MLQoL	Multiple Ligament Quality of Life Questionnaire
MOP	Manual of Operating Procedures
MOS	Military Occupational Specialty
NMES	Neuromuscular Electrical Stimulation
NPRS	Numeric Pain Rating Scale
NWB	Non-Weight Bearing
OA	Osteoarthritis
ORP	Office of Research Protections
PASC	Publications and Ancillary Studies Committee
PASS	Patient Acceptable Symptom State
PCL	Posterior Cruciate Ligament
PF	Physical Function
PFL	Popliteofibular Ligament
PEB	Physical Evaluation Board
PI	Principal Investigator
PLC	Posterolateral Corner
POL	Posterior Oblique Ligament
PRO	Patient Reported Outcome
PROMIS	Patient Reported Outcome Measurement Information System
PTOA	Post-Traumatic Osteoarthritis
PWB	Partial Weight-Bearing
QA	Quality Assurance
QC	Quality Control
QCC	Quality Control Coordinators
QCI	Qualified Clinical Investigator
QM	Quality Management
RC	Research Coordinator
ROM	Range of Motion
SAE	Serious Adverse Event
SID	Study Identification Number
TBI	Traumatic Brain Injury
TSK	Tampa Scale for Kinesiophobia
TTWB	Toe-Touch Weight-Bearing
UP	Unanticipated Problem

arthrofibrosis, residual laxity, complications/adverse events, re-injury and additional surgical procedures.

3.2.1 Primary Outcome

The primary outcome will be time return to full pre-injury military duty, work and sports. For military personnel, to assess return to duty we will ask three questions from the Injury Surveillance Survey (ability to perform Annual Physical Fitness Test; deployability, ability to perform specific military occupational specialty [MOS] duties). Additionally, we will record the military subject's MOS physical demand classification. The physical demands of work and sports activity will be assessed using the Cincinnati Occupational Rating[58] and Marx Activity Scales,[59] respectively. To further assess return to work, we will also record the individual's current employment status and specific occupation. To assess sports participation, we will record the type (very strenuous, strenuous etc.) and frequency (4-7 times per week, 1-3 times per week etc.) of sports.

Because of the expected heterogeneity of pre-injury activity level of individuals that sustain a MLKI we will combine return to pre-injury military duty, work and sports into an overall Return to Activity and Participation variable. Individuals will be classified as having returned to activity if and when they have returned to their pre-injury level of military duty, work and sports. Successful return to activity will be assessed using the patient-reported measures of military duty, work and sports and will be compared to the individual's pre-injury level of military duty, work and sports.

Individuals in the military will achieve a "Full Return to Activity and Participation" designation if and when they indicate they have returned to full pre-injury level of military duty, work and sports without any restrictions based on their:

- Reported ability to pass an Annual Physical Fitness Test at a level similar to pre-injury and are as deployable and mission capable as they were prior to injury (per the ISS);
- Achievement of the same or better score on the Cincinnati Occupational Rating Scale and;

- Achievement of the same or better score on the Marx Activity Rating Scale and participation in the same type and frequency of sports as prior to injury.

Individuals who are not in the military will achieve a “Full Return to Activity and Participation” designation if and when they have returned full pre-injury work and sports without any restrictions based on their:

- Achievement of the same or better score on the Cincinnati Occupational Rating Scale and;

- Achievement of the same or better score on the Marx Activity Rating Scale and participation in the same type and frequency of sports as prior to injury.

Any individual who does not meet all of these criteria will be designated as having “Not Returned to Full Activity and Participation”. Participants reporting that they have returned to military duty, work and sports in a limited or modified role will be considered as having “Not Returned to Full Activity and Participation”.

3.2.2 Co-Primary Outcome – Patient Reported Physical Function

The Multiple Ligament Quality of Life (MLQoL) Questionnaire[60] is a condition-specific patient-reported outcome measure for individuals that have sustained a MLKI. It was developed with stakeholder input from patients with a MLKI and clinicians that treat those patients to address the limitations of existing knee-specific patient-reported outcome measures that do not represent the full spectrum of content that is pertinent to individuals with a MLKI. The MLQoL questionnaire consists of 52 items that are divided into 4 domains: physical impairment (19 items), emotional impairment (15 items), activity limitations (12 items) and social involvement (6 items). Lower scores represent the best outcomes for each subscale.

To measure physical function, we selected the Activity Limitation scale of the MLQoL Questionnaire as the primary outcome based on input from patients with a MLKI that indicated items contained in this scale were most important and relevant over the long-term.[60] Psychometric testing of the Activity Limitation scale in individuals with a MLKI

found no floor or ceiling effects, internal consistency (Cronbach's Alpha) was 0.94 and test re-test reliability (intra-class correlation coefficient[ICC]) was 0.91. Furthermore, the Activity Limitations scale demonstrated construct validity as evidenced by satisfying seven of eight a priori hypotheses.

3.2.3 Secondary Outcomes

3.2.3.1 Secondary Knee-Specific Patient-Reported Outcome Measures

The MLQoL Questionnaire Physical Impairment, Emotional Impairment and Social Involvement Scales will serve as MLKI-specific secondary measures of patient-reported outcome. These scales contain content that is relevant for individuals with a MLKI, have no floor or ceiling effects and acceptable levels of internal consistency (Cronbach's Alpha 0.94, 0.93 and 0.91 respectively), test re-test reliability (ICC 0.89, 0.86 and 0.88 respectively) and construct validity.[60]

International Knee Documentation Committee Subjective Knee Form (IKDC-SKF) is an 18-item knee-specific patient-reported measure of symptoms, function and sports activities for individuals with a variety of knee conditions, including MLKIs. The IKDC-SKF has undergone extensive psychometric testing.[61-63] and normative data in a representative sample of the United States population has been determined.[64] Test re-test reliability was high (ICC 0.94) with a standard error of measurement of 4.6. The IKDC-SKF is related to concurrent measures of physical function (r=.47 to .66) but not emotional function (r=.16 to .26). A change score of 11.5 was found to distinguish between those who were improved and those who were not over an average of 19 months follow-up.[62] Most recently, the threshold for the patient acceptable symptom state (PASS) for the IKDC-SKF for individuals 1 to 5 years after ACL reconstruction has been established.[65]

3.2.3.2 General Measures of Patient-Reported Physical Function

The Patient Reported Outcome Measurement Information System (PROMIS) Physical Function (PF) Scale was developed by the PROMIS Network, which was an NIH Roadmap Initiative, to assess physical function regardless of the health condition present. The PROMIS PF item bank has been shown to be well suited to assess patient-reported outcomes in those with a variety of orthopaedic disorders. PROMIS PF CATs have been used for patients with foot and ankle disorders,[66] following ACL reconstruction[67], osteoarthritis,[68] knee osteoarthritis[69] and have demonstrated adequate internal consistency,[66] test re-test reliability,[68] decreased ceiling and floor effects,[66] and shorter completion times.[66,67] As part of an NIAMS-funded study, we recently demonstrated the PROMIS PF CAT had moderate test re-test reliability (ICCs 0.55 to 0.68) over 1 and 3 month time periods in a stable cohort of individuals 2 or more years after ACL reconstruction and large effect sizes (ES) from before to 12 (ES 1.85) and 24 months (ES 1.80) after ACL reconstruction. To minimize response burden we will administer the PROMIS PF scale as a CAT that is offered through the REDCap library.

3.2.3.3 Patient-Reported Multi-Dimensional Quality of Life

The PROMIS Global 10 scale is a 10-item patient-reported measure of physical and emotional health.[70] Exploratory and confirmatory analyses indicated the global health items fit a two factor model that included global physical and global mental health. The scales had an internal consistency of 0.81 and 0.86 respectively and the global physical health scale was more strongly correlated (r=0.76) with the EQ-5D then was the global mental health scale (r=.59). We are including the PROMIS Global 10 as a measure of global health because global health items are predictive of future health care utilization and mortality.

