholder Panel, as well as the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) [66], which recommends measurement of four pain outcome domains: pain intensity (WOMAC pain subscale), physical functioning (WOMAC function scale, Satisfaction with Physical Function Scale, and Short Physical Performance Test Protocol), emotional functioning (Patient Health Questionnaire-8), and participant global impression of change. We have also included secondary outcomes and process measures related to physical activity.

C.7.1 Primary Outcomes: Western Ontario and McMasters Universities Osteoarthritis Index. The primary outcome measure for this study is the WOMAC, a measure of lower extremity pain (5 items), stiffness (2 items), and function (17 items). All items are 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 [67]. In patients with hip or knee OA, Bellamy et al. reported internal consistency coefficients (Cronbach's alpha) between 0.86 and 0.95 on WOMAC pain, stiffness, and function subscales. Construct validity has been confirmed by a significant association with the Lequesne Algofunctional Index for Knees [67]. The WOMAC has been widely used in trials behavioral interventions for patients with knee OA, confirming its sensitivity to change in these interventions.

C.7.2 Secondary Outcomes.

Satisfaction with Physical Function Scale. This is a validated 5-item questionnaire that assesses patients' satisfaction with their ability to complete basic functional tasks that are often affected by lower extremity OA, including stair-climbing, walking, doing housework (light and heavy, and lifting and carrying [68]. All items are rated on a 7 point scale ranging from Very Dissatisfied (-3) Very Satisfied (+3).

Objective Physical Function. We will objectively assess physical function using seven tests. This group of tests is relevant to the proposed study because they assess aspects of daily function that require lower extremity strength, and that are often impacted by knee or hip OA. This battery examines balance (4 tests including a side by side stand, semi-tandem stand, tandem stand, and a unilateral stand), time to rise from a chair and return to the seated position for 30 seconds, timed up and go-rising from a seated position, walking a short distance and returning to seated position, and a 2 minute step test. For each test, the possible range of scores is 0-4, for a total range of 0-20.

Depressive Symptoms – Patient Health Questionnaire-8. We have chosen to include depressive symptoms as a secondary outcome because of the close association of these symptoms with pain. Depressive symptoms

and severity will be assessed using the PHQ-8, a reliable and valid measure of depression[71]. The PHQ-8 is an eight-item survey derived from the Primary Care Evaluation of Mental Disorders (PRIME-MD) diagnostic tool, and consists of items corresponding to the depression criteria listed in the *Diagnostic and Statistics Manual Fourth Edition* (DSM-IV). Each of the eight questions is scored as 0 (not at all) to 3 (nearly every day), so that total scores range from 0 to 24.

The Knee injury and Osteoarthritis Outcome Score (KOOS). The KOOS is a patient-reported outcome measurement instrument, developed to assess the patient's opinion about their knee and associated problems. The KOOS evaluates both short-term and long-term consequences of knee injury and also consequences of primary osteoarthritis (OA) }. It holds 42 items in five separately scored subscales: **KOOS Pain**, **KOOS Symptoms**, Function in daily living (**KOOS ADL**), Function in Sport and Recreation (**KOOS Sport/Rec**), and knee-related Quality of Life (**KOOS QOL**). Some of these items overlap with those with the WOMAC, and in those instances questions will only be asked once.

The PROMIS Sleep-related Impairment Instrument. The PROMIS adult sleep related impairment item bank focuses on self-reported perceptions of alertness, sleepiness, and tiredness during usual waking hours, and the perceived functional impairments during wakefulness associated with sleep problems or impaired alertness. It assesses sleep-related impairment over the past seven days. This scale includes 8 items, each measured on a 5-point Likert scale.

The PROMIS Fatigue Instrument. The PROMIS Fatigue instruments evaluate a range of self-reported symptoms, from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally in family or social roles. Fatigue is divided into the experience of fatigue (frequency, duration, and intensity) and the impact of fatigue on physical, mental, and social activities. It assesses fatigue over the past seven days, This scale includes 8 items, each measured on a 5-point Likert scale.

Patient Global Assessment of Change. We will use the Patient Global Impression of Change scale to evaluate participants' perspectives on overall changes in their joint pain during the study period. This single-item measure asks participants to describe their change in pain on a 7-point rating scale with the following options: "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," and "very much worse." This scale has been widely used in clinical trials of chronic pain treatments and is specifically recommended by IMMPACT [66].

