**Complete Title:** Preventing Posttraumatic Osteoarthritis with Physical Activity Promotion

**Short Title:** Tar Heel Walks

**Drug or Device Name(s):** N/A

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PROTOCOL TITLE: Preventing Posttraumatic Osteoarthritis with Physical Activity Promotion

Short Title: Tar Heel Walks

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Protocol Version: 1

Version Date: 4/26/2023

I confirm that I have read this protocol and understand it.

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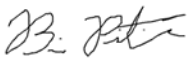
Principal Investigator Signature: 

Date: 4/26/2023

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# Abbreviations and Definitions of Terms

| Abbreviation | Definition |
|---|---|
| ACL | Anterior Cruciate Ligament |
| ACLR | Anterior Cruciate Ligament Reconstruction |
| AE | Adverse Event |
| API | Application Programming Interface |
| FDA | Food and Drug Administration |
| HIPPA | Health Insurance Portability and Accountability Act |
| IRB | Institutional Review Board |
| KOOS | Knee Injury and Osteoarthritis Outcomes |
| KOOS-QOL | Knee Injury and Osteoarthritis Outcomes Score Quality of Life Subscale |
| MOTION | MusculOskeleTal Injury preventiON |
| MRI | Magnetic Resonance Imaging |
| ms | millisecond |
| MSU | Michigan State University |
| OA | Osteoarthritis |
| PA | Physical Activity |
| PI | Principal Investigator |
| PID | Participant Identifier |
| PTOA | Posttraumatic Osteoarthritis |
| SAE | Serious Adverse Event |
| SMS | Short Message Service |
| SQL | Structured Query Language |
| UNC-CH | University of North Carolina at Chapel Hill |

## PROTOCOL SYNOPSIS

| | |
|---|---|
| Study Title | Preventing Posttraumatic Osteoarthritis with Physical Activity Promotion |
| Funder | North Carolina Translational and Clinical Sciences Institute |
| Clinical Phase | Pilot Study |
| Study Rationale | Osteoarthritis (OA) is a leading cause of disability worldwide resulting in severe limitations in daily activities and chronic pain. It is estimated that 35% of posttraumatic OA (PTOA) cases occur after knee injuries and surgeries such as anterior cruciate ligament (ACL) injury and ACL reconstruction (ACLR). Optimal free-living mechanical loading, which refers to the forces acting on the knee caused by daily activities, plays an essential role in maintaining knee articular cartilage health. After ACLR, individuals take fewer steps per day as compared to uninjured controls. This results in insufficient free-living mechanical loading to joint tissues and is associated with early PTOA development. Adequate physical activity (PA) is recommended to help reduce risk of PTOA, but it is unclear how changes in PA acutely impact knee joint cartilage health. The overall objective of this pretest-posttest experimental pilot study is to determine how optimizing free-living mechanical loading through Daily step (i.e., PA) promotion intervention improves cartilage composition in individuals who demonstrate insufficient free-living mechanical loading after ACLR. A daily step promotion intervention will be delivered over 8 weeks using commercially available PA monitors and the patients' own smartphone to provide daily personalized and achievable step goals to increase daily step counts to a level consistent with healthy PA participation. We hypothesize that Magnetic Resonance Imaging (MRI) markers of proteoglycan density associated with PTOA development will improve after 8-weeks of daily step promotion intervention. We also hypothesize that greater changes in steps per day will be associated with improved proteoglycan density. The proposed work is innovative, in that this study will use a novel combination of outcomes that will lead to unprecedented insight into the influence of daily step promotion in mitigating early PTOA development. |
| Study Objective(s) | Primary<br>• Determine the change in MRI markers of proteoglycan density (i.e., cartilage composition) after 8-weeks of the daily step promotion intervention. |

| | |
|---|---|
| | • Determine the associations between change in free-living mechanical loading and change in MRI markers of proteoglycan density (i.e., cartilage composition) after 8-weeks of the daily step promotion intervention.<br>Secondary<br>• Determine the change in self-reported knee function after 8-weeks of daily step promotion intervention.<br>• Determine daily step promotion intervention retention and compliance. |
| Test Article(s)<br>*(If Applicable)* | Daily Step Promotion Intervention |
| Study Design | Single Arm Pre-test Post-test Clinical Trial |
| Subject Population<br>key criteria for Inclusion and Exclusion: | Inclusion Criteria: Completed all other formal physical therapy, between the ages of 18 and 35, underwent an ACLR no earlier than 6 months and no later than 5 years prior to enrollment, demonstrate < 8,000 steps per day, demonstrate clinically relevant-knee symptoms<br>Exclusion Criteria: Underwent an ACLR revision surgery, multiple ligament surgery, lower extremity fracture diagnosed with osteoarthritis in either knee, cochlear implant, metal in body, claustrophobia, history of seizures |
| Number Of Subjects | We anticipate needing to consent up to 30 participants inorder to enroll 10 of those participants after the daily step screening phase (i.e., individuals taking less than 8000 steps). |
| Study Duration | Each participant who fully screens into the study will complete four visits that will last up to 12 weeks<br>• Screening Visit = 45 minutes and 1 week of monitoring in free-living settings<br>• Baseline Visit = 2 hours and 2 weeks of monitoring in free-living settings<br>• Intervention = 8 weeks<br>• Follow Up Visit = 1.5 hours and 1 week of monitoring in free-living settings<br>The entire study is expected to last from May 2021 to April 2023. |
| Study Phases<br>Screening<br>Study Treatment<br>Follow-Up | (1) Screening Visit: The initial visit will include initial screening (i.e. screening question and fill out Knee Injury and Osteoarthritis Outcomes Score quality of life (KOOS-QOL) subscale, enrollment, walking biomechanics assessment, and instructional use of actigraph PA monitor which will be worn for 7 days during all waking hours. |

| | |
|---|---|
| | (2) Baseline: The second visit will include Fitbit and smartphone initialization, collection of patient reported outcomes and MRI scan of their knee. Participants will wear the fitbit monitor on their non-dominant wrist for 2 weeks during all waking hours in free-living settings in preparation for the intervention.<br>(3) Intervention/Treatment: Between the second and third visit, participants will receive daily short message service (SMS) message with daily step count goals on their smart phone for 8 weeks. The daily step goal is based on an adaptive step goal paradigm in which their daily goal is based on the top 60th percentile of steps over the last 10 days.<br>(4) Follow up: The third visit will include the completion of surveys, returning the fitbit monitor, instructional use of the actigraph monitor for second wear period over 7 days, and MRI. |
| Efficacy Evaluations | Cartilage Composition: Cartilage composition (i.e. proteoglycan density) will be measured using T1ρ relaxation times (millisecond; [ms]) of medial and lateral tibiofemoral articular cartilage from MRI imaging.<br>Daily Steps: Objective daily step counts measured via Triaxial accelerometer and averaged over 7 days or wear<br>Self-Reported Knee Function: Knee-related quality of life assessed via the KOOS-QOL questionnaire.<br>Feasibility Outcomes: intervention retention rates (%) and intervention compliance (%) |
| Pharmacokinetic Evaluations | *N/A* |
| Safety Evaluations | Medical Monitor & IRB, Routine Safety Reports, Expedited Safety Reports |
| Statistical And Analytic Plan | Estimation of effect sizes for pretest and posttest MRI measures of proteoglycan density (i.e., cartilage composition) changes will be analyzed with pooled Cohen's d effect sizes and corresponding 95% confidence intervals to determine the magnitude of outcome differences between time points. The relationship between daily step changes and MRI measures of proteoglycan density (i.e., cartilage composition) changes will be analyzed using bivariate Pearson product moment correlation coefficients and 95% confidence intervals will be constructed using Fisher's transformations to estimate the strength of the associations. |
| DATA AND SAFETY MONITORING PLAN | Data tracking, entry, editing, updating and reporting will be completed by study investigators.<br>All data quality control will be performed by the Principal Investigator (PI). |

# 1 STUDY OBJECTIVES

## 1.1 Introduction

OA is a leading cause of disability worldwide[10] that affects millions of Americans each year.[24] Patients with knee OA report many challenges to daily life including greater days in lost work,[1] poor mental health,[13] and persistent pain.[3] Patients with PTOA, which occurs after knee injury, make up as many as 35% of total knee OA cases.[8] PTOA significantly impacts patients after ACL injury and ACLR surgery with approximately 50% of patients developing PTOA within 20 years of injury or surgery.[30] Physical activity (i.e., daily step) promotion through is a focus of current clinical guidelines for prevention of OA progression following a musculoskeletal injury.[34]

Approximately 57% of North Carolinians with a history of knee injury have a lifetime risk of symptomatic PTOA.[33] Optimal free-living mechanical loading (i.e. steps per day) is critical for maintaining ideal knee joint health. After ACLR, altered mechanical loading is linked to PTOA development.[4,35] Patients with ACLR take 25% less steps per day (~2000 steps) compared to uninjured controls as early as 6 months post-ACLR which results in insufficient free-living mechanical loading that can persist for years if not addressed.[5] Our preliminary cross sectional data demonstrate that lesser steps per day is associated with MRI measures of poor proteoglycan density related to PTOA development after ACLR. Reestablishing optimal free-living mechanical loading through daily step promotion may prevent irreversible cartilage damage and address a critical gap in PTOA prevention.[16,34] Pilot data linking sufficient free-living mechanical loading and healthy joint biology is needed to develop PTOA prevention interventions that is scalable to larger populations via existing technology.

This novel pilot study will provide essential proof-of-concept data linking mechanical loading in real-world settings with biology through cartilage proteoglycan density assessment. Previous research has incorporated MRI measures of proteoglycan density in observational studies. However, this is the first experimental study to our knowledge to incorporate cutting-edge in vivo MRI assessment of proteoglycan density to test a PTOA prevention strategy. Furthermore, physical activity promotion used in this study targets step counts which are easily interpretable and can be monitored by health care professionals or the general population. We have purposefully incorporated the use of commercially available, cost-effective activity monitors and smart phones to promote accessibility when developing future randomized control trials and translation for use by patients. This study provides the first step in translating small scale observational and feasibility studies into larger randomized control trials to develop interventions that mitigate the risk of PTOA in patients after ACLR.