3.2.3.4 Additional Secondary Outcomes from Clinical Follow-Up Visits

Information gathered during standard of care clinical follow-up visits will be prospectively collected at 1, 3, 6 and 9 to 12 months after the date of surgery. This information will be documented on a Clinical Visit Form and will serve to provide

additional secondary outcomes related to post-operative recovery. The information will include pain, pain medication usage, joint effusion, wound and neurovascular status, ROM, WB status, use of a post-operative rehabilitation brace, imaging and/or laboratory tests ordered and completed, complications and adverse events, additional surgical procedures and military duty, work and sports status. Knee laxity will also be assessed at the final clinical follow-up 9 to 12 months after surgery.

randomization and at 6, 12 and 24 months after randomization. Return to pre-injury activity and patient-reported outcome will be collected electronically through surveys administered by the Data Coordinating Center at the University of Pittsburgh.

Additional secondary outcomes, including recovery of ROM, arthrofibrosis, residual laxity, complications/adverse events, re-injury and additional surgical procedures, will be determined through standardized, structured usual-care clinical follow-up visits 1, 3, 6 and 9 to 12 months after surgery. These data will be recorded on electronic Clinical Visit Forms completed by the clinical and research staff at each participating clinical site.

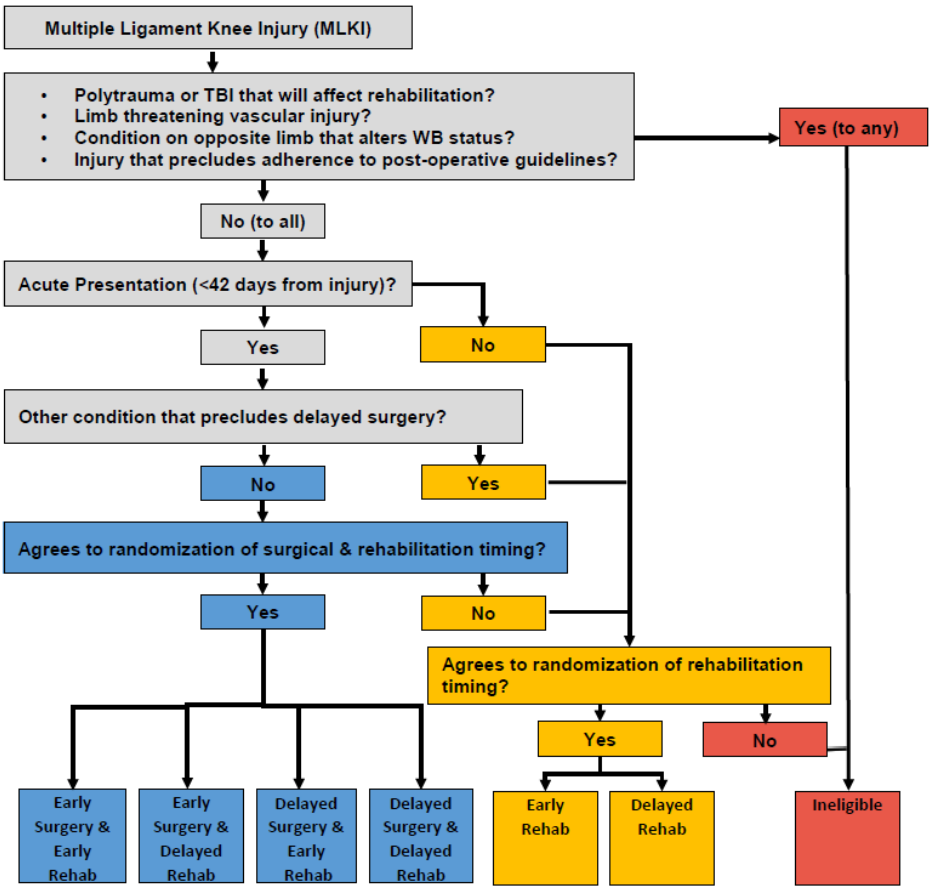

Figure 1 - Subject Presentation, Eligibility, and Randomization. Blue boxes are associated with Aim 1. Yellow boxes are associated with Aim 2.

7 STUDY SCHEDULE

7.1 Subject Identification, Prescreening, and Informed Consent Processes

We expect to recruit and randomize 690 military personnel and civilians (392 for Specific Aim 1 and 298 for Specific Aim 2) with a MLKI from 5 military and 20 civilian (17 US and 3 Canadian) centers of excellence for treatment of MLKIs.

Patients presenting with a MLKI to a surgeon-investigator's office or Emergency Department at a participating clinical study site will undergo pre-screening that will consist of review of the medical record to determine if the individual is potentially eligible to participate in the study. This review will be performed by members of the clinical care team that would otherwise have access to the medical record information that is being reviewed. The identification and pre-screening of potential study participants could occur in either in the surgeon's office or in the Emergency Department in consultation with the orthopaedic trauma service.

If the pre-screening process reveals that the patient is potentially eligible for participation in the study, he/she will be approached by a member of the clinical care team to ask the patient if he/she would be interested in learning more about the study. At that point if the individual is interested in learning more about the study, the surgeon-investigator and/or the research coordinator will provide additional information regarding participation in the study.

If the pre-screening indicates that the patient is not potentially eligible for participation, no interaction between the study team and the patient will occur, however the results of the pre-screening process, including the reason(s) why the patient was not eligible for participation will be stored in a separate, de-identified table in the REDCap database.

For the individuals that are potentially eligible and interested in learning more about the study, the surgeon-investigator and/or the research coordinator will provide detailed information regarding the study. This will include a discussion of the reason for the study, research procedures, risks and benefits of participation and compensation. Prior to providing informed consent, all of the potential subject's questions will be answered

by the surgeon-investigator and/or research coordinator. If the individual agrees to participate in the study, the participant will review and sign the informed consent form, which will also be signed by the surgeon-investigator. For individuals that are 16 or 17 years of age, written signed informed consent will be obtained from the individual's parent or legal representative and the participant will provide attestation. A copy of the signed informed consent form will be given to the participant and the original copy will be stored by the research team. Additionally, a copy of the signed informed consent for will be included in the electronic health record.

7.2 Screening

Patients with MLKI that have provided informed consent will undergo further screening to determine eligibility for participation in the study. Screening procedures for the study entail collection of demographics and participant information, review of medical records and the baseline clinical examination performed by the surgeon-investigator. At the conclusion of the screening process, subjects will be informed as to whether or not they are eligible for participation in the study.

7.3 Baseline Visit

Participants deemed eligible for the study will complete baseline patient-reported outcomes (see Section 8) prior to randomization, to minimize missing baseline data and to avoid selection bias. Eligible participants will complete a list of patient-reported outcomes using the REDCap system.

7.4 Randomization and Scheduling and Completion of Surgery

Subjects will be randomized in 1:1 allocation for both factors (timing of surgery and timing of rehabilitation) in the two by two trial (Aim 1) and for timing of post-operative rehabilitation in the one arm trial (Aim 2). Randomization will be conducted by the DCC

7.6 Research Follow-Ups

Research follow-up assessments will assess the participant's current military duty, work participation, and sports participation on a monthly basis. This will begin 6 months **after randomization** and continue through 24 months from randomization. Additionally, we will collect knee-related physical function and health related quality of life patient-reported outcome measures 6, 12, and 24 months after randomization.

The research follow-ups will be conducted remotely by the Data Coordinating Center. Participants will be asked to complete follow-up surveys electronically using a REDCap link (with instructions to access the surveys) that will be sent to their preferred method of contact method (via e-mail and/or text message). Multiple contact attempts to complete the patient-reported measures will be sent to maximize response rate. If the participant does not respond to the first two automated e-mail/messages, a member of the research staff will call the participant to remind them to complete the surveys. Each participant will receive at most three phone calls from the research staff to remind them to complete the surveys. The research coordinator from the site at which the participant was recruited will be enlisted to assist with participant contact as necessary for participants who do not respond to requests from the Coordinating Center. Completion of the patient-reported measures of knee-specific and general measures of physical function and health-related quality of life will take approximately 30 minutes (estimated time). Participants will also be compensated $35 for their time to complete the measures at 6, 12 and 24 months.

populate the Inclusion/Exclusion Criteria form and will determine individual's eligibility to participate in the study.

