Improving Physical Activity and Gait Symmetry After Total Knee Arthroplasty Protocol

NCT number NCT04090125
Document Date 10/06/2022

Physical Activity and Gait Symmetry: Randomized Trial of an Intervention for Patients Following Total Knee Arthroplasty

Protocol Number: 19-0568

NCT Number: 04090125

Principal Investigator: Kelli D. Allen, PhD

Sponsor: University of North Carolina at Chapel Hill

Grant Title: Improving Physical Activity and Gait Symmetry after Total Knee Arthroplasty

Grant Number: R21-AR074149

Funded by:
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

Version Number: 11.0

6 October 2022

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
1.1, 1.2, 4.1, 9.1, 9.2 and 9.4	Change made to reduce the sample size from 72 to 60 for the study	Sample size reduced due to challenges with enrollment

Table of Contents

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator or Clinical Site Investigator:
Signed: _____ Date: _____
Name:

Title:

Investigator Contact Information
Affiliation: University of North Carolina at Chapel Hill
Address: 3300 Thurston Bldg., CB #7280, Chapel Hill, NC 27599-7280
Telephone:919-966-0558
Email: kdallen@med.unc.edu

1 PROTOCOL SUMMARY

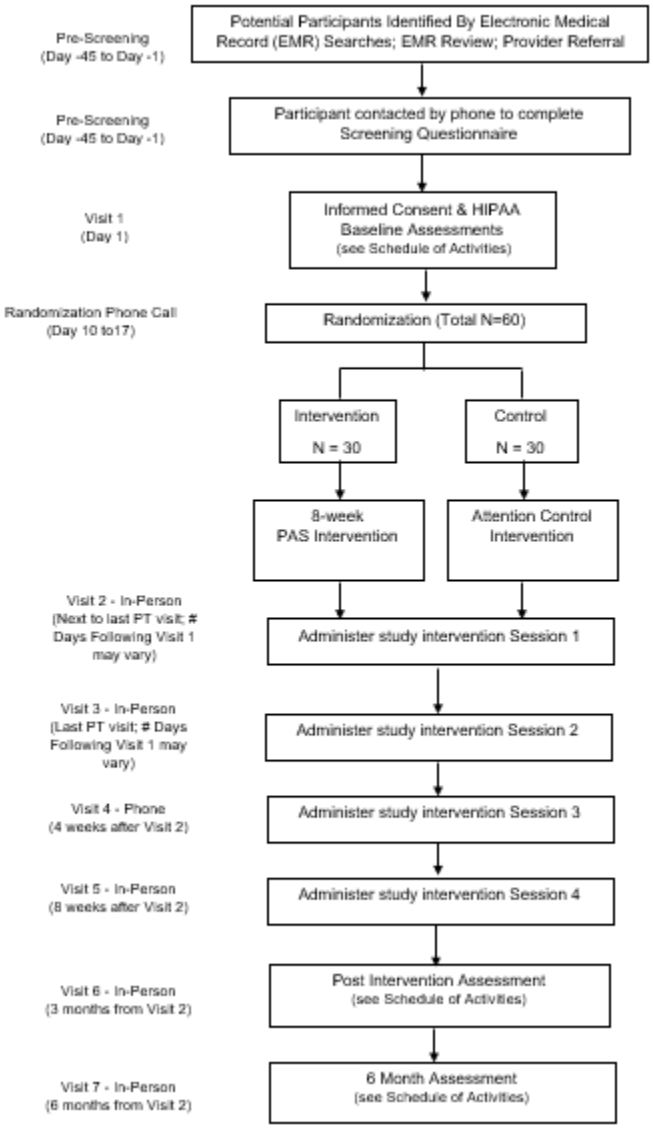
1.1 SYNOPSIS

Title:	Improving Physical Activity and Gait Symmetry after Total Knee Arthroplasty
Grant Number:	R21-AR074149
Study Description:	The overall objective of this study is to gather preliminary evidence on the efficacy, feasibility and acceptability of the Physical Activity and Symmetry (PAS) intervention. Specific hypotheses are as follows: H1: The PAS group will have greater improvement in objectively assessed physical activity (PA) at the 3-month and 6-month assessments, compared to the attention control (ATT) group. The main co-primary metric of interest is minutes of moderate to vigorous physical activity; other secondary metrics will include step count, minutes of any PA, and sedentary minutes. H2: The post-total knee arthroplasty (TKA) exercise group will have greater improvement in peak load symmetry during walking at the 3-month and 6-month assessments, compared to the ATT group.
Objectives*:	Specific Aim 1: Obtain preliminary data on the efficacy of the PAS program with respect to the change in objectively assessed physical activity, measured via accelerometers. Specific Aim 2: Obtain preliminary data on the efficacy of the PAS program with respect to change in peak load symmetry during walking, measured by a novel 3-sensor insole device. Specific Aim 3: Assess the feasibility and acceptability of the PAS program following TKA.

Endpoints*:	Primary Endpoints: One co-primary primary end- point / outcome is objectively assessed PA, measured via accelerometer. The primary metric of interest is minutes of moderate to vigorous physical activity (MVPA). This will be assessed at both 3-month and 6-month follow-up time points. The other co-primary primary end- point / outcome is peak load symmetry during gait. This will be assessed at both 3-month and 6-month follow-up time points. Secondary Endpoints: In addition to minutes of MVPA, secondary metrics of physical activity will include step count, minutes of any PA, and sedentary minutes. In addition to peak load symmetry during gait, peak load symmetry will be assessed during physical performance tests including the 30-second stair stand test, 40m fast-paced walk, stair climb test, and Timed Up and Go (TUG) test. Feasibility metrics include recruitment, retention, intervention delivery, and outcome assessment. Perceptions of acceptability will be obtained from patients and physical therapists using open-ended questions. Exploratory outcomes include self-reported PA, physical performance tests, balance, knee symptoms, and kinesiophobia.
Study Population:	N = 60 participants receiving post-TKA physical therapy (PT) at a University of North Carolina (UNC) Healthcare System or at physical therapy clinics outside of UNC. We will enroll both males and females, 18 years of age and older from all racial and ethnic backgrounds.
Phase* or Stage:	Based on the Obesity-Related Behavioral Intervention Trials (ORBIT) framework, this study is a Phase II Preliminary Testing trial.
Description of Sites/Facilities Enrolling Participants:	We will only be enrolling patients receiving post-TKA PT at a UNC Healthcare System clinic or at physical therapy clinics outside of UNC.

Description of Study Intervention/Experimental Manipulation:	The PAS program significantly augments usual post-TKA PT, specifically addressing critical gaps of physical inactivity and joint loading asymmetry. The PAS program will be initiated during the final usual care PT visits, allowing integration and capitalizing on the existing patient-provider relationship. PAS content will be included within the last two routine PT visits (Session 1 and 2, see Table 1, Section 6.1 Study Intervention Administration). Then, PAS participants will receive a follow-up call after 4 weeks (to assist with activity progression and problem-solving) and an additional visit after 8 weeks (conducted in-person if possible or remotely via an IRB approved video platform or by phone).
Study Duration*:	18 months
Participant Duration:	6 months

1.2 SCHEMA


Pre-Screening (Day -45 to Day -1)
Potential Participants Identified By Electronic Medical Record (EMR) Searches; EMR Review; Provider Referral
Pre-Screening (Day -45 to Day -1)
Participant contacted by phone to complete Screening Questionnaire
Visit 1 (Day 1)
Informed Consent & HIPAA Baseline Assessments (see Schedule of Activities)
Randomization Phone Call (Day 10 to17)
Randomization (Total N=60)
Intervention N = 30
Control N = 30
8-week PAS Intervention
Attention Control Intervention
Visit 2 - In-Person (Next to last PT visit; # Days Following Visit 1 may vary)
Administer study intervention Session 1
Visit 3 - In-Person (Last PT visit; # Days Following Visit 1 may vary)
Administer study intervention Session 2
Visit 4 - Phone (4 weeks after Visit 2)
Administer study intervention Session 3
Visit 5 - In-Person (8 weeks after Visit 2)
Administer study intervention Session 4
Visit 6 - In-Person (3 months from Visit 2)
Post Intervention Assessment (see Schedule of Activities)
Visit 7 - In-Person (6 months from Visit 2)
6 Month Assessment (see Schedule of Activities)

1.3 SCHEDULE OF ACTIVITIES

	Pre-screening (Pre-consent)	Visit 1 Day 1	Randomization Phone Call (Day 10 to 17)	Visit 2 (Next to last PT visit)	Visit 3 (Last PT visit)	Visit 4 (4 weeks after Visit 2)	Visit 5 (8 weeks after Visit 2)	Visit 6 (3-Months from Visit 2)	Visit 7 (6-Months from Visit 2)
EMR Review Eligibility or Provider Referral	X								
Screening Phone Call	X								
Informed Consent		X							
Outcome Measures									
Objectively Assessed Physical Activity (accelerometer)		X						X	X
Peak Joint Load Symmetry During Walking		X						X	X
Physical Performance Tests:									
-30-second stair stand test		X						X	X
-40m fast-paced walk		X						X	X
-Stair climb test		X						X	X
-Timed Up and Go (TUG) test		X						X	X
-Berg Balance Scale		X						X	X
-Brief Balance Evaluation Systems Test		X						X	X
Patient Reported Measures:									
-Modified version of CHAMPS		X						X	X
-Knee injury and Osteoarthritis Outcome Score (KOOS)		X						X	X
-Tampa Kinesiophobia Scale		X						X	X
Acceptability									X
Patient Characteristics		X							
Symptoms and Events in the Non-Surgical Limb		X						X	X
Randomization			X						
Control & Experimental Interventions - Physical Therapist Visits or Phone Calls (refer to Table 1 in Protocol)				x	x	x	x		
Adverse Event Reporting		x	x	x	x	x	x	x	x

2 INTRODUCTION

2.1 STUDY RATIONALE AND BACKGROUND

2.1.1. CLINICAL SIGNIFICANCE

TKA Rates are High and Increasing Rapidly. TKA is the most common surgical procedure involving a hospital stay in the United States. In 2012, TKAs accounted for >700,000 hospital stays, and rates increased 66% from 2003-2012 [1]. Demand for TKA is expected to rise to 3.48 million procedures by 2030 [2]. About 40% of patients with unilateral TKA will progress to a TKA on the contralateral side within 10 years [3,4]. As a result of the high surgical volume and the progression of disease in the contralateral limb, it is imperative that post-TKA outcomes are optimized through effective rehabilitation strategies.

There are Critical Deficits in Post-TKA Outcomes. Studies have identified two key deficits in individuals' activity-related trajectories following TKA. *First, despite major improvements in joint pain for most patients, overall PA levels remain very low [5,6].* Although some studies suggest that patients perceive they are more active after surgery than before, accelerometer-based studies demonstrate that PA levels do not increase meaningfully following TKA, remaining well below Department of Health and Human Services (DHHS) guidelines[7] as well as PA levels of healthy individuals [5,8-14]. For example, participants in one study spent 8.1% of the day in movement-related activity prior to TKA, and this increased to only 9.1% 6 months following surgery [10]. This has negative implications not only for function and joint health but also for managing common comorbid diseases and improving overall physical and psychological health. Increases in body weight are also common during the year following TKA [15,16], and increasing PA can help to mitigate this risk. *The second post-TKA deficit highlighted in recent studies involves joint loading asymmetries.* Although patients show improvements in pain and some aspects of physical performance following TKA and outpatient rehabilitation [17,18], many patients continue to demonstrate movement asymmetries that result in greater load on the non-surgical limb [19]. Importantly, this likely contributes to the increased risk for TKA on the contralateral limb within 10 years of the primary TKA procedure [17]. *Research indicates that joint loading asymmetries are adopted as a result of pre-operative pain and weakness, and the compensatory movement mechanics persist following surgery despite resolution of pain and completion of traditional rehabilitation programs* [20]; this indicates the importance of a re-training process, in which patients learn to correct maladaptive movement patterns that perpetuate joint loading asymmetries.

