Surgical Timing and Rehabilitation for Multiple Ligament Knee Injuries: A Multicenter Integrated Clinical Trial

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the Terms and Conditions US Army Medical Research Acquisition Activity (USAMRAA). All personnel involved in the conduct of this study have completed human subjects protection training.

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SIGNATURE PAGE

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

I will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

"Surgical Timing and Rehabilitation for Multiple Ligament Knee Injuries: A Multicenter Integrated Clinical Trial"

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LIST OF ABBREVIATIONS

ACL	Anterior Cruciate Ligament
ADL	Activities of Daily Living
AE	Adverse Event
AEAC	Adverse Event Adjudication Committee
CAT	Computerized Adaptive Test
CCC	Clinical Coordinating Center
Co-I	Co-Investigator
CMP	Clinical Monitoring Plan
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTSI	Clinical and Translational Science Institute
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DoD	Department of Defense
DMP	Data Management Plan
DSMB	Data Safety and Monitoring Board
DSMP	Data Safety and Monitoring Plan
EHR	Electronic Health Record
ES	Effect Size
ESC	Executive Steering Committee
FCI	Functional Comorbidity Index
GCP	Good Clinical Practice
GRC	Global Rating of Change
HRPO	Human Resources Protection Office
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IKDC	International Knee Documentation Committee
IKDC-SKF	International Knee Documentation Committee Subjective Knee Form
IRB	Institutional Review Board
ITB	Iliotibial Band
LCL	Lateral Collateral Ligament
MCL	Medial Collateral Ligament
MLKI	Multiple Ligament Knee Injury

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

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

PROTOCOL SUMMARY

Title:

Surgical Timing and Rehabilitation for Multiple Ligament Knee Injuries: A Multicenter Integrated Clinical Trial

Précis:

Military personnel and civilians between the ages of 16 and 55 with a multiple ligament knee injury (MLKI) without a history of prior knee ligament reconstruction that do not have a peri-articular fracture, vascular injury, poly-trauma or a traumatic brain injury will be eligible to participate in this multicenter randomized clinical trial. Participants will be randomly assigned to timing of surgery (early – within 6 weeks of injury vs. delayed – surgery 3 to 4 months after injury) and timing of post-operative rehabilitation (early – weightbearing as tolerated [WBAT] gait and unrestricted range of motion [ROM] exercises starting within one week of surgery or delayed – non-weightbearing [NWB] gait and limited ROM for four weeks). Subjects that cannot be randomized to timing of surgery will be randomized to only timing of rehabilitation in a separate parallel trial. Participants return to pre-injury military duty, work and sports participation and patient-reported physical function will be monitored over 24 months follow-up.

Objectives:

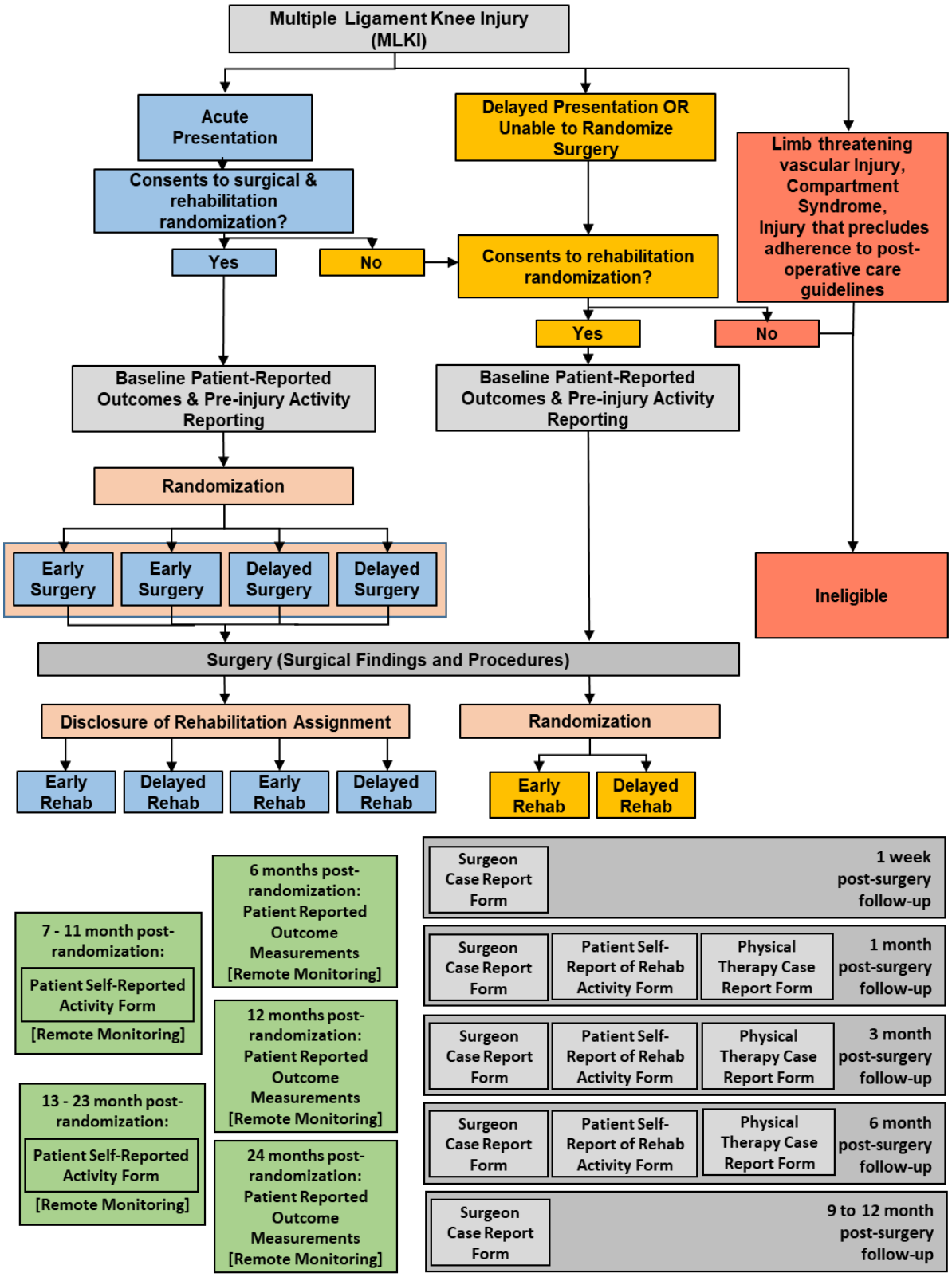
To investigate the effects of timing of surgery (early vs. delayed) and timing of post-op rehabilitation (early vs. delayed) for the treatment of military personnel and civilians that have sustained a MLKI on time to return to pre-injury level of military duty, work and sports participation and patient reported physical function. Secondary outcome measures will include additional knee-specific and general patient-reported measures of physical function and health related quality of life, recovery of range of motion (ROM), arthrofibrosis, residual laxity, complications/adverse events, re-injury and additional surgical procedures. The specific aims 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 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.
Population:	A total of 690 (392 for Aim 1 and 298 for Aim 2) male and female military personnel and civilians between the ages of 16 and 55 with a MLKI (complete grade III injury of two or more ligaments) without a history of prior knee ligament reconstruction will be eligible to participate in the clinical trials. Individuals with a torn or avulsed patellar or quadriceps tendon, fracture that precludes adherence to post-operative care guidelines or use of an external fixator to maintain reduction of the knee for greater than 10 days, that are unable to WB on the contralateral uninjured leg or have a traumatic brain injury (TBI) that limits their ability to participate in their post-operative care will be excluded from participation in these studies.
Phase:	III
Number of Sites:	25
Description of Intervention:	To address Aim 1, individuals with a MLKI that present within 6 weeks of injury will be randomized to early (within 6 weeks of injury) or delayed (12 to 16 weeks after injury) surgery and early (WB and unrestricted ROM exercises starting first week after surgery) vs. delayed (non-WB and knee locked in extension for the first four post-op weeks) rehabilitation. To address Aim 2, individuals with a MLKI that present greater than 6 weeks after injury, have an injury that precludes randomization to early or delayed surgery as well as those that refuse surgical randomization will be eligible to participate in the trial that compares only early vs. delayed rehabilitation.
Study Duration:	48 months
Subject Participation Duration:	24 months
Estimated Time to Complete Enrollment:	21 months

Schematic of Study Design:



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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

2.1.1 Overview of Multiple Ligament Knee Injuries

Multiple ligament knee injuries, including knee dislocations, represent a spectrum of injury from disruption of two ligaments (one cruciate ligament and one collateral ligament) to all four ligaments (both cruciates and both collateral ligaments). These injuries are potentially devastating and are often associated with significant injury to multiple structures of the knee including the capsule, tendons, menisci, chondral surfaces, bone, nerves and blood vessels. Concomitant injuries may include those to the popliteal artery,[1] tibial nerve, peroneal nerve,[1,2] joint capsule, patellar, quadriceps, biceps and/or popliteus tendons, iliotibial band, medial or lateral menisci and/or fractures.[3] Because of the extensive nature of injury, treatment for MLKIs creates multiple complex problems fraught with complications[4-6] As such, MLKIs often have adverse effects on the long-term health of the knee[7,8]and frequently lead to restricted participation in military duty, work and sports.[9,10] and early separation from the military. While multiple studies have reported treatment algorithms and outcomes for MLKIs, many of these studies are retrospective in nature with small sample sizes. Only a few prospective studies have been published and to date there are no randomized controlled studies that have investigated optimal treatment methods for these complex knee injuries.