8.1.2.1 Demographics and Participant Information

Demographics and participant information, including primary and secondary contact information will be collected. Access to any the participant's identifiable information will be limited to the local research team and to the research personnel at the Data Coordinating Center (except for the Canadian sites). Demographic information will include age, sex, weight, height, marital status, educational level, pre-injury military duty, work activity, and sports activity, smoking history and insurance status.
Further screening to determine eligibility for the study will entail the surgeon-investigator (or his/her designee) documenting the results of the standard of care initial examination on the Baseline Clinical Visit form.

8.1.2.2 Pre-injury activity measures

- **Military Duty**

To measure military duty prior to injury we will record the physical demand classification of the military occupational specialty (MOS) [72] and will ask three questions from the Injury Surveillance Survey (ability to perform Annual Physical Fitness Test; Deployability and Specific MOS Duties). These questions were developed based on input from members of a working group at the Office of the Surgeon General and are being incorporated in the Medical Readiness Assessment Tool (MRAT). Additionally, the questions are also scheduled to be added to the new DoD/VA electronic medical record that is to be released in 2016.[73] These questions have also been included as an outcome measure in a prospective study to develop predictive models for spine and lower extremity injury after discharge from rehabilitation (see *https://clinicaltrials.gov/ct2/show/NCT02776930*).

- **Work Activity**

To measure work activity prior to injury, we will use the Cincinnati Occupational Rating Scale, which has demonstrated high test-retest reliability in both patients (ICC=.97) and

uninjured individuals (ICC=.87).[58] Additionally we will record the individual's pre-injury employment status (work regular duty full time, work regular duty part-time etc.) and occupation.

- **Sports Activity and Participation**

We will use the Marx Activity Rating Scale[59] to measure the participant's level of sports activity in the year prior to injury. Test re-test reliability for this scale over a two-week period was high (ICC=.97) and it had moderately strong correlations with the Cincinnati and Lyhsolm scores.[59] To assess sports participation, we will also record the type (very strenuous, strenuous etc.) and frequency (4-7 times per week, 1-3 times per week etc.) of sports participation as well as the specific sport(s) the individual participated in prior to injury.

8.1.2.3 Baseline Clinical Examination

A standard of care history and clinical examination and review of standard of care imaging studies will be performed by the surgeon-investigator to confirm the diagnosis of a MLKI and determine eligibility for inclusion in the study. This information will be documented on a Baseline Clinical Visit Form. Data that will be collected on the Baseline Clinical Visit form will include current level of pain, ROM, imaging and/or laboratory tests ordered and completed, knee ligament testing, neurovascular status, and plan for pre-operative management.

- <u>Pain</u>

Pain intensity will be recorded utilizing an 11-point numeric pain rating scale (NPRS) that ranges from 0 (no pain) to 10 (worst imaginable pain). Pain ratings of 4 to 6 represent moderate pain. Current pain intensity will be recorded. The minimal clinically important difference for a change that is deemed quite a bit better is 2.17 on the 0 to 10 pain scale.[74]

- <u>Active and Passive Range of Motion of the Knee</u>

and observe for a fluid wave on the medial side of the knee. Inter-tester reliability for the stroke test was found to have 73% agreement with a Kappa value of 0.75.[79]

- Wound Status

At each clinical follow-up visit the status of the wound will be recorded as healed, healing, draining, open, erythema or presence of a superficial wound infection.

- Adherence to Prescribed Rehabilitation

Assessment of Participant's Adherence to Allocated Rehabilitation Program
At each clinical follow-up visit, the surgeon's perspective on participant's adherence with allocated post-operative rehabilitation program will be recorded as fully adherent, partially adherent or not adherent for both ROM and weight bearing status.

- Use of Assistive Devices

The use of assistive devices for ambulation will be recorded as yes or no.

- Use of Post-Operative Brace

Use of a post-operative brace will be recorded as yes or no. If the brace is being used, the type of brace will be recorded. If a hinged brace is being used, the range of motion limits of the brace will be recorded. If the brace is no longer being used, the date that brace use was discontinued will be recorded.

- Additional Diagnostic Tests

At each follow-up visit we will record any additional diagnostic tests that have been performed including radiographs, stress radiographs, MRI, CT-scan, ultrasound, vascular testing and/or EMG/nerve conduction velocity. The date and indication for any additional diagnostic test will be recorded.

- Knee Ligament Examination

A manual knee ligament examination will be performed at the clinical follow-up visits at the discretion of the surgeon. The ligament laxity tests will be assessed during the clinical follow-up visits in the same manner as describe for the baseline clinical visit (see Section 8.1.2.3).

The PROs collected during the research follow-up assessments will be administered and monitored remotely by the DCC.

8.1.7 Assessment of Outcomes

8.1.7.1 Primary Outcome

- **Return to Pre-Injury Military Duty, Work and Sport**

Because of the expected heterogeneity of pre-injury activity level of individuals that sustain a MLKI, similar to our work related to return to pre-injury sports activity and participation for individuals following anterior cruciate ligament (ACL) reconstruction, we will combine return to pre-injury military duty, work and sports into an overall Return to Activity and Participation variable. Individuals will be classified as having returned to activity if and when they have returned to their pre-injury level of military duty, work and sports. Successful return to activity will be assessed using the patient-reported measures of military duty, work and sports described above and will be determined based on comparison of the individual's pre-injury level of military duty, work and sports.

Individuals in the military will achieve a "Full Return to Activity and Participation" designation if and when they indicate they have returned to full pre-injury level of military duty, work and sports without any restrictions based on their:

- Reported ability to pass an Annual Physical Fitness Test at a level similar to pre-injury status and are as deployable and mission capable as they were prior to injury (per the ISS);
- Achievement of the same or higher Military Occupational Specialty Physical Demand Classification
- Achievement of the same or better score on the Cincinnati Occupational Rating Scale and;
- Achievement of the same or better score on the Marx Activity Rating Scale and participation in the same type and frequency of sports as prior to injury.

Individuals who are not in the military will achieve a “Full Return to Activity and Participation” designation if and when they have returned to full pre-injury work and sports without any restrictions based on their:

- Achievement of the same or better score on the Cincinnati Occupational Rating Scale and;
- Achievement of the same or better score on the Marx Activity Rating Scale and participation in the same type and frequency of sports as prior to injury.

Any individual who does not meet all these criteria will be designated as having “Not Returned to Full Activity and Participation”. Participants reporting that they have returned to military duty, work and sports in a limited or modified role will be considered as having “Not Returned to Full Activity and Participation”.

Longitudinal Collection of Return to Military Duty, Work and Sports Activity and Participation Outcomes – To more precisely measure time to return to military duty, work and sports, we will administer a brief Return to Activity Monitoring Survey on a monthly basis, starting 6 months after randomization continuing through the 24-month follow-up. To promote compliance with data collection and ease the burden of completion that is placed on study participants, the Return to Activity Monitoring Survey is a responsive branching survey. At each follow-up time point, participants will be presented with three simple questions about returning to military duty, work and sports. They will be asked to indicate if they have not returned, returned in a limited fashion, or returned without any restrictions. Participants indicating that they have returned in a limited role or without restrictions will be asked to complete the three-question scale from the Injury Surveillance System and Cincinnati Occupational Rating and Marx Activity Rating scales, as appropriate (see Figure 5). This responsive branching design seeks to limit the questions asked in the monthly, recurring survey while still providing sufficient detail to make a true determination of the participant’s return to military duty, work and sports status.

consistency (Cronbach's Alpha .94) and test re-test reliability (ICC .91). Evidence for construct validity was demonstrated by acceptance of seven of eight a priori hypotheses for the Activity Limitations scale.[60]

8.1.7.2 Secondary Outcomes – Patient-Reported Outcomes

We will also collect several patient-reported measures of physical functions and health-related quality. These patient-reported outcome measures will be collected at baseline, 6, 12 and 24 months follow-up from time of randomization. The measures are described in detail below.