Gaps in the Post-TKA Rehabilitation Process. Although outpatient PT is a standard practice following TKA, there is very little guidance regarding the most appropriate post-TKA rehabilitation regimen [17,21], and, as a result, there is substantial variability in post-TKA PT [22-24]. *Importantly, neither deficit described above – overall PA and joint loading asymmetry – is adequately addressed in current post-TKA rehabilitation paradigms* [22,23]. Specifically, studies show lack of attention to cardiovascular training (e.g. general aerobic activity), guidance in exercise progression, and balance interventions [22,23]. *This highlights the need to optimize the post-TKA rehabilitation process so that these key outcomes are adequately addressed.*

Goal and Importance of this Exploratory Trial. To address these critical gaps, we will conduct an exploratory trial of a novel PAS intervention that focuses on the persistent deficits of physical inactivity and joint loading asymmetry following TKA. Randomized pilot study methods will be used to test hypotheses related to PAS efficacy (Aims 1 and 2) and feasibility and acceptability (Aim 3). This exploratory study is required prior to a larger trial because: 1) Preliminary data on the PAS intervention are needed; although we hypothesize that it will result in meaningful improvements in PA and symmetry, if this is not confirmed then further investment in a large trial would not be warranted. 2) The PAS intervention will be integrated in real-world PT settings, and preliminary work is needed to establish logistical procedures.

2.1.2. PREMISE

The PAS intervention is based on previous studies of effective strategies for improving PA and joint loading symmetry in various patient populations. With regard to improving PA, the PAS intervention will utilize goal setting, brief motivational interviewing (MI) and connection of patients with community programs and other PA

resources [25-30]. With respect to mitigating loading asymmetries, the PAS intervention will employ balance exercises for two reasons. First, since 60% of the gait cycle is spent in single leg stance, inability to balance on one leg impacts gait outcomes as well as gait stability. Studies have added balance exercises to early post-TKA rehabilitation and shown improvements in multiple outcomes [18,24,31-33], but *our target of joint loading symmetry has not been examined*. Second, teaching patients specific gait retraining strategies to address loading asymmetries is very challenging in research settings and would be even more difficult with a home exercise program. Small studies have used biofeedback (similar to our proposed strategy) to help patients learn to place equal amounts of force on right and left legs after TKA, resulting in improvements in knee movement during gait [34-36]. However, these studies used technologies that are not practical to implement widely in clinical and home settings; our approach addresses this limitation.

2.1.3. PRIOR STUDIES AND RATIONALE FOR DEVELOPMENT

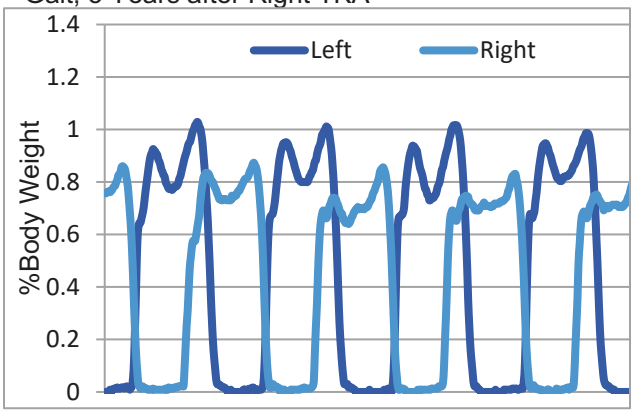
Dr. Allen (lead principal investigator [PI]) is an exercise scientist and health services researcher who has led eight trials of interventions for patients with osteoarthritis (OA) [37-43]. Dr. Queen (multiple PI) is a biomechanist who has led long-term outcomes studies in a variety of orthopaedic populations, as well as studies assessing loading and movement symmetry [44-54]. Dr. Hill is a physical therapist whose clinical and research interests focus musculoskeletal conditions. Dr. Schwartz is a biostatistician with expertise in analyses of randomized trials [37,55-66]. Dr. Hales is an expert in the use of accelerometers to measure PA [67,68].

Drs. Allen and Queen recently collaborated on a pilot study of functional movement retraining following total hip arthroplasty in Veterans (Department of Veterans Affairs, I21RX001033). Participants (n=15) showed improvements in single leg stance time, functional tests and self-reported hip symptoms. The intervention included elements similar to the PAS program, including tailoring of exercises to patients' progression. Our experience with delivering this intervention, as well as recruiting and retaining this post-surgical group (87% follow-up completed), provide valuable experience for the proposed study.

Drs. Allen, Hill and Schwartz collaborated on a randomized trial comparing PT with internet-based exercise training for individuals with OA [37]. Of high relevance to the proposed study, four PT practices (UNC and surrounding communities) delivered the study intervention to participants; this illustrates our ability to engage physical therapists in this type of research and address logistical issues related to integrating research into clinical practice. This study also used similar analytic strategies, including multiple imputation.

Dr. Queen has pilot tested novel 3-sensor insoles (*loadsol*®, Novel Electronics, St. Paul, MN) that will be used for measuring joint loading symmetry. This has included: 1) A 10-participant study showing that the maximum force generated during walking was comparable when measured by *loadsol*® insoles and an embedded force plate (Intra-class Correlation Coefficient (ICC) = 0.924); *loadsol*® insoles also had excellent between-day reliability (ICC = 0.876). 2) A study of five patients with knee OA, demonstrating side-to-side asymmetries, measured with the *loadsol*® during walking and stair climbing. 3) Of high relevance to the proposed study, measurement of joint loading asymmetries during gait among patients following TKA. *Figure 1 is an example of a patient with joint asymmetry persisting five years after a successful right TKA.*

Figure 1. *Loadsol*-Measured Joint Load During Gait, 5 Years after Right TKA



2.2 RISK/BENEFIT ASSESSMENT

2.2.1 KNOWN POTENTIAL RISKS

Emotional distress: it is unlikely that the types of questions participants will be asked in this study will result in emotional distress, but we understand that participants may be uncomfortable with answering questions about some aspect of their health or other things about them. To minimize this risk, we will let participants know they may choose not to answer any study questions and can still be involved in the study.

Breach of confidentiality: we will be collecting some elements of personal health information (PHI) necessary for the study. To minimize breaches of confidentiality, all data will be stored on a secure UNC server or a UNC IRB approved platform for sharing PHI (with Virginia Tech), and paper information will be stored in locked filing cabinets in the office of a study team member. Only approved study personnel will have access to those data.

Risks of Exercise: Injury associated with mild-to-moderate physical activity is rare or infrequent. Because participants will all be post TKA, mild-to-moderate PA may be associated with short-term increases in pain or discomfort; we estimate short-term likelihood to be "common." However, longer-term increases in pain or discomfort after this type of activity is "infrequent" when PA is done appropriately. To minimize all of these risks, we will ensure that participants are given instructions for safe and appropriate physical activity levels and techniques for individuals post TKA. Participants will be given information on how to manage activity-related pain or discomfort. They will also be instructed that if pain is still elevated two hours after PA, they should reduce the intensity level during the next activity session.

2.2.2 KNOWN POTENTIAL BENEFITS

Participants may experience improved physical function, decreased pain, increased PA and improved joint loading symmetry. It is possible that this study may not benefit participants directly, but participation in this study may lead to information that can benefit others receiving post-TKA PT.

2.2.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

This is a minimal risk study with risks that are comparable to those that would be encountered during typical PT or exercise programs in clinical or community settings. Functional tests also mirror activities conducted during normal daily routines (e.g., walking, chair stands). Although muscle or joint soreness may occur following assessments or intervention sessions, all of the activities being conducted are necessary for the scientific rigor of the study. In particular, the function tests being conducted are those recommended by the Osteoarthritis Research Society International (OARSI). Section 8.2 on Safety Assessments describes the study team's plans to minimize risks associated with intervention sessions and outcome assessment. Given the high and increasing rate of TKAs, the persistent deficits of physical inactivity and joint loading asymmetry, and the lack of a standard, evidence-based approach to address these deficits in rehabilitation settings, we believe the value of the information to be gained outweighs the risks of participation in the study.

3 STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Obtain preliminary data on the efficacy of the PAS program with respect to the change in objectively assessed physical activity, measured via accelerometers. H_1: The PAS group will have greater improvement in objectively assessed physical activity at the 3-month and 6-month assessments, compared to the ATT control group. The main co-primary metric of interest is MVPA.	One co-primary primary end-point / outcome is objectively assessed PA, measured via accelerometer. This will be assessed at both 3-month and 6-month follow-up time points. The rationale for these time points is described in the Overall Design section, and the rationale for sample size and analysis including co-primary outcomes is described in the Statistical Considerations Section.	This is a co-primary outcome because it addresses one of the key deficits being addressed in the PAS intervention: physical inactivity. MVPA was particularly chosen as the primary metric because it corresponds to DHHS PA recommendations.
Obtain preliminary data on the efficacy of the PAS program with respect to change in peak load symmetry during walking, measured by a novel 3-sensor insole device. H_2: The post-TKA exercise group will have greater improvement in peak load symmetry during walking at the 3-month and 6-month assessments, compared to the ATT control group. The main co-primary outcome of interest will be the peak load - limb symmetry index during level walking.	The other co-primary primary end- point / outcome is peak load symmetry during walking. This will be assessed at both 3-month and 6-month follow-up time points. The rationale for these time points is described in the Overall Design section, and the rationale for sample size and analysis including co-primary outcomes is described in the Statistical Considerations Section.	This is a co-primary outcome because it addresses one of the key deficits being addressed in the PAS intervention: joint load asymmetry during gait.
Secondary		
Obtain preliminary data on the efficacy of the PAS program with respect to the change in secondary metrics of objectively assessed PA,	In addition to minutes of MVPA, secondary metrics will include step count, minutes of any PA, and sedentary minutes	These secondary metrics will be assessed because they measure aspects of PA that are complementary to minutes of MVPA and also have clinical relevance.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
measured via accelerometers		
Obtain preliminary data on the efficacy of the PAS program with respect to change in peak load symmetry during additional activities, measured by a novel 3-sensor insole device.	In addition to peak load symmetry during gait, peak load symmetry will be assessed during physical performance tests including the 30-second stair stand test, 40m fast-paced walk, stair climb test, and TUG test.	These secondary metrics of load symmetry are being included because they are complement the primary measure of load symmetry during gait. The physical performance tests being assessed represent typical daily activities, in which it is important to understand patterns of joint loading.
Assess the feasibility and acceptability of the PAS program following TKA.	Feasibility metrics include recruitment, retention, intervention delivery, and outcome assessment. Perceptions of acceptability will be obtained from patients and physical therapists using open-ended questions.	This information if important for planning for a future, larger trial and for refining the PAS intervention as needed.
Tertiary / Exploratory		
Obtain preliminary data on the efficacy of the PAS program with respect to the change in exploratory outcomes relevant to post-TKA recovery.	Exploratory outcomes include self-reported PA, physical performance tests, balance, knee symptoms, and kinesiophobia.	These exploratory outcomes were chosen because they are recommended for trials involving knee OA and / or represent patient-centered outcomes relevant to post-TKA recovery.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The overall objective of this study is to gather preliminary evidence on the efficacy, feasibility and acceptability of the PAS intervention. Specific aims are:

Specific Aim 1: Obtain preliminary data on the efficacy of the PAS program with respect to the change in objectively assessed physical activity, measured via accelerometers.
H_1: The PAS group will have greater improvement in objectively assessed PA at the 3-month and 6-month assessments, compared to the ATT control group. The main co-primary metric of interest is minutes of MVPA; other secondary metrics will include step count, minutes of any PA, and sedentary minutes.