## 1.2 Name and Description of Investigational Product or Intervention

Daily Step Promotion Paradigm: All participants will be outfitted with a Fitbit Charge 2 activity monitor. The monitor will be worn during all waking hours, and compliance will be considered as a day with ≥ 1,000 steps. Participants will complete a 14-day "run-in" observation period while wearing the Fitbit but no PA promotion will occur. Individuals who are noncompliant during the "run in" period (<10 days with <1,000 steps) will be removed. For the intervention, participants will receive a text message each morning with a personalized, daily step count goal and a link used to confirm receipt of the goal for 8 weeks. The preceding 10 days of step data will be rank ordered and the 60th percentile step count will be set as the goal for the next day.

## 1.3 Risk-Benefit Ratio

- Potential Benefits: This novel pilot study will provide essential proof-of-concept data linking mechanical loading in real-world settings with knee joint biology. The daily step promotion intervention used in this study targets step counts which are easily interpretable and can be monitored by health care professionals or the general population. We have purposefully incorporated the use of commercially available, cost-effective activity monitors and smart phones to promote accessibility when developing future randomized control trials and translation for use by patients. This study provides the first step in translating small scale observational and feasibility studies into larger randomized control trials to develop interventions that mitigate the risk of PTOA in patients after ACLR.

There is the possibility that the subject may receive no direct benefit from participation. Using a PA monitor, like a Fitbit, has the potential to enhance the amount or intensity of PA in which a person participates. While all participants may not experience an improvement in their activity participation, it is possible that participation in this study may benefit some participants individually.

- Potential Risks:

- Risk of pain or injury from MRI
    - How to Minimize Risk: Participants will be screened at time of consent and the day before each MRI as per the protocol of the Biomedical Imaging Research Center to exclude those with cochlear implant, metal in body (i.e., non-surgical), claustrophobia, history of seizures, pacemaker, liver disease, high blood pressure, or diabetes from receiving an MRI. Participants will also wear ear plugs and offered MRI-safe headphones to protect their ears from loud noises. Both scanners are Food and Drug Administration (FDA)-approved and all new sequences will contain the same safeguards as standard (FDA-approved) clinical sequences to prevent harm to participants.
- Risk that someone outside of approved research personnel could know participant information (breach of confidentiality).
    - How to Minimize Risk: The following actions will be taken to protect a participant's private information: 1) Study personnel will have access to private consenting and research collection areas or participant interactions. 2) Data will only be inputted and reviewed by Institutional Review Board (IRB)-approved study personnel. 3) Paper records will be stored in locked filing cabinets and electronic files will be stored on REDCap and password-restricted, secure cloud-based storage maintained by a dedicated IT staff member in the Department of Exercise and Sport Science that can only be accessed by IRB-approved study personnel.

## 1.4 Relevant Literature and Data

Individuals With Traumatic Knee Injuries Are a Representative High-Risk Population to Examine Mechanical Mechanisms of OA. OA is a leading cause of disability worldwide[10] that affects millions of Americans each year.[24] Approximately, 50% of individuals with a traumatic knee injury and surgery will develop radiographic OA within 20 years.[30] OA significantly impacts individuals with ACL injury and ACLR at younger ages[14] and leads to greater years lived with disability. Individuals post-ACLR demonstrate worse knee cartilage health[25,45,48,50] and take an average of 1600 fewer daily steps compared to uninjured individuals[28], both of which, may persist for years if not addressed. Therefore, individuals post-ACLR are a representative population to determine the effects of increasing loading

frequency through daily steps on cartilage health because they have an increased risk of OA development[6,9,26,30] and persistently take fewer daily steps compared to uninjured individuals.[5,28] Addressing underloading mechanisms in individuals at high-risk for OA is a unique opportunity to use non-pharmacological interventions to reduce the risk of OA and long-term disability.

Low Loading Frequency is an Understudied Component of Altered Mechanical Loading on Knee Joint Health in Individuals at Risk for OA. OA has been historically and inaccurately described as a chronic disease of "wear and tear" implicating only overloading as the primary mechanical mechanism. However, animal models[12,15,31,47] demonstrate that *insufficient loading* results in poor knee joint health providing a scientific basis to assess links of underloading and cartilage health in human models. Current evidence only supports that biomechanical underloading (i.e., lesser ground reaction force and knee moments) during a single step is associated with systemic biomarkers of cartilage degradation, poor cartilage composition measured via MRI T1ρ relaxation times, and OA post-ACLR.[17,21,29,36-38,49,56] In comparison, only a few cross-sectional or longitudinal studies have linked low loading frequency with poor cartilage composition in individuals at risk[7] or living with idiopathic knee OA.[27,55] No studies to our knowledge have assessed the effects of increasing daily steps to recondition cartilage.

Scientific Rigor of Using 8000 Steps to Classify Low Daily Step Group and Implementing Adaptive Daily Step Goals to Increase Loading Frequency. Individuals who take at least 7000-8000 daily steps consistently meet national weekly aerobic physical activity guidelines[52,53] which provides empirical evidence to support the lower limit classification of 8000 daily steps to determine whether individuals 6-12 months post-ACLR engage in low daily steps for. Adaptive daily steps goals are a feasible framework to increase loading frequency by over 2,000 daily steps in individuals at high risk for OA in as few as 8 weeks following initiation of the intervention.[2,19] Furthermore, a previous study reports excellent compliance (97%) with this adaptive daily step goals framework in ACLR individuals.[22] Approximately, 50% of individuals 6-12 months post-ACLR take fewer than 8000 daily steps demonstrating that a substantial proportion of ACLR individuals will benefit from a daily step promotion. Therefore, individuals post-ACLR who take <8000 daily steps will be the target population for this study.

Tibiofemoral Cartilage is Deconditioned and Less Resilient Following Traumatic Knee Injury and Surgery but Not Addressed in Recovery. Tibiofemoral cartilage T1ρ relaxation times increase after knee surgery[23,45] (i.e., decreased proteoglycan density) and are greater in ACLR limb compared to the contralateral limb and limb of healthy controls (i.e., lower proteoglycan density).[25,45,48,50] These results indicate that cartilage composition is compromised 6-12 months post-ACLR. Depletion of proteoglycan density in the extracellular matrix dampens the articular cartilage's ability to resist loading.[11,18,46] If cartilage is deconditioned and less resilient, then the tibiofemoral joint cannot resist excessive forces and may result in cartilage degeneration and increased risk of OA over time. There is a critical need to recondition the affected cartilage by increasing proteoglycan density (i.e., decreasing T1ρ relaxation times) in ACLR individuals.

The Proposed Study Will Address Current Gaps by Establishing Proof of Concept Data if Increasing Daily Steps Can Recondition Cartilage by Improving Knee Joint Health. Previous studies in sedentary, otherwise healthy individuals report that progressively increasing loading frequency over 10-16 weeks increases cartilage proteoglycan density[41,54] which supports the scientific rationale for implementing daily step promotion paradigm in the proposed study.

# 1 STUDY OBJECTIVES

The overall objective of this pretest-posttest experimental pilot study is to determine how optimizing free-living mechanical loading through daily step promotion improves cartilage composition in individuals who demonstrate insufficient free-living mechanical loading after ACLR.

## 1.4 Primary Objective

Aim 1. Determine the change in magnetic resonance imaging (MRI) markers of proteoglycan density after 8-weeks of daily step promotion. Hypothesis: Exposure to individualized physical activity promotion will decrease T1rho relaxation times (i.e. improve in vivo estimates of proteoglycan density) from pretest to posttest.

Aim 2. Determine the associations between change in free-living mechanical loading and change in MRI markers of proteoglycan density after 8-weeks of daily step promotion. Hypothesis: Greater increases in steps per day will be associated with greater decreases in T1rho relaxation times (i.e. improve in vivo estimates of proteoglycan density) from pretest to posttest.

## 1.5 Secondary Objective

Aim 3. Determine the change in self-reported knee function after 8-weeks of daily step promotion. Hypothesis: Self-reported knee function measured via the Knee Injury and Osteoarthritis Outcome Score Quality of Life Subscale will increase from pretest to posttest indicating improved knee related quality of life

Aim 4: Determine intervention retention and compliance. Hypothesis: Participants will demonstrate ≥90% retention and ≥95% compliance with monitor wear.

# 2 INVESTIGATIONAL PLAN **(brief overview)**

## 2.1 Study Design

Type of design: Single-arm pre-test post-test clinical trial

- Screening Visit: The initial visit will include initial screening (i.e. screening question and fill out KOOS-QOL subscale), enrollment, walking biomechanics assessment, and instructional use of actigraph physical activity monitor which will be worn for 7 days during all waking hours.

- Baseline: The second visit will include Fitbit and smartphone initialization with MSU Researcher, collection of patient reported outcomes and MRI scan of their knee. Participants will wear the fitbit monitor on their non-dominant wrist for 2 weeks during all waking hours in free-living settings in preparation for the intervention.

- Intervention/Treatment: Between the second and third visit, participants will receive daily SMS message with daily step count goals on their smart phone for 8 weeks. The daily step goal is based

on an adaptive step goal paradigm in which their daily goal is based on the top 60$^{th}$ percentile of steps over the last 10 days.

- Follow up: The third visit will include the completion of surveys, returning the fitbit monitor, instructional use of the actigraph monitor for second wear period over 7 days, and MRI.

**2.2 Allocation to Treatment Groups and Blinding (if applicable)**

This study is a single arm study. All participants received the treatment so neither the participants nor the researchers were blinded to treatment allocation.