- **International Knee Documentation Committee (IKDC) Subjective Knee Form**

The International Knee Documentation Committee Subjective Knee Form (IKDC-SKF) is an 18-question measure of symptoms, function and sports activities for individuals with a variety of knee conditions, including MLIKs injuries. Individuals complete the IKDC Subjective Knee Form from the perspective of "the past 4 weeks or since your injury". Each item is scored using an ordinal scale, such that a score of 0 is given to responses that represent the highest level of symptoms or the lowest level of function or activity. The IKDC-SKF is scored by summing the scores for the 18 items and then transforming the score to a scale from 0 to 100 by dividing the sum of the scores by the maximum possible score, which is 87 if the individual responds to all 18 questions. Higher IKDC-SKF scores indicate the absence of symptoms and higher levels of function and sports activities.

If there are missing item responses, the IKDC-SKF score can still be calculated if there are responses to at least 90% of the items (i.e. when responses have been provided for at least 16 of the questions). In the presence of up to 2 missing item responses, the IKDC-SKF score is calculated as the (sum of the completed items)/(maximum possible sum of the completed items) times 100.

The IKDC-SKF has undergone extensive psychometric testing[61-63] and normative data in a representative sample of the US population has been determined.[64] Test re-test reliability was high (ICC .94) with a standard error of measurement of 4.6. The IKDC-

SKF is related to concurrent measures of physical function (r=.47 to .66) but not emotional function (r=.16 to .26). A change score of 11.5 was found to distinguish between those who were improved and those who were not over an average of 19 months follow-up.[62] Since its development, the IKDC-SKF has be found to include questions that are important to individuals with an ACL injury[82]. Most recently, the threshold for the patient acceptable symptom state (PASS) for the IKDC-SKF for individuals that are 1 to 5 years after ACL reconstruction have been established.[65]

- **Physical Impairment, Emotional Impairment and Social Involvement Scales of the MLQoL Questionnaire**

We will also administer the other three scales as secondary outcomes to capture the full range of physical and emotional impairments and social impact that a MLKI has on people's lives.

The psychometric testing for the physical impairment, emotional impairment, and social involvement scales found no floor and ceiling effects and acceptable levels of internal consistency (Cronbach's Alpha 0.94, 0.93 and 0.91, respectively) and test re-test reliability (ICC 0.89, 0.86 and 0.88, respectively).[60]

- **Patient Reported Outcome Measurement Information System (PROMIS) Physical Function Scale**

The Patient Reported Outcome Measurement Information System (PROMIS) Physical Function Scale was developed by the PROMIS Network, which was an NIH Roadmap Initiative, to assess physical function regardless of the health condition present. In contrast to classical test theory, which focuses on the total scale score, IRT focuses on individual items and models the probability of a response to an item as a function of the properties of the item and the ability level of the individual responding to the item.

The PROMIS PF item bank consists of 121 items and can be administered as a computer adaptive test (CAT) or through short forms. The CAT version of the PROMIS Physical Function Scale utilizes a computer algorithm to adaptively select items that provide the most information about an individual. Selection of each item is dependent

on an individual's responses to prior items and items are administered until either a fixed number items are administered or until the individual's physical function is estimated with a pre-specified level of precision. The advantage of the CAT version of the PROMIS Physical Function Scale is that it allows for shorter, more efficient and potentially more precise measurement of an individual's level of physical function. The PROMIS Physical Function scores are presented as standardized T-scores that are normalized to the United States population. A T-score of 50 is equal to the population average with a standard deviation of 10. Thus, a score of 55 represents an individual with a physical function score that is one-half of a standard deviation above the population average. We will utilize the CAT version of the PROMIS Physical Function Scale that is available free through the REDCap library.

The PROMIS PF Scale has been shown to be well suited to assess patient-reported outcomes in those with a variety of orthopaedic disorders. The PROMIS Physical Function CATs have been used for patients with foot and ankle disorders[66], following ACL reconstruction[67], osteoarthritis,[68] and knee osteoarthritis[69]and have demonstrated adequate internal consistency,[66] test re-test reliability,[68] decreased ceiling and floor effects,[66] and shorter completion times,[66,67] As part of an NIAMS-funded study, we recently demonstrated the PROMIS Physical Function CAT had moderate test re-test reliability (ICCs 0.55 to 0.68) over a 1 and 3 month time period in a stable cohort of individuals two or more years after ACL reconstruction and large effect sizes (ES) from before to 12 (ES 1.85) and 24 months (ES 1.80) after ACL reconstruction (unpublished data).

- **PROMIS Global 10**

The PROMIS Global 10 is a 10-item patient-reported measure of physical and emotional health.[70] It consists of a self-rated health item (global-1), single pure physical health (global-3) and mental health (global-4) items and an item representing overall quality of life (global-2), which is strongly related to mental health. The other items provide global ratings of physical function (global-6), fatigue (global-8), pain (global-7), emotional distress (global-10) and social health (global-5 and global-9).

- **Brief Resilience Scale**

Resilience is a measure of an individual's ability to "bounce back" or recover from ongoing health-related stresses.[94] The Brief Resilience Scale is a 6-item questionnaire, in which individuals indicate their level of agreement to each statement using a 5-point Likert scale that ranges from "strongly disagree" to "strongly agree". The score is created by calculating the mean of the 6 items, after reverse coding the scores for items 2, 4 and 6. The scores range from 1 to 5, where higher scores indicate positive resilience capabilities. The Brief Resilience Scale was evaluated in four samples and it was found to be an unidimensional and reliable measure (Cronbach's alpha ranging from .80 - .91).[94] We hypothesize that individuals with higher resilience will have a quicker return to return to pre-injury level of military duty, work and sports and higher levels of patient-reported physical function.

- **Functional Comorbidity Index**

Health status is likely to contribute to overall outcomes after surgery for a MLKI, therefore we will assess for the presence of medical comorbidities using the 18-item Functional Comorbidity Index (FCI). Using medical comorbidities is an important factor in creating risk-adjustment models for orthopedic trauma.[95] The FCI is a self-administered report of medical comorbidities that has been shown to be associated with physical function,[96] whereas other comorbidity outcomes focus on mortality. The FCI measures the full spectrum health related to musculoskeletal, cardiopulmonary, sensory, neuromuscular, endocrine and mental health. The FCI was found to demonstrate a stronger association with that SF-36 physical function subscale (R2 = 0.29) than the Charleston (R2 = 0.18) and Kaplan-Feinstein (R2 = 0.07) indices.[96] A simple count of the number of comorbidities performed similarly to a weighted count of the comorbidities and thus for simplicity, the simple count of the number of co-morbidities is recommended. When individuals were classified into high and low function based on the SF-36 physical function score, the FCI correctly classified 77% of the cases.

9.1.3 Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

If determined on the AE form that the event was a serious adverse event, additional questions will become available to collect information pertinent to the SAE including:

- Unexpected serious adverse event;
- Outcome of serious adverse event;
- Action required because of the serious adverse event.

9.2 Time Period and Frequency for Event Assessment and Follow-Up

Unanticipated problems will be recorded in the data collection system throughout the study. The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each clinical visit and through the electronic surveys, the research team will actively query participants on the occurrence of any potential health related event since last contact. Events will be followed for outcome information until resolution or stabilization.

9.3 Characteristics of an Adverse Event

9.3.1 Relationship to Study Intervention

To assess relationship of an event to the study intervention, the following guidelines will be used:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

9.3.2 Expectedness of SAEs

An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention in the protocol-related documents, such as the IRB-approved research protocol and informed consent document.