Specific Aim 2: Obtain preliminary data on the efficacy of the PAS program with respect to change in peak load symmetry during walking, measured by a novel 3-sensor insole device.
H_2: The post-TKA exercise group will have greater improvement in peak load symmetry during walking at the 3-month and 6-month assessments, compared to the ATT control group. The main co-primary outcome of interest will be the peak load - limb symmetry index during level walking; secondary outcomes will be peak load - limb symmetry index values during additional physical performance tasks.

Specific Aim 3: **Assess the feasibility and acceptability of the PAS program following TKA.**
3a. Measure feasibility metrics related to recruitment, retention, intervention delivery, and outcome assessment.
3b. Assess perceptions of acceptability of the intervention from patients and physical therapists and refine the intervention based on this feedback.

This will be an exploratory, single site randomized controlled trial with 60 patients equally allocated to the PAS intervention or an ATT control group (see Schema section above). Based on the ORBIT framework (which has application beyond the topic area of obesity), this study is a Phase II Preliminary Testing trial. Randomization will be stratified according to gender and presence of self-reported pain (≥3 on a 10 point scale) in any lower extremity joint (hip, knee or ankle) in addition to the surgical knee, to ensure that the groups are balanced in these respects. We chose patient-level randomization because it is a straight-forward design that avoids potential biases and challenges of cluster randomization, such as imbalances in participant characteristics across study arms and attrition of study physical therapists [41,42]. With this design, each study therapist can treat patients in both study arms. Although the PAS program will involve discrete components that are distinct from usual post-TKA PT (which will be delivered to the ATT control group), we acknowledge the risk of contamination of intervention delivery. To mitigate this risk, we will employ an intensive fidelity monitoring process, described below and in the Intervention Documents. If we find in this exploratory study that contamination is a concern, clinic-level randomization will be considered for a larger trial. The typical length of post-TKA PT is about 12 weeks. We will enroll patients approximately 4 weeks from initiation of outpatient PT, allowing time for randomization and notification of the treating therapist to begin the PAS intervention before PT is complete. Follow-up assessments will be conducted 3 months after the beginning intervention visits (shortly following to the end of the PAS intervention) and after 6 months (sustainability end point). Regarding the 3-month follow-up time point, we selected this interval because it will: 1) allow for several weeks for participants to act on content delivered in the 8-week intervention visit and 2) allow sufficient time for scheduling first follow-up assessments after all intervention visits have been complete. Longer term outcomes will be included in a larger trial.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The ATT control group was selected to account for potential effects of intervention-related contacts (e.g., "attention") that are not specific to the PAS program components (e.g., the specific rehabilitation and exercise program being delivered in the PAS intervention). Additional comments regarding rationale for the study design are described in Section 4.1.

4.3 JUSTIFICATION FOR INTERVENTION

The intervention is described in detail in Section 6. The number, frequency and types of contacts were selected based on ability to deliver the PAS content, as well as feasibility of administration in real-world clinical settings. We chose for the first 2 PAS visits to be included within the context of routine post-TKA PT so that it would be integrated into routine care. The 4-week and 8-week contacts were selected to include a reasonable, feasible amount of contact – beyond the typical post-TKA time period – to follow up with patients regarding their progress with components of the PAS intervention. Because this intervention includes only 4 contacts, we have not defined a separate "minimum-acceptable" participation in the intervention. Ideal participation includes participation in all visits. As part of this exploratory trial, we will be monitoring the feasibility and rates of visit completion, in preparation for a larger trial. In this study, primary analyses will include all randomized participants, regardless of amount of intervention completion. However, we may conduct additional exploratory analyses that account for different patterns of intervention completion.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed 6-month follow-up assessment. As noted above, there is no minimum number of intervention visits required to meet at definition of "completion," but patterns of intervention completion will be assessed.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

All participants must be receiving post-TKA PT from a physical therapist at a UNC Healthcare System clinic or at physical therapy clinics outside of UNC. We will include individuals with OA in other lower extremity joints to maximize generalizability and help inform the larger trial.

5.2 EXCLUSION CRITERIA

Exclusion criteria are: significant cognitive impairment, neurological disorders affecting gait, systemic rheumatic disease; hospitalization for a cardiovascular condition the past six months; psychosis; substance abuse disorder; lower extremity surgery in the past year; planning total joint replacement in next 6 months; any other health conditions determined to be contraindications to a home exercise program.

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are not subsequently assigned to the study intervention or entered in the study. Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting one or more exclusion criteria (e.g., development of an exclusionary health condition) will not be rescreened. This is because of the brief period of time in which participants are eligible to participate in the study (e.g., time between initial screening and beginning of the intervention, which starts at the end of routine post-TKA PT). It is unlikely that any exclusionary health conditions, resulting in screen failure, will resolve during that period of time.

5.5. STRATEGIES FOR RECRUITMENT AND RETENTION

For UNC Healthcare clinics, we will identify potential participants though regular medical record searches of patients initiating outpatient post-TKA PT. About 10 patients initiate post-TKA PT at our target clinics monthly. Although we expect this will be sufficient to meet our sample size goal, we also have existing partnerships with and processes for working with other local PT clinics [37]. Potentially eligible patients will be mailed a recruitment letter (including an opt-out telephone number) from the study team, followed by a telephone call about 1 week later from a study team member to assess eligibility and interest. A UNC provider (physical therapist or orthopedic surgeon) may also discuss the study with a patient and will notify a study team member, if the patient agrees to be contacted. For non UNC Healthcare physical therapy clinics, staff will provide verbal information and / or recruitment flyers to participants regarding the study. With patients' verbal permission, a clinic team member may provide our UNC study team with contact information (telephone number, address) for the patient, so that we may contact them about the study. Patients may also directly contact the UNC study team, using the phone number provided on the flyer. Interest and eligibility of these patients will also be assessed via telephone.

Eligible patients will be asked to meet with a study team member to complete a baseline visit including informed consent, Health Insurance Portability and Accountability Act of 1996 (HIPAA) authorization and baseline assessments. We may review the informed consent and HIPAA over the phone prior to the baseline visit. At the end of the baseline visit, participants will be given an accelerometer to wear for one week and return via mail. Following receipt of the accelerometer, participants will be called by an un-blinded study team member with their randomization assignment, and the treating therapist will be notified accordingly.

6.0 STUDY INTERVENTIONS

6.1 STUDY INTERVENTION ADMINISTRATION

PAS Intervention Administration

Overview. Traditional post-TKA PT focuses on reducing pain and swelling and increasing range of motion (ROM) and strength. *The PAS program significantly augments usual post-TKA PT, specifically addressing critical gaps of physical inactivity and joint loading asymmetry*. The PAS program will be initiated during the final usual care PT visits, allowing integration and capitalizing on the existing patient-provider relationship. This is strategic timing because patients typically make substantial progress in traditional metrics (strength, ROM, pain) by this time point and are embarking on the independent phase of the recovery process. We will aim for PAS content to be included within the last two routine PT visits and will orchestrate this timing with study physical therapists. The course of PT may end slightly sooner or later than expected, and this exploratory study will allow us to fine tune processes for beginning delivery of PAS. PAS participants will then receive a follow-up call after 4 weeks (to assist with activity progression and problem-solving) and an additional visit (conducted in-person if possible or remotely via an IRB approved video platform or by phone if needed) after 8 weeks (to visually monitor exercise performance and re-assess proportional weight-bearing ability). Each of the contacts for the PAS intervention is summarized in Table 1 and described below. Participants will be asked to track performance of specific exercises and overall PA through Physiotec, a web-based tracking page. Physical therapists will have access to these pages to facilitate accountability and intervention delivery. If participants prefer not to log their exercise using Physiotec the study team will offer paper logs that can be used instead. In these cases, participants will be reminded to bring in their exercise logs for in-person sessions, and physical therapists will ask participants to refer to their logs during the 4-week phone call. For participants who do not have regular internet access (expected 9-10%) [37], we will provide an iPad and data plan for the intervention period. Physical therapists will also track information from PAS sessions through a study clinic note template in the participant's medical record.

Table 1. Overview of PAS Intervention Session Content

Session #	PA Counseling Content	Balance Exercise (Loading Symmetry) Content	Total Minutes
1 (In-Person or via video platform or phone if needed))	Overview of PA post-TKA, goal-setting, MI	--	15-20
2 (In-Person, or via video platform or phone if needed)	--	50% weight-bearing exercise, assign home exercises	20-25
3 (Phone) 4-weeks	Assess PA, address barriers, goal-setting, MI, community resources	Assess progress with exercises, advise on progression	25
4 (In-Person, or via video platform or phone if needed) 8-Weeks	Assess PA, dealing with setbacks, MI long-term goal setting	Demonstration of exercises, advise on progression	40

PAS Content: Counseling to Increase General Physical Activity

Specific content will be as follows:

Session 1 (In-Person if possible, or via video platform or phone if needed): The PT will: (1) Emphasize the importance of PA in TKA recovery using key points. (2) Work with participants to establish a SMART (Specific, Measurable, Attainable, Relevant, Time-bound) goal regarding overall PA. (3) Incorporate MI principles to elicit motivations and / or ambivalence toward PA [69-71]. (4) Provide a list of community-based and other resources to support overall PA. These materials will be emailed to the participant if the visit is conducted remotely.

Session 3 (4-Week Phone Session): The PT will: (1) Assess progress with overall PA using standard questions, referring to the web-based PA log. (2) Help participants to develop strategies to address any barriers they experienced in their PA. (3) Apply MI principles to elicit motivations and / or ambivalence toward PA. (4) Work with participants to establish a new SMART PA goal for the next four weeks, with appropriate progression. (5) Discuss PA resources and facilitate connection of participants to these resources.

Session 4 (8-Week Session In-Person if possible or remotely via an IRB approved video platform or by phone if needed): Activities will mirror those for Session 3 with two modifications. First, the physical therapist will discuss strategies for dealing with setbacks in PA. Second, SMART goal setting will be more long term in nature, focusing on the next six months.