**2.3 Study Duration, Enrollment and Number of Subjects**

Study Duration: The duration of an individual's participation will last up to 12 weeks (3 months). The screening visit will last 45 minutes in-person and participants will wear the Actigraph physical activity monitor for 1 week in free-living settings. If participants screen into the study, then they will complete an in-person baseline visit which will last 2 hours and wear a fitbit on their wrist in free-living settings for 2 weeks. The intervention will last 8 weeks. The follow-up visit will last 1.5 hours in person and participants will wear the Actigraph physical activity monitor for 1 week in free-living settings.

Enrollment: Once a potential participant has been identified and has indicated that he/she is interested in participating in the study, a study team member will then administer a screening questionnaire via telephone or in person at the orthopaedic clinic or laboratory to further assess eligibility. We will obtain participants' verbal consent to ask a limited number of questions that include inclusion/exclusion criteria.

Participants will be asked screening questions to determine if they are eligible for the study.

If the individual meets self-reported screening criteria, score less than 87.5 on the KOOS-QOL, and are interested in participating, participants will provide written informed consent and sign a HIPPA form at the clinic. They will be outfitted with a research-grade actigraph accelerometer to monitor daily during free-living settings for 7 days and fill out the demographic form, knee injury history form. The actigraph will be secured on a belt and placed on the right hip. Participants will be instructed to wear the device for 7 days (removed for water activity and sleep). After 7 days, participants will return to the laboratory. If participants average <8000 steps per day over the wear period then they will continue with the baseline visit.

Number of Subjects: We anticipate needing to consent up to 30 participants in order to enroll 10 participants after the daily step screening phase (i.e., individuals taking less than 8000 steps) for the project because preliminary data suggested that 2/3rd of patients up to 5 years post-ACLR take less than 8000 daily steps.

**2.4 Study Population**

We will include individuals who:

- Provide informed consent and sign a HIPPA form prior to any study procedures are performed.
- Have completed all other formal physical therapy and therapeutic exercise regimens, and will not be engaging in any other formal therapy for their ACLR during the study
- Are between the ages of 18 and 35.
- Underwent an ACLR no earlier than 6 months and no later than 5 years prior to enrollment.
- Demonstrate < 8,000 steps per day during the screening phase of the study as assessed using the Actigraph GT9X Link monitor[51]
- Demonstrate clinically relevant-knee symptoms, defined as a KOOS-QOL subscale score < 72.2.[20] This criteria was updated and approved by the IRB on 5/5/2022 to expand criteria to include individuals reporting KOOS QOL score <87.52.[20]

Participants will be excluded if:

- The participant underwent an ACLR revision surgery due to a previous ACL graft injury
- Multiple ligament surgery was indicated at the time of ACLR surgery.
- A lower extremity fracture was suffered during the ACL injury.
- The participant has been diagnosed with osteoarthritis in either knee.

Due to the MRI outcomes participants will be excluded if they have:

- Cochlear implant
- Metal in body
- Claustrophobia
- History of seizures

# 3 STUDY PROCEDURES

## 3.1 Screening Procedures

Once a potential participant has been identified and has indicated that he/she is interested in participating in the study, a study team member will then administer a screening questionnaire via telephone or in person at the orthopaedic clinic or the laboratory to further assess eligibility. We will obtain participants' verbal consent to ask a limited number of questions that include inclusion/exclusion criteria. If the individual meets self-reported screening criteria, score less than 87.5 on the KOOS quality of life subscale, and are interested in participating, participants will provide written informed consent and sign a HIPPA form at the clinic. They will be outfitted with a research-grade actigraph accelerometer to monitor daily during free-living settings for 7 days and fill out the demographic form, knee injury history form. The actigraph will be secured on a belt and placed on the right hip. Participants will be instructed to wear the device for 7 days (removed for water activity and sleep). After 7 days, participants will return to the laboratory. If participants average <8000 steps per day over the wear period then they will continue with the baseline visit.

## 3.2 Baseline Visit Procedures

If participants average <8000 steps per day over the wear period then they will undergo an MRI at the Biomedical Imaging Research Center, complete surveys (KOOS) and be outfitted with a Fitbit Charge 2 monitor on their wrist by a researcher.

After this process is complete, participants will be connected to a member of the Michigan State University study team using a HIPAA compliant video conferencing platform. The investigator from MSU will guide the participant through monitor initialization and sync the monitor with the participant's personal mobile device. The Fitbit Versa 2 is well suited for our study design based on its ability to display SMS messages on a digital interface, ease of charging, ability to wirelessly sync data using a smartphone, and ability to continuously capture daily steps using the Fitbit Application Programming Interface (API). Monitor will be worn during all waking hours, and compliance will be considered as a day with = 1,000 steps recorded. At this visit participants will be provided a handout that describes the physical activity promotion exposure, dates of the physical activity promotion (8 weeks), and a reminder card indicating the date of their follow-up visit.

### 3.3 Intervention/Treatment procedures

Detailed procedures can be found in "Appendix A. Extended Intervention Document." Following monitor initialization and registration, participants will complete a 14-day "run-in" period during which they will wear the Fitbit (=10 days of compliance) but no physical activity promotion will occur. This establishes participant compliance, understanding of the Fitbit, and baseline daily step data to generate the first individualized step goals for the physical activity promotion period. Individuals who do not meet compliance requirements needed to set the daily goals (>10 days with at least 1,000 steps). Participants who are compliant will be exposed to physical activity promotion for 8 weeks. During this period of time, participants will receive an SMS message (or email if they don't have a smart phone) each morning containing a personalized step count goal for the day and a link which they will click to confirm receipt of the goal. To set the daily goal, the preceding 10 days of step data will be rank ordered and 60th percentile step count will be set as the goal for the following day. Calculation of daily goals will be automated, and will occur prior to our standard goal communication time (8 AM).

### 3.4 Follow-up procedures

After the intervention, participants will be outfitted at the laboratory with the research-grade actigraph accelerometer to monitor daily during free-living settings for 7 days and fill out the surveys (KOOS). The actigraph will be secured on a belt and placed on the right hip. Participants will be instructed to wear the device for 7 days (removed for water activity and sleep). Participants will also undergo another MRI of the surgical limb at the Biomedical Imaging Research Center.

### 3.5 Unscheduled visits – N/A

### 3.6 Concomitant Medication documentation – N/A

### 3.7 Rescue medication administration (if applicable) – N/A

### 3.8 Subject Completion/ Withdrawal procedures

A participant may be withdrawn from the study at any time if the participant or the investigator feels that it is not in the subject's best interest to continue. All participants are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice. A participant will be withdrawn from the study for non-compliance of the protocol or lost to follow-up. Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals.

### 3.9 Screen failure procedures:

A participant will screen out from the study if:

1) They don't meet screening criteria (<8000 steps per day over 7 days during the initial actigraph physical activity monitoring period)
2) They are non-compliant with the Fitbit monitoring "run in" observation period over 14 days. A participant will be determined non-compliant if they fail to accumulate 1,000 daily steps for more than 5 days during this period of time.

Participants will be notified that they failed the screening to qualify for the intervention, return the actigraph or fitbit monitor, and not continue with the baseline visit, intervention, or follow-up visit.

## 4 STUDY EVALUATIONS AND MEASUREMENTS

### 4.1 Efficacy Evaluation (if applicable)

Cartilage Composition: Cartilage composition will be measured using T1ρ relaxation times (ms) of medial and lateral tibiofemoral articular cartilage from MRI imaging. The measurement demonstrates excellent test-retest and inter-rater reliability.[39] T1ρ relaxation times are inversely related to cartilage proteoglycan density. Lower T1ρ relaxation times or decreases in T1ρ relaxation times indicate greater proteoglycan density or increase proteoglycan density respectively.

Daily Steps: Objective daily step counts measured via Triaxial accelerometer and averaged over 7 days or wear (i.e., Actigraph Link or Fitbit Charge 2)[5,22,32]

Self-Reported Knee Function: The Knee Injury and Osteoarthritis Outcomes Score (KOOS) Questionnaire assesses the participant's opinion about their pain, other symptoms, function in activities of daily living, function in sport and recreation and knee related quality of life. We will focus the primary analysis on the KOOS-QOL subscale, as it represents the most responsive KOOS subscale.[42] The KOOS is a valid[42] and reliable[44] self-reported questionnaire of outcomes following knee specific injury and has been used previously by the PI.[39,40] All other KOOS subscales will be collected and analyzed alternative analyses.[43] KOOS QOL is measured on a scale of 0-100 with a greater score indicating better self-reported knee function.

Feasibility Outcomes: intervention retention rates (%) and intervention compliance (%)

### 4.2 Pharmacokinetic Evaluation (if applicable) - N/A

### 4.3 Safety Evaluations

Medical Monitor:

All adverse events will be reported to Dr. Troy Blackburn from the MOTION Science Institute at the University of North Carolina at Chapel Hill (UNC-CH). Dr. Troy Blackburn, Co-Director of the (MusculOskeleTal Injury preventiON) MOTION Science Institute, will be responsible for the independent safety monitoring since he is not a co-investigator or collaborator on this project. Dr. Troy Blackburn has previous experience as a PI in clinical trials for patients with knee injuries (NCT02605876) and therefore has the experience and knowledge regarding the scientific area of study and study design, which will be important in understanding the analysis and interpretation of the data to ensure participant safety as well as ethical, scientifically rigorous study conduct.

Institutional Review Board

The research described in this proposal meets the definition of human subject's research of a biomedical or behavioral nature. As such, we have approval from human subjects research from the IRB for Biomedical Research at UNC-CH. This approval has been obtained prior to the recruitment or enrollment of study participants and the collection of any study-related data. The Michigan State University (MSU) study team and IRB for Biomedical Research will rely on the UNC-CH IRB for Biomedical Research as the single IRB for the duration of the proposed study.