The Brief Fear of Movement Scale. The Brief Fear of Movement Scale is a six item scale for assessing fear of movement in OA. The scale specifically assesses activity avoidance due to pain-related fear of movement. All items are measured on a 4-point scale from "strongly agree" to "strongly disagree."

Physical Activity Measures

Physical Activity Scale for the Elderly. The Physical Activity Scale for the Elderly (PASE) is a self-report, 12-item scale that measures level occupational, household, and leisure activity during a one-week period. [73] This scale was particularly developed for use among older adults; although all participants in the proposed study will not be age 65 or over, patients with knee OA typically have more limited physical activity than the general population. Therefore we believe this scale will be more applicable to our participant group than scales that were developed for younger adults.

Additional Self-Report Physical Activity Items. In addition to the assessment of overall physical activity that will be provided by the PASE, we are particularly interested in purposeful exercise behaviors that correspond to the IBET intervention and those typically prescribed in the context of standard PT for knee OA. We will ask participants, at each assessment point, to report the number of times and minutes per week, on average, they are completing strengthening, stretching, and aerobic exercises

Use of IBET Website / Number of PT Visits Attended. As described above, participants' use of the IBET website will be logged within the site. Therefore we will be able to compare use (e.g., number of log-ins and records of completion of exercise weekly) throughout the 12-month time period for participants in that study arm. Similarly, for patients in the Standard PT group, we will document the number of visits and the proportion of scheduled visits attended.

C.7.3 Process Measures. We will include two key process measures that have been associated with change in physical activity behavior. These will help us to understand potential mechanisms underlying any observed improvement in the IBET and / or standard PT interventions.

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.
Social Support for Exercise Scale. [76] 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 [76].
C.7.4 Demographic and Clinical Characteristics. For Specific Aim#3, we will focus on evaluating potential differential effects of the IBET and / or standard PT interventions, with particular interest in differences according to participant age and baseline physical function. We are interested in potential age-related differences for two reasons. First, we are interested in understanding whether older individuals respond differentially to an internet-based exercise program, since they may be less comfortable with this technology compared to younger adults. Second, older individuals typically have more comorbid health problems and activity limitations, and we are interested in understanding whether this results in any differential effectiveness of the two types of interventions. We are similarly interested in potential differences according to patients' baseline functional status, so that we can understand whether patients with more severe disease may respond differentially two the two types of interventions.

We may also explore differential effects according to some of the following additional participant characteristics, which are also important for describing the study sample: race / ethnicity, gender, household financial state, education level, work status, marital status, and internet use / comfort, health literacy, body mass index (BMI), joint involvement (i.e., report of all joints affected by arthritis), duration of OA symptoms, general self-rated health, and comorbid illnesses (Self-Administered Comorbidity Questionnaire [78]).
C.7.5. OA Treatment Use. We will also assess participants' OA treatment use at each time point, via self-report, to evaluate whether there are any changes during the study period. For example, we are interested in understanding whether patients in the intervention groups may reduce pain medications if their symptoms improve. In addition, these data will provide information about whether other new treatment occurred (e.g., joint injection) that may have an impact on outcomes during the study period. Specific treatment aspects will include: pain medications for OA (prescription and non-prescription), knee braces, walking aids, physical therapy and joint injections. At the two follow-up time points we will also ask participants to indicate whether they think they currently use more, less, or about the same amount of pain medication to control their OA symptoms since starting the study.
C.7.6 Participant Feedback on IBET and Standard PT Arms. We will ask participants in the IBET group to complete the same Program Satisfaction questions described in the pilot study, at the 4-month assessment point. We will develop similar questions that pertain to the standard PT arm. In addition, we will ask participants to answer open-ended questions regarding both interventions. For example, we will ask participants which aspects of the interventions were most and least helpful, usability of the IBET website, content of the PT sessions, and ways we may be able to further improve the interventions.

C.8.0 Data Analyses

C.8.1 General Overview. Our statistical approach is guided by the PCORI Methods Report. For the superiority hypotheses (H1, H3), analyses will be conducted on an intent-to-treat (ITT) basis; patients will be analyzed in the arm to which they were randomized, regardless of adherence, using all data up to the 12-month follow-up or last available measurement prior to exclusion or dropout [79]. Additional exploratory analyses focusing on alternative, more restrictive analytic cohorts (e.g., as treated) may be considered for the superiority hypotheses, to provide additional information about the impact of magnitude of exposure to the interventions. For non-inferiority hypotheses (H2, H4), the ITT analysis would not be the conservative approach; therefore, it is recommended to perform analysis on both an intent-to-treat and per-protocol basis [80,81].
C.8.2 Descriptive statistics. Descriptive statistics, including graphical displays, will be used to summarize all study variables overall and by randomization arm. We will construct individual and mean trajectory plots of the

longitudinal outcome variables to understand their general trends over the study period. In addition, we will explore the variability and correlation structure of the longitudinal outcome variables. All statistical analyses will be performed using the SAS (Cary, NC) software package / R (www.r-project.org).