The lack of high-level evidence related to treatment of MLKIs is due to both the heterogeneity of the injury and the relatively low incidence of MLKIs compared to isolated ligament injury. A precise estimate of the number of knee dislocations has not been determined, however it has been estimated that for every 1400 orthopaedic injuries there is one knee dislocation.[11] Furthermore, the incidence of MLKIs is likely under-estimated because many of the knee dislocations spontaneously reduce and are misdiagnosed. Because of the physical demands in the military and the 10 fold greater risk of ACL injuries in the military compared to civilian population,[12] the risk of a knee

dislocation or MLKI in the military population is likely greater than the risk in the civilian population.

Despite their relatively low incidence, MLKIs and knee dislocations are associated with a high rate of adverse outcomes due to poor wound healing, arthrofibrosis, neurovascular injuries, persistent pain and instability and PTOA, resulting in residual disability and high direct and indirect health care costs. Functionally, patients have few limitations with activities of daily living but are frequently limited with higher demand activities such as those associated with military training, physical labor and sports.[9]

2.1.2 Impact of Multiple Ligament Knee Injuries on Military Duty, Work, and Sports

Multiple ligament knee injuries result in significant time lost from military duty, work and sports.[9,13-15] In many cases, patients are unable to return to their pre-injury military duty, work, or sports. In fact, the return to duty rate after combat-related MLKIs has been reported as low as 41% [13]to 50%[9] and is substantially lower than the average reported civilian return to work rate of 81%.[10,16,17] The most commonly cited reasons for individuals not being able to return to work after a MLKI are knee pain (53%), instability (26%) and concurrent injuries (26%).[16] While these studies indicate the majority of civilians with a MLKI return to work, neither the influence of the physical work demands or the precise time for return to work have been considered, which are both needed to fully understand the economic and societal costs of these devastating injuries.

Reported return to sports rates after MLKI are generally lower than return to work rates, ranging from 17% to 81%, with a mean of 50%.[10] For competitive athletes, only 22% were able to return to the same level of competitive sports.[18] A similarly low return to sports rate of 17% was observed among military service members after MLKI.[9] The ability to return to sports after a MLKI appears to depend on the pre-injury level of sports in which the individual participates. A greater percentage of individuals with a low level of pre-injury activity were able to return to a similar level of activity compared to patients with a higher pre-injury activity level.[18] Factors associated with the inability to return to

sports include pain (55%), instability (19%), concurrent injuries (14%) and swelling (12%).[16]

While studies have reported the rates of return to military duty, work, and sports, relatively few have provided information regarding the time from surgery to return to activity. Furthermore, the majority of the studies are retrospective in nature with limited sample sizes and none have prospectively determined the time required to return to pre-injury military duty, work and sports, which from the military's perspective is of primary interest and highly relevant to unit readiness and return to duty capabilities.

2.1.3 Association Between Multiple Ligament Knee Injuries and Premature Development of Arthritis

Post-traumatic osteoarthritis arthritis (PTOA) is the most common long-term complication of a MLKI.[8,19] At a minimum of two years follow-up, 87% of knees with a MLKI had grade 2 or worse Kellgren & Lawrence arthritic changes on radiographs, in contrast to only 35% of uninjured knees.[8] Richter et al. reported similar rates of arthritis (68% Grade 2 or worse) at a mean of 8-years follow-up, and perhaps most importantly found an inverse relationship between PTOA and knee stability at follow-up, suggesting that surgical restoration of native knee stability may decrease the risk of PTOA.