PAS Content: Balance Exercises to Improve Joint Loading Symmetry.
Although usual post-TKA PT aims to improve overall function, the PAS intervention differs substantially in its targeted approach to help patients detect side-to-side joint loading asymmetries and re-learn how to equalize loads across limbs. The content for this component of PAS will be as follows:

Session 2 (Second Session In-Person if possible, remotely via an IRB approved video platform or by phone if needed): If session is conducted in person, participants will undergo a process enabling them to detect when 50% weight bearing is achieved on each leg. The foot of the post-surgical limb will be placed on an analog bathroom scale and the contralateral foot on a small step of equivalent height. The participant will then shift weight between legs so that it feels as if 50% of weight is on each foot. The therapist will inform the participant of the actual weight distribution and assist the participant with achieving 50% weight bearing stance through verbal and tactile cues. The participant will then perform a series of 10 weight shifts off of the post-surgical limb and attempt to return to 50% weight bearing for a 10 second hold in that position. Participants who cannot successfully assume equal weight bearing within 5% for 8 of 10 trials will be given a scale and a step of equal height to continue practice at home by performing 10 repetitions of the weight shifting activity daily.

Table 2. PAS Intervention Balance and Functional Strength Exercises

STATIC BALANCE	DYNAMIC BALANCE*	
Initial Exercise: most challenging position that can be held for 3 repetitions, 10 seconds	**Initial Exercise:** most challenging activity that can be performed for 10 consecutive repetitions without a loss of balance	
Progression Criterion: hold for 30 seconds, 3 repetitions	**Progression Criterion:** perform 3 sets of 10 repetitions without a loss of balance	
***Exercises** (in order of difficulty)*		
Staggered stance	Weight shift in staggered stance	Forward lunge to 45 degrees knee flexion and return
Narrow staggered stance	Weight shift in tandem stance	Walking forward lunge
Tandem stance	Tandem walk with arms outstretched	March with single leg hold for 3 seconds
Single leg stance	Tandem walk with arms crossed over chest	Walking forward lunge with 3 seconds hold during transition
*Physical therapist will assign 1 exercise from each column.		

Next, the PT will prescribe balance exercises – one static and two dynamic (see Intervention Documents) - which supplement the general strengthening exercises assigned as part of usual post-TKA PT. The initial balance exercises prescribed will be the highest level at which the participant can perform at a minimal standard (defined in Table 2). If the visit is conducted remotely, the PT will be instructed to begin with the lowest level of balance exercises and to increase the level once they meet the progression criterion shown in Table 2. Participants will be given or emailed handouts and access to a website that displays proper exercise form. Participants will be instructed to perform exercises once daily. *Static balance exercises* will be performed bilaterally in an alternating leg manner for three repetitions, 30-seconds each, with use of hand support as needed to maintain balance. *Dynamic balance exercises* will be performed bilaterally for 10 repetitions per set for three sets, with use of hand support as needed.

Session 3 (4-Week Telephone Session): The PT and participant will discuss recent performance of balance exercises (e.g, frequency, progression, problems with specific exercises) using standard questions (see Intervention Documents). This will ensure exercise performance is of appropriate intensity and frequency to achieve improvement. The therapist will encourage the participant to advance to the next level of an exercise has become too easy, based on criteria in Table 2.

Session 4 (8-Week Session In-Person if possible or remotely via an IRB approved video platform or by phone if needed): The PT and participant will discuss performance of balance exercises using standard questions (see Intervention Documents). Participants will demonstrate current exercises if the session is conducted in person or via video platform, and the therapist will correct form as needed. Progression of exercises will be promoted as described above. If session is delivered in-person, the therapist will also reassess participants' abilities to stand with equal weight bearing as described above in Session 2.

ATT Control Intervention Administration . The ATT control group will receive usual in-person post-TKA care, without the additional PAS components described for Sessions 1 and 2 in Table 1. To account for non-specific effects (e.g. therapists "attention") of the two additional visits in the PAS intervention (4-week phone call and 8-week visit), the ATT control group will receive visits at the same intervals but differing in content. Specifically, the 4-week phone call will include: information on typical recovery benchmarks for this time point, assessment of participants' daily activities, and reminders about symptoms that should trigger contacting a medical professional. The 8-week visit (conducted in-person if possible or remotely via an IRB approved video platform or by phone) will be primarily evaluative, including assessment of ROM, strength, and function when possible. If the visit is delivered via video, performance tests will be conducted, when feasible. Participants will be given or emailed a report summarizing these assessments. Participants will also be instructed to continue the home exercise program prescribed by their PT at discharge. This information may be delivered whether the visit is conducted in-person, via video or by phone. Neither of these contacts will include PA counseling or promotion of symmetrical loading of lower extremities, which are key components of the PAS intervention.

6.2 FIDELITY

Physical therapists will be trained by Drs. Allen (PA counseling) and Hill (balance exercises) and will conduct mock sessions of all PAS visits prior to study initiation. The study team and physical therapists will establish a formal description of usual care PT components, to help ensure the in-person ATT visits are distinct from the PAS visits. Study physical therapists will also be trained in delivery of the 4- and 8-week ATT control sessions. Since contamination between interventions is a challenge of this study design, we will aim to conduct monitoring of 75% of PT sessions to evaluate fidelity and the feasibility of using this approach for a larger trial.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The randomization scheme will be generated by the study statistician and stored within the study database. The database will be configured so that blinded study personnel (e.g., those conducting follow-up assessments) will not have access to randomization information. The participants will not be notified of randomization assignment until all baseline assessments are complete. In addition an individual participant's randomization assignment will not be known to any study personnel until baseline assessments are complete. Randomization will be stratified according to gender and presence of self-reported pain (≥3 on a 10 point scale) in any lower extremity joint (hip, knee or ankle) in addition to the surgical knee, to ensure that the groups are balanced in these respects.

6.4 STUDY INTERVENTION ADHERENCE

The study database will be used to track participants' completion of all assessment visits, as well as all intervention visits. Intervention visits will be logged in the UNC electronic medical record (EMR), and the study coordinator or other unblinded study team member will monitor these records for study participants to determine intervention adherence (and document the information in the study database). The study team will also maintain close communication with study physical therapists. If participants miss intervention visits, an unblinded study team member may assist the study physical therapist in contacting and rescheduling visits, as needed.

6.5 CONCOMITANT THERAPY

Participants will be permitted to continue any other post-TKA treatment (e.g., pain medications) during the course of the study.

7 STUDY INTERVENTION/ DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

When a participant discontinues from the PAS intervention but not from the study, remaining study procedures will be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed; the treating study physical therapist may be involved with these recommendations. Any new clinically relevant finding will be reported as an adverse event (AE). The data to be collected at the time of study intervention discontinuation will include the reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue a participant from the study for the following reasons:

- Lost-to-follow up; unable to contact subject
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded in the study database. Participants who discontinue or are withdrawn will be replaced up to the point of randomization assignment being given to the participant. Once participants are given their randomization assignment, they will be counted toward the total study sample size and not replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for the final, 6-month follow-up assessment. If a participant misses intervention visits or misses the 3-month follow-up assessments and cannot be contacted during the time frame, the study team will still attempt to contact the participant for remaining visits / assessments. The study team must attempt to contact a participant at least 3 times, on different days of the week, different times of day, and across at least 2 weeks, before they are considered to have missed a visit / assessment or are lost to follow-up. These contact attempts will be documented in the study database.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Measures will be collected at baseline, 3 months and 6 months by a trained research assistant blinded to randomization assignment. Participants will be paid $50 for completing baseline questionnaire and $15 for wearing and returning an accelerometer. Then, up to $40 at 3 month and 6 month time point: $25 for completing questionnaires and functional measures and $15 for wearing and returning an accelerometer.

Due to COVID-19 safety measures, we may conduct a briefer set of measures focused on the primary functional assessments. We will explain to the participant during the consent process that the measures may

be more limited in order to minimize in-person visit time. Also, we may schedule a time to call the participant after the in-person visits (at baseline and 3 month and 6 month follow-up) to complete the questionnaires over the phone.

Efficacy (Aims 1 and 2)
Co-Primary Efficacy Outcome: Objectively Assessed Physical Activity (accelerometer). Our specific primary outcome of interest is MVPA per week, since this corresponds to DHHS recommendations and is a known predictor of outcomes in patients with OA [7]. We will also examine step counts, minutes of any PA and sedentary minutes as secondary outcomes [72,73]. Participants will wear the waist-worn Actigraph GT3X+ (Pensacola, FL) for 7 days [74]. Following previously established thresholds, outcomes will only be computed for participants who wear the accelerometer for 4+ days with 10+ hours of wear. Accelerometers will be given to participants during in-person visits at each time point and mailed back to the study team, using our procedures from prior studies that have resulted in very high adherence rates (89-93%). If participants are not able to complete follow-up assessments in person but complete questionnaires by telephone, we may mail an accelerometer for wear and return via mail. Accelerometer data will be processed using standard procedures [75-78].
Co-Primary Efficacy Outcome: Peak Joint Load Symmetry During Walking. We will use a novel, 3-sensor in-shoe load measurement device (*loadsol*) to measure joint load symmetry. The *loadsol*® builds on the reliable pedar-X® in-shoe measurement system [79] but importantly collects data on a handheld device without any external cabling, facilitating measurement during a variety of dynamic tasks. The *loadsol*® requires minimal training, making it ideal for clinical settings. Participants will complete a 10 meter walking test (three trials averaged) [80], while load beneath each foot is recorded. Walking speed will also be recorded and will be used as a covariate since this may impact the loading metrics. Loading symmetry (peak ground reaction force) will be assessed using the limb symmetry index (LSI (|Surgical/Non-Surgical|*100), which has been associated with adverse outcomes such as re-injury of the anterior cruciate ligament (ACL); values lower than 100% indicate less loading of the surgical limb [81-84]. LSI was selected based on its current use in the clinical setting and the ease of calculation.
Secondary Efficacy Outcomes
Self-reported Physical Activity: Modified version of the CHAMPS (Community Health Activities Model Program for Seniors) Physical Activity Measure [85]. This measure complements the accelerometer-based data by providing additional information on the contexts and types of activities in which participants are engaging. This modified version of the CHAMPS includes items tailored for this participant group. For each item, participants first indicate whether they have done the activity for 10 or more minutes during the past week. If they respond "yes," they will be asked the number or days and minutes per week. This questionnaire will be supplemented with individual items to assess sitting behavior and sleep.

Physical Performance Tests. We will administer tests recommended by OARSI for clinical trials of knee OA: 30-second stair stand test, 40m fast-paced walk, stair climb test, and TUG test [86] . Participants will wear the *loadsol* bilaterally for all functional tests. This will allow us to assess loading symmetry while patients are performing each of these common daily tasks. In addition, for the 30-second chair stand test, TUG, and 10m walk (described above), we will collect additional measures for the purpose of developing field-based methods for assessing knee joint kinematics and spatiotemporal gait mechanics.

Data capture via video cameras discontinued in December 2021 Three high speed cameras will be used to record participants completing the function tests. All cameras will be placed on tripods held 60 cm off the floor. One camera will be placed facing the participant and 150 cm beyond the line in which they turn during the TUG. The other two cameras will be placed to the left and right of the middle of the TUG path approximately 350 cm away from the path. Participants will be equipped with 6 reflective markers, which will be placed bilaterally over the lateral aspect of the femoral epicondyle, in the middle of the shank in-line with the lateral femoral epicondyle and lateral malleoli, and in the middle of the thigh in-line with the lateral femoral epicondyle and greater trochanter. Each camera will be equipped with an external light source (flash), which will cause the reflective markers to shine very brightly and be easily tracked throughout the video. The cameras will collect

wide view videos at 120 frames per second. The wide view video will result in a 'Fish-Eye' effect in the video data, which will be corrected and converted to a linear image using previously developed methods[23, 26] and the individual cameras lens coefficients. Each marker will be tracked in both the frontal and sagittal view videos after de-warping the fish-eye effect. The XY position of each marker will be used to create knee angles. Before movement trials, a 1 second static trial will be recorded from both views, and the knee angle during quiet stance will be used to normalize knee angle during the movement trials (i.e. knee flexion and valgus will be considered zero during quiet stance).

