University of South Carolina Study Protocol v.7

Study Title: Technology Interventions to Improve Outcomes After Knee Replacement

Grant Title: Reducing Sedentary Time using an Innovative mHealth Intervention among Total Knee Replacement Patients

Principal Investigator Name: Christine Pellegrini, PhD

Statement of Compliance: This trial will be conducted in compliance with the protocol, International Council for Harmonization/Good Clinical Practice requirements (ICH/GCP), and applicable state, local and federal regulatory requirements

NCT: NCT04482400

Version Date: June 14, 2023

A. SPECIFIC AIMS

The objective of this study is to expand our previous and current work by examining an innovative, just-in-time mHealth sedentary behavior intervention for TKA patients. The specific aims of the project are:

Aim 1: To examine the effects of the NEAT!2 mHealth sedentary reduction intervention on sedentary time in TKR patients at the end of treatment (2 months) and following a maintenance period (5 months).

Aim 2: To evaluate changes in total physical activity time (light, moderate, and vigorous), physical function, and pain in TKR patients after participating in the NEAT!2 mHealth sedentary reduction intervention at the end of treatment (2 months) and following a maintenance period (5 months).

Aim 3: To examine the dose-response relationship between adherence to NEAT!2 and changes in sedentary time, total physical activity time, physical function, and pain. Measures of adherence include the percentage of calls completed/total possible (5 calls), days of app use/total days (56 days), and number of activity transitions following NEAT!2 prompt/total number of NEAT!2 prompts.

B. BACKGROUND AND SIGNIFICANCE

Adults with TKR are an important population, accounting for over $13 billion/year in US healthcare costs.[1–3] More than 675,000 adults undergo TKR annually.[4] TKR results in significant improvements in physical function and pain among the majority of patients,[5,6] yet these improvements do not translate to increases in physical activity. Most TKR patients fail to increase physical activity above pre-operative levels after surgery, with >90% remaining below federal physical activity recommendations two years after TKR. [7–10]

Physical activity interventions for TKR patients have shown success, but the increases in activity were modest compared to changes in the general population.[11,12] After TKR, we found patients face additional barriers to activity, including continued pain, physical limitations, and a lack of motivation to be active.[13] As a result, patients continue to spend >60% of the day in sedentary behaviors after surgery, which is similar to adults with knee osteoarthritis.[14,15] This is concerning because among those with knee osteoarthritis, excess sedentary behavior is strongly associated with functional declines,[15,16] physical frailty,[17] and disability.[18] Sustained high levels of sedentary behavior after TKR may lead to impaired long-term function and undermine the overall success of the surgical treatment. Intervening to reduce sedentary behavior may be a more feasible, first step approach for TKR patients who may not yet be ready to increase activity.

This study leverages TKR as a teachable moment[19] to implement an innovative strategy to decrease sedentary behavior using a mobile health (mHealth) just-in-time intervention. *NEAT!2* (Non-Exercise Activity Thermogenesis version 2) builds on our *NEAT!* study.[20] Our *NEAT!* app successfully interrupted prolonged bouts of sitting, decreased sedentary time by 8.1±4.5% (45.7 min/day), and increased light activity by 7.9±5.5% in adults with type 2 diabetes.[20] The *NEAT!2* app was updated and adapted with TKR patient input and preferences.

To our knowledge, no prior studies have examined a sedentary reduction intervention specifically designed for TKR patients after surgery. The expected outcome from this study includes determining if an mHealth sedentary reduction intervention is an effective approach to decrease sedentary time in patients after TKR. The results of this study will build on our previous and current work to improve health behaviors after TKA. Specifically, we expect to identify potentially effective and scalable strategies to help TKR patients become more physically active following surgery and ultimately lead to improved long-term functional outcomes.

C. PRELIMINARY STUDIES

Our Steps to Health study[21] recruited 401 adults with arthritis (56.3 years, 86% women, 64% white) in Columbia, SC to a 12-week exercise program. Retention at 12 weeks and 9 months was 80% and 74%, respectively. For our Patient-Centered Weight Loss (PACE) pilot study, 16 patients (63.3±7.5 years, BMI 36.5 ± 5.1 kg/m2) scheduled for TKR were randomized to start a 14-week weight loss program either before (PACE) or after surgery (Delayed PACE). Retention at 26 weeks was 76%. To minimize

attrition in the proposed study, we will randomize after TKR, since 60% of drop-outs in the previous study occurred prior to surgery

Nine adults (53.1±10.7 years, BMI 37.4±9.9kg/m2) with diabetes used the NEAT! app on 21.9±8.0 days/month. NEAT! interrupted continuous bouts (≥20 minutes) of sitting by providing prompts to engage in light-intensity activity for ≥2 minutes. Prompts to interrupt sedentary time were given 5.8±3.5 times/day. Participants reduced their sedentary time by 8.1±4.5% (45.7 min/day) between baseline and 1 month,[20] and is above our definition of a clinical meaningfulness of change (i.e., -5%; -30 min/day). Nearly 88% of participants indicated they would use NEAT! again in the future, suggesting high acceptability of NEAT!.

The research team has experience with recruitment of TKR patients in the Columbia, SC area and specifically with Prisma Health Orthopedic Center. Currently, we have recruited 26 patients who underwent a TKR to participate in an ongoing study examining a physical therapist led physical activity intervention on objectively measured physical activity levels (USC ASPIRE-I funded – PRO00081254). To date, 20 participants have completed the 12-week assessment.