The robust link between MLKI and premature development of knee osteoarthritis (OA) is especially pertinent for the military population. Knee OA represents an exceptionally large occupational burden for military personnel,[7] and affects military service members at higher rates than their civilian counterparts.[20,21] The overall rate of arthritis in military service members has been rising, and the incidence of PTOA in the military has risen 100% since 2005.[7] A recent review of U.S. Physical Evaluation Board (PEB) data for 1566 combat-injured service members reported that 100% of battlefield knee injuries resulted in PTOA.[21] The implications of this rising incidence are staggering considering that the most common reason for disability-related medical separation for military service members is OA.[21,22]

The development of PTOA following a MLKI is at least in part due to the inability to restore normal structure and function of the knee. Joint contracture, residual instability,

muscle weakness and/or poor neuromuscular control may all contribute to abnormal knee kinematics leading to altered loading of the knee with subsequent development of PTOA in the long term. We believe that determining the optimal time for surgery and initiation of post-op rehabilitation may reduce residual knee impairments that contribute to development of PTOA. Because of the extended time to develop PTOA, PTOA as an outcome measure will not be included in this study, however we will consider follow-on studies to assess long-term outcomes, including PTOA, of the subjects that participate in this study. Rivera et al. [21] provided a fitting summary for this study by stating that "PTOA is common in the battlefield population," and recommended that future studies should focus on "identification of clear treatment-related factors" that contribute to the development of PTOA, including "timing of surgery for intra-articular injuries" and "optimum rehabilitation strategies."

2.1.4 Controversies in Surgical Management of Multiple Ligament Knee Injuries

While there are a number of controversies related to treatment of MKLIs, the literature has consistently demonstrated that operative management is superior to non-operative management of MLKIs.[10,16,23,24] Patients treated surgically were significantly more likely to return to work[25,26]and sports.[16,26,27] Furthermore, patients who underwent operative treatment for MLKI have shown lower rates of endstage arthritis and higher patient-reported outcomes (PROs) scores than those who underwent non-operative management for the same types of injury.[16] However, the optimal timing of surgery is less well understood and remains the subject of intense debate.

2.1.5 Postoperative Rehabilitation of Multiple Ligament Knee Injuries

The timing of rehabilitation after surgery for a MLKI has not been investigated. The best available evidence for the timing of post-operative rehabilitation for knee ligament surgery is based on evidence from the ACL literature. Early (accelerated) rehabilitation (immediate WB, ROM, quadriceps exercises) after ACL reconstruction is the current standard of care.[28] Early (accelerated) rehabilitation has been found to reduce post-operative stiffness,[29] and is either superior or equivalent to delayed rehabilitation in

terms of PROs and resolution of ROM and strength deficits without adversely affecting knee joint laxity.[30-32]

Post-operative rehabilitation after surgery for a MLKI typically involves a period of non-weightbearing and delayed initiation of ROM exercises to protect the repaired/reconstructed structures[33,34] however these guidelines are based on Level V expert opinion and have not been tested in a trial.

2.2 Rationale

The timing of surgical intervention is a crucial consideration for treatment of MLKIs, and the ideal timing for surgery has yet to be conclusively determined. While certain circumstances require early intervention (irreducible knee dislocation, vascular injury, etc.), the majority of MLKIs create a treatment conundrum. Recently, authors have suggested early surgical intervention within 3 to 6 weeks of injury, because within this time period tissue planes are more easily identifiable, tissue quality is sufficient to hold sutures for repair, and retraction of tissues such as ruptured tendons is minimized.[24] However, other authors have agreed with the conventional wisdom that delayed surgery for MLKI can decrease perioperative risks, such as compartment syndrome (from capsular fluid extravasation during surgery) and arthrofibrosis.[35-37] Although several studies have compared the results of early vs. delayed surgery for MLKIs, the overwhelming majority of these studies were retrospective.[3,38-42] Notably, no Level I prospective randomized trials have compared outcomes of early vs. delayed surgery for MLKI, and results from existing studies vary widely.

A systematic review of 12 retrospective studies found no difference in outcomes based on the International Knee Documentation Committee (IKDC) Knee Ligament grade between early (58.4% good/excellent) and delayed (45.5% good/excellent) surgical management of KD-III injuries.[36] However, the authors pooled results across studies that did not directly compare early vs. delayed surgery. A second systematic review of 24 Level III and IV retrospective studies that compared early vs. delayed surgery found increased post-op anterior laxity and more frequent flexion deficits in those undergoing

early surgery for a MLKI, but no difference in posterior, varus or valgus instability, average ROM, or patient reported outcomes. There were a greater number of patients ultimately needing manipulation under anesthesia for post-op stiffness in the early compared to delayed surgery group.[43] A third systematic review of five retrospective studies involving 130 patients that underwent early (within 3 weeks of injury) or delayed surgery for a MLKI found that that early surgery resulted in higher Lysholm scores (90 versus 82) and a greater percentage of "excellent/good" IKDC results (47% verus 31%). No differences in ROM between the early and delayed surgery groups were found.[24]