9.3.3 Severity of Event

The following scale will be used to grade adverse events:

1. Mild: no intervention required; no impact on activities of daily living (ADL);

2. Moderate: minimal, local, or non-invasive intervention indicated; moderate impact on ADLs;

3. Severe: significant symptoms requiring invasive intervention; subject seeks medical attention, needs major assistance with ADLs;

4. Life-threatening: urgent intervention indicated;

5. Death related to AE.

9.4 Internal and External Review and Adjudication of AE and SAE documentation

Close monitoring of the AE and SAE CRFs documentation will take place throughout the implementation of the study. Two AE review committees have been created to provide a two-level review process for all filed AEs. The first-level review will be conducted by the University of Pittsburgh Internal Review Committee, which is comprised of three voting members and three non-voting members. The second-level review will be conducted by the External AE Adjudication Committee, which is comprised of three voting members. Refer to table 3 for the composition of these two committees.

Table 3: Internal and Extern AE Review Committees composition

1st Level Review – University of Pittsburgh Internal Review Committee		
Voting Members		
Dr. Irrgang (PI)	Dr. Musahl (Co-PI & Qualified Clinical Investigator)	Dr. Lynch (Co-I & Qualified Clinical Investigator for Rehabilitation)
Non-Voting members		
Dr. Moore (Co-I & DCC Director),	Dr. Gil (Co-I & Quality Control Coordinator),	Beatriz Catelani (STaR Trial Project Coordinator)
2nd Level Review – External Adjudication Committee		
Dr. Kurt Spindler, MD; Department of Orthopaedic Surgery, Cleveland Clinic	Dr. Kelley Fitzgerald, PT, PhD, FAPTA; Professor at Department of Physical Therapy, University of Pittsburgh	Susan Spillane, RN CCRP; Clinical Research Coordinator, Center for Clinical Trials & Data Coordination, University of Pittsburgh

All AE and SAEs will be documented into the REDCap electronic database on an ongoing basis (Figure 6). For the first-level review, weekly reports will be generated and reviewed during the weekly Pittsburgh site research team meeting. At least two voting members of the University of Pittsburgh Internal Adverse Events Review Committee will need to be present for the review. This internal review of AEs and SAEs will determine

10 STUDY OVERSIGHT

10.1 Composition of the Data and Safety Monitoring Board

In addition to the PIs' responsibility for oversight, study oversight will be under the direction of an independent Data and Safety Monitoring Board (DSMB) comprised of seven individuals. Dr. Steven Svoboda, MD was appointed the chair of the DSMB for the study, and he will be responsible for generating minutes from each meeting. The committee includes three orthopaedic surgeons with expertise related to treatment of complex knee injuries, three physical therapists with expertise related to rehabilitation of the knee, and a biostatistician. When selecting the members of the DSMB, we ensured that there was one orthopaedic surgeon and one physical therapist each to represent the interests of the US military and civilian practices in the US and Canada included on the DSMB. Written documentation attesting to absence of conflict of interest has been obtained to ensure that the members of the DSMB are independent of the investigators and have no financial, scientific, or other conflict of interest with the STaR Trial. Members of the DSMB, including their credentials are listed below in Table 4.

Table 4. DSMB Committee Members

	Address	**Contact: Phone**
US Military Members		
Steven Svoboda, MD – Chair	MedStar Georgetown University Hospital 1133 21st Street Northwest Washington, DC 20036	Tel: (202) 416-2000 Cell: (210) 882-6413 Email: stevensvoboda@mac.com
Richard Westrick, PT, DPT, DSc, OCS, SCS	Associate Professor Department of Physical Therapy MGH Institute of Health Profession 36 1st Avenue Boston, MA 02129	Tel: (617) 724-4846 Email: rwestrick@mghihp.edu
US Civilian Members		
Annunziato Amendola, MD	Department of Orthopaedic Surgery Duke University	Tel: (919) 613-6711 Fax: (919) 681-6357 Email: ned.amendola@duke.edu

meeting date and time commitment well in advance. The agenda will contain a list of topics in order of the presentation, the expected duration of each discussion item and the name of individual who will lead the discussion.

The following pre-requisites should be completed prior to the site initiation visit:

- Protocol and consent have been reviewed and approved by the DSMB, site local IRB, University of Pittsburgh IRB, and HRPO;
- All necessary site staff have been identified; and
- All staff have been completed training on utilization of REDCap database.

The QCC will utilize the following list of activities as a starting point for the Initiation Visit Agenda:

- Protocol Overview
    - Type of study
    - Study objectives
    - Key inclusion/exclusion criteria
        - Completion of Screening and Eligibility Scenarios
    - Study procedures
    - Enrollment goals
    - Recruitment Plans
    - Informed Consent Discussion
    - Study visit schedule/schedule of events
- Safety: Definitions, Collection, and Reporting
    - Review of Adverse Events (AEs), Serious AEs (SAEs), and Unanticipated Problems (UPs)
    - Completion of Reportable Events Scenarios
    - Review of timeline related to Reportable Events
    - Queries resulting from the above
- Site Specific Study Procedures
    - Review of site specific study implementation

11.3.3 For-Cause Visits

For-Cause Visits will be conducted to address any unanticipated issues that arise which require training, remediation or other situations for which the site requires assistance. For-Cause Visits can be conducted remotely or on-site if mandated by the Quality Control Coordinator, PI, or Director of the DCC or requested by the site.

11.3.4 Close-Out Visit

The Close-Out Visit will be conducted to ensure that all study data and other study documentation is complete and accurate and that all study records have been reconciled. Study closure activities may require several remote visits which will include conference calls and communication via email. Close-Out Visits may be conducted at study completion or earlier in the case of termination of the site's participation in the study or termination of the study overall as determined by IRB, HRPO, Data and Safety Monitoring Board, or Executive Steering Committee.

11.4 Research Records and Documents to be Monitored

Table 7 below summarizes the research records and documents to be monitored including the number of records to be monitored and method of monitoring.

Table 7 – Monitoring of Research Records and Documents

Records and Documents to Be Monitored	# Records	Remotely	On-site visit
Site Human Subject Protection Training Records	100%	✓	
IRB and HRPO Initial Approval and Annual Renewal Letters	100%	✓	
Signed Informed Consent Forms	100%		✓
Eligibility Criteria	100%	✓	
Surgical Source Documentation vs. CRFs	100%		✓

Clinical Follow-up Visits Source Documentation vs. CRFs	10%		✓
CRFs or Data Queries	10%		✓
Process to Contact PTs when CRFs Were Not Submitted	10%	✓	
Missed Visits and Missing Data	100%	Interim reports biannually	
Documentation and Reporting of AEs, SAEs, Protocol Deviations Documentation	100%	✓	✓
Withdrawals and Dropouts Documentation	100%	✓	
Site Regulatory Documents	100%	At close-out visits	At initiation and interim visits

Ligament Findings and Procedures		X									
Articular Cartilage Findings and Procedures		X									
Peroneal Nerve Findings		X									
Complications Reporting		X	X	X	X	X	X				
Clinical Visit Form			X	X	X	X	X				
Additional Surgeries – Clinical			X	X	X	X	X				
Additional Surgeries – Patient Reported								X	X	X	
Return to Activity Monitoring Survey [4]								X	X	X	X
Physical Therapy Case Report				X	X	X					
Patient Reported Rehabilitation				X	X	X					
1 week Home Exercise Post-Op Log			X								
Post-Operative Home Exercise Log				X							
Adverse Event/ Serious Adverse Event	AS NEEDED										
Protocol Deviation	AS NEEDED										
Change in Status	AS NEEDED										
Unanticipated Problems	AS NEEDED										

[1] Clinical Follow-Up: additional clinical visits will also be recorded as Interim Visits, and data would include: Concomitant Medications, Complications Reporting, Clinical Visit Form, Additional Surgeries, and Rehabilitation information should be collected.

[2] IKDC-SKF and MLQoL will be completed at baseline by participants who are greater than 6 weeks from injury at the time of screening/baseline. Participants who are screened that are less than 6 weeks from injury will only complete the MLQoL Activity Limitations Subscale.