Balance. We are conducting a limited set of tests due to COVID precautions. We will administer two tests from the Berg Balance Scale: tandem stance and 10 sec single leg stance [87]. We will also administer one test from the Brief Balance Evaluation Systems Test: Stance With Eyes Closed, on Foam Surface [88].

Knee injury and Osteoarthritis Outcome Score (KOOS). The KOOS is a widely used and validated patient-reported outcome that includes five separately scored subscales (42 items total): pain, symptoms, activities of daily living, sports and recreation, and knee-related quality of life [90]. The KOOS pain subscale will also be assessed at each intervention visit, so that we can assess potential associations between pain and PA.

Tampa Scale for Kinesiophobia. Fear of movement is a key concern for patients following TKA, associated with poorer clinical outcomes [91,92]. This is a 17-item measure of multiple domains of fear of movement [93].
Feasibility and Acceptability (Aim 3)

Feasibility Metrics, The following are feasibility metrics, as well as "targets" that will indicate success, when appropriate:
- Number of potentially eligible patients identified from the medical record during the recruitment period. There is no standard benchmark for "success" for this metric. Rather, this information is important in planning for a future, larger trial. When planning for that trial, a sample size / power analysis will be conducted. Based on information gathered from this metric, we will be able to ascertain the feasibility of conducting a single site trial vs. moving to a multi-site trial (and understanding the number / size of sites that would be needed).
- *Proportion of patients who are eligible and enroll, along with ineligibility and refusal reasons*. Similarly, there is no standard benchmark for success for this metric, but it will be used to determine feasibility and site(s) for a future trial. However, based on our prior studies, we expect an enrollment rate of at least 20%[39,94]. An enrollment rate below this threshold will signal a need to closely evaluate study requirements for participants, as well as recruitment and enrollment methods. Information gathered on ineligibility and refusal reasons will guide this process.
- *Proportion of participants completing each intervention contact and follow-up assessment (overall and by study arm)*. Because this is a brief intervention, completion of all 4 visits is optimal. However, we recognize there are reasons that participants cannot complete visits. With regard to the first two intervention visits (which take place during routine post-TKA PT), we will consider the approach to be successful if ≥80% of participants complete both visits; a proportion below this threshold will signal a need to re-evaluate our approach of how these interventions are embedded into routine post-TKA PT. With regard to the 4-week and 8-week follow-up intervention visits, we will also consider the approach to be successful if 80% of participants complete both visits; a proportion below this will signal a need to re-evaluate aspects including the timing of the visits and whether the final visit should remain in-person vs. via telephone. Our participant questionnaires on intervention feedback will provide insight into these issues.

Acceptability. We will ask study participants and therapists a series of open-ended questions to assess intervention acceptability and obtain suggestions for improving the intervention[95,96].

Patient Characteristics. We will collect information on age, race / ethnicity, education, work and marital status, body mass index, comorbid illnesses [97], joints with arthritis symptoms, and duration of knee symptoms.

Symptoms and Events in the Non-Surgical Limb. Although the 6-month follow-up period is not sufficient to fully assess impacts on the non-surgical limb, we will measure changes in pain (10-point visual analog scales

specific to the contralateral knee, assessing average, worst and least pain in the past 2 weeks), injuries, and progression in plans for TKA. This will be assessed for a longer period in the subsequent larger trial.

8.2 SAFETY ASSESSMENTS

Study physical therapists will be experienced clinical personnel who are familiar with standard clinical practice for protecting patient safety during visits. Study-specific intervention content is within the scope of PT practice, so we do not believe any special procedures are needed to protect participants' safety, beyond adherence to usual procedures. For the weight-shifting exercise to be conducted in 2 of the PAS visits, we will provide physical therapists with in-person training and a video (to refer to at later points) to show procedures, including prevention of falls if a participant loses their balance during the test. In addition, when participants are shown balance exercises, the physical therapists will instruct them to perform these in a place where they can easily grab on to a stable item if they begin to lose balance. Any AEs that occur during PT visits or in the course of participants' home exercise will be documented on the Adverse Events form, as described below.

For the Physical Performance Tests, the testing administrator will be trained to monitor patient safety during testing. This will include following slightly behind and off to one side of the patient but not to pace or impede them, as well as allowing the patient to stop and rest if they become tired, if necessary.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from DHHS Office for Human Research Protections (OHRP): Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

This protocol uses the definition of serious adverse event from DHHS OHRP: any adverse event that results in death; is life-threatening (places the subject at immediate risk of death from the event as it occurred); results in inpatient hospitalization or prolongation of existing hospitalization; results in a persistent or significant disability/incapacity; results in a congenital anomaly/birth defect; or based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

All AEs will be assessed by the PI or co-investigators, if the PI is not available. The following guidelines will be used to describe severity:

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".]

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All AEs will have their relationship to study procedures, including the intervention, assessed by the PI or co-investigators based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Related** – The AE is known to occur with the study procedures, there is a reasonable possibility that the study procedures caused the AE, or there is a temporal relationship between the study procedures and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study procedures and the AE.
- **Not Related** – There is not a reasonable possibility that the study procedures caused the event, there is no temporal relationship between the study procedures and event onset, or an alternate etiology has been established.

8.3.3.3 EXPECTEDNESS

A clinician with appropriate expertise in post-TKA patients and recovery (Olcott or Hill) will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an AE or serious adverse event (SAE) may come to the attention of study team members during study visits. All AEs, not otherwise precluded per the protocol, will be captured on the Adverse Event Form. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

The Project Coordinator will record events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. Participants are identified in the EMR as a study participant and for each AE/SAE occurrence, research team members will receive an alert through EMR. AEs or SAEs may also be reported to study physical therapist

during the course of intervention visits. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Once Dr. Allen (or a co-investigator) is contacted about the adverse event, she / he will make a determination about the reporting requirements in accordance with UNC IRB guidelines.

The PI will report all adverse events to the Safety Officer (SO) on a biannual basis, or as requested. Additionally, the PI or a co-investigator will report any AEs that suggest new or increased risk to participants or others within 7 calendar days of when the PI became aware of the information. For AEs that are not related to participation in the research and do not suggest new or increased risks to the participant, these will be reported at continuing review.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Once Dr. Allen (or a co-investigator) is contacted about a serious adverse event, she / he will make a determination about the reporting requirements in accordance with UNC IRB guidelines. This will include notification of the UNC IRB, as well as the SO, within 24-hours if a study-related death and within 48 hours if another SAE.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4. UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

Unanticipated Problems (UPs) are not included in the 45 CFR part 46, but are defined by the OHRP as any incident, experience or outcome that meets all of the <u>following requirements:</u>

(1) Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

(2) Related or possibly related to participation in the research. *Possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

(3) Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

OHRP recognizes that it may be difficult to determine whether a particular incident, experience, or outcome is unexpected and whether it is related or possibly related to participation in the research. OHRP notes that an incident, experience, or outcome that meets the three criteria above generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of participants or others.

The following corrective actions or substantive changes that could be considered in response to an unanticipated problem include:

- Changes to the research protocol initiated by the investigator prior to obtaining IRB approval to eliminate apparent immediate hazards to subjects;
- modification of inclusion or exclusion criteria to mitigate the newly identified risks;
- implementation of additional procedures for monitoring subjects; suspension of enrollment of new subjects;
- suspension of research procedures in currently enrolled subjects;
- modification of informed consent documents to include a description of newly recognized risks;
- provision of additional information about newly recognized risks to previously enrolled subjects.

Only a small subset of adverse events occurring in human subjects participating in research will meet these three criteria for an unanticipated problem. Furthermore, there are other types of incidents, experiences, and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

All UPs will be reported to the NIAMS and the SO (through KAI) within 48 hours of the PI becoming aware of the event.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Participants will be given any new information gained during the course of the study that might affect their willingness to continue participation in the study.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Specific Aim 1: Obtain preliminary data on the efficacy of the PAS program with respect to the change in objectively assessed physical activity, measured via accelerometers.

H_1: The PAS group will have greater improvement in objectively assessed physical activity at the 3-month and 6-month assessments, compared to the ATT control group. The main co-primary metric of interest is MVPA; other secondary metrics will include step count, minutes of any PA, and sedentary minutes.

Table 3. Statistical power according to effect size, assuming 27 patients per group

Effect Size (SD units)					
0.5	**0.6**	**0.7**	**0.8**	**0.9**	**1.0**
0.44	0.66	0.58	0.82	0.90	0.95

Specific Aim 2: Obtain preliminary data on the efficacy of the PAS program with respect to change in peak load symmetry during walking, measured by a novel 3-sensor insole device.

H_2: The post-TKA exercise group will have greater improvement in peak load symmetry during walking at the 3-month and 6-month assessments, compared to the attention control group. The main co-primary outcome of interest will be the peak load - limb symmetry index during level walking; secondary outcomes will be peak load - limb symmetry index values during additional physical performance tasks.

9.2 SAMPLE SIZE DETERMINATION

No adjustment for co-primary outcomes is made since this is a pilot study. We do not necessarily expect this exploratory study to be highly powered. Table 3 shows a range of effect sizes and corresponding statistical power for a comparison of intervention versus control group means, for the projected total of n=54 participants at the two-sided 0.05 significance level. We chose n=54 because this is reasonable to complete within the time frame of this exploratory trial and will allow sufficient experience to inform a larger trial. We are allowing for a 10% attrition rate, so n=60 participants will be enrolled. Data from this study are crucial for informing sample size estimates for a larger trial; however, preliminary calculations indicate that for a standardized effect size of 0.35-0.40 standard deviation units, a sample size of 100-130 per group may be required. This sample size is reasonable to enroll within the time frame of this exploratory trial, and it will allow sufficient experience with intervention delivery to inform the larger trial. Our analytic strategy (described below) will also accommodate dropout, missed visits, and loss-to-follow-up. Information regarding the actual observed extent of dropout, missed visits, and loss-to-follow-up in this study will also be useful for the subsequent large-scale trial.

9.3 POPULATIONS FOR ANALYSES

The primary analyses will be conducted using an intent-to-treat approach. Supportive exploratory analyses may be conducted to consider samples with greater completion of study intervention visits. Since this is a preliminary, exploratory analysis, the nature of these supportive analyses will be based on observed patterns of intervention visits. However, likely approach is to assess outcomes among participants who completed at least 3 of the 4 study visits.

9.4 STATISTICAL ANALYSES PLAN

Preliminary analyses will include generating descriptive statistics for demographic variables, as well as baseline characteristics and follow-up measures. This includes means and standard deviations for continuous variables, and frequencies and percentages for categorical variables. Ranges will also be examined for outliers and to ensure data integrity. Demographics and baseline characteristics will also be described separately by randomized group. Statistical tests will be performed to compare each of these by randomized group to determine the extent of random imbalance by t-test of chi-square testing, as appropriate. However, the p-values generated by these tests are considered as descriptive rather than as inferential. We would

expect some imbalance between the groups by random chance, owing to the limited sample size. Variables exhibiting imbalance may be considered as covariates in the statistical models described below.