Routine Safety Reports and Expedited Safety Reports

Dr. Lisee or Dr. Pietrosimone will report all adverse events (both serious and non-serious), unanticipated problems, study progress, and protocol deviations to the safety officer, Dr. Troy Blackburn (who is not affiliated with the study), on a biannual basis (every 6 months) or as requested in a detail and summary format. All adverse events (both non-serious and serious) will be collected, analyzed, and monitored in the study's adverse event log, which is kept in Dr. Lisee and Dr. Pietrosimone's regulatory files on a secured server. Dr. Troy Blackburn will also ensure the enrollment rate is consistent with the project timeline, verify that the participants meet enrollment criteria, and that each subject has been consented. Please see Section 7: Safety Management for more details.

## STATISTICAL CONSIDERATIONS

### 4.4 Primary Endpoint

1.) T1rho relaxation times in the medial femoral condyle at pre-intervention: MRI marker of T1rho relaxation times of medial femoral articular cartilage (i.e proteoglycan density) at pre-intervention
2.) T1rho relaxation times in the medial femoral condyle at post-intervention: MRI marker of T1rho relaxation times of medial femoral articular cartilage (i.e proteoglycan density) at post-intervention
3.) T1rho relaxation times in the lateral femoral condyle at pre-intervention: MRI marker of T1rho relaxation times of lateral femoral articular cartilage (i.e proteoglycan density) at pre-intervention
4.) T1rho relaxation times in the lateral femoral condyle at post-intervention: MRI marker of T1rho relaxation times of lateral femoral articular cartilage (i.e proteoglycan density) at post-intervention

5.) T1rho relaxation times in the medial tibial condyle at pre-intervention: MRI marker of T1rho relaxation times of medial tibial articular cartilage (i.e proteoglycan density) at pre-intervention
6.) T1rho relaxation times in the medial tibial condyle at post-intervention: MRI marker of T1rho relaxation times of medial tibial articular cartilage (i.e proteoglycan density) at post-intervention
7.) T1rho relaxation times in the lateral tibial condyle at pre-intervention: MRI marker of T1rho relaxation times of lateral tibial articular cartilage (i.e proteoglycan density) at pre-intervention
8.) T1rho relaxation times in the lateral tibial at post-intervention: MRI marker of T1rho relaxation times of lateral tibial articular cartilage (i.e proteoglycan density) at post-intervention
9.) Change in daily steps: change in average steps per day over 7 day physical activity monitor wear pre-intervention (baseline) to approximately 8-weeks (post-intervention) after physical activity promotion intervention
10.) Change in T1rho relaxation times in the medial femoral condyle: change in MRI marker of T1rho relaxation times of medial femoral articular cartilage (i.e proteoglycan density) from pre-intervention (baseline) to approximately 8-weeks (post-intervention) after physical activity promotion intervention
11.) Change in T1rho relaxation times in the medial tibial condyle: change in MRI marker of T1rho relaxation times of medial tibial articular cartilage (i.e proteoglycan density) from pre-intervention (baseline) to approximately 8-weeks (post-intervention) after physical activity promotion intervention
12.) Change in T1rho relaxation times in the lateral femoral condyle: change in MRI marker of T1rho relaxation times of lateral femoral articular cartilage (i.e proteoglycan density) from pre-intervention (baseline) to approximately 8-weeks (post-intervention) after physical activity promotion intervention
13.) Change in T1rho relaxation times in the lateral tibial condyle: change in MRI marker of T1rho relaxation times of lateral tibial articular cartilage (i.e proteoglycan density) from pre-intervention (baseline) to approximately 8-weeks (post-intervention) after physical activity promotion intervention

### 4.5 Secondary Endpoint

1.) KOOS-QOL subscale at pre-intervention
2.) KOOS-QOL subscale at post-intervention
3.) Daily step promotion intervention retention: percentage of patients retained at post-intervention visit
4.) Daily step promotion intervention compliance: percentage of days participant is compliant with fitbit monitor wear (>1,000 steps per day)

### 4.6 Statistical Methods

Owing to the preliminary nature and small sample size, we will emphasize estimation of effect sizes rather than formal inferential statistical hypothesis testing for future grant proposals. Pretest and posttest outcomes will be analyzed with pooled Cohen's *d* effect sizes and corresponding 95% confidence intervals to determine the magnitude of outcome differences between time points. The relationship between outcome changes will be analyzed using bivariate Pearson product moment

correlation coefficients and 95% confidence intervals will be constructed using Fisher's transformations to estimate the strength of the associations.

### 4.7 Sample Size and Power

We will enroll 10 individuals allowing for 18% attrition (n=2 individuals not completing the study) for a total of 8 participants. With 8 ACLR individuals at each time point, we will be powered (80% power, two-tailed alpha level of 0.05) to detect a strong time effect in proteoglycan density (*d*=1.2) and strong correlation (r=0.77) between change in steps and change in proteoglycan density.

### 4.8 Interim Analysis

We are only collecting 8-10 participants as a proof-of-concept study for pilot data to support grant applications for larger clinical trials. Therefore, an interim analysis is not necessary.

## 5 STUDY INTERVENTION (DEVICE, DRUG, OR OTHER INTERVENTION)

Detailed procedures can be found in "Appendix A. Extended Intervention Document." Following monitor initialization and registration, participants will complete a 14-day "run-in" period during which they will wear the Fitbit (=10 days of compliance) but no physical activity promotion will occur. This establishes participant compliance, understanding of the Fitbit, and baseline daily step data to generate the first individualized step goals for the physical activity promotion period. Individuals who do not meet compliance requirements needed to set the daily goals (>10 days with at least 1,000 steps). Participants who are compliant will be exposed to physical activity promotion for 8 weeks. During this period of time, participants will receive an SMS message (or email if they don't have a smart phone) each morning containing a personalized step count goal for the day and a link which they will click to confirm receipt of the goal. To set the daily goal, the preceding 10 days of step data will be rank ordered and 60th percentile step count will be set as the goal for the following day. Calculation of daily goals will be automated, and will occur prior to our standard goal communication time (8 am).

## 6 STUDY INTERVENTION ADMINISTRATION (IF APPLICABLE)

N/A

## 7. SAFETY MANAGEMENT

Definitions:

- *Adverse Event (AE)* - An adverse event is any unfavorable and unintended diagnosis, sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the study intervention, which may or may not be related to the intervention. AEs include any new events not present during the pre-intervention period or events that were present during the pre-intervention period, which increased in severity.
- *Serious Adverse Event (SAE)* – A serious adverse event is any untoward medical occurrence that results in death, is life-threatening, requires or prolongs hospitalization, causes persistent or significant disability/incapacity, results in congenital anomalies/birth defects, or, in the opinion of the investigators, represents other significant hazards or potentially serious harm to research

participants or others.

- *Unanticipated Problems* – Unanticipated problems 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 following requirements: 1) unexpected events that are 2) related or possibly related to participation in the research that 3) place subjects or others at greater risk of harm than was previously known or recognized. All three criteria above must be met to qualify the event as an unanticipated problem.

Monitoring Roles:

- *Medical Monitor* - A physician or other designated medical practitioner who is responsible for the day-to-day safety aspects of the study and can be consulted regarding individual participants.
- *IRB* - A committee established the grantee/sponsoring Institution to review and approve research involving human subjects. The IRB ensures human subject research is conducted in accordance with all federal, institutional, and ethical guidelines.

The research described in this proposal meets the definition of human subject's research of a biomedical or behavioral nature. As such, we have approval from human subjects research from the IRB for Biomedical Research at UNC-CH. This approval has been obtained prior to the recruitment or enrollment of study participants and the collection of any study-related data. The MSU study team and IRB for Biomedical Research will rely on the UNC-CH IRB for Biomedical Research as the single IRB for the duration of the proposed study. The proposal is considered a low-risk study and an early phase clinical trial. As such, a formal Data Safety Monitoring Board may not be required. However, the final determination of the need for a Data Safety Monitoring Board will be made in collaboration with NC TraCS.

Dr. Lisee and Dr. Pietrosimone will oversee data collection monitoring and all issues related to participant safety, data collection protocols, and participant confidentiality. Dr. Lisee and Dr. Pietrosimone will collect all adverse events for any study-related issues pertaining to safety and all adverse events will be reported to Dr. Troy Blackburn from the MOTION Science Institute at the UNC-CH. Dr. Troy Blackburn, Co-Director of the MOTION Science Institute, will be responsible for the independent safety monitoring since he is not a co-investigator or collaborator on this project. Dr. Troy Blackburn has previous experience as a PI in clinical trials for patients with knee injuries (NCT02605876) and therefore has the experience and knowledge regarding the scientific area of study and study design, which will be important in understanding the analysis and interpretation of the data to ensure participant safety as well as ethical, scientifically rigorous study conduct.

It is not anticipated that there will be any significant physical or psychological risks associated with this study. However, federal regulations require prompt reporting to the IRB at UNC-CH, all injuries, adverse events, or other unanticipated problems involving risks to patients or others that occur during a patient's participation in this research study. Study team members who become aware of any adverse event or unanticipated problems related to the study will notify Dr. Lisee or Dr. Pietrosimone, immediately. Study team members will have contact information for both PIs for daytime, evening, and weekend hours. If both Dr. Lisee and Dr. Pietrosimone are not available for contact when a study team member becomes

aware of a study-related adverse event, Dr. Spang, the Medical Monitor on the study, will be contacted. Once Dr. Pietrosimone or the PI at MSU are contacted about the event, Dr. Pietrosimone will make appropriate reports in accordance with the UNC-CH IRB guidelines. This will include notification of the UNC-CH IRB and the Safety Officer.