D. RESEARCH DESIGN AND METHODS AND DATA ANALYSIS

Study Design: This study is a randomized controlled trial examining effects of the NEAT!2 mHealth sedentary reduction intervention on sedentary time in TKR patients at the end of treatment (2 months) and following a maintenance period (5 months). Subject participation will last approximately 6 months. The project timeline is displayed in Figure 1, which highlights study procedures, enrollment, data collection and data analysis over the grant period. Figure 2 displays the study design.

	Year 1				Year 2				Year 3				Year 4 (NCE)				Year 5 (NCE)			
	4/20	5/20-7/20	8/20-10/20	11/20-1/21	2/21-4/21	5/21-7/21	8/21-10/21	11/21-1/22	2/22-4/23	5/22-7/22	8/22-10/22	11/22-1/23	2/23-4/23	5/23-7/23	8/23-10/23	11/23-1/24	2/24-4/24	5/24-7/24	8/24-10/24	11/24-1/25
Project Start-Up																				
Finalized study protocol																				
Finalized informed consent form																				
Finalized REDCap surveys																				
NEAT!2 app finalized																				
Training of Study Staff																				
Register trial on ClinicalTrials.gov																				
Enrollment																				
Study Opens to Enrollment																				
Recruitment (# per quarter)				3*	2*	3*	0	8	8	8	8	8	8	9	9	9	9			
Intervention																				
Assessments																				
Baseline																				
3 Month																				
6 Months																				
Project Completed																				
Data cleaning, managing, and analysis																				
Writing primary results manuscript																				
Submit to present results at conference																				
Submit results to ClinicalTrials.gov																				

* = Actual

Figure 1. Updated Study Timeline

Figure 2. Updated Study Design

Study Week(s) & Events	*NEAT!2* App	*NEAT!2* Call	Control App	Control Call
BASELINE ASSESSMENT				
RANDOMIZATION				
1	*NEAT!2*	Coaching #1	MyKneeGuide	Control Call #1
2	*NEAT!2*		MyKneeGuide	
3	*NEAT!2*	Coaching #2	MyKneeGuide	Control Call #2
4	*NEAT!2*		MyKneeGuide	
5	*NEAT!2*	Coaching #3	MyKneeGuide	Control Call #3
6	*NEAT!2*		MyKneeGuide	
7	*NEAT!2*	Coaching #4	MyKneeGuide	Control Call #4
8	*NEAT!2*		MyKneeGuide	
9	*NEAT!2*	Coaching #5	MyKneeGuide	Control Call #5
END OF TREATMENT ASSESSMENT (2 Months)				
10-12	*NEAT!2* (optional)		MyKneeGuide (optional)	
13	*NEAT!2* (optional)	Maintenance #1	MyKneeGuide (optional)	Maintenance #1
14-16	*NEAT!2* (optional)		MyKneeGuide (optional)	
17	*NEAT!2* (optional)	Maintenance #2	MyKneeGuide (optional)	Maintenance #2
18-20	*NEAT!2* (optional)		MyKneeGuide (optional)	
21	*NEAT!2* (optional)	Maintenance #3	MyKneeGuide (optional)	Maintenance #3
MAINTENANCE ASSESSMENT (5 Months)				

Procedures:

a) ***Recruitment:*** The study will recruit and identify patients within one year of their total knee replacement. See Section E2 below for more details on recruitment.

b) Screening: Participants may be screened online (via REDCap), via telephone, or in-person, based on preference and recruitment method, to assess the study's inclusion and exclusion criteria. Eligible candidates who completed the online screener will be contacted by telephone, to further discuss the study, and answer questions. Eligible candidates will be mailed or emailed the consent document to read prior to the visit.

c) Informed Consent: A study member will go through the informed consent process prior to starting the baseline assessment. During the informed consent process, study staff will discuss full details of the study, risks/benefits, and answer any questions they may have. Interested participants and staff will only sign the consent after going through all details of the study and confirming they have read the consent document. After signing the informed consent form, participants will be provided a copy.

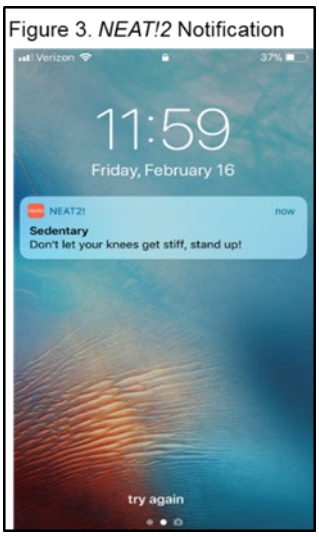
d) Baseline Assessment: The baseline assessment will be completed at either the University of South Carolina or Prisma Health Orthopedics. During the assessment, participants will be asked to complete three physical function tests and will be provided with the two activity monitors to wear for 7 days (procedures for these measures are described below). We anticipate this will take approximately 20 minutes. Participants will also be provided with paper surveys or a link to complete the surveys online. It is anticipated that it will take approximately 10 minutes to complete the surveys. Following the 7-day wear period, participants will return the monitors via mail with a prepaid stamped envelope.