The co-primary outcome of MVPA will be analyzed across the follow-up time points through a general linear mixed model (GLMM). Specifically, the MVPA values at 8 weeks and at 6 months for a given patient will form their response vector for this model. Fixed effects for the primary model will include an indicator for PAS group, an indicator for the 6-month follow-up time point, their interaction (group by time), and baseline MVPA value; a supporting model will also include any covariates that exhibit random imbalance between groups at baseline. Random effects for patients will account for the within-patient correlation induced by the repeated measures design. Formal statistical testing of the group by time interaction term will provide assessment for whether efficacy varies by follow-up time point. A term representing the interaction of PAS-by-baseline value will be included and tested to explore whether participants' starting point might impact how much they improve; it will be removed if non-significant attention. Statistical contrasts will be constructed in order to estimate the effect of PAS versus attention control, separately at 8 weeks and at 6 months; these estimates will inform the sample size estimation of the subsequent trial. Estimated correlations among follow-up time points will also be useful in this regard.
The approach outlined above will be repeated for the co-primary outcome of peak joint loading symmetry during gait, through fitting a separate GLMM. The main difference will be to include walking speed as an additional covariate, as justified in the research strategy. Secondary outcomes will also be analyzed using the same approach, each with its own GLMM.

An exploratory analysis will include KOOS pain scores as a (time-dependent) main effect, as well as their interaction with PAS, to evaluate whether this variable has an impact on intervention effects. This exploratory analysis will be repeated, but using participant-specific changes in KOOS pain scores, to examine how our primary outcomes (MVPA and peak load symmetry during walking) are associated with those changes.

If any of the co-primary or secondary outcomes exhibit distributions that deviate markedly from normality, alternatives will be considered. First, transformations, such as the natural logarithm, will be applied in an attempt to normalize the distribution. If this is not successful in remedying the non-normality, alternatives such as categorizing the variable and applying appropriate categorical data analysis, such as logistic mixed models (with a similar specification as described above for the GLMMs) or logistic models utilizing generalized estimating equations methodology can be fitted.

A two-sided 0.05 significance level will be applied to each co-primary outcome, as well as each secondary outcome; no adjustment for multiple comparisons will be applied. This is consistent with the trial's objective as a pilot study to generate estimates useful for the large-scale trial to follow.

An additional advantage to using the GLMM approach is its ability to accommodate missing data (including dropouts, missed visits, and lost-to-follow-up) under a missing at random paradigm. All available follow-up data will be utilized in an intent-to-treat manner. If a participant is missing one of the follow-up time points, that participant is not completely excluded from the analysis. A supportive analysis will be conducted using multiple imputation to produce multiple datasets that have complete data for all n=60 participants, where missing values (due to dropouts, missed visits, and lost-to-follow-up) have been imputed. The statistical models will be fitted to each of the complete datasets; results of each model will be synthesized in a manner that accounts for both between and within imputation variation to produce final estimates to address the research questions.

Feasibility metrics will be computed as proportions, along with 95% confidence intervals to describe the level of uncertainty of the estimates. Lower confidence bounds of these proportions will be useful in considering worst-case scenarios when planning the subsequent large-scale trial. Acceptability data are primarily open-ended questions, and responses will be summarized to inform appropriate modifications to the PAS intervention. For the brief questionnaires on acceptability, appropriateness, and feasibility [95,96], we will calculate mean and median scores and distributions across each domain.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be given to the participant and written documentation of informed consent will be completed prior to starting the study intervention. The following consent materials are submitted with this protocol: Adult Consent Form.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Once a potential participant meets the medical record and telephone screening criteria for eligibility, and is interested in participating, a study team member will email or mail the potential participant a copy of the informed consent form and HIPAA for them to review. The study team member will set up a time to call the potential participant no more than 24 hours before the baseline visit to conduct the COVID-19 wellness screening. During the phone call, the study team member will review the IRB approved consent form with the potential participant and provide an opportunity for him/her to ask any questions that they may have about the research study.

We will use a UNC IRB approved consent form with included language that satisfies the HIPAA requirements and outlines the protection of health information utilized in the study. No other study activities will occur until the consent process is completed.

We anticipate this process to take approximately 20 minutes, but this time will not be limited should a participant have additional questions or concerns regarding the study. During this phase of the consent process, it will be stressed that the participant is not obligated to participate in the study, that participation is completely voluntary, and that he/she may withdrawal from the study at any time without penalty. Also, potential risks from participating in the study will be outlined in the consent form, as are the measures taken to protect against study specific risks. Once the information in the consent from is fully reviewed and understood by the individual, he/she will be asked to decide at that time if they would like to voluntarily participate in the research study. If the individual does choose to participate in the study, they will be asked to print, sign and date the consent form and HIPAA, and bring the documents with them to the baseline visit. If the participant is unable to print or bring the documents, copies will be available at the baseline visit for them to complete. Both the individual and the study team member will sign and date the consent form. Each enrolled participant will then receive a signed copy of their consent form to keep for their records.

If after reviewing the consent form, the potential participant is not sure they would like to participate in the study at this time, they may choose to consider the study further at home, and then contact the study team if they decide later that they would like to participate.

Participants will only be included if they have capacity to give legally effective consent. Additionally, this study will only recruit participants whom are English speakers.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and sponsor/funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB or other relevant regulatory or oversight bodies (OHRP, SO).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible in the EXSS Lab or at a study PT clinic.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the IRB, regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study.

The study participant’s contact information will be securely stored on a secure study database for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored on a secure UNC server. The study data entry and study management systems used by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived on a secure UNC server.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies

It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

10.1.4 FUTURE USE OF STORED DATA

Data collected for this study will be analyzed and stored on a secure UNC server. After the study is completed, the de-identified data will be made available to other researchers, available by request to the PI. Investigators requesting study data must adhere to regulatory requirements for data use (e.g., IRB approvals, data use agreements). No biological samples are collected for this study.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator	**Independent Safety Monitor**
Kelli D. Allen, PhD	Kurt P. Spindler, M.D. Vice-Chair of Research, Orthopaedic & Rheumatologic Institute (ORI)
University of North Carolina at Chapel Hill	*Cleveland Clinic Sports Health Center*
3300 Thurston Bldg, CB #7280 Chapel Hill, NC 27599-7280	5555 Transportation Blvd. Garfield Heights, OH 44125
919-966-0558	
kdallen@med.unc.edu	

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of the NIAMS appointed SO. The SO will be independent from the study conduct and free of conflict of interest. On a biannual basis, the PI will provide to the SO a study summary, a report of all AEs, and any problems or issues that have been identified.

10.1.7 CLINICAL MONITORING

Since this is a single site study there will not be site visits conducted by the PI or co-investigators. However, we will employ an intensive fidelity monitoring process for the study physical therapists. Physical therapists will be trained by the PI and a co-investigator (Hill) and will conduct mock sessions of all PAS and ATT control intervention sessions prior to study initiation. Since contamination between interventions is a challenge of this study design, we will aim to conduct monitoring of 75% of PT sessions to evaluate fidelity and the feasibility of using this approach for a larger trial. KAI may conduct a site visit on behalf of the NIAMS, however, KAI will not have the responsibility of the overall clinical monitoring for this study.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented as follows:

Informed consent --- During the consenting process, the study team member will review the completed consent document to ensure the participant has signed and dated the consent form accurately prior to completing any other study activities.

Source documents and the electronic data --- Data from the Physical Performance Tests will be initially captured on source documents and will ultimately be entered into the study database; all other data from study measures will be entered directly into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2**

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Study data will be stored on a secure UNC server in a folder accessible only to IRB-approved study team members. We will use REDCap to store all patient information and dispositions, responses to screening and outcome assessments. REDCap is a secure web application supported at UNC that can be used to build and manage case report forms, surveys, and other data capture mechanisms. Additionally, a data set will be shared with Dr. Queen at Virginia Tech for the purpose of this research. This data set will include information from the *loadsol* measurements, for which Dr. Queen has specialized programs for analysis, along with a participant ID so that the processed *loadsol* data can be linked back with other participant data at UNC. There will be no additional identifiable data elements included in the data set sent to Virginia Tech.

10.1.9.2 STUDY RECORDS RETENTION

Research study records will be maintained for no less than 6 years following the completion of the study, after which time personal identifying information will be removed. Research information in a subject's medical record will be kept indefinitely. No records will be destroyed without the written consent of the sponsor/funding agency, if applicable. It is the responsibility of the sponsor/funding agency to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol,

ICH GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations that impact participant safety to the NIAMS and the SO (through KAI) within 48 hours of the PI becoming aware of the event and to the UNC IRB within 7 business days of the time the PI becomes aware to the event, if the protocol deviation harmed participant(s) or others or placed participant(s) or others at increased risk of harm. Otherwise, protocol deviations/violations that occur but do not affect participant safety will be submitted with the routine safety reports as noted. Protocol deviations will be sent to the reviewing IRB per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

- National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal

manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers after the completion of the primary endpoint by contacting the study PI. Considerations for ensuring confidentiality of these shared data are described in Section **Error! Reference source not found.**

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIAMS has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS

ACL	Anterior Cruciate Ligament
AE	Adverse Event
ATT	Attention Control
DHHS	Department of Health and Human Services
CoC	Certificate of Confidentiality
CHAMPS	Community Health Activities Model Program for Seniors
CFR	Code of Federal Regulations
EMR	Electronic Medical Record
EXSS	Exercise and Sports Science
GLMM	General Linear Mixed Model
GCP	Good Clinical Practice
HHS	Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICH	International Council on Harmonisation
IRB	Institutional Review Board
KOOS	Knee injury and Osteoarthritis Outcome Score
LSI	Limb Symmetry Index
MOP	Manual of Procedures
MI	Motivational Interviewing
MVPA	Moderate to Vigorous Intensity Physical Activity
NIH	National Institutes of Health
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OHRP	Office for Human Research Protections
ORBIT	Obesity-Related Behavioral Intervention Trials
PA	Physical Activity
PAS	Physical Activity and Symmetry
PT	Physical Therapy
PI	Principal Investigator
QC	Quality Control
ROM	Range of Motion
SAE	Serious Adverse Event
TKA	Total knee arthroplasty
UNC	University of North Carolina