Dr. Lisee or Dr. Pietrosimone will report all adverse events (both serious and non-serious), unanticipated problems, study progress, and protocol deviations to the safety officer, Dr. Troy Blackburn (who is not affiliated with the study), on a biannual basis (every 6 months) or as requested in a detail and summary format. All adverse events (both non-serious and serious) will be collected, analyzed, and monitored in the study's adverse event log, which is kept in Dr. Lisee and Dr. Pietrosimone's regulatory files on a secured server. Dr. Troy Blackburn will also ensure the enrollment rate is consistent with the project timeline, verify that the participants meet enrollment criteria, and that each subject has been consented.

## 8. DATA COLLECTION AND MANAGEMENT

All data storing and sharing methods will be approved by the UNC-CH's Institutional Review Board.

In Person Study Data Protections: Prior to performing any study related activities, potential adult participants will provide written informed consent. All consent procedures will be completed by qualified and trained members of the study team. This includes informing each potential participant of the purpose of the project, possible risks, their personal rights, and potential benefits of the study. All possible exclusion criteria will be verified following informed consent. Extreme care will be taken to ensure that there will be no breach of participant confidentiality.

Outcomes Data: All outcomes data will be managed using REDCap, which is a secure online platform for building and managing online databases provided at no cost to investigators at UNC-CH. The study team has been using REDCap for the past 5 years and is versed in building, acquiring and securing data using this database. REDCap also provides automated export to statistical packages (e.g. R, SPSS, and SAS) that will be used to analyze data from this study. UNC-CH also offers REDCap training twice a month as well as onsite support for assistance in building or managing REDCap databases. All pre-processed and post-processed Actigraph physical activity data, magnetic resonance imaging data, patient-reported outcome data will be stored electronically on a secure password-protected server maintained by UNC-CH. Only investigators with IRB and PI clearance will be given access to the password-protected folders on the secure server. All individuals must have current UNC-CH online access credentials to access the server and personal access will be reviewed annually to purge or renew personnel access. The PI can remove access to the server for individuals if necessary.

- Data Entry: data will be entered into REDCap from electronic files by investigators (i.e. processed magnetic resonance imaging data and joint tissue metabolism) or directly by study participants (i.e. demographics, patient-reported outcomes). Outcome measures will be cut and pasted from electronic files or collection software into REDCap to minimize data entry error. All outcome measure data will be entered by two individual investigators.
- Data Editing: means and standard deviations for datasets will be calculated each month and crossed referenced between databases for each investigator. If means are different investigators will look to determine which outcomes differ. In the case that investigators cannot come to a consensus on the correct outcome measure, the PI will act as an arbiter.

- Updating: data may need to be updated due to an error in data entry. After the incorrect data point has been determined the PI should be notified and the Signature Log should be signed indicating who changed data in the spread sheet, what data was changed, for what reason was it changed as well as the time and date it was changed. A new database with the current date should be created. The previous database with the error will not be deleted.
- Statistical Analyses: data will be reported directly from REDCap to statistical analysis software for statistical analysis.

Fitbit Data: Each participant will be assigned a unique participant identifier (PID) code generated and stored in the Microsoft Structured Query Language (SQL) database following the informed consent process. This PID code will be used to label participant data so that the data remain de-identified. Only investigators with IRB and PI clearance will be given access to the password-protected folders on the secure server which will be administered by a Co-Investigator.

Fitbit Data Protections: We will be storing participant demographics, mobile device information, and Fitbit Versa 2 PA monitor-related data using Microsoft SQL Server database software. Data for each participant will be de-identified and stored with a unique study identifier to maintain confidentiality. We will utilize a normalized schema design which will facilitate indexing (for performance), strong data types (for stability and data integrity), and User-Level security to allow us to maintain access control lists for accessing data, reading data, writing data. Data backups will be done utilizing the software's built-in backup scheduling mechanism. This will create daily, full, backup files that will reside in a designated storage location and access will be governed by an access control list which will allow us to maintain a need-to-know policy within the study team. This approach, using Microsoft SQL Server, will also allow us to take advantage of industry best-practice and facilitate the scaling of these practices in the future development of larger-scale clinical trials. For redundancy, we will backup files to separate external solid-state password protected hard drives on a weekly basis at both research sites.

Methods and Systems to Ensure Data Confidentiality and Subject Privacy

The privacy and confidentiality of research participants are to be respected and protected at all times. The proposed research study will comply with the HIPAA Privacy Rule as well as all other state, federal, and institutional regulations intended to protect the rights, safety, and welfare of human participants involved in research studies. We will attempt to minimize the collection, storage, and transmission of information containing patients' personal identifiers, and, whenever identifiers are necessary, protect against unauthorized access or disclosure. In addition, we will employ several rigorous procedures for protecting against risks to participant privacy and confidentiality of data. We will only collect and store information about study participants that is relevant to the research as outlined in the protocol. All electronic data will be collected and stored on secure password-protected computers. Some paper documents, such as the consent form, will be required, and these will be stored in a locked file cabinet in a locked office of a study team member. We will establish a shared folder on a secure UNC-CH server to house all study data. This folder, as well as all study databases, will be password-protected, and only study team members who need access to these data will have permissions. Individual patient data will not be shared with individuals outside the study team, except as required by law and/or for regulatory purposes. All individuals on the study team must regularly fulfill certification requirements in Human Subjects Protection training. Study personnel are also regularly trained in stringent computer and information security procedures. All electronic study data will be securely backed up on a nightly, monthly, and biannual schedule. Monthly and biannual backups will be kept on static media throughout the duration of the study and for at least 5 years after study completion. Research study records will be

maintained for no less than 7 years following the completion of the study, after which time personal identifying information will be removed. Research information in a participant's medical record will be kept indefinitely.

Process for Locking Final Data

Following completion of the study, the PI will conduct a final evaluation to ensure all data has been inputted into the REDCap database. The PI, with assistance from MSU study team members will conduct a final evaluation to ensure all Fitbit data has been inputted into and stored in the SQL database. Then, the PI will notify the University REDCap Administrator to lock the REDCap study database and co-investigator to lock the SQL study database.

Planned Procedures for Data Access and Sharing

At the conclusion of the study, datasets will be locked for the required amount of time as outlined by the University's Institutional Review Board. At the conclusion of this period, data will be destroyed in accordance to the University's Institutional Review Board. The UNC-CH has offices responsible for ensuring privacy and confidentiality standards and safeguarding data security at the recipient site to avoid manipulation of data with the intent of identifying participants. The UNC-CH is HIPAA compliant; therefore, any datasets generated from human participants will be free of any identifiers that would allow linkages to individual participants and variables that could lead to deductive disclosure of individual participants. The final dataset will include a comprehensive group of outcome measures (demographics, injury and surgical data, physical activity data, patient-reported outcomes, and magnetic resonance imaging of knee tissues). The entire dataset will link the outcomes and demographics but will be devoid of patient identifying information. We will make our data available to other investigators that contact the PI and provide written commitment to: 1) only use the data for purposes currently unplanned by the investigators, 2) only use the data for research purposes and not to contact patients or potential future research participants, as well as 3) destroy or return raw data following completion of data analysis.

Data Request Process: Prior to authorizing data transfer the requesting PI must provide written specific aims for the study and regulatory approval from their institution for study of de-identified data. The PI of this study will decide on approving data transfer for the specific aims requested. The requestor must additionally request data use if new specific aims arise. The request process is meant to limit duplication of analyses.

Data Sharing Process: Data will be stored on a secure server at MSU. Cleaned processed and unprocessed data will be stored in its original form and using the SQL database infrastructure. We will transfer de-identified data using a secure electronic server. This process will take place in 2 weeks of the initial request unless additional data cleaning is required.

Privacy: De-identified data will always be transferred.

## 9. RECRUITMENT STRATEGY

We will complete the following recruitment strategies for the proposed study:

- Potential participants will be recruited verbally from classes following approval by individual course instructors. At this time, potential participants will be read a standard recruitment script detailing the inclusion criteria, procedures, duration, benefits, and potential risks associated with participation, and will be allowed to ask any questions pertaining to the investigation. All recruitment procedures will be conducted by members of the research team at the end of the specified class meetings. This will allow nonparticipating students the option of leaving the classroom, thereby alleviating pressure to participate. Individuals who are interested in participating and who meet the inclusion criteria will be provided with the PI's contact information and asked to contact the PI to address any additional questions regarding the study and to schedule data collection.
- Participants will be recruited via informational, IRB-approved flyers posted on the UNC-CH campus and in local rehabilitation clinics.
- Participants will be recruited via an informational email posted on the UNC-CH server. In the event UNC students are recruited and enrolled in the study, they will be made aware their participation is completely voluntary, and their decision to enroll in the study, or to withdraw from the study at any time will not affect their grades or status as a student. Additionally, if a UNC employee is recruited and enrolled they will be made aware their participation in the study is completely voluntary and their decision to enroll or withdraw at any time will not affect their status as an employee.
- Participants will be recruited using EPIC and physician referral from UNC Orthopedics or Campus Health (Co-investigators, Jeff Spang, Ganesh Kamath, and Robert Creighton). All subjects must receive physician approval to return to regular, unrestricted physical activity to be eligible for participation. Drs. Spang, Kamath and Creighton will provide subjects with information regarding participation in the study following the subject's clinical visit at which this approval is obtained.
- Participants will be recruited usingthe Carolina Data Warehouse. We will receive a list of patients with ACL reconstruction within the past 5 years from the Carolina Data Warehouse. This patient list will include names and multiple forms of contact information that will be used to contact potential subjects via telephone, letter/US Mail, or email depending on the available contact information to determine the individual's interest in participating in the study.

## 10. CONSENT PROCESS

The screening and consenting process will be done in a private room. The study coordinator or research assistant will ask the potential participant screening questions based on the inclusion/exclusion criteria for the study. Participants will be included if they answer yes to the following questions:

- Have completed all other formal physical therapy and therapeutic exercise regimens, and will not be engaging in any other formal therapy for their ACLR during the study
- Are between the ages of 18 and 35.
- Underwent an ACLR no earlier than 6 months and no later than 5 years prior to enrollment

Participants will be excluded if they answer yes to the following questions:

- The participant underwent an ACLR revision surgery due to a previous ACL graft injury.
- Multiple ligament surgery was indicated at the time of ACLR surgery.
- A lower extremity fracture was suffered during the ACL injury.