In addition, to ensure compatibility and eliminate the potential of technological issues, participants with an iPhone will download both the MyKneeGuide (https://www.mykneeguide.com) and NEAT!2 apps on their phone. All participants will be able to use the MyKneeGuide app prior to randomization; however, the NEAT!2 app will remain idle. Participants will not receive notifications about sedentary time until after randomization. In the event the participant does not have an iPhone, they will be asked to use MyKneeGuide on the website since the app is not compatible with Androids. The NEAT!2 app is compatible with both Android and iOS platforms.

e) ***Randomization:*** A study staff member will call the participant once all baseline assessment items have been completed. In addition to reminding participants of the study details, an equipoise induction will be conducted to review the benefits and barriers to both general research study participation and specific study participation.[21] Study staff will have the participant discuss the pros and cons of the study randomized conditions (NEAT!2 and Tech Ed [control]) and staff will review the importance of a control group and how attrition bias can alter the results. The equipoise induction will be done to highlight why the research is being conducted, the importance of attending assessments, regardless of adherence to the intervention, and to help prevent differential attrition. Participants who express continued interest in participating will be randomized (stratified by age,

<65 years and ≥65 years) on a rolling basis using randomly permuted blocks to one of two conditions: (1) NEAT!2, or (2) Tech Ed (Control).

f) Randomized Conditions:



NEAT!2. Participants randomized to *NEAT!2* will have their *NEAT!2* app turned on after randomization. The *NEAT!2* app, designed to target automatic processes, works by promoting awareness of prolonged sedentary behavior. NEAT!2 uses the internal accelerometer and Android OR iOS activity recognition libraries to classify the smartphone's patterns of movement. When 30 minutes of continuous sedentary time are detected using machine learning algorithms, the NEAT!2 app triggers an audible tone/vibration and places a notification on the phone's lock/home screen (see Figure 3). When the app detects movement of a predefined magnitude and threshold (e.g., using the phone while seated would be below the threshold, whereas walking with the phone would be above the threshold), the 30-minute timer will restart; thus, the app will only provide notifications when prolonged bouts of minimal to no movement are objectively detected. Reminders will only occur during waking hours and each notification will consist of a different message. Participants will be asked to use the app until 3 months after randomization.

NEAT!2 participants will be given an initial goal to reduce sedentary time by 30 minutes/day, ultimately progressing to a 90 minute/day reduction by 2 months after randomization. To assist with goal attainment and target controlled processes, participants will receive biweekly coaching calls for the first 2 months. Coaching calls will be completed by trained coaches, be semi-scripted, and last ~10-15 minutes. During calls, coaches will use motivational interviewing, discuss goal progression and educational handouts, problem solve, and set a SMART (specific, measurable, attainable, realistic/reward, timely) goal related to reducing sedentary time. All calls will be recorded and timed to assess treatment fidelity. After the 2-month assessment, participants will have the option to continue using the app until 5 months. Additionally, participants will receive monthly calls between 2 and 5 months, unrelated to the intervention and focused on surgery recovery, to maintain contact and help with retention during follow-up. The maintenance calls are expected to last approximately ~5 minutes.

Tech Ed (Control). Participants randomized to Control will receive an attention-matched education program. Control participants will be asked to continue using the control app or website (MyKneeGuide) until 2 months after randomization. MyKneeGuide is a commercially-available app/website and provides pre- and post-operative information for TKR patients, tracks appointments, connects to local rehabilitation facilities, and can connect with other patients who have recently had TKR. Control participants also will receive biweekly calls for the first 2 months. During calls, study staff will discuss surgery recovery (e.g., range of motion, sleep, stretching, reducing risk of injury, and emotional self-care) and avoid topics relating to sedentary behavior and physical activity. All calls will last approximately 10-15 minutes and will be recorded to evaluate whether any unintended content was discussed (e.g., reducing sedentary time, physical activity). Control participants will receive similar monthly calls between 2-5 months. Following the 5-month assessment, participants in Control will be offered the NEAT!2 app.

g) Treatment Fidelity: Telephone sessions will be audiotaped, and a 15% sample rated for treatment fidelity on a quarterly basis. If fidelity falls <80%, coaches will be retrained. Fidelity checklists will assess SMART goal setting, intended session content (e.g., sedentary behavior goals for *NEAT!2* or stiffness for Control) and unintended session content (i.e., discussing physical activity or sedentary behavior with Control participants). Drs. Pellegrini and Wilcox will train the coaches on

intervention procedures and the project coordinator will serve as primary fidelity evaluator. Coaches will meet every other week with Drs. Pellegrini and Wilcox to review treatment delivery.

h) ***Follow-Up Assessments:*** In addition to the baseline assessment, assessments will be completed at 2 months (end of treatment) and 5 months (maintenance). The 2 and 5 month assessments will be at either the University of South Carolina TecHealth Center (915 Greene Street, Columbia, SC), Prevention Research Center (921 Assembly St, Columbia, SC) or Prisma Health Orthopedics. Detailed descriptions and a timeline of outcomes are provided below in the text and Table 1. Briefly, at all three assessments, participants will be asked to complete surveys (demographics, brief medical history, KOOS, WOMAC) which should take approximately 10 minutes to complete. Based on participant preferences, surveys will be able to be completed on paper or online via REDCap. Participants will also be asked to wear an Actigraph Link accelerometer and an ActivPAL for 7 days at each assessment. At the end of the 7 days these monitors will be dropped off or mailed in a prepaid envelope to the University of South Carolina TecHealth Center. In addition to the surveys and monitor, at each assessment participants will complete functional tests which will take approximately 20 minutes to complete. Participants will receive $15 completing the 2 and 5 month assessments ($30 total).