In summary, there is a trend in published studies toward improved patient-reported outcomes and laxity in early compared to delayed surgery, but there is an increased risk of postoperative stiffness. However, non-randomized and retrospective studies that have investigated the timing of surgery for MLKIs are inherently limited because patients were selected for early versus delayed surgery based on the time of presentation and the expected or perceived soft tissue quality. As such, it is not possible to directly compare the early vs. delayed surgery and inferences from the data must be made with caution. Furthermore, none of the studies that examined early vs. delayed surgery precisely measured time to return to military duty, work and sports as an outcome, which of paramount importance from the perspective of unit readiness and the social and economic impact of these injuries. Due to the conflicting evidence regarding early versus delayed surgical management of MLKIs, there is a need for a large randomized controlled trial to determine the optimal timing of surgery for these devastating injuries that can only be achieved in a large multicenter trial.

2.2.1 Rational for Early vs. Delayed Post-Operative Rehabilitation for Multiple Ligament Knee Injuries

Mook and colleagues systematically reviewed the available literature through 2008 concerning the timing of post-operative rehabilitation. In individuals treated with early surgery and immediate motion compared to immobilization, there were fewer instances of posterior, varus and valgus laxity, loss of flexion >10º, loss of extension >5º, and poor outcome scores.[43] These results are specific only to the mobility component of

rehabilitation – early mobility was defined as allowing greater than 30^{o} motion prior to 3 weeks after surgery. It should be noted that all of the studies included in the review by Mook et al were non-randomized comparative or single cohort retrospective studies. Currently there are no randomized trials comparing early vs. delayed motion.

Mook and colleagues[43] did not review the effects of weight bearing status. Many published rehabilitation protocols for MLKIs call for an extended period of non-weight bearing (NWB) ranging from 4 weeks to 6 weeks.[33,44-50] Very few protocols recommend weight bearing as tolerated (WBAT)[51] and some recommend early partial weight bearing (PWB)[3,8,16,34,40,52,53] or toe-touch weight bearing (TTWB).[54-56] Considering the variability with the current expert recommendations for weight bearing (ranging from NWB, TTWD, PWB tor WBAT) and the lack of established outcomes after MLKI surgery, there is little evidence to support the need for non-weight bearing status. Conversely, controlled weight bearing benefits cartilage and meniscus nutrition,[57] can provide beneficial proprioceptive input to the knee joint, and promote muscle activity. Given the variability in weight bearing after MLKI surgery and its potential benefits, we will test a method to dose early weight bearing for the reconstructed knee based on the cardinal signs of inflammation (effusion, pain, warmth & redness).

Therefore, given the above information, we have designed this study to determine if early controlled WB and ROM exercises within the first week after surgery will allow for restoration of normal ROM of the knee with no increased risk of laxity or instability, leading to an earlier and more complete return to military duty, work and sports. We hypothesize that early WB and ROM exercises initiated within the first week after surgery will shorten the time to return to pre-injury level of military duty, work and sports.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

Participants in this study will undergo multiple knee ligament reconstruction surgery as part of their standard of care treatment. The surgery will be performed by surgeons who are experienced in reconstructing structures of the knee. The risks of surgery will be

discussed during the clinical surgery consent process. The risks of surgery include the risks associated with anesthesia as well as post-operative pain and swelling, loss of motion or joint stiffness, recurrent laxity and instability, infection, deep vein thrombosis and injury to neurovascular structures. Because subjects participating in this study would be undergoing surgery regardless of whether they participate in this study, the risks associated with the surgery itself are no greater than the risks had the subject not participated in this study.

While the current standard of care for MLKIs includes early or delayed surgery and early or delayed post-operative rehabilitation, there is no definitive evidence of the risks associated with these methods of treatment. However, randomization to these standard of care methods for surgical treatment and rehabilitation of MLKIs may carry associated risks that are currently unknown. These may include the risk of joint stiffness and contracture for those in the early surgery and/or delayed rehabilitation groups as well as increased joint laxity and instability of the knee for those undergoing delayed surgery and/or early rehabilitation. To mitigate these risks, we will closely monitor post-operative recovery of the individual and will intervene as necessary. This could include additional surgery and/or physical therapy to address arthrofibrosis or instability.

Follow-up activities involved with this study include the completion of patient-reported outcome measures and evaluation of return to activity by subjects at multiple intervals throughout the duration of the study. These follow-up activities will be completed by the subjects remotely via Internet-based data collection methods. Although data security measures will be implemented, there is a risk of breach of confidentiality.