[3] Pre-op PROs only expected if pre-op date is greater than 28 days from baseline date. If the participant was less than 6 weeks from injury at baseline but is greater than 6 weeks at pre-operative visit, they will get the full MLQoL and IKDC at the pre-operative visit even if the pre-operative visit is less than 28 days from baseline.

[4] Return to Activity contains questions from the following:
Return to Activity Monitoring Survey
Return to Work Activity
Return to Sports Activity
Return to Military Activity
Cincinnati Occupational Rating Scale
Marx Activity Rating Scale

US	United States
USAMRMC	United States Army Medical Research and Materiel Command
WBAT	Weight-Bearing As Tolerated

4 STUDY DESIGN

To address the controversies and lack of evidence related to the timing of surgery and post-operative rehabilitation for treatment of individuals with a MLKI we will conduct two parallel phase 3 unblinded multicenter randomized clinical trials (Figure 1). In the first trial, we will randomize 392 individuals to four groups (98 per group): early surgery/early rehabilitation, early surgery/delayed rehabilitation, delayed surgery/early rehabilitation and delayed surgery/delayed rehabilitation. In the second trial, which will be conducted concurrently with the first trial, we will randomize 298 individuals (149 per group) with a MLKI whose surgery cannot be randomized due to presentation greater than 6 weeks after injury or vascular or other injury requiring immediate surgery as well as those that refuse randomization to surgery to either early or delayed post-operative rehabilitation.

Participants will be recruited at 25 clinical sites, including 5 United States (US) military sites and 3 Canadian and 17 US civilian sites. Randomization will be done using permuted blocks with random block sizes stratified by site and injury pattern. Randomization will be concealed to those responsible for recruitment and determining subject eligibility. Recruitment is expected to occur over 21 months and participants will be followed for 24 months.

Early surgery will be defined as surgical treatment of the MLKI within 6 weeks of injury and delayed surgery will be performed 12 to 16 weeks after injury. Early post-operative rehabilitation will consist of WBAT gait and unrestricted ROM exercises starting within 1 week after surgery. For delayed post-operative rehabilitation, participants will use a NWB gait and the knee brace locked in extension for the first 4 weeks after surgery followed by progressive WB and ROM exercises.

The primary outcome will be the time to return to pre-injury military duty, work and sports, which will be assessed monthly starting 6 months after randomization through 24 months. The Activity Limitations Scale of the Multi-Ligament Quality of Life Scale which is a knee-specific patient-reported measure of physical function, will serve as a co-primary outcome and other knee-specific and general health related quality of life PROs that will serve as secondary outcomes will be collected at the time of

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Subject Inclusion Criteria

5.1.1 Inclusion Criteria for Participants Enrolled Aims 1 and 2

Male and female military personnel and civilians between the ages of 16 and 55 with a MLKI (defined as a complete grade III injury of two or more ligaments) without a history of prior knee ligament reconstructions will be eligible to participate in the clinical trials for Aim 1 or 2. Individuals with a nerve injury or biceps or popliteus tendon rupture/avulsion **will not** be excluded from participation in either trial (Table 1).

5.1.2 Inclusion Criteria for Participants Enrolled in Aim 1 - Randomization to Both Timing of Surgery and Post-Operative Rehabilitation

To be eligible to participate in the trial that randomizes individuals to both the timing of surgery and timing of post-operative rehabilitation, individuals with a MLKI must present to the orthopaedic surgeon in time to undergo definitive surgery within 6 weeks of injury if randomized to the early surgery group.

5.1.3 Inclusion Criteria for Aim 2 - Randomization to Only Timing or Post-Operative Rehabilitation

Subjects with a MLKI that present to orthopaedic surgery at a time that precludes randomization to early surgery or have an injury that precludes randomizing the timing of surgery (such as a vascular injury) as well as those that refuse randomization to the timing of surgery will be eligible to participate in the study for Aim 2 which randomizes subjects to only early vs. delayed rehabilitation.

5.2 Subject Exclusion Criteria

5.2.1 Exclusion Criteria for Enrollment of Participants in Trials for Either Aims 1 or 2

Individuals will be excluded from both trials if they:

1. Have a history of prior knee ligament surgery of the involved knee:

statisticians using permuted blocks with random block sizes stratified by site and injury pattern. The randomization lists will be created using SAS Enterprise Guide version 6.1 and uploaded using the REDCap randomization module. This module permits allocation concealment such that the allocation to the treatment arm is only viewed once certain criteria are entered into the system. The same approach will be used for the randomized trial of early versus delayed post-operative rehabilitation. Once the study coordinator has obtained and entered all screening information, he/she can request a randomization assignment by clicking on the 'Randomize' field which will then provide the allocation for only that participant.

For those individuals participating in the trial for Aim 1, randomization will be performed after final confirmed eligibility and collection of baseline patient-reported outcomes. The surgery will be scheduled based on the allocation for timing of surgery. Those assigned to early surgery will undergo surgical procedure for MLKI within 6 weeks of injury, and for those assigned to delayed surgery, the surgical procedure will be performed between 12 to 16 weeks after injury. To prevent the allocated rehabilitation intervention from influencing the surgical intervention, allocation of early vs. delayed rehabilitation will be disclosed at the completion of the surgical intervention, and it will be shared with the participant during his/hers first post-operative clinical follow-up visit.

Participants that cannot or refuse to be randomized to timing of surgery will only by randomized to timing of rehabilitation. For those individuals, surgery will be scheduled and performed at the discretion of the surgeon. Randomization to early vs. delayed rehabilitation will be performed after surgery to ensure that the individual is still eligible to participate in the study and to avoid any bias in the performance of surgery based knowledge of the assigned post-operative rehabilitation.

For individuals that undergo surgery greater than 4 weeks after collection of the baseline patient-reported forms, the patient-reported outcome measures (i.e. the MLQoL, IKDC-SKF and PROMIS PF) will be re-administered within 1 week of the date surgery, either during a pre-operative clinical visit or on the day of surgery in the pre-operative holding area. These pre-operative patient-reported outcome measures will

8 STUDY PROCEDURES /EVALUATIONS

8.1 Study Procedures/Evaluations

8.1.1 Consent Process

Potential patients that present to surgeon's office or in the Emergency Department with a MLKI will be informed of the study. Patients with MLKI who are interested in participating in the study will be introduced to the research staff for detailed information about the study. This will include a discussion of the reason for the study, research procedures, risks and benefits of participation and compensation. Prior to providing informed consent, all patient's questions related to the study procedures will be answered by the surgeon-investigator and/or research coordinator. If the individual agrees to participate in the study, the participant will review and sign the informed consent form, which will also be signed by the surgeon-investigator. For individuals that are 16 or 17 years of age, written signed informed consent will be obtained from the individual's parent or legal representative and the participant will provide attestation. A copy of the signed informed consent form will be given to the participant and the original copy will be stored by the research team. Additionally, a copy of the signed informed consent for will be included in the electronic health record.

For active military personnel, no individuals in the participant's chain of command will be involved in the recruitment process.

8.1.2 Screening

Screening of patients will occur at surgeon-investigator's office after signing informed consent, and the process consists of demographics, history and physical examination performed by the orthopaedic surgeon and imaging to determine if individual has a MLKI.

Final eligibility for the individuals participation in the study will be determined at the conclusion of the screening activities. Participants will not be able to be randomized until final eligibility for participation in the study has been determined. Data elements from the screening process will be entered into the REDCap database and will auto-

The range of active and passive extension and flexion of both knees will be measured with a goniometer with the individual lying supine on the examination table. Range of motion of the knee should be visually estimated prior to using a goniometer to measure the motion. Range of motion will be measured to the to the nearest 1° with a large (11.5 inch arms) clear plastic goniometer marked in 1° increments. Range of motion of the non-involved knee will be measured first followed by measurement of the involved knee. The side to side difference in passive knee extension and flexion will be calculated and will be used to determine the IKDC Knee Ligament Rating System classification of range of motion.[75]. Intra- and inter-tester reliability coefficients are .98 and .86 for passive knee extension and .99 and .90 for knee flexion respectively. [76]

- Diagnostic Tests

Standard of care diagnostic tests including radiographs, stress radiographs, MRI, CT-scan, ultrasound, vascular testing and/or EMG/nerve conduction velocity will be recorded on the Baseline Clinical Examination form. The date and indication for each diagnostic test will be recorded.