Table 1. Study Outcomes and Measures

Concept	Variable	Measure	Data Collection
Aim 1 Outcome			
Sedentary Behavior	- Objectively measured sedentary behavior	-Minutes and % of daily sedentary time[22,23]	- ActiGraph GT9X Link worn on hip - ActivPAL worn on thigh
Domain Specific Sedentary Behavior (exploratory)	- Self-report sedentary behavior	-SIT-Q[24]	-RedCap survey
Aim 2 Outcomes			
Total Physical Activity Time	- Objectively measured physical activity	- Minutes of total activity (light, moderate, and vigorous)/week[22,23]	- ActiGraph GT9X Link worn on hip - ActivPAL worn on thigh
Physical function	- Objectively measured physical function	- Six-minute walk (feet); chair stands/30 seconds; timed up and go (seconds) using Osteoarthritis Research Society International (OARSI) procedures[25]	- In-person assessment
Pain	- Self-reported pain	- Western Ontario and McMaster Universities Arthritis Index (WOMAC)[26] pain scale	- REDCap survey
Aim 3 Outcome			
NEAT!2 Adherence	- Intervention adherence	- % of calls completed; days of app use; number of activity transitions following NEAT!2 prompt	- *NEAT!2* coach interface
Demographic, Health Status, and Process Variables			
Demographics	- Age, sex, race, ethnicity, marital status, living status, education	- Demographic questionnaire	- REDCap survey (pre-op only)
Health Status	- Height, weight, BMI - Medical history	- Stadiometer and electronic scale - Brief medical history	- In-person assessment - REDCap survey
Knee Symptoms	- Self-reported knee symptoms	- Knee injury and Osteoarthritis Outcome Score (KOOS)[27]	- REDCap survey
Habit formation	- Habit strength related to sitting	- Adapted Self-Report Habit Index[23]	- REDCap survey
Patient-reported outcomes	- Self-reported general health, sleep disturbance, and mobility	- Patient-Reported Outcomes Measurement Information System (PROMIS).[28]	- REDCap survey
Covid-19 impact	-Self-reported impacts from the COVID-19 pandemic	-Modified Epidemic-Pandemic Impacts Inventory (EPII)[29]	-Paper survey

Measures

1. **Sedentary behavior (Aim 1) and total physical activity time (Aim 2)** will primarily be assessed with the ActiGraph GT9X Link (Pensacola, FL). Participants will be asked to wear the Actigraph accelerometer on their hip using a waistband for 7 days during waking hours (except water activities). Following best practice recommendations,[30–33] at least four valid days of the 7 days will be required to be included in analyses, with a valid day defined as participants wearing the accelerometer for at least 10 hours/day.[22] Non-wear time is defined as ≥90 minutes with zero activity counts, allowing for up to 2 minutes of <100 counts/min.[23] Sedentary time for the Actigraph is defined as <100 counts/min and total activity as ≥100 counts/min).[22] Average daily sedentary time (minutes/day), percentage of the waking day spent in sedentary time, and weekly total physical activity will be calculated. Data from the Actigraphs will be processed using ActiLife 6 (Pensacola, FL). Sedentary time will also be assessed using an ActivPAL™ PAL Technologies Ltd, (Glasgow, UK) which can better distinguish body position (e.g., sitting and standing). At the same time participants are wearing the Actigraph, participants will be asked to wear the ActivPAL on their thigh (non-surgery leg) using waterproof tape. They will be asked to wear the monitor for 24 hours/day. The time spent sitting/lying, standing, and walking, transitions and step counts will be determined using the ActivPAL software. Participants will also complete a 7-day log indicating times either device was worn and taken off.

2. **Physical function (Aim 2)** measures will include the chair stand, timed up and go, and 6-minute walk test. All physical function tests will be completed following Osteoarthritis Research Society International (OARSI) recommendation procedures.[24] During the chair stand test, patients are asked to complete as many chair stand repetitions as possible during a 30-second period. The Timed Up and Go Test assesses the time in seconds taken to rise from a chair, walk 3-meters, turn, walk back to the chair, and sit down. The Six Minute Walk Test evaluates the maximal distance a patient can cover during a 6-minute period.

3. **Pain (Aim 2)** and related self-reported outcomes will be assessed using two methods: 1) Knee Injury and Osteoarthritis Outcome Score (KOOS) on this participants will self-report on symptoms, stiffness, pain, daily function, and active function of their knee from the past week; 2) Western Ontario and McMaster Universities Arthritis Index (WOMAC) is a 15-item survey assessing pain and stiffness over the last 48-hours on a 5-point Likert scale.[25]

4. **Adherence to *NEAT!2* intervention (Aim 3)** will be examined by (a) percentage of coaching calls completed/total calls prescribed by intervention (5 calls), (b) total days the *NEAT!2* app was used/total days possible (56 days), and (c) response to *NEAT!2* notifications. The response to *NEAT!2* notifications will be defined as (1) the percentage of notifications in which a transition from sitting to standing/walking was detected within 5 minutes of the prompt divided by total number of notifications, and (2) average time from notification to activity transition. All *NEAT!2* app data will be obtained and exported from the *NEAT!2* coaching interface.

5. **Demographic, Process, or Exploratory Measures**

    a. Weight will be measured at all assessments. Measurements will be taken without shoes, wearing light clothing on a calibrated beam balance scale. Height will also be measured using a stadiometer, and body mass index (BMI) will be calculated as weight in pounds/(height in inches)²) x 704.5.

    b. Patient-reported outcomes will be assessed using Patient-Reported Outcomes Measurement Information System (PROMIS).[28] PROMIS utilizes a computer adaptive test via RedCap.[34] We will assess general health, sleep disturbance, and mobility.

c. Adapted Self-Report Habit Index[23] assesses habit strength related to sitting, stretching, and exercising. Participants answer the questions on a 1-7 Likert scale ranging from "Strongly Disagree" to "Strongly Agree".

d. Sedentary behavior will also be assessed with the SIT-Q.[24] This will be assessed as part of the web screening to estimate how many hours individuals spent sitting on an average day over the last 3 months. The survey assesses time spent sleeping and sitting time during multiple domains (e.g., meals, transportation, work, leisure). The survey will also be administered at each assessment to explore changes in domain specific sedentary time.

e. COVID-19 impact will be assessed using a modified version of the Epidemic-Pandemic Impacts Inventory (EPII) survey.[29] The survey is a tool designed to assess tangible impacts of epidemics and pandemics across many domains. The adaptations made to the survey were made to provide a shorter version that only assessed COVID-19 related concerns for this project. This will be administered at the 2 and 5-month appointments.