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
2.0	2/13/20	Added language for provider referrals; added additional enrollment site; removed phone call language from fidelity checks	Changes made to assist with recruitment efforts; Removed phone call language since patients are not consented for recordings
3.0	3/24/20	Added language to allow for intervention sessions to be conducted remotely via an IRB approved video platform or by phone if an in-person visit is not possible	Change made in response to Temporary UNC Policy on Human Subjects-Related Research Visits at UNC-Chapel Hill during COVID-19 Outbreak
4.0	5/12/20	Added language to further explain data being shared with Virginia Tech, which includes video recordings and that participant faces will be blurred prior to sending.	Change made in response to New Safety Information (NSI) submission to IRB
5.0	5/20/20	Personnel change	Changes made in response to Daniel Del Gaizo, MD no longer on the project personnel listing as a Co-Investigator for this study; Christopher Olcott, MD added to the project personnel listing as a Co-Investigator
6.0	11/20/20	Included language to state we may conduct a briefer set of measures focused on the primary functional assessments and not conduct the balance tests	Change made to shorten duration of in-person visits due to COVID-19 safety precautions
		Included language to state we will email or mail the consent and HIPAA forms for the potential participant to review before the baseline visit	Change made to shorten duration of baseline visit due to COVID-19 safety precautions
		Video recordings shared with VA Tech will include full PHI (i.e. facial images)	Amendment made to the subaward to include disclosure of full PHI
7.0	3/23/21	Added language to allow study to recruit patients from non-UNC Healthcare clinics	Change made to assist with recruitment efforts
8.0	10/12/21	Added additional exclusion criteria	Change made to eliminate need for the study to withdraw patients who may have joint replacement

			surgery scheduled in next 6 months and which it would make them unsafe to continue participating
9.0	1/5/22	Updated and removed language related to video camera data capture	Video camera data collection was discontinued
10.0	2/21/22	Updated language to state we will conduct a limited set of balance tests	Balance tests were paused due to COVID restrictions and now introducing a limited set of tests to conduct

REFERENCES

1. Fingar K, Stocks C, Weiss A, Steiner C. Most Frequent Operating Room Procedures Performed in U.S. Hospitals, 2003-2012. HCUP Statistical Brief #186. 2014. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb186-Operating-Room-Procedures-United-States-2012.pdf. .
2. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am.* 2007;89(4):780-785.
3. McMahon M, Block JA. The risk of contralateral total knee arthroplasty after knee replacement for osteoarthritis. *J Rheumatol.* 2003;30(8):1822-1824.
4. Ritter M, Mamlin LA, Melfi CA, Katz BP, Freund DA, Arthur DS. Outcome implications for the timing of bilateral total knee arthroplasties. *Clinical Orthopaedics & Related Research.* 1997(345):99-105.
5. Paxton RJ, Melanson EL, Stevens-Lapsley JE, Christiansen CL. Physcial activity after total knee arthroplasty: a critical review. *World Journal of Orthopedics.* 2015;6(8):614-622.
6. Hammett T, Simonian A, Austin M, et al. Changes in physical activity after total hip or knee arthroplasty: A systematic review and meta-analysis of 6 and 12 month outcomes. *Arthritis Care Res (Hoboken).* 2017.
7. U.S. Department of Health and Human Services. *2008 Physical Activity Guidelines for Americans.* Washington, DC2008.
8. Kersten RF, Stevens M, van Raay JJ, Bulstra SK, van den Akker-Scheek I. Habitual physical activity after total knee replacement. *Phys Ther.* 2012;92(9):1109-1116.
9. Arnold JB, Walters JL, Ferrar KE. Does Physical Activity Increase After Total Hip or Knee Arthroplasty for Osteoarthritis? A Systematic Review. *J Orthop Sports Phys Ther.* 2016;46(6):431-442.
10. de Groot IB, Bussmann HJ, Stam HJ, Verhaar JA. Small increase of actual physical activity 6 months after total hip or knee arthroplasty. *Clin Orthop Relat Res.* 2008;466(9):2201-2208.
11. Brandes M, Ringling M, Winter C, Hillmann A, Rosenbaum D. Changes in physical activity and health-related quality of life during the first year after total knee arthroplasty. *Arthritis Care Res (Hoboken).* 2011;63(3):328-334.
12. Harding P, Holland AE, Delany C, Hinman RS. Do activity levels increase after total hip and knee arthroplasty? *Clin Orthop Relat Res.* 2014;472(5):1502-1511.
13. Vissers MM, de Groot IB, Reijman M, Bussmann JB, Stam HJ, Verhaar JA. Functional capacity and actual daily activity do not contribute to patient satisfaction after total knee arthroplasty. *BMC Musculoskelet Disord.* 2010;11:121.
14. Walker DJ, Heslop PS, Chandler C, Pinder IM. Measured ambulation and self-reported health status following total joint replacement for the osteoarthritic knee. *Rheumatology (Oxford).* 2002;41(7):755-758.
15. Zeni JA, Jr., Snyder-Mackler L. Most patients gain weight in the 2 years after total knee arthroplasty: comparison to a healthy control group. *Osteoarthritis Cartilage.* 2010;18(4):510-514.
16. Pellegrini CA, Song J, Semanik PA, et al. Patients Less Likely to Lose Weight Following a Knee Replacement: Results From the Osteoarthritis Initiative. *J Clin Rheumatol.* 2017.
17. Meier W, Mizner RL, Marcus RL, Dibble LE, Peters C, Lastayo PC. Total knee arthroplasty: muscle impairments, functional limitations, and recommended rehabilitation approaches. *J Orthop Sports Phys Ther.* 2008;38(5):246-256.
18. Piva SR, Gil AB, Almeida GJ, DiGioia AM, 3rd, Levison TJ, Fitzgerald GK. A balance exercise program appears to improve function for patients with total knee arthroplasty: a randomized clinical trial. *Phys Ther.* 2010;90(6):880-894.
19. Alnahdi AH, Zeni JA, Snyder-Mackler L. Gait after unilateral total knee arthroplasty: frontal plane analysis. *J Orthop Res.* 2011;29(5):647-652.
20. Mandeville D, Osternig LR, Chou LS. The effect of total knee replacement on dynamic support of the body during walking and stair ascent. *Clin Biomech (Bristol, Avon).* 2007;22(7):787-794.
21. Westby MD, Brittain A, Backman CL. Expert consensus on best practices for post-acute rehabilitation

after total hip and knee arthroplasty: a Canada and United States Delphi study. *Arthritis Care Res (Hoboken).* 2014;66(3):411-423.
22. Oatis CA. Exercise After Total Knee Arthroplatsy: Progressive Resistance. How "Progressive" Are We? What Phyiscal Therapy Records Show. Paper presented at: American College of Rheumatology2014; San Francisco, CA.
23. Jones CA, Martin RS, Westby MD, Beaupre LA. Total joint arthroplasty: practice variation of physiotherapy across the continuum of care in Alberta. *BMC Health Serv Res.* 2016;16(1):627.
24. Bruun-Olsen V, Heiberg KE, Wahl AK, Mengshoel AM. The immediate and long-term effects of a walking-skill program compared to usual physiotherapy care in patients who have undergone total knee arthroplasty (TKA): a randomized controlled trial. *Disabil Rehabil.* 2013;35(23):2008-2015.
25. Boehler CE, Milton KE, Bull FC, Fox-Rushby JA. The cost of changing physical activity behaviour: evidence from a "physical activity pathway" in the primary care setting. *BMC Public Health.* 2011;11:370.
26. Bull FC, Milton KE. A process evaluation of a "physical activity pathway" in the primary care setting. *BMC Public Health.* 2010;10:463.
27. Barrett EM, Hussey J, Darker CD. Feasibility of a physical activity pathway for Irish primary care physiotherapy services. *Physiotherapy.* 2016.
28. AuYoung M, Linke SE, Pagoto S, et al. Integrating Physical Activity in Primary Care Practice. *Am J Med.* 2016.
29. Sallis JF, Cervero RB, Ascher W, Henderson KA, Kraft MK, Kerr J. An ecological approach to creating active living communities. *Annu Rev Public Health.* 2006;27:297-322.
30. Gilbert AL, Lee J, Ehrlich-Jones L, et al. A randomized trial of a motivational interviewing intervention to increase lifestyle physical activity and improve self-reported function in adults with arthritis *Semin Arthritis Rheum.* 2017;In Press.
31. Liao CD, Lin LF, Huang YC, Huang SW, Chou LC, Liou TH. Functional outcomes of outpatient balance training following total knee replacement in patients with knee osteoarthritis: a randomized controlled trial. *Clin Rehabil.* 2015;29(9):855-867.
32. Liao CD, Liou TH, Huang YY, Huang YC. Effects of balance training on functional outcome after total knee replacement in patients with knee osteoarthritis: a randomized controlled trial. *Clin Rehabil.* 2013;27(8):697-709.
33. Jogi P, Overend TJ, Spaulding SJ, Zecevic A, Kramer JF. Effectiveness of balance exercises in the acute post-operative phase following total hip and knee arthroplasty: A randomized clinical trial. *SAGE Open Med.* 2015;3:2050312115570769.
34. Zeni J, Jr., Abujaber S, Flowers P, Pozzi F, Snyder-Mackler L. Biofeedback to promote movement symmetry after total knee arthroplasty: a feasibility study. *J Orthop Sports Phys Ther.* 2013;43(10):715-726.
35. Levinger P, Zeina D, Teshome AK, Skinner E, Begg R, Abbott JH. A real time biofeedback using Kinect and Wii to improve gait for post-total knee replacement rehabilitation: a case study report. *Disabil Rehabil Assist Technol.* 2016;11(3):251-262.
36. Christiansen CL, Bade MJ, Davidson BS, Dayton MR, Stevens-Lapsley JE. Effects of Weight-Bearing Biofeedback Training on Functional Movement Patterns Following Total Knee Arthroplasty: A Randomized Controlled Trial. *J Orthop Sports Phys Ther.* 2015;45(9):647-655.
37. Williams QI, Gunn AH, Beaulieu JE, et al. Physical therapy vs. internet-based exercise training (PATH-IN) for patients with knee osteoarthritis: study protocol of a randomized controlled trial. *BMC Musculoskelet Disord.* 2015;16:264.
38. Schrubbe LA, Ravyts SG, Benas BC, et al. Pain coping skills training for African Americans with osteoarthritis (STAART): study protocol of a randomized controlled trial. *BMC Musculoskelet Disord.* 2016;17(1):359.
39. Allen KD, Bongiorni D, Bosworth HB, et al. Group Versus Individual Physical Therapy for Veterans With Knee Osteoarthritis: Randomized Clinical Trial. *Phys Ther.* 2016;96(5):597-608.
40. Allen KD, Oddone EZ, Coffman CJ, et al. Telephone-based self-management of osteoarthritis: a randomized, controlled trial. *Annals of Internal Medicine.* 2010;153:570-579.