- Knee Ligament Examination

A manual knee ligament examination will be performed determine the knee ligament injury pattern. The ligament laxity tests that will be performed include the Lachman test, total anterior-posterior (A-P) translation at 25° and 70° of knee flexion, varus and valgus stress tests at 20° of knee flexion, external rotation at 30° and 90° of knee flexion and pivot shift tests. The ligament laxity test will be graded according to the IKDC Knee Ligament Rating System guidelines.[75] All ligament laxity tests will be graded based on the side to side difference between the MKLI-injured and contralateral normal knee.

- Neurovascular Status

Assessment of neurovascular status will include assessment of pulses, sensation to pain and distal motor function. The dorsal pedal and posterior tibialis pulses will be recorded as symmetrical, diminished or absent in comparison to the non-involved leg.

- Military Duty

The surgeon's recommendations regarding current military duty will be recorded as no duty, limited or modified duty or full duty.

- Work/School Status

The surgeon's recommendations on work/school status will be recorded as no work, limited or modified work or full work.

- Sports Activity

The surgeon's recommendation on sports activity status will be recorded as no sports, limited or modified return to sports or return to sports without restrictions.

During the clinical follow-up visits, in addition to the Clinical Visit Form, the research team will also collect data on Complications, Additional Surgeries – clinical form, and Concomitant Medications.

8.1.6 Research Follow-Up Visits

The primary outcome will be time return to full pre-injury military duty, work and sports. We will also assess patient-reported physical function as measured with the Multiple Ligament Quality of Life (MLQoL) Questionnaire 6, 12 and 24 months after randomization. To more precisely measure the time to return to military duty, work and sports, we will administer a brief Return to Activity Monitoring Survey monthly starting 6 months after randomization and continuing through the 24-month follow-up. Secondary outcome measures will include additional knee-specific and general patient-reported measures of physical function and health-related quality of life. We will also collect measures of kinesiophobia, resiliency and functional comorbidities because these constructs may impact return to military duty, work and sports. Below we provide the details for each of the outcome evaluations to be made.

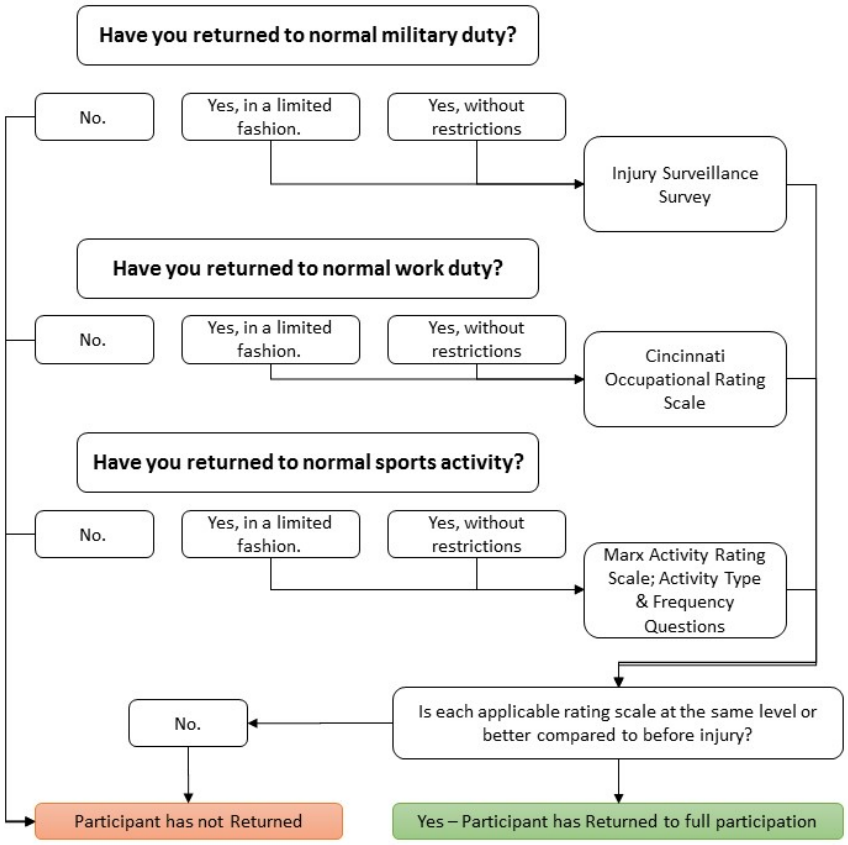

Figure 5. Determination of Return to Pre-Injury Activities

To administer the monthly Return to Activity Monitoring Survey we will utilize customized survey software (Twilio) administered through REDCap. Individuals will be contacted based on their preferred method (e-mail or text message) 1 week prior to the target date (based on the date they were randomized). An automated reminder (e-mail and text message) will be sent on the exact target date of completion. If the individual has not responded after the initial contact, a research assistant from the University of Pittsburgh will make up to three phone calls to contact the individual to administer the questionnaires over the phone or remind them to complete the questionnaire online. Similar methods have been used to track activity after ACL reconstruction with excellent reliability[80] and follow-up completeness (93% complete follow-up on 100 patients up to 2 years after ACL reconstruction)[81].

Scoring the PROMIS Global 10 requires recoding three items (global-7 [average pain], global-8 [average fatigue] and global-10 [frequency of emotional problems]). The global physical health score is created by summing the responses to four items (global-3, global-6, recoded global-7 and recoded global-8). The global emotional health score is created by summing the responses to 4 items (global-2, global-4, recoded global-5 and recoded global-10). The raw scores are converted to T scores using a look-up table. The T-score distribution is standardized such that a score of 50 represents the mean of the US general population with a standard deviation around the mean of 10 points. Therefore, a person that has T-scores of 60 for the Global Physical Health and Global Mental Health scales has physical and mental health scores that are one standard deviation better than the US population average.

Exploratory and confirmatory analyses indicated the global health items fit a two-factor model that included global physical and global mental health. The scales had an internal consistency of 0.81 and 0.86 respectively and the global physical health scale was more strongly correlated (r=0.76) with the EQ-5D then was the global mental health scale (r=.59). We are including the PROMIS Global 10 as a measure of global health because global health items are predictive of future health care utilization and mortality

- **Patient Acceptable Symptom State/Global Rating of Change**

The Patient Acceptable Symptom State (PASS) is a single question that measures an individual's satisfaction with their health state. The PASS is assessed by asking the participant the question: "Taking into account all the activity you have during your daily life, your level of pain and also activity limitations and participation restrictions, do you consider the current state of your knee satisfactory?" with the responses of "yes" or "no". The PASS question has shown to be have sufficient test re-test reliability in patients after ACL reconstruction, with a kappa coefficient of 0.78.[65]
The Global Rating of Change is a fifteen-point global rating of change (GRC) and will be administered at 6, 12, and 24 months after randomization. The global rating of change asks the individual to compare their current functional status to the time of

9 ASSESSMENT OF SAFETY

9.1 Specification of Safety Parameters

All surgeries and post-operative rehabilitation will be performed according to established standards of care for individuals undergoing treatment for a MLKI. All clinical assessments performed in this study are considered to be part of standard clinical practice. At each clinical visit and through the electronic surveys, the research team will actively query participants on the occurrence of any potential health related event since last contact.

9.1.1 Unanticipated Problems

The Human Research Protection Office (HRPO) and the University of Pittsburgh IRB consider unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Per this definition, only a subset of adverse events would be characterized as unanticipated problems involving risks to subjects or others. There are other types of incidents, experiences, and outcomes that are not considered adverse events, but are characterized as unanticipated problems (e.g., breach of confidentiality or other incidents involving social or economic harm).

the event term, severity, relatedness, seriousness, and expectedness. Changes to the AE and SAE designations will be made as needed.