Statistical Analysis: The primary analysis will examine changes in sedentary time (minutes/day, percentage/day) between NEAT!2 and Control. Secondary analyses will examine changes in total physical activity (daily minutes objectively-measured from ActiGraph accelerometers), physical function (walking distance from the 6-minute walk test), and self-reported pain (WOMAC). Due to multiple statistical testing for each pre-specified hypothesis, we will adjust for errors and keep the overall nominal significance (alpha) level at 0.05. SAS V9.4 (Cary, NC) will be the primary statistical analysis program. Multiple linear regression with generalized estimating equation (GEE) methodology accounting for follow-up assessments will be used to evaluate whether participants randomized to NEAT!2 sedentary reduction intervention had greater improvements in sedentary time, physical activity, physical function, and pain than Control at 2- and 5- months. The model will be adjusted for potential covariates (i.e., age, sex, BMI, comorbidities). Regression coefficients and corresponding confidence intervals (CIs) to compare those in NEAT!2 and Control at 2- and 5-months will be computed for each outcome (Aims 1 and 2). For Aim 3, multiple linear regression models will be used to evaluate the association between adherence and reductions in sedentary time, higher total physical activity time, improved physical function, and less pain accounting for baseline differences and adjusted for potential covariates. Regression coefficients and corresponding CIs of adherence will be computed for each outcome. Descriptive analyses of baseline demographic and process data will be conducted.

Sample Size: The sample size of this study was chosen to allow for 40 subjects to receive *NEAT!2* intervention and the same number to serve as the Control (a total of 80). We will recruit 92 subjects into the study, expecting that no more than 15% of these subjects will fail to return at 2 or 5 month post-surgery assessment yielding at least 80 subjects for change from baseline to follow-up assessments. To estimate power for Aim 1, we used PACE data where an average of 70.1% of the day was spent in sedentary behavior before surgery. We expect to detect an 8.1% reduction in sedentary time in participants in *NEAT!2* with modest or no reduction in Control. With 40 participants in each group, we have 90% power to detect an 8.1% reduction in sedentary time (i.e., effect size of 0.7) between participants in *NEAT!2* and Control group from baseline and 2- or 5-month assessment. For the secondary outcomes in Aim 2, we will have 80% power to detect a minimum detectable effect size of 0.7 (i.e., 230.6 minutes increase in weekly total physical activity time, 213.5 ft improvement in physical function, and 2 point reduction in pain).

Data Management: All surveys will be administered either on paper or online via REDCap (secure, web application for building and managing online surveys and database – managed by the University of South Carolina). Paper surveys will be stored in a locked filing cabinet in the TecHealth Center at University of South Carolina. All computer files will be password protected. Only the study team will have access to the data.

E. PROTECTION OF HUMAN SUBJECTS

1. TARGET POPULATION:

After initial identification of potential participants by surgeons and staff, research staff will send recruitment letters and materials via email and mail. Participants can complete the screening online (via REDCap), via telephone, or in-person, based on preference and recruitment method. Eligibility criteria is as follows:

Inclusion criteria:

Eligible participants will 1) be 40-79 years of age, 2) have had a primary unilateral TKR within a year of the baseline assessment, 3) have an Android or iOS smartphone that is accessible and near them the majority of the day, 4) be willing to download the study applications on their smartphone, 5) spend at least 7 hours/day sitting, and 7) be English-speaking

Exclusion criteria: As all patients will be under physicians' supervision post-TKR, participants will only be excluded if they 1) have any contraindications to activity, 2) have a mobility limiting comorbidity (e.g., spinal stenosis), 3) have a scheduled surgery (i.e., TKR on contralateral knee) within the next 6 months, or 4) do not have ≥4 days of valid accelerometer wear at baseline.

2. RECRUITMENT PLANS:

Adults after knee replacement will be recruited using several recruitment approaches. Approved flyers will be hung, available in the waiting rooms, and distributed to potential candidates at Prisma Health Orthopedics. Prisma staff will regularly identify candidates who had knee replacement and provide the candidates name, address, phone number, and/or email address to study staff. Study staff will then make outreach via phone, email, or mail with approved recruitment materials to introduce the study to the candidate. Contact information will be destroyed following contacting the participant and assessing interest in participating. Additional recruitment strategies include: 1) Posting flyers and electronic blurbs for the UofSC campus (e.g., UofSC Today emails, TecHealth website); 2) posting flyers or postcards at local Columbia area businesses, health centers, and physical therapy clinics (e.g., Prisma Health Orthopedics Rehabilitation Centers); 3) electronic and social media blurbs (e.g., Twitter, Facebook); and 4) promotions in publications with low or no advertising cost.

All recruitment materials will contain IRB approved information about the study, a link to our website to access the web screener, and study phone number in which participants can contact one of the study personnel if they have any questions regarding the study. Participants may be screened online (via REDCap), via telephone, or in-person, based on preference and recruitment method, to assess the study's inclusion and exclusion criteria. Eligible candidates who completed the online screener will be contacted by telephone, to further discuss the study, and answer questions.

3. EXISTING DATA/SAMPLES:

Not applicable.

4. CONSENT/ASSENT:

Eligible participants will be provided with a copy of the informed consent. Study staff will discuss full details of the study and answer any questions. Participants will be reminded that participation is voluntary. Disclosure will be made of the nature and potential risks of participating and all participants will be asked if they have any questions about their participation to ensure they understand the procedures. Participants will also be provided with a copy of the signed informed consent document at either the initial or the baseline appointment.