Subjects will complete several instruments (PROMIS Global 10 Health Scale and the Emotional Impairments Scale of the Multiple Ligament Quality of Life Questionnaire) that inquire about behavioral health status. While these instruments are not direct measures of emotional distress (depression, anxiety etc.), responses to some of these questions could indicate the participant is in emotional distress. On the PROMIS Global 10 Health Scale, this includes questions 4 (In general, how would you rate your mental health, including your mood and ability to think?) and 8 (How often have you been

bothered by emotional problems such as feeling anxious, depressed or irritable?) and question 34 (How often are you depressed or sad due to knee pain or nerve pain?) on the Emotional Impairment Scale of the Multiple Ligament Quality of Life Questionnaire. Responses of "poor" to question 4 or "always" to question 8 on the PROMIS Global 10 Health Scale or a response of "always" to question 34 on the Emotional Impairment Scale of the Multiple Ligament Quality of Life Questionnaire could indicate that the participant is in emotional distress. The responses to these questions will be monitored and will provide feedback to the participant regarding appropriate intervention, if needed and if the situation affects the immediate safety of the subject, we will communicate this to the research team who will assist in facilitating immediate evaluation at the Emergency Department or through a crisis center.

2.3.2 Potential Benefits

Participants in this study may benefit from being followed more closely during the conduct of the study. This would allow for more timely progression of the post-operative recovery process as well as more timely identification and treatment of any complications associated with multiple ligament knee injuries. This study also has the potential to improve the surgical and rehabilitation care for future patients undergoing treatment of a multiple ligament knee injury.

3 OBJECTIVES

3.1 Study Objectives

The overall objective of this project is 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:

3.1.1 Specific Aim 1

To determine the effects of timing of surgery and post-op 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.

3.1.2 Specific Aim 2

To determine the effects of timing of 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.

3.2 Study Outcome Measures

The primary outcome will be time return to full pre-injury military duty, work and sports. Patient-reported physical function as measured with the Activities Limitation Scale of the Multiple Ligament Quality of Life (MLQoL) Questionnaire will be assessed as a co-primary outcome 6, 12 and 24 months after randomization. Secondary outcome measures will include additional knee-specific and general patient-reported measures of physical function and health related quality of life, recovery of range of motion (ROM),

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.

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

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.