- The participant has been diagnosed with osteoarthritis in either knee.

The study coordinator or research assistants will verbally discuss the general protocol with the patient using the consent form as a guide. They will also briefly review the purpose of the project and any potential risks of the study. The consent form will be given to the patient to read. The participant will be reminded that engagement in research in voluntary and they can stop the study at any time. All major points about the study purpose, the study protocol including the daily step promotion intervention and data collection procedures, and risks to participating in the study will be reviewed verbally between the patient and the study coordinator or research assistants. The subject will be given time to consider the study and to discuss further with the study coordinator or research assistant if desired. After all questions have been answered and the subject shows verbal understanding of the study, signatures will be obtained and the subject will be given a copy to keep. The study member will also sign the consent form as the person obtaining consent.

The PI or the Study Coordinator will be obtaining consent from subjects. The surgeons will not consent any of their own patients during the study.

## 11. PLANS FOR PUBLICATION

The investigators of this study plan to publish the results of the study as a technical note or short report in the one of the following journals: Arthritis Care and Research, Journal of Athletic Training, or the Journal of Sports Rehabilitation.

## 12. REFERENCES


1. United States Bone and Joint Initiative: The Burden of Musculoskeletal Diseases in the United States (BMUS). https://www.boneandjointburden.org/. Accessed 5/25/2019.
2. Adams MA, Sallis JF, Norman GJ, et al. An adaptive physical activity intervention for overweight adults: a randomized controlled trial. *PLoS One.* 2013;8(12):e82901.
3. Alkan BM, Fidan F, Tosun A, Ardicoglu O. Quality of life and self-reported disability in patients with knee osteoarthritis. *Mod Rheumatol.* 2014;24(1):166-171.
4. Andriacchi TP, Mundermann A. The role of ambulatory mechanics in the initiation and progression of knee osteoarthritis. *Curr Opin Rheumatol.* 2006;18(5):514-518.
5. Bell DR, Pfeiffer KA, Cadmus-Bertram LA, et al. Objectively measured physical activity in patients after anterior cruciate ligament reconstruction. *Am J Sports Med.* 2017;45(8):1893-1900.
6. Bodkin SG, Werner BC, Slater LV, Hart JM. Post-traumatic osteoarthritis diagnosed within 5 years following ACL reconstruction. *Knee Surg Sports Traumatol Arthrosc.* 2019.
7. Brenneman Wilson EC, Gatti AA, Keir PJ, Maly MR. Daily cumulative load and body mass index alter knee cartilage response to running in women. *Gait Posture.* 2021;88:192-197.
8. Brown TD, Johnston RC, Saltzman CL, Marsh JL, Buckwalter JA. Posttraumatic osteoarthritis: a first estimate of incidence, prevalence, and burden of disease. *J Orthop Trauma.* 2006;20(10):739-744.
9. Cinque ME, Dornan GJ, Chahla J, Moatshe G, LaPrade RF. High Rates of Osteoarthritis Develop After Anterior Cruciate Ligament Surgery: An Analysis of 4108 Patients. *Am J Sports Med.* 2018;46(8):2011-2019.

10. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis.* 2014;73(7):1323-1330.
11. Dare D, Rodeo S. Mechanisms of Post-traumatic Osteoarthritis After ACL Injury. *Curr Rheumatol Rep.* 2014;16(10):448.
12. Fitzgerald GK, Piva SR, Irrgang JJ. A modified neuromuscular electrical stimulation protocol for quadriceps strength training following anterior cruciate ligament reconstruction. *J Orthop Sports Phys Ther.* 2003;33(9):492-501.
13. Furner SE, Hootman JM, Helmick CG, Bolen J, Zack MM. Health-related quality of life of US adults with arthritis: analysis of data from the behavioral risk factor surveillance system, 2003, 2005, and 2007. *Arthritis Care Res (Hoboken).* 2011;63(6):788-799.
14. Golightly Y SK, Nocera M, Guermazi A, Cantrell J, Renner J, Padua D, Cameron K, Svoboda S, Jordan J, Loeser R, Kraus V, Lohmander S, Beutler A, Marshall S. Association of Traumatic Knee Injury with Knee Function, Symptoms, and Radiographic Osteoarthritis in Military Officers [abstract]. *Arthritis Rheumatol (Hoboken, NJ).* 2019;71 (suppl 10). .
15. Hagiwara Y, Ando A, Chimoto E, et al. Changes of articular cartilage after immobilization in a rat knee contracture model. *J Orthop Res.* 2009;27(2):236-242.
16. Harkey MS, Blackburn JT, Davis H, et al. The association between habitual walking speed and medial femoral cartilage deformation following 30minutes of walking. *Gait Posture.* 2018;59:128-133.
17. Harkey MS, Blackburn JT, Hackney AC, et al. Comprehensively Assessing the Acute Femoral Cartilage Response and Recovery after Walking and Drop-Landing: An Ultrasonographic Study. *Ultrasound Med Bio.* 2018;44(2):311-320.
18. Hayes WC, Bodine AJ. Flow-independent viscoelastic properties of articular cartilage matrix. *J Biomech.* 1978;11(8-9):407-419.
19. Hurley JC, Hollingshead KE, Todd M, et al. The Walking Interventions Through Texting (WalkIT) Trial: Rationale, Design, and Protocol for a Factorial Randomized Controlled Trial of Adaptive Interventions for Overweight and Obese, Inactive Adults. *JMIR Res Protoc.* 2015;4(3):e108.
20. Ingelsrud LH, Granan LP, Terwee CB, Engebretsen L, Roos EM. Proportion of Patients Reporting Acceptable Symptoms or Treatment Failure and Their Associated KOOS Values at 6 to 24 Months After Anterior Cruciate Ligament Reconstruction: A Study From the Norwegian Knee Ligament Registry. *Am J Sports Med.* 2015;43(8):1902-1907.
21. Khandha A, Manal K, Wellsandt E, et al. Gait mechanics in those with/without medial compartment knee osteoarthritis 5 years after anterior cruciate ligament reconstruction. *J Orthop Res.* 2017;35(3):625-633.
22. Kuenze C, Pfeiffer K, Pfeiffer M, Driban JB, Pietrosimone B. Feasbilitiy of a wearable-based physical activity goal-setting intervention among individuals with anterior cruciate ligament reconstruction. *J Athl Train.* 2022;56(6):555-564.
23. Kumar D, Su F, Wu D, et al. Frontal Plane Knee Mechanics and Early Cartilage Degeneration in People With Anterior Cruciate Ligament Reconstruction: A Longitudinal Study. *Am J Sports Med.* 2018;46(2):378-387.
24. Lawrence RC, Felson DT, Helmick CG, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. *Arthritis Rheum.* 2008;58(1):26-35.
25. Li X, Kuo D, Theologis A, et al. Cartilage in anterior cruciate ligament-reconstructed knees: MR imaging T1{rho} and T2--initial experience with 1-year follow-up. *Radiology.* 2011;258(2):505-514.
26. Lie MM, Risberg MA, Storheim K, Engebretsen L, Oiestad BE. What's the rate of knee osteoarthritis 10 years after anterior cruciate ligament injury? An updated systematic review. *Br J Sports Med.* 2019.

27. Lin W, Alizai H, Joseph GB, et al. Physical activity in relation to knee cartilage T2 progression measured with 3 T MRI over a period of 4 years: data from the Osteoarthritis Initiative. *Osteoarthritis Cartilage.* 2013;21(10):10.1016/j.joca.2013.1006.1022.
28. Lisee C, Montoye AH, Lewallen NF, et al. Assessment of free-living cadence using actigraph accelerometers among individuals with and without ACL reconstruction. *J Athl Train.* 2020;2020.
29. Luc-Harkey BA, Franz JR, Hackney AC, et al. Lesser lower extremity mechanical loading associates with a greater increase in serum cartilage oligomeric matrix protein following walking in individuals with anterior cruciate ligament reconstruction. *Clin Biomech (Bristol, Avon).* 2018;60:13-19.
30. Luc B, Gribble PA, Pietrosimone BG. Osteoarthritis prevalence following anterior cruciate ligament reconstruction: a systematic review and numbers-needed-to-treat analysis. *J Athl Train.* 2014;49(6):806-819.
31. Maldonado DC, Silva MCPd, Neto SE-R, de Souza MR, de Souza RR. The effects of joint immobilization on articular cartilage of the knee in previously exercised rats. *J Anat.* 2013;222(5):518-525.
32. Migueles JH, Cadenas-Sanchez C, Ekelund U, et al. Accelerometer Data Collection and Processing Criteria to Assess Physical Activity and Other Outcomes: A Systematic Review and Practical Considerations. *Sports Med (Auckland, NZ).* 2017.
33. Murphy L, Schwartz TA, Helmick CG, et al. Lifetime risk of symptomatic knee osteoarthritis. *Arthritis Rheum.* 2008;59(9):1207-1213.
34. Palmieri-Smith RM, Cameron KL, DiStefano LJ, et al. The Role of Athletic Trainers in Preventing and Managing Posttraumatic Osteoarthritis in Physically Active Populations: a Consensus Statement of the Athletic Trainers' Osteoarthritis Consortiuma. *J Athl Train.* 2017;52(6):610-623.
35. Pfeiffer SJ, Spang J, Nissman D, et al. Gait Mechanics and T1rho MRI of Tibiofemoral Cartilage 6 Months Post ACL Reconstruction. *Med Sci Sports Exerc.* 2019;.(4):630-639.
36. Pfeiffer SJ, Spang J, Nissman D, et al. Gait Mechanics and T1rho MRI of Tibiofemoral Cartilage 6 Months after ACL Reconstruction. *Med Sci Sports Exerc.* 2019;51(4):630-639.
37. Pietrosimone B, Blackburn JT, Harkey MS, et al. Greater mechanical loading during walking is associated with less collagen turnover in individuals with anterior cruciate ligament reconstruction. *Am J Sports Med.* 2016;44(2):425-432.
38. Pietrosimone B, Loeser RF, Blackburn JT, et al. Biochemical markers of cartilage metabolism are associated with walking biomechanics 6-months following anterior cruciate ligament reconstruction. *J Orthop Res.* 2017;35(10):2288-2297.
39. Pietrosimone B, Nissman D, Padua DA, et al. Associations between cartilage proteoglycan density and patient outcomes 12months following anterior cruciate ligament reconstruction. *Knee.* 2018;25(1):118-129.
40. Pietrosimone B, Seeley MK, Johnston C, et al. Walking ground reaction force post-ACL reconstruction: analysis of time and symptoms. *Med Sci Sports Exerc.* 2019;51(2):246-254.
41. Roos EM, Dahlberg L. Positive effects of moderate exercise on glycosaminoglycan content in knee cartilage: a four-month, randomized, controlled trial in patients at risk of osteoarthritis. *Arthritis Rheum.* 2005;52(11):3507-3514.
42. Roos EM, Roos HP, Lohmander LS, Ekdahl C, Beynnon BD. Knee Injury and Osteoarthritis Outcome Score (KOOS)--development of a self-administered outcome measure. *J Orthop Sports Phys Ther.* 1998;28(2):88-96.
43. 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.