5. POTENTIAL RISKS:

Risks associated with interrupting sedentary time with brief bouts of light-intensity physical activity such as standing or light ambulation are minimal. Since participants will have recently undergone total knee replacement, we will assess any type of events or adverse events that may occur, such as a fall. It is expected that some participants will still be experiencing pain and soreness from the surgery at the

start of the intervention; thus, the proposed study includes individual telephone calls with participants to allow the tailoring of goals related to reducing sedentary time that are consistent with participants recovery from knee replacement. Prior to the start of the intervention, participants will be encouraged to notify study staff of any event (study-related or not-study related) that occurs. The research team will not make any diagnoses nor have access to participants' medical records. Potential risks that may occur are:

- Feelings of muscle soreness, fatigue, or pain may occur during physical function testing. Participants will be allowed to take breaks at any time during function tests. Standard procedures will be used to monitor participants and ensure safety. These procedures have been used in previous studies and no adverse events or outcomes have occurred implementing these assessments.
- The use of the MyKneeGuide smartphone application or website poses a risk of loss of privacy. Participants will be provided with a confidential study name and email address to register on MyKneeGuide; however, participants will have the ability to post messages to other knee replacement patients on the app/website. Participants will be informed that they do not need to use a username that identifies them in the posts.
- Participants may experience skin irritation from wearing the activPAL accelerometer for 7 days at each assessment. In the event the participant experiences skin irritation, we will ask the participant to remove the device. We will provide them with additional tape, with multiple options available to accommodate individual reactions and preferences to medical grade tape, to reaffix to the other leg.

6. POTENTIAL BENEFITS:

Participants may or may not directly benefit from participating in this study. Participants may gain skills and knowledge regarding how to decrease sedentary behavior or general education related to recovery from total knee replacement. Participants who are adherent to the intervention and reduce sedentary time may have greater reductions in pain and improvements in physical function. If the intervention is effective, it may provide an innovative approach to reduce sedentary time following total knee replacement.

7. CONFIDENTIALITY

To ensure participants information is confidential, all participants will be assigned a study ID, which will be used on all paper or electronic forms and the NEAT!2 smartphone application. All study files will be stored in locked cabinets or on password-protected computer data files or secure-websites that only authorized study personnel can access. All results will be presented in aggregate form and participants will not be identified personally in any scientific report or presentation. All study personnel will undergo or have completed the most up to date clinical training, human subjects, and confidentiality training prior to assisting with any aspect of the study.

8. COMPENSATION:

Participants will earn $15 for completing each of the 2- and 5-month assessments ($30 total).

9. WITHDRAWAL:

Participants will be informed they can leave the research at any time without penalty. If a participant decides to withdraw, no more information will be collected. The participants will be made aware of this during the consent process.

Any data collected during their participation may be used by the investigators for the purposes described above. Choosing not to be in the study will not result in any penalty or loss of benefit to which participants are entitled. Specifically, the choice not to be in this study will not negatively affect a participant's right to any present or future medical treatment or his/her present or future employment.

10. SAFETY REPORTING:

Definitions - An adverse event (AE) is any untoward medical occurrence in a subject during participation in the clinical study. An adverse finding can include a sign, symptom, abnormal assessment, or any combination of these. An Unexpected Adverse Event is any adverse event in which the specificity or severity of the event was not expected and not consistent with the risk information described in the protocol or consent form.

A serious adverse event (SAE) is any adverse event that results in one or more of the following outcomes:

- Death
- A life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly or birth defect
- An important medical event based upon appropriate medical judgment

An unanticipated problem (UP) is an incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- 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
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Classification of Expectedness – An event will be classified as unexpected if it occurs in one or more subjects or others participating and the event's nature, severity, or frequency is not consistent with either:

a. The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in the protocol-related documents, such as the IRB-approved research protocol and the current IRB-approved informed consent document; or
b. the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

Expected adverse events are events that may be expected. Expected adverse events for the current trial include skin irritation from the activity monitors, muscle soreness, pain, fatigue or injury during the physical function tests, and falls.

Classification of AE Severity - AEs will be labeled according to severity, which is based on their impact on the patient. An AE will be termed “mild” if it does not have a major impact on the patient, “moderate” if it causes the patient some minor inconvenience, “severe” if it causes a substantial disruption to the patient’s well-being, “life threatening or disabling” if it is life threatening or disables the patient in any way, or “fatal” if death occurs.

AE Attribution Scale - AEs will be categorized according to the likelihood that they are related to the study intervention. Specifically, they will be labeled definitely unrelated, unlikely related, possibly related, probably related, or definitely related to the study intervention.

Reporting and Follow-up - See DSMB Template – May 2020 for reporting template and Appendix A for all Reporting Forms. All DSMB reports (and the DSMB's deliberations) will also be shared with NIAMS. We will assess events at on the Health Events Forms at 2 and 5ms, as well as when we become aware of any event in between assessments. We will follow up with participants as needed to ensure full details of each event are obtained.

AE Reporting:

- All non-serious AE's will be reported on the semi-annual report to DSMB and NIAMS. during the semi-annual DSMB. In the AE report, the DSMB will state that they have reviewed all AE reports.
- All non-serious AE's will be reported to IRB during annual reviews, unless they constitute an unanticipated problem involving risks to subjects or others.

SAE Reporting:

- Deaths will be reported to IRB within 24 hours of learning about the death. All other SAE's besides death will be reported to IRB during annual reviews, unless they constitute an unanticipated problem involving risks to subjects or others.
- All SAEs, including participant deaths, will be reported to NIAMS and the DSMB within 48 hours of the PI becoming aware of the event. The DSMB feedback will also be shared with NIAMS.