41. Allen KD, Oddone EZ, Coffman CJ, et al. Patient, Provider, and Combined Interventions for Managing Osteoarthritis in Primary Care: A Cluster Randomized Trial. *Ann Intern Med.* 2017.
42. Allen KD, Yancy WS, Jr., Bosworth HB, et al. A Combined Patient and Provider Intervention for Management of Osteoarthritis in Veterans: A Randomized Clinical Trial. *Ann Intern Med.* 2016;164(2):73-83.
43. Allen KD, Sanders LL, Olsen MK, et al. Internet Versus DVD Decision Aids for Hip and Knee Osteoarthritis. *Musculoskeletal Care.* 2016;14(2):87-97.
44. Queen RM, Attarian DE, Bolognesi MP, Butler RJ. Bilateral symmetry in lower extremity mechanics during stair ascent and descent following a total hip arthroplasty: a one-year longitudinal study. *Clin Biomech (Bristol, Avon).* 2015;30(1):53-58.
45. Butler RJ, Ruberte Thiele RA, Barnes CL, Bolognesi MP, Queen RM. Unipedal balance is affected by lower extremity joint arthroplasty procedure 1 year following surgery. *J Arthroplasty.* 2015;30(2):286-289.
46. Queen RM, Butler RJ, Adams SB, Jr., DeOrio JK, Easley ME, Nunley JA. Bilateral differences in gait mechanics following total ankle replacement: a two year longitudinal study. *Clin Biomech (Bristol, Avon).* 2014;29(4):418-422.
47. Queen RM, Appleton JS, Butler RJ, et al. Total hip arthroplasty surgical approach does not alter postoperative gait mechanics one year after surgery. *PM R.* 2014;6(3):221-226; quiz 226.
48. Queen RM, Sparling TL, Butler RJ, et al. Patient-Reported Outcomes, Function, and Gait Mechanics After Fixed and Mobile-Bearing Total Ankle Replacement. *J Bone Joint Surg Am.* 2014;96(12):987-993.
49. Somers TJ, Blumenthal JA, Guilak F, et al. Pain coping skills training and lifestyle behavioral weight management in patients with knee osteoarthritis: a randomized controlled study. *Pain.* 2012;153(6):1199-1209.
50. Queen RM, De Biassio JC, Butler RJ, DeOrio JK, Easley ME, Nunley JA. J. Leonard Goldner Award 2011: changes in pain, function, and gait mechanics two years following total ankle arthroplasty performed with two modern fixed-bearing prostheses. *Foot Ankle Int.* 2012;33(7):535-542.
51. Queen RM, Butler RJ, Watters TS, Kelley SS, Attarian DE, Bolognesi MP. The effect of total hip arthroplasty surgical approach on post-operative gait mechanics. *Journal of Arthroplasty.* 2011;26 (6 Suppl):66-71.
52. Queen RM, Watters TS, Abbey AN, Sabesan VJ, Vail TP, Bolognesi MP. Gait symmetry: a comparison of hip resurfacing and jumbo head total hip arthroplasty patients. *J Arthroplasty.* 2011;26(5):680-685.
53. Sims EL, Keefe FJ, Kraus VB, Guilak F, Queen RM, Schmitt D. Racial differences in gait mechanics associated with knee ostoarthritis. *Aging Clinical and Experimental Research.* 2009;21(6):463-469.
54. Queen RM, Watters TS, Abbey AN, Sabesan VJ, Vail TP, Bolognesi MP. Gait symmetry: a comparison of hip resurfacing and jumbo head total hip arthroplasty patients. *J Arthroplasty.*26(5):680-685.
55. Nelson AE, Golightly YM, Renner JB, et al. Variations in Hip Shape Are Associated with Radiographic Knee Osteoarthritis: Cross-sectional and Longitudinal Analyses of the Johnston County Osteoarthritis Project. *J Rheumatol.* 2016;43(2):405-410.
56. An H, Marron JS, Schwartz TA, et al. Novel statistical methodology reveals that hip shape is associated with incident radiographic hip osteoarthritis among African American women. *Osteoarthritis Cartilage.* 2016;24(4):640-646.
57. Barbour KE, Hootman JM, Helmick CG, et al. Meeting physical activity guidelines and the risk of incident knee osteoarthritis: a population-based prospective cohort study. *Arthritis Care Res (Hoboken).* 2014;66(1):139-146.
58. Broderick JE, Keefe FJ, Bruckenthal P, et al. Nurse practitioners can effectively deliver pain coping skills training to osteoarthritis patients with chronic pain: A randomized, controlled trial. *Pain.* 2014;155(9):1743-1754.
59. Callahan LF, Cleveland RJ, Shreffler J, et al. Evaluation of active living every day in adults with arthritis. *J Phys Act Health.* 2014;11(2):285-295.
60. Koch GG, Schwartz TA. An overview of statistical planning to address subgroups in confirmatory clinical trials. *J Biopharm Stat.* 2014;24(1):72-93.
61. Cleveland RJ, Schwartz TA, Prizer LP, et al. Associations of educational attainment, occupation, and

community poverty with hip osteoarthritis. *Arthritis Care Res (Hoboken).* 2013;65(6):954-961.
62. Allen KD, Chen JC, Callahan LF, et al. Racial differences in knee osteoarthritis pain: potential contribution of occupational and household tasks. *J Rheumatol.* 2012;39(2):337-344.
63. Callahan LF, Shreffler JH, Altpeter M, et al. Evaluation of group and self-directed formats of the Arthritis Foundation's Walk With Ease Program. *Arthritis Care Res (Hoboken).* 2011;63(8):1098-1107.
64. Allen KD, Helmick CG, Schwartz TA, DeVellis B, Renner JB, Jordan JM. Racial differences in self-reported pain and function among individuals with radiographic hip and knee osteoarthritis: The Johnston County Osteoarthritis Project. *Osteoarthritis & Cartilage.* 2009;17(9):1132-1136.
65. Jordan JM, Helmick CG, Renner JB, et al. Prevalence of knee symptoms and radiographic and symptomatic knee osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. *The Journal of Rheumatology.* 2007;31(4):172-180.
66. Goeppinger J, Armstrong B, Schwartz T, Ensley D, Brady TJ. Self-managment education for persons with arthritis: managing comorbidity and eliminating health disparities. *Arthritis Care and Research.* 2007;57(6):1081-1088.
67. Evenson KR, Wen F, Hales D, Herring AH. National youth sedentary behavior and physical activity daily patterns using latent class analysis applied to accelerometry. *Int J Behav Nutr Phys Act.* 2016;13:55.
68. Hales D, Vaughn AE, Mazzucca S, et al. Development of HomeSTEAD's physical activity and screen time physical environment inventory. *Int J Behav Nutr Phys Act.* 2013;10:132.
69. Miller WR, Rollnick S. *Motivational Interviewing: Preparing People for Change, 2nd Ed.* New York: Guilford Press; 2002.
70. O'Halloran PD, Blackstock F, Shields N, et al. Motivational interviewing to increase physical activity in people with chronic health conditions: a systematic review and meta-analysis. *Clin Rehabil.* 2014;28(12):1159-1171.
71. Rubak S, Sandbaek A, Lauritzen T, Christensen B. Motivational interviewing: a systematic review and meta-analysis. *British Journal of General Practice.* 2005;55:305-312.
72. Semanik PA, Lee J, Song J, et al. Accelerometer-monitored sedentary behavior and observed physical function loss. *Am J Public Health.* 2015;105(3):560-566.
73. White DK, Tudor-Locke C, Zhang Y, et al. Daily walking and the risk of incident functional limitation in knee osteoarthritis: an observational study. *Arthritis Care Res (Hoboken).* 2014;66(9):1328-1336.
74. Carr LJ, Mahar MT. Accuracy of intensity and inclinometer output of three activity monitors for identification of sedentary behavior and light-intensity activity. *J Obes.* 2012;2012:460271.
75. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. *Medicine and Science in Sports and Exercise.* 2008;40(181-188).
76. Choi L, Ward SC, Schnelle JF, Buchowski MS. Assessment of wear/nonwear time classification algorithms for triaxial accelerometer. *Med Sci Sports Exerc.* 2012;44(10):2009-2016.
77. Matthews CE. Calibration of accelerometer output for adults. *Med Sci Sports Exerc.* 2005;37(11 Suppl):S512-522.
78. Ward DS, Rodgers AB. Objective monitoring of physical activity: closing the gaps in the science of accelerometry. *Medicine and Science in Sports and Exercise.* 2005;37(11):S582-588.
79. Price C, Parker D, Nester C. Validity and repeatability of three in-shoe pressure measurement systems. *Gait Posture.* 2016;46:69-74.
80. Unver B, Baris RH, Yuksel E, Cekmece S, Kalkan S, Karatosun V. Reliability of 4-meter and 10-meter walk tests after lower extremity surgery. *Disabil Rehabil.* 2016:1-5.
81. Ageberg E, Roos HP, Silbernagel KG, Thomee R, Roos EM. Knee extension and flexion muscle power after anterior cruciate ligament reconstruction with patellar tendon graft or hamstring tendons graft: a cross-sectional comparison 3 years post surgery. *Knee Surg Sports Traumatol Arthrosc.* 2009;17(2):162-169.
82. Adams D, Logerstedt DS, Hunter-Giordano A, Axe MJ, Snyder-Mackler L. Current concepts for anterior cruciate ligament reconstruction: a criterion-based rehabilitation progression. *J Orthop Sports Phys Ther.* 2012;42(7):601-614.
83. Barber SD, Noyes FR, Mangine RE, McCloskey JW, Hartman W. Quantitative assessment of functional

limitations in normal and anterior cruciate ligament-deficient knees. *Clin Orthop Relat Res.* 1990(255):204-214.
84. Rohman E, Steubs JT, Tompkins M. Changes in involved and uninvolved limb function during rehabilitation after anterior cruciate ligament reconstruction: implications for Limb Symmetry Index measures. *Am J Sports Med.* 2015;43(6):1391-1398.
85. Stewart AL, Mills KM, King AC, Haskell WL, Gillis D, RItter PL. CHAMPS physical activity questionnaire for older adults: outcomes for interventions. *Medicine and Science in Sports and Exercise.* 2001;33(7):1126-1141.
86. Dobson F, Hinman RS, Roos EM, et al. OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. *Osteoarthritis Cartilage.* 2013;21(8):1042-1052.
87. Berg K, Maki B, Williams JI, Holliday P, Wood-Dauphinee S. A comparison of clinical and laboratory measures of postural balance in an elderly population. *Archives of Physical Medicine & Rehabilitation.* 1992;73:1073-1083.
88. Chan AC, Pang MY. Assessing Balance Function in Patients With Total Knee Arthroplasty. *Phys Ther.* 2015;95(10):1397-1407.
89. Horak FB, Wrisley DM, Frank J. The Balance Evaluation Systems Test (BESTest) to differentiate balance deficits. *Phys Ther.* 2009;89(5):484-498.
90. Roos EM, Toksvig-Larsen S. Knee injury and Osteoarthritis Outcome Score (KOOS) - validation and comparison to the WOMAC in total knee replacement. *Health Qual Life Outcomes.* 2003;1:17.
91. Brown ML, Plate JF, Von Thaer S, et al. Decreased Range of Motion After Total Knee Arthroplasty Is Predicted by the Tampa Scale of Kinesiophobia. *J Arthroplasty.* 2016;31(4):793-797.
92. Dominick GM, Zeni JA, White DK. Association of Psychosocial Factors With Physical Activity and Function After Total Knee Replacement: An Exploratory Study. *Arch Phys Med Rehabil.* 2016;97(9 Suppl):S218-225.
93. Miller RP, Kori SH, Todd DD. *The Tampa Scale.* Tampa, FL1991.
94. Allen KD, Arbeeva L, Callahan LF, et al. Physical therapy vs internet-based exercise training for patients with knee osteoarthritis: results of a randomized controlled trial. *Osteoarthritis Cartilage.* 2018;26(3):383-396.
95. Lewis CC, Weiner BJ, Stanick C, Fischer SM. Advancing implementation science through measure development and evaluation: a study protocol. *Implement Sci.* 2015;10:102.
96. Weiner BJ, Dorsey C, Stanick CF, Halko HM, Powell BJ, Lewis CC. Psychometric assessment of three newly developed implemenation outcome measures. 9th Annual Conferene on the Science of Dissemination and Implementation; 2016; Washington, DC.
97. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The self-administered comorbidity questionnaire: a new method to assess comorbidity for clinical and health services research. *Arthritis & Rheumatism.* 2003;49(2):156-163.