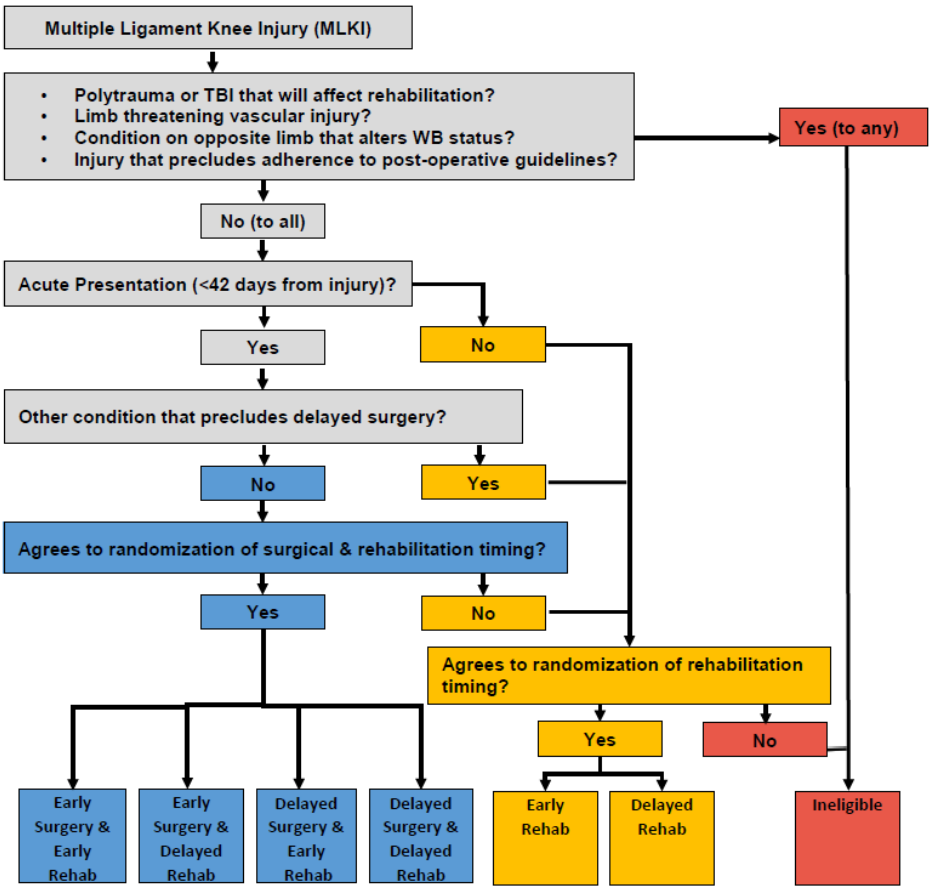

Figure 1 - Subject Presentation, Eligibility, and Randomization. Blue boxes are associated with Aim 1. Yellow boxes are associated with Aim 2.

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:

2. Have a torn or avulsed patellar or quadriceps tendon;
3. Have a periarticular or long bone fracture that is anticipated to preclude weight bearing after surgery;
4. Require use of an external fixator to maintain reduction of the knee or soft tissue/open wound management for greater than 10 days;
5. Planned staged surgical treatment for MLKI;
6. Are unable to WB on the contralateral uninjured leg;
7. Have a traumatic brain injury (TBI) that limits their ability to participate in their post-operative care or any condition that would preclude the ability to comply with post-operative guidelines;
8. Skin or soft tissue injury that precludes early surgery and/or early rehabilitation;
9. Surgical procedure that precludes early WB & ROM (i.e. surgery for extensor mechanism rupture or avulsion, vascular graft surgery).
10. Have multiple trauma that limits ability to participate in early rehabilitation;

5.2.2 Exclusion of Participants in Trial for Aim 1 - Randomization to Both Timing of Surgery and Post-Operative Rehabilitation

Individuals will be excluded from the trial that randomizes both the timing of surgery and post-operative rehabilitation if they:

1. Have a vascular injury that dictates the timing of surgery;
2. Have multiple trauma that precludes surgery within 6 weeks of injury;

5.2.3 Exclusion of Participants in Trial for Aim 2 – Randomization to Only Post-Operative Rehabilitation

Individuals will be excluded from the trial that randomizes only the timing post-operative rehabilitation if they:

1. Have vascular surgery that precludes early rehabilitation;
2. Have a skin or soft tissue injury that precludes early weightbearing or range of motion.

Table 1: Summary of Eligibility Criteria for Each Clinical Trial	
Specific Aim 1 – Randomize Timing of Surgery & Post-Operative Rehabilitation	**Specific Aim 2 – Randomize Timing of Post-Operative Rehabilitation**
Inclusion Criteria	**Inclusion Criteria**
• Male and female military personnel & civilians with MLKI (grade III injury of 2 or more ligaments)	• Male and female military personnel & civilians with MLKI (grade III injury of 2 or more ligaments)
• 16 to 55 years of age	• 16 to 55 years of age
• **Present for treatment in time to be randomized to early surgery (within 6 weeks of injury)**	
Exclusion Criteria	**Exclusion Criteria**
• Prior ligament reconstruction of ipsilateral knee	• Prior ligament reconstruction of ipsilateral knee
• Torn or avulsed patellar or quadriceps tendon	• Torn or avulsed patellar or quadriceps tendon
• Have a periarticular or long bone fracture that is anticipated to preclude weight bearing after surgery	• Have a periarticular or long bone fracture that is anticipated to preclude weight bearing after surgery
• External fixator for greater than 10 days	• External fixator for greater than 10 days
• Planned staged surgical treatment	• Planned staged surgical treatment
• Inability to WB on contralateral leg	• Inability to WB on contralateral leg
• Traumatic brain injury that limits ability to participate in post-op care	• Traumatic brain injury that limits ability to participate in post-op care
• **Vascular injury that dictates timing of surgery** • **Polytrauma that precludes surgery within 6 weeks of injury**	• **Vascular surgery that precludes early rehabilitation** • **Polytrauma that limits ability to participate in post-op care**
• **Skin or soft tissue injury that precludes early surgery and rehabilitation**	• **Skin or soft tissue injury that precludes early rehabilitation**
• Surgical procedure that precludes early WB & ROM	• Surgical procedure that precludes early WB & ROM