UP Reporting:

- UPs will be reported to NIAMS and the DSMB within 48 hours of the PI becoming aware of the event. The DSMB feedback will also be shared with NIAMS.
- UPs will be reported to IRB no later than 10 working days after the event or notification to the investigator that the event has occurred.

11. Protocol Deviations:

Definitions - A Protocol Deviation is any departure from the procedures and treatment plans as outlined in the protocol version submitted and approved by the USC Institutional Review Board (IRB). A protocol deviation is considered **major** if it:

- Is intended to eliminate apparent immediate hazard to a research participant,
- Impacts the health, safety or welfare of subjects or places subject at increased risk of harm (physical, psychological, economic, or social),
- Concerns possible serious or continued non-compliance (see USC IRB Guidance re: NonCompliance at: http://www.orc.research.sc.edu/PDF/Non-compliance.pdf).

A protocol deviation is considered **minor** if it does NOT:

- Impact the health, safety or welfare of subjects or alters the risk/benefit ratio,
- Compromise the scientific integrity of the data collected for the study,
- Affect subjects' willingness to continue participating in the study.

Protocol Deviation Reporting:

- Major protocol deviations will be reported to the IRB, NIAMS, and the DSMB within 48 hours of the PI becoming aware of the event. The DSMB feedback will also be shared with NIAMS.
- Minor protocol deviations will be reported to IRB during continuing reviews and to the DSMB during semi-annual meetings. All reports from DSMB and their feedback will be given to NIAMS.

12. Safety & Precautions from COVID-19

The study team will follow all current UofSC and/or Prisma Health COVID-19 safety guidelines and procedures.

Screening: If a study team member experiences any of the symptoms, has a temperature over 100°, or was in contact with anyone with COVID-19, they should remain at home and not come to campus or any study site locations. As with staff, if any participant meets the criteria above, we will cancel the in-person appointment. Some Prisma Health study site locations may also require all individuals to undergo screening (symptom & temperature check) prior to entering the facilities.

Social Distancing: All unvaccinated study team members will be required to wear a face mask that covers their nose and mouth, except when in an office alone. Masks are required for everyone (staff and participants) at Prisma healthcare settings. Appointment times will be spaced out to avoid overlapping and allow timing for proper cleaning and disinfecting.

Cleaning & Disinfecting. Study team members will wash their hands before and after each participant contact. Hand sanitizer will also be available for each in-person interaction. Frequently touched areas (e.g., desks, chairs, door handles, computer keyboard) and equipment (e.g., scale, stadiometer, cones, and stop watches) will be cleaned and disinfected using recommended EPA-registered disinfectants and/or alcohol-based wipes containing at least 70% alcohol in between each participant or use. New pens will be provided for each participant and cleaned and disinfected after each use. Activity monitors will be cleaned and disinfected and all activity bands and pouches will be washed using warm water in a washing machine before given to a participant. Activity monitors will be sealed in a storage bag after initialization and given or mailed to participants. Study staff will use a different set of monitors to explain how to wear them correctly.

F. REFERENCES/LITERATURE CITATIONS

1. Losina E, Paltiel AD, Weinstein AM, et al. Lifetime Medical Costs of Knee Osteoarthritis Management in the United States: Impact of Extending Indications for Total Knee Arthroplasty. *Arthritis Care Res Hoboken*. 2015;67(2):203-215. doi:10.1002/acr.22412

2. Losina E, Thornhill TS, Rome BN, Wright J, Katz JN. The Dramatic Increase in Total Knee Replacement Utilization Rates in the United States Cannot Be Fully Explained by Growth in Population Size and the Obesity Epidemic. *J Bone Jt Surg Am*. 2012;94(3):201-207. doi:10.2106/jbjs.j.01958

3. Molloy IB, Martin BI, Moschetti WE, Jevsevar DS. Effects of the Length of Stay on the Cost of Total Knee and Total Hip Arthroplasty from 2002 to 2013. *J Bone Jt Surg Am*. 2017;99(5):402-407. doi:10.2106/JBJS.16.00019

4. Steiner C, Andrews R, Barrett B, Weiss A. HCUP Projections: Mobility/Orthopedic Procedures 2003 to 2012. Published online September 20, 2012. https://www.hcup-us.ahrq.gov/reports/projections/2012-03.pdf

5. Mizner RL, Petterson SC, Clements KE, Zeni JA, Irrgang J, Snyder-Mackler L. Measuring Functional Improvement after Total Knee Arthroplasty Requires both Performance-Based and Patient-Report Assessments: A Longitudinal Analysis of Outcomes. *J Arthroplasty*. 2011;26(5):728-737. doi:10.1016/j.arth.2010.06.004

6. Vina ER, Hannon MJ, Kwoh CK. Improvement following total knee replacement surgery: Exploring preoperative symptoms and change in preoperative symptoms. *Semin Arthritis Rheum*. 2016;45(5):547-555. doi:10.1016/j.semarthrit.2015.10.002

7. de Groot I, Bussmann H, Stam H, Verhaar J. Small Increase of Actual Physical Activity 6 Months After Total Hip or Knee Arthroplasty. *Clin Orthop*. 2008;466(9):2201-2208. doi:10.1007/s11999-008-0315-3

8. 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. doi:10.2519/jospt.2016.6449

9. Harding P, Holland AE, Delany C, Hinman RS. Do activity levels increase after total hip and knee arthroplasty? *Clin Orthop*. 2014;472. doi:10.1007/s11999-013-3427-3