44. Salavati M, Akhbari B, Mohammadi F, Mazaheri M, Khorrami M. Knee injury and Osteoarthritis Outcome Score (KOOS); reliability and validity in competitive athletes after anterior cruciate ligament reconstruction. *Osteoarthritis Cartilage.* 2011;19(4):406-410.
45. Shimizu T, Samaan MA, Tanaka MS, et al. Abnormal Biomechanics at 6 Months Are Associated With Cartilag Degeneration at 3 Years After Anterior Cruciate Ligament Reconstruction. *Arthroscopy.* 2018;35(2):511-520.
46. Song Y, Carter DR, Giori NJ. Cartilage nominal strain correlates with shear modulus and glycosaminoglycans content in meniscectomized joints. *J Biomech Eng.* 2014;136(6):064503.
47. Souza RB, Baum T, Wu S, et al. Effects of unloading on knee articular cartilage T1rho and T2 magnetic resonance imaging relaxation times: a case series. *J Orthop Sports Phys Ther.* 2012;42(6):511-520.
48. Su F, Hilton JF, Nardo L, et al. Cartilage morphology and T1ρ and T2 quantification in ACL-reconstructed knees: a 2-year follow-up. *Osteoarthritis Cartilage.* 2013;21(8):1058-1067.
49. Teng HL, Wu D, Su F, et al. Gait characteristics associated with a greater increase in medial knee cartilage T1rho and T2 relaxation times in patients undergoing anterior cruciate ligament reconstruction. *Am J Sports Med.* 2017;45(14):3262-3271.
50. Theologis AA, Haughom B, Liang F, et al. Comparison of T1rho relaxation times between ACL-reconstructed knees and contralateral uninjured knees. *Knee Surg Sports Traumatol Arthrosc.* 2014;22(2):298-307.
51. Tudor-Locke C, Craig CL, Brown WJ, et al. How many steps/day are enough? For adults. *Inter J Behav Nutr Phys Act.* 2011;8:79-79.
52. Tudor-Locke C, Johnson WD, Katzmarzyk PT. Accelerometer-determined steps per day in US adults. *Med Sci Sports Exerc.* 2009;41(7):1384-1391.
53. Tudor-Locke C, Leonardi C, Johnson WD, Katzmarzyk PT, Church TS. Accelerometer steps/day translation of moderate-to-vigorous activity. *Prev Med.* 2011;53(1-2):31-33.
54. Van Ginckel A, Baelde N, Almqvist KF, et al. Functional adaptation of knee cartilage in asymptomatic female novice runners compared to sedentary controls. A longitudinal analysis using delayed Gadolinium Enhanced Magnetic Resonance Imaging of Cartilage (dGEMRIC). *Osteoarthritis Cartilage.* 2010;18(12):1564-1569.
55. Voinier D, Neogi T, Stefanik JJ, et al. Using Cumulative Load to Explain How Body Mass Index and Daily Walking Relate to Worsening Knee Cartilage Damage Over Two Years: The MOST Study. *Arthritis Rheumatol (Hoboken, NJ).* 2020;72(6):957-965.
56. Wellsandt E, Gardinier ES, Manal K, et al. Decreased Knee Joint Loading Associated With Early Knee Osteoarthritis After Anterior Cruciate Ligament Injury. *Am J Sports Med.* 2016;44(1):143-151.

# APPENDIX

## Appendix A. Extended Intervention Document

### 5.1. INTERVENTION DOCUMENTS

**Investigator's Brochure of Product Label/Package Insert**
Not applicable to the proposed investigation.

**Monitoring Manual**
The purpose of this collaborative project is to determine if increasing daily steps will lead to increased tibiofemoral cartilage proteoglycan density following anterior cruciate ligament reconstruction (ACLR). The proposed research will be carried out at collaboratively at the University of North Carolina – Chapel Hill (UNC, PI: Lisee, Mentor: Pietrosimone) and Michigan State University (MSU, Co-I: Kuenze) which will facilitate timely recruitment and enrollment of a maximum of 12 participants from our targeted clinical population over the proposed 1-year study period. The proposed research team has experts in knee joint cartilage health after ACLR (Pietrosimone), PA measurement and promotion after ACLR (Kuenze), mobile intervention design and database management (Pfeiffer), biostatistics (Schwartz), orthopedics (Spang), and MRI (Lalush) which will enable the proposed research to be executed in a scientifically rigorous manner.

***Personnel***
Dr. Lisee (PI) and the members of the UNC research team, will be responsible for all participant recruitment and enrollment, data collection, data processing, and data analysis related to the proposed study. Dr. Kuenze will oversee all aspects of the physical activity exposure. His responsibilities will include but are not limited to management of intervention documentation, scheduling, administering the physical activity promotion exposure, monitoring fidelity of the physical activity promotion exposure, and managing potential adverse effects. Lastly, Co-I Pfeiffer will assist with technical training for the research assistants to allow them to navigate the SQL database and provide basic technical support to participants enrolled in the study. To ensure continuity between personnel administering the intervention, standard procedures (outlined below) will be followed by all personnel.

***Description of Required Equipment***
The personalized physical activity (PA) promotion will be delivered using an automated text messaging approach that has been developed and integrated into the custom SQL database environment by the study team (Pfeiffer) and a Fitbit Charge 2 PA monitor that is Bluetooth paired with the participants personal mobile device. Rationale for these selections are as follows:

- Participation in the proposed study will be limited to individuals that have access to a mobile device capable of sending and receiving text messages, downloading the most recent version of the Fitbit mobile application, and pairing a Fitbit Charge 2 PA monitor using Bluetooth. Based on our inclusion criteria, it is estimated that >95% of potential participants will have access to a device that meets these technical requirements.
- The Fitbit Charge 2 monitor is well suited for long-term monitoring based on the ease of charging, the ability to wirelessly sync data using a smartphone, ability to send, receive, and interact with text messages on the monitor display, and the ability to integrate PA monitor data into our SQL database using the Fitbit Application Programming Interface (API) in a continuous, automated manner. It is a future goal of the research team to re-develop the personalized PA promotion intervention for the full series of current generation Fitbit PA monitors, as well as monitors manufactured by other companies, in order to enable a greater number of individuals to utilize the personalized PA promotion intervention using their own preferred PA monitor.

***Instructions for Syncing the Fitbit Charge 2 Monitor and Initializing the Run-in Period***
Participants will be connected to a member of the MSU study team using a HIPAA compliant video conferencing platform (Zoom or Webex) in a quiet, private environment. The investigator or research assistant from MSU will instruct the participant to un-box the Fitbit Charge 2 monitor, access the Fitbit online portal (https://www.fitbit.com/login), and pair the Fitbit using a study email address + the unique participant identifier. This technique allows for multiple monitors to be associated with a single laboratory email address to prevent collection of extraneous Fitbit data or unwanted Fitbit features from being accessed by study participants. Specific directions for this process can be found below:

1. Retrieve the unique participant identifier from our SQL database through a custom-built web-based portal that will also be utilized for data entry following the enrollment study visit.
2. Access https://www.fitbit.com/login
3. Click "Main Menu" in options menu.
4. Choose "Set up a New Fitbit Device".
5. Choose "Existing User".
6. Enter in the Fitbit account information (email/password) you want to associate with the device.
7. For each Fitbit account append a "+Participant Identifier" to the study email address.
8. Follow the instructions to select the device and sync.
9. Access the Fitbit mobile application on the App Store and download the file.
10. Open the application and click register.
11. Complete the registration process using the participant identifier.

12. Confirm Bluetooth pairing of the Fitbit Charge 2 monitor and the Fitbit mobile application.
13. Send a test text message via the SQL database environment in order to confirm connectivity of the participants personal mobile device.
14. Confirm connectivity of the participants personal mobile device by having the participant interact with a standardized link included in the text message and check that this interaction was logged in the SQL database.
15. Fit the participant appropriately with the Fitbit Charge 2 monitor.
16. Provide the participant with the following information:
17. Participants should wear the monitor at all times unless participating in water-based sports. Any activities completed when the monitor is not being worn should be recorded in the physical activity log within the Fitbit mobile application activity log.
18. Participants should always keep the Fitbit mobile application open in the background of their mobile device. In addition, participants should interact with the application daily to ensure data syncing. If they do not sync data within a 48-hour period, they will receive a notification to do so.
19. Participants should charge the monitor when the battery level falls below 50% which is indicated on the monitor interface and in the Fitbit mobile application. If the monitor charge level falls below 50% for 3 consecutive days, they will receive a notification to charge the monitor within 24 hours.
20. If the monitor fails or they are not able to connect the monitor to their mobile device, they should contact the study team immediately for technical assistance. Contact can be made by responding to their most recent text message from the study team or via email, text, or phone call to the study team based on participant preference.
21. Guide the participant through each screen within the application and answer any questions they may have.
22. Inform the participant that activity data will be monitored by the study team over the next 10 days (run-in period) to confirm that they are compliant (following instructions) with study procedures.