C.8.3 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 outcome measures due to dropout, death, a missed interim assessment, or item non-response. Given a thorough understanding of the missing data mechanism, it is possible to use all of the available information in analysis, rather than using only subjects with completely observed information. Our main analysis technique for the primary outcomes, general linear mixed models via maximum likelihood estimation, implicitly accommodates missingness when it is due either to treatment, to prior outcome, or to other baseline covariates included in the model, defined as missing at random [82]. Therefore, inferences will be valid even if we have differential dropout by intervention arm. If the missing values are related to other measured patient factors, such as age or comorbidity, then multiple imputation (MI) provides a framework for incorporating information from these variables, while still preserving a parsimonious main treatment effect model [83], and is described as a significant advantage in recommendations from Panel on Handling Missing Data in Clinical Trials [84]. 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/). If the probability of dropout is related to the actual missing response (which is unobserved because it is missing) or to other unobserved quantities, the missing data due to dropout is considered missing not at random (MNAR) or nonignorable [85]. There is a possibility that data may be MNAR, and we propose as additional sensitivity analyses to explore MNAR methods, including selection and pattern-mixture models [85].

C.8.4. Specific Aim #1. *H1 (Superiority): Patients who receive either IBET or standard PT will have clinically relevant improvements in pain, stiffness, and function, measured by the WOMAC at 4-month follow up, compared with patients in the WL control group; H2 (Non-Inferiority): The IBET intervention will be non-inferior to the standard PT intervention at 4-month follow-up, indicated by a mean WOMAC score less than 5 points higher than standard PT*. For Specific Aim #1, we will use a linear mixed model (LMM) that accounts for the correlation between a participant's repeated measurements over time. Because of the small number of time points, 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: $Y_{it} = \beta_0 + \beta_1 4month + \beta_2 IBET*4month + \beta_3 PT*4month$, where Y_{it} is the WOMAC score for subject i at t=0 and 4 months. 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 H1, we will test for a difference in mean WOMAC scores between the IBET and/or PT group and the WL group at the primary time point of 4 months by testing that $\beta_2=0$ and/or $\beta_3=0$. For H2, we chose a non-inferiority limit of 5 points for mean WOMAC scores because it is reasonable and on the border of what would be considered a clinically important effect [86] . The null hypothesis in the non-inferiority framework is that IBET is inferior to standard PT in management of OA symptoms. We will test the non-inferiority hypothesis by examining the estimate of the contrast $\beta_2-\beta_3$. Specifically, we will examine the 95% CI of the estimated contrast $\beta_2-\beta_3$, and if the upper limit of the interval is less than the threshold value of 5 points, we will conclude non-inferiority of IBET to PT [81]. If we conclude non-inferiority, we test will for superiority of IBET to PT at 4 months by examining the 95% CI of the estimate of $\beta_2-\beta_3$ for inclusion of 0 and the p-value for the test of the contrast $\beta_2-\beta_3=0$. Time is coded in this 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 the treatment arms [87]. In this way, the cLDA model is comparable to an ANCOVA model; the two models are equivalent when there is no missing data. However, unlike an ANCOVA, participants who are missing follow-up measurements are included in the cLDA model because baseline is part of the response vector. For improvement in precision, the model will also be adjusted for enrollment site (stratification variable) [88]. Similar procedures will be used to assess all continuous secondary outcomes.

C.8.5. Specific Aim #2: *H1 (Superiority): Patients who receive either IBET or standard PT will have clinically relevant improvements in pain, stiffness, and function, measured by the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) at 12-month follow up, compared with patients in the WL control group; H2 (Non-Inferiority): The IBET intervention will be non-inferior to the standard PT intervention at 12-month follow-up, indicated by a mean WOMAC score less than 5 points higher than standard PT .* As

described above, will use a linear mixed model (LMM), adding in the 3 parameters for the 12-month period (12month, IBET*12month, PT*12month). We will follow the same testing procedures for the 12-month parameters as described for the 4-month. Similar procedures will be used to assess longer term effects of all continuous secondary outcomes at 12-months.