10. Kahn TL, Schwarzkopf R. Does Total Knee Arthroplasty Affect Physical Activity Levels? Data from the Osteoarthritis Initiative. *J Arthroplasty*. 2015;30(9):1521-1525. doi:10.1016/j.arth.2015.03.016

11. Losina E, Collins JE, Deshpande BR, et al. Financial Incentives and Health Coaching to Improve Physical Activity Following Total Knee Replacement: A Randomized Controlled Trial. *Arthritis Care Res*. 2018;70(5):732-740. doi:10.1002/acr.23324

12. Piva SR, Almeida GJ, Gil AB, DiGioia AM, Helsel DL, Sowa GA. Effect of Comprehensive Behavioral and Exercise Intervention on Physical Function and Activity Participation After Total Knee Replacement: A Pilot Randomized Study. *Arthritis Care Res*. 2017;69(12):1855-1862. doi:10.1002/acr.23227

13. Pellegrini CA, Ledford G, Chang RW, Cameron KA. Understanding barriers and facilitators to healthy eating and physical activity from patients either before and after knee arthroplasty. *Disabil Rehabil*. 2018;40(17):2004-2010. doi:10.1080/09638288.2017.1323026

14. Webber SC, Strachan SM, Pachu NS. Sedentary Behavior, Cadence, and Physical Activity Outcomes after Knee Arthroplasty. *Med Sci Sports Exerc*. 2017;49(6):1057-1065. doi:10.1249/MSS.0000000000001207

15. 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. doi:10.2105/AJPH.2014.302270

16. Lee J, Chang RW, Ehrlich-Jones L, et al. Sedentary Behavior and Physical Function: Objective Evidence From the Osteoarthritis Initiative. *Arthritis Care Res*. 2015;67(3):366-373. doi:10.1002/acr.22432

17. Song J, Lindquist LA, Chang RW, et al. Sedentary Behavior as a Risk Factor for Physical Frailty Independent of Moderate Activity: Results From the Osteoarthritis Initiative. *Am J Public Health*. 2015;105(7):1439-1445. doi:10.2105/AJPH.2014.302540

18. Dunlop D, Song J, Arnston E, et al. Sedentary Time in U.S. Older Adults Associated With Disability in Activities of Daily Living Independent of Physical Activity. *J Phys Act Health*. Published online 2014.

19. Warner DO. Surgery as a Teachable Moment: Lost Opportunities to Improve Public Health. *Arch Surg*. 2009;144(12):1106-1107. doi:10.1001/archsurg.2009.205

20. Pellegrini C, Hoffman S, Daly E, Murillo M, Iakovlev G, Spring B. Acceptability of smartphone technology to interrupt sedentary time in adults with diabetes. *Transl Behav Med*. 2015;5(3):307-314. doi:10.1007/s13142-015-0314-3

21. Goldberg JH, Kiernan M. Innovative techniques to address retention in a behavioral weight-loss trial. *Health Educ Res*. 2005;20(4):439-447. doi:10.1093/her/cyg139

22. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. *Med Sci Sports Exerc*. 2008;40(1):181-188. doi:10.1249/mss.0b013e31815a51b3

23. Choi L, Liu Z, Matthews CE, Buchowski MS. Validation of accelerometer wear and nonwear time classification algorithm. *Med Sci Sports Exerc*. 2011;43(2):357-364. doi:10.1249/MSS.0b013e3181ed61a3

24. Lynch BM, Friedenreich CM, Khandwala F, Liu A, Nicholas J, Csizmadi I. Development and testing of a past year measure of sedentary behavior: the SIT-Q. *BMC Public Health*. 2014;14:899. doi:10.1186/1471-2458-14-899

25. 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. doi:10.1016/j.joca.2013.05.002

26. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*. 1988;15(12):1833-1840.

27. Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): from joint injury to osteoarthritis. *Health Qual Life Outcomes*. 2003;1(1):64. doi:10.1186/1477-7525-1-64

28. Cella D, Yount S, Rothrock N, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH Roadmap cooperative group during its first two years. *Med Care*. 2007;45(5 Suppl 1):S3-S11. doi:10.1097/01.mlr.0000258615.42478.55

29. Grasso DJ, Briggs-Gowan MJ, Ford JD, Carter AS. The Epidemic – Pandemic Impacts Inventory (EPII). Published online 2020. https://drive.google.com/file/d/1GiPgkOVZU9BBsd9Jh0dEhj2c_i2uSOmb/view

30. Napolitano MA, Borradaile KE, Lewis BA, et al. Accelerometer use in a physical activity intervention trial. *Contemp Clin Trials*. 2010;31(6):514-523. doi:10.1016/j.cct.2010.08.004

31. Berlin JE, Storti KL, Brach JS. Using activity monitors to measure physical activity in free-living conditions. *Phys Ther*. 2006;86(8):1137-1145.

32. Matthews CE, Ainsworth BE, Thompson RW, Bassett DR. Sources of variance in daily physical activity levels as measured by an accelerometer. *Med Sci Sports Exerc*. 2002;34(8):1376-1381. doi:10.1097/00005768-200208000-00021

33. Esliger DW, Copeland JL, Barnes JD, Tremblay MS. Standardizing and Optimizing the Use of Accelerometer Data for Free-Living Physical Activity Monitoring. *J Phys Act Health*. 2005;2(3):366-383. doi:10.1123/jpah.2.3.366

34. Obeid JS, McGraw CA, Minor BL, et al. Procurement of shared data instruments for Research Electronic Data Capture (REDCap). *J Biomed Inform*. 2013;46(2):259-265. doi:10.1016/j.jbi.2012.10.006