The second-level review will be conducted by the External Adjudication Committee. Every two months, a cumulative report of AEs and SAEs will be send to the External AE Adjudication Committee with recommendations. The Committee will meet by conference call to discuss the overall report and any AE or SAE of concern. Once approved as the final status, the Research Coordinator responsible for processing AEs and SAEs will record the final status of each AE and SAE in the REDCap STaR Trial database. Every 6 months, the Data Coordinating Center (DCC) will review how often there are changes to AE/SAE terms, severity, relatedness, seriousness, and expectedness for each site. This will be reported to the PI and the Quality Control Co-Investigator. This two-level review process will help identify sites that are not documenting AEs appropriately, and will trigger additional training of the AE documentation.

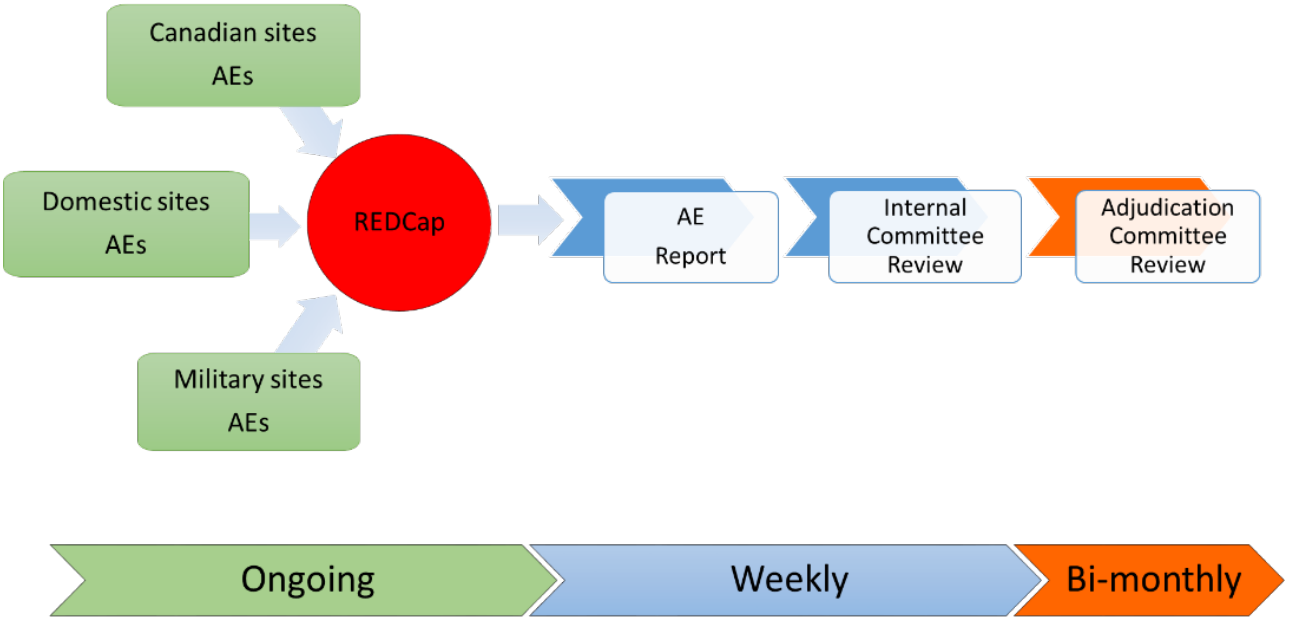

Figure 6 - AEs Internal and External Adjudication Flow Chart

	Duke Sports Science Institute 3475 Erwin Road DUMC Box 3639 Durham, NC 27705	
Steven Z. George, PT, PhD	Professor Director of Musculoskeletal Research Duke Clinical Research Institute Vice Chair of Clinical Research Orthopaedic Surgery **Duke University** OFFICE: 8020 North Pavilion MAIL: PO Box 17969, Durham, NC 27715 DEL: 2400 Pratt Street, Room 0311 Terrace Level, Durham NC 27705	Tel: (919) 668-0825 Email: steven.george@duke.edu
Canadian Members		
Peter B, MacDonald, MD, FRCS	University of Manitoba Pan Am Clinic 75 Poseidon Bay Winnipeg, MB R3M 3E4 Canada	Tel: (204) 925-7480 Fax: (204) 453-9032 Email: pmacdonald@panamclinic.com
Michael Hunt, BHK, MPT, MSc, PhD	Associate Professor and Director, Motion Analysis and Biofeedback Lab Department of Physical Therapy University of British Columbia, 212 Friedman Building 2177 Wesbrook Mall, Vancouver, British Columbia, CA V6T 1Z3	Tel: (604) 827-4721 Fax: (604) 822-2870 Email: michael.hunt@ubc.ca
Biostatistician Member		
Stephen R. Wisniewski, PhD	Vice Provost for Data and Information, Office of the Provost Co-director, Epidemiology Data Center, Epidemiology	Tel: (412) 624-2246 2nd Tel: (412) 624-5218 Fax: (412) 624-3775 Email: stevewis@pitt.edu

- Review creation and retention of source documentation
- Review procedures for data entry.
- Review of action items for Reportable Events
- Discuss site specific communication plan with participants, physical therapists, site PI, local IRB and Clinical Coordinating Center.

- Clinical Monitoring
  - Contacts
  - QCC and site responsibilities
  - Frequency
  - Close out procedures
- Site Essential Documents File Review
  - Structure of the Regulatory Binder as well as Essential Documents to include: IRB approval documents: protocol, patient handouts, advertisements, consent document
  - Document updates
- Tour of Facilities
- Summary/Review of Action Items

A site can be activated only after all of the requirements of the Clinical Terms of Award list (see Table 6 below) have been met.

Table 6 – Site Activation Requirements Check List

Item	Date
1. IRB Approval Received for Protocol, Consent Form, and Other Applicable Documents	
2. Site Essential Document File Approved	
3. Study Materials on Site	
4. Site Initiation Visit Completed • Trained on protocol, study procedures (MOP), electronic systems. (Note this requirement includes re-training, if site activation is more than 8 weeks after the site initiation visit. The re-training will be conducted remotely via conference calls/webinars)	

12 STATISTICAL CONSIDERATIONS

12.1 Study Hypotheses

The overall objective of this study us to investigate the effects of timing of surgery (early vs. delayed) and timing of post-op rehabilitation (early vs. delayed) for the treatment of military personnel and civilians that have sustained a MLKI. To achieve this objective, we will conduct two parallel randomized controlled trials. The aims and hypotheses for these trials are:

***Aim 1*: Determine the effects of timing of surgery and post-operative rehabilitation on time to return to pre-injury level of military duty, work and sports and patient-reported physical function.**

We hypothesize that early surgery, early rehabilitation and the combination of early surgery with early rehabilitation will lead to an earlier and more complete return to pre-injury military duty, work and sports and better patient-reported physical function.

***Aim 2*: Determine the effects of timing of post-operative rehabilitation on time to return pre-injury level of military duty, work and sports and patient-reported physical function.**

We hypothesize that early rehabilitation will lead to an earlier and more complete return to pre-injury military duty, work and sports activity and better patient-reported physical function.

12.2 Sample Size Considerations

Based on our preliminary retrospective study, we estimate that across 25 clinical sites there will be 1213 MLKIs over a 2-year recruitment period. After the exclusions for participation in the trial that randomizes timing of surgery and rehabilitation (Aim 1), we estimate that there will be approximately 650 eligible individuals with a MLKI that present to orthopaedics in time to make it possible to perform surgery within 6 weeks if randomized to early surgery. If approximately 60% of the eligible subjects agree to participate in the study, this would provide a total sample size of 392 (n= 98 per cell).

APPENDIX C: STUDY FORMS