C.8.6. Specific Aim #3: Examine whether individual patient characteristics (particularly age and baseline functional status) are associated with differential improvement in the IBET and / or standard PT interventions. Patients may vary in their response to the intervention programs; this variation is known as heterogeneity of treatment effects (HTE). We will be conducting a descriptive HTE analyses [89]. We have two a priori defined patient characteristics (noted above) and will conduct a separate descriptive HTE for each characteristic for primary and secondary outcomes, as defined in the PCORI Methods Report. We will initially treat age as a continuous variable and evaluate whether treatment response varies with increasing age; we will also evaluate treatment response within discrete age categories (e.g., by decade). With respect to functional status, we will evaluate potential differential response on the basis of participants' baseline scores on the SPPT (objective physical function test), since this is a separate measure from our primary outcome (WOMAC). We will initially treat baseline SPPT composite scores as a continuous variable (0-12). We will also evaluate treatment response within discrete baseline SPPT score categories of <5, 5-8, and >8, which have been shown to predict adverse outcomes. We will construct individual and mean trajectory plots of the longitudinal outcome variables by patient characteristics and treatment arm to understand their general trends over the study period. Our general steps in this secondary analysis will be to add the patient characteristics main effect, as well as the interaction variables, to the linear mixed model defined above. We will examine the parameter and 95% CI of the parameter estimates for the 3-way interactions treatment*time*patient characteristic (e.g. IBET*4month*age) to determine whether there is evidence of HTE for that characteristic. New state-of-the art modeling methods have taken the exploration of HTE to the next level, making it possible to explore and identify multidimensional subgroups exhibiting heterogeneous treatment effects. We will explore whether the a priori defined patient characteristics define multidimensional subgroups that exhibit HTE. We will utilize two different analytic strategies for doing so: multivariable logistic regression[90,91] and recursive partitioning [92,93]. Each has unique strengths as well as limitations, and each approaches the problem of identifying the multidimensional subgroups differently. Our general steps in this secondary analysis will be: construction of outcome variables; identification of multidimensional subgroups via logistic regression and recursive partioning; and, finally, examination of treatment effects within the multidimensional subgroups.

C.8.7. Additional Exploratory Analyses. We may also conduct exploratory analyses of associations among other measures collected as part of this study. This may include associations among variables at baseline, potential roles of baseline variables as moderators or mediators of treatment effects, or association of baseline variables with intervention uptake and outcomes.

C.8.8 Sample size. The sample size estimate of n=350 patients, 140 per each of the IBET and standard PT arms and 70 in the WL arm, is based on H2, the non-inferiority hypothesis, as this is the most conservative [80,94,95], and on a randomization of 2:2:1 [96]. In our proposed analysis, this involves testing the IBET*4month and PT*4month interactions in our model. Sample size calculations are based on this comparison and use methods appropriate for ANCOVA analyses, which are equivalent in terms of efficiency to our linear model as noted above, in randomized trials [87]. For the non-inferiority test the method is based on performing a one-sided two-sample t-test sample size calculation at the alpha=0.025 level for the between group difference at the 4 month time point, multiplied by a factor 1-(rho)^2, where rho represents the Pearson correlation between baseline and follow-up time point outcome measures [97].This sample size is then adjusted to compensate for potential missing observations due to attrition. Based on data from our other OA studies, we assume a correlation of 0.6 between WOMAC scores at baseline and at 4 months and an SD for WOMAC scores of 17.5. With 80% power, alpha=0.025, SD=17.5, rho=0.60, and a 10% attrition rate by 4 months, 140 patients in each of the IBET and standard PT groups, need to be enrolled at baseline to identify less than a 5 point difference in mean WOMAC scores between the two treatment groups. We selected the 10% attrition rate based our prior research of behavioral interventions for OA of similar duration [54]. For H1, with alpha=0.05, SD= 17.5, rho=.6, and approximately 10% attrition rate by 4 months, we have 80% power to detect moderate effect size of 0.35, corresponding to a 6.1 point difference (approximately 13% improvement, which corresponds to a clinically relevant difference) in mean total WOMAC scores at 4 months for either of the 2 intervention compared to WL

control. For the remaining secondary outcomes we will also be powered to detect a moderate 0.35 effect size difference for either of the two intervention compared to the WL control group. We did not conduct a power analysis for the HTE analysis for Aim #3 because we are proposing a descriptive HTE [89] and have followed the PCORI Methods Report on this issue. However, our analyses for Aim #3 will provide meaningful and practical data to Stakeholders and organizations with potential to incorporate the IBET program – for example, whether patients with different characteristics differentially benefit from IBET vs. standard PT for knee OA.