***Description of Instructions for Administering the Physical Activity Promotion Exposure***

Following the screening, automated, scheduled percentile-based goals will be delivered to the participant every morning via a personalized text message. The goal setting feature functions via automated processing of daily participant-level steps per day data which is used to develop a daily steps goal. Visual representation of the daily goal setting text message can be seen in Figure 1.

After screening, participants will be made aware of that the physical activity promotion period has started and a study team member will describe the specifics of the Daily Step Promotion intervention. This will include the following descriptions and instructions:

1. The participant will receive a daily text message in the morning which will include their daily step goal and a link that they will need to click to confirm receipt of the text message.
2. The link will provide access to a personalized dashboard that will display their step counts during the study period and number of days during which they achieved their step goals.
3. If they do not click the link, they will be reminded to do so later in the day via follow-up text message.
4. If they do not click the link for 2 consecutive days, they will be contacted by a study team member via phone.
5. The PA data collected by the Fitbit Charge 2 monitor will update throughout the day without any additional required effort.
6. The PA goal will change daily.
7. The participant should attempt to meet or exceed their daily PA goal.

Following this communication, the participant will complete the 8-week intervention period with minimal contact from the study team with exception of a weekly "check-in" phone call or text message, participant non-compliance, or technical difficulty. During week 6 of the study period, participants will be contacted by a study team member to schedule an appointment to complete the 8-week study visit and they will receive a reminder via text 1 week prior to the date of the visit. At the time of the 8-week study visit, a study team member will provide instructions regarding de-registration of the Fitbit Charge 2 monitor from the study account in order to re-purpose the device for personal use. The study team member will also confirm the appropriate method for delivery of study renumeration.


**Figure 1.** Example of text messages received by participants.

**Table 1:** Description of automated text messages in physical activity promotion exposure

| Text Message Purpose | Text Message Scheduling | Text Message Template |
|---|---|---|
| **Personalized PA Promotion Intervention** | | |
| Goal setting message | Frequency: daily<br>Schedule: 8:00am EST | Good morning! Your goal is to take at least <insert personalized goal> steps today. Good Luck! Please click the link below to confirm that you have received your daily goal: <insert single use personalized link> |
| Motivational status update message | Frequency: daily<br>Schedule: when the participant reaches 50% of their daily step goal. | Keep going! You are halfway to your goal of <insert personalized goal> steps today. |
| Goal achievement message | Frequency: daily<br>Schedule: at the time of goal achievement | Congratulations! You have achieved your step goal for today. Keep up the great work! |
| **Technical Support Messages** | | |
| Monitor battery charging reminder | Frequency: as needed<br>Schedule: when battery level falls below 50% of maximum charge. | We noticed that your Fitbit battery is getting a little low. Please charge your Fitbit while you are sleeping tonight. If you are experiencing technical difficulties, please respond to this text and a study team member will contact you ASAP. |
| Monitor wear compliance reminder | Frequency: as needed<br>Schedule: when an invalid <<1,000 steps> is logged | We noticed that you may not have been wearing your Fitbit yesterday. If you forgot to do so, please make sure to wear your Fitbit today. If you are experiencing technical difficulties, please respond to this text and a study team member will contact you ASAP. |

***Physical Activity Promotion Exposure Adherence and Compliance Monitoring and Promotion***

The study team has developed a participant retention plan that will utilize Fitbit Charge 2 PA monitor power level data and PA data to alert an unblinded member of the MSU study team to periods during which a participant has not been compliant with study procedures. Participant data will be monitored by the study team and participants will be contacted by phone or text message in the following situations: 1) monitor charge status below 50% for 2 consecutive days, 2) 2 consecutive days with no logged PA data and 3) 2 consecutive days of no interaction with the personalized text message link. Participant contact, via phone or text message, will continue until compliance is restored or the participant has informed the study team of their desire to withdraw from the study protocol. The total number of participant prompts will be recorded and reported as a measure of compliance with the intervention. Additionally, an unblinded MSU study team member will check in on the participants weekly to remind the participants about the study and make sure the participants have not sustained a secondary knee injury or any other complications.

***Management of Physical Activity Promotion Data***

We will also track physical activity promotion usage and compliance via automated metrics derived from the Fitbit API and our custom participant dashboard interface. In summary, we will track: 1) the percentage of patients retained at each weekly data capture timepoint, and 2) patient adherence (number of days of PA data). Data will be stored using Microsoft SQL Server database software on a secure server at MSU. This database will be developed and managed by a study team member (Pfeiffer) who is a graduate-trained computer scientist with expertise in platform and database development, management, and security. We will utilize a normalized schema design to facilitate indexing (for performance), strong data types (for stability and data integrity), and User-Level security to allow us to maintain access control lists (ACL) for data access and writing. Data backups will be done using built-in backup scheduling mechanism. This will create daily, full, backup files that will reside in a designated storage location on the server and access will be governed by an ACL which will allow us to maintain a need-to-know policy within the study team.

***Monitoring Physical Activity Promotion Exposure Fidelity***

Fidelity of the physical activity promotion exposure will be maintained by providing standard instructions on administering the physical activity promotion, utilizing an investigative team with experience in delivering online physical activity promotion, completing standard study team training prior to involvement in study activities, and convening of weekly conference calls of the full study team to discuss current study progress. All documentation will be stored in locked office within a locked cabinet at in the office of the MSU team leader (Kuenze).

*Review of Intervention Documentation:* The standard physical activity promotion documentation will be reviewed by the investigators (Kuenze and Lisee), database and application expert (Pfeiffer), and research assistants on a weekly basis as these individuals will be responsible for delivery of the intervention.

*Monitoring of Application Technical Errors:* Participants in the study will be asked to communicate with the study team via an "in-application" feedback portal which will generate an email to Tier 1 support, or participants can opt to contact the study team directly via email, phone, or text message (depending on participant preference) in the event that a technical error occurs within the Fitbit Mobile application, Fitbit Charge 2 PA monitor, or the text messaging interface. Reporting of all issues via text message, email, or phone will ensure that Co-I (Pfeiffer) is alerted via secure email and mobile notification of the ongoing issue regardless of severity. These reports will be utilized to: 1) determine if a technical error is actually present, 2) assess the source or cause of the error, 3) create long or short term solutions to the error in order to continue physical activity promotion delivery, and 4) summarize the error and solution for PI (Lisee) in order to maintain consistency across the study team. Upon receiving notification of a technical error, the study team will then utilize the tier-based application support hierarchy and support strategy provide (Table 2) in order to appropriately categorize and route the issue to ensure prompt and appropriate troubleshooting. During this process, Tier 1 issues (simple and expected) will be addressed by the local study team as these technical issues have consistent and basic solutions that do not require advanced technical training. Tier 2 issues are categorized as challenging and related to study-specific equipment or applications. Tier 2 issues that are reported at either data collection site will be immediately routed to Co-I Pfeiffer who will work with the unblinded study team at MSU to develop and implement both short- and long-term solutions. Co-I Pfeiffer will maintain daily communication with the participant via text or secure email for 72 hours following the initial resolution of the technical issue to ensure that the implemented solution remains effective. Tier 3 issues are categorized as highly technical and related to university infrastructure used to support data storage or personalized text messaging functionality. Co-I Pfeiffer has built a series of scheduled system checks to monitor the status of the MSU network and the server on which our data will be housed for the duration of the study period. In the case that Co-I Pfeiffer is alerted to a network or system outage or fault, he will immediately contact University IT services to develop and implement a rapid solution to the underlying technical issue. Co-I Pfeiffer has been an active consultant with the MSU and UNC investigators for the last 3 years, has developed strong relationships with professional in central IT service at MSU, and has a commitment from the IT services team responsible for maintenance of MSU College of Education services to prioritize access and support in the case of technical issues with the aforementioned servers or university networks. For technical support issue in tiers 1, 2, and 3, PI Lisee will be immediately informed and Co-I Pfeiffer will summarize the

underlying issues and implemented solutions on the weekly study team conference call described in the next section of this document.

*Study Team Interactions:* The study team will convene weekly conference calls to review of study progress.

**Table 2. Application support hierarchy and participant support strategy.**

| Support Level | Support Function | Study Team Members |
|---|---|---|
| **Tier 1** | Basic assistance with:<br>• Participant training<br>• Participant text message use<br>• Participant mobile device syncing<br>• Initial review of questions or reports of issues from participants | UNC: PI (Lisee) and Mentor (Pietrosimone)<br>MSU: Co-I (Kuenze) |
| **Tier 2** | In-depth support including:<br>• Text message and mobile device sending and receipt<br>• Fitbit application and Fitbit Charge 2 monitor updates<br>• Troubleshooting based on mobile operating system updates<br>• Database design, management, and migration<br>• Basic issues if a tier 1 team member is unavailable or unable to resolve the issue | MSU: (Co-I) M. Pfeiffer.<br>PI Lisee and Co-I Kuenze will be informed of all ongoing issues |
| **Tier 3** | Highly technical support including:<br>• Maintenance and troubleshooting of University technical infrastructure including servers<br>• Support if tier 1 and tier 2 team members are unavailable | MSU: Co-I M. Pfeiffer in consultation with MSU information technology services<br>PI (Lisee) and Co-I (Kuenze) will be informed of all ongoing issues by Co-I (M. Pfeiffer) |