C.9.0 Data Management and Quality Control. Study tracking data will be entered into a database created by expert programmers at the UNC Sheps Center for Health Services Research, which has been developed and refined over many years in the context of other clinical trials. This database includes safeguards for ensuring tracking data are collected reliably for all participants (e.g., required fields, limited sets of appropriate responses) and will be thoroughly tested by the study team prior to beginning the clinical trial. This database can be easily customized for the proposed project. We are also able to randomize participants within this database. Customized reports allow the research assistant and project coordinator to identify daily tasks in need of completion, as well as generate flow charts to monitor overall study progress. Screening and outcome measures will be recorded in this same database. As with the tracking database, screening and outcome measures will be programmed to ensure reliable data (e.g., required fields, set ranges of responses) and will be thoroughly tested by the study team before beginning the study. The study team will conduct regular checks and cleaning of screening and outcomes data, throughout the study period, to monitor data quality. The database will also house information on study PT visits, including the initial evaluation form and progress notes for all visits.

C.10.0 Project Timeline and Management Plan. We are proposing a 3-year study. The first 4 months will be devoted to start-up activities, including additional stakeholder input on the IBET program and incorporation of modifications accordingly. This phase will also involve training of personnel and finalization of study databases. Enrollment will take place over the next 16 months (through year 2, month 8), with 4-month follow-up completed by year 3 month 1 and 12-month follow-up completed by year 3, month 9. The final 3 months of the project will be devoted to final analyses and dissemination and implementation related activities. This timeline will require us to enroll 21-22 participants per month, and this is very reasonable based on our experience with prior clinical trials and the resources requested for this project (particularly research assistant effort).

C.11.0. Participant Retention.

We will utilize strategies to promote participant retention that have been successful in our prior and ongoing clinical trials of patients with symptomatic OA (which include diverse groups of patients in terms of gender, health status, education level, and race / ethnicity)[54-56]. First, we have chosen a wait list control group, versus a usual care control group that receives no treatment. We have found that this helps with fostering retention in any study group that is "inactive" at the beginning of the trial period. Second, we are providing compensation that will be adequate to support participants' time and travel for study assessments. Third, we will be working with at least three different PT clinics to deliver that intervention arm; this will minimize driving distances for participants. Fourth, we will make any reasonable accommodation possible for participants to complete their baseline and follow-up assessments. We are selecting assessment sites with convenient parking and at central locations, and we will conduct assessments outside of normal business hours when needed. Although we plan for study assessments to occur in-person, if participants are unable to come to a study location for a follow-up assessment point (but are otherwise eligible to continue the study), we will allow telephone-based assessment in order to minimize loss-to-follow-up. Our main outcome measures (WOMAC) has been validated for telephone administration.

D. Demonstrate the patient-centeredness of the application (*Criterion 4*)

The proposed project is highly relevant to patients because knee OA is a leading cause of pain and disability [98,99], outcomes of great importance to patients [100-102]. OA-related pain also has a detrimental impact on other important patient-centered outcomes such as depression, anxiety, employment, relationships, sleep, fatigue, employment, and quality of life [12,18,103,104]. In addition, arthritis (including knee OA) is a key barrier to engaging in other healthy behaviors, such as physical activity, and it is strongly associated with obesity [105-107]. Therefore interventions that help patients manage knee OA-related pain also have tremendous potential for

affecting other health outcomes of importance to patients. This project addresses two key PCOR questions:
1. *"What can I do to improve the outcomes that are most important to me?"* Specifically, information generated from this project will enable patients with knee OA to know whether participating in an internet-based exercise program may be as effective of an option as standard PT for improving physical activity and associated patient-centered outcomes. Since some patients experience barriers to access to PT for knee OA (e.g., insurance or related, availability of physical therapists, schedule constraints), it is important for patients to know whether there are alternative resources that will help them to improve outcomes like pain and function via support of an appropriate physical activity program.
2. *"Given my personal characteristics, conditions and preferences, what should I expect will happen to me?"* Results of this project (Specific Aim #3) will help patients and providers understand whether patient characteristics (particularly age and baseline physical function) are associated with differential effectiveness of IBET vs. standard PT among patients with knee OA.

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