5.3 Strategies for Recruitment and Retention

5.3.1 Recruitment of Participants for the Trial for Aim 1 that Randomizes Both the Timing of Surgery and Rehabilitation

Based on our preliminary retrospective study, we estimate that across 25 clinical sites there will be 1213 MLKIs over a 2-year recruitment period. Additionally, based upon the preliminary retrospective study we expect that approximately 78% of the patients will present to orthopaedics within 6 weeks of injury, making it possible to randomize the individual to early surgery, defined as surgery within 6 weeks of injury. We utilized the prevalence of polytrauma; soft tissue and skin, vascular and quadriceps and patellar tendon injuries and use of an external fixator to estimate the number of individuals we would expect to meet our eligibility criteria for Aim 1. In doing so, we estimated that 50% of the individuals with polytrauma would be able to undergo surgery within six weeks of injury if randomized to early surgery. After these exclusions, we estimated that there will be approximately 650 eligible individuals with a MLKI that present to orthopaedic surgery 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). Assuming 10% lost to follow-up over two years, we expect to have 352 subjects (n=88 per cell) for the final analysis. To achieve the required sample size for the trial that randomizes both timing of surgery and post-operative rehabilitation, with 25 clinical sites, we expect that each site will recruit and randomize approximately 16 subjects.

5.3.2 Recruitment of Participants for the Trial for Aim 2 that Randomizes Timing of Rehabilitation

After accounting for those included in the trial that randomizes surgery and rehabilitation and applying the exclusions described above we estimate that approximately 440 individuals with a MLKI will be eligible for participation in the trial that randomizes only timing of post-op rehabilitation. If approximately 68% of the eligible subjects agree to participate in the study that randomizes only timing of post-operative rehabilitation, this

would provide a total sample size of 298 (n= 149 per cell). Assuming 10% lost to follow-up over two years, we expect to have 268 subjects (n=134 per cell) for the final analysis. To achieve the required sample size for the trial that randomizes only the timing of post-operative rehabilitation, with 25 clinical sites, we expect that each site will recruit and randomize approximately 12 subjects.

5.3.3 Recruitment Process

Potentially eligible patients will be informed of the study by their orthopaedic surgeon or the surgeon's clinical designee, either during an office visit or in the Emergency Department. To identify potentially eligible individuals that present to the Emergency Department, the study team will work closely with the orthopaedic residents and orthopaedic trauma attending surgeons and fellows to identify and inform individuals with a MLKI that are eligible for the study. Individuals with a MLKI interested in learning more about the study will be introduced to a research coordinator who together with the surgeon-investigator will explain the study details to the participant. If the individual is willing to participate in the study, he/she will review and sign the consent form, which will also be signed by the surgeon-investigator. The participant will be given as much time as necessary to review the consent form and ask questions. Prior to signing the consent form, all questions will be answered to the satisfaction of the individual by research coordinator and/or surgeon-investigator.

For active duty military personnel, no individuals in the participant's chain of command will be involved in the recruitment process. Because the surgeon is also an investigator in the study, we recognize that the surgeon may be conflicted in their attempts to recruit the individual into the study. During the recruitment and consent process, subjects will be informed of this potential conflict and offered the opportunity to discuss their care with another surgeon that is not associated with the study. Once informed consent has been obtained, screening procedures will be performed to confirm final eligibility for participation in the trial for Aim 1 or 2.

5.3.4 Efforts to Monitor and Maximize Subject Recruitment

A number of strategies have been and will be used to ensure that we meet the recruitment targets. We will review all study procedures with an emphasis on successful recruitment methods at the first in-person Investigators' Meeting as well as to the Research Coordinator during the Site Initiation Visit. Recruitment materials, such as flyers, recruitment scripts and laminated reference cards that summarize eligibility criteria will be developed and distributed to the sites. To keep all study personnel engaged we will produce and distribute a quarterly newsletter that highlights study successes, provides recruitment tips and lists the recruitment results for each site.

As part of the Clinical Monitoring Plan, we will closely monitor monthly recruitment at each of the sites. Sites that achieve or exceed the recruitment goals will be encouraged to recruit additional subjects beyond their targeted enrollment and will be rewarded accordingly based on the budget model that reimburses sites based on the number of subjects enrolled and followed.

For those sites that lag in recruitment, we will work closely with them to increase enrollment. Strategies to improve recruitment will vary based upon the barriers encountered by the site. Site participation in the study will be reconsidered if recruitment drops below 50% of site target enrollment after 3 quarters of recruitment (i.e. enrolled less than 6 subjects by the end of year 1). If overall recruitment for the study lags behind targeted enrollment we will consider adding sites and will re-allocate financial support for additional sites from those sites that are not meeting recruitment projections or have been terminated from the study.

A Recruitment Committee has been established and consists of investigators and research coordinators from the Coordinating Center and the collaborating clinical research sites. The Recruitment Committee will establish a plan for and monitor recruitment throughout the duration of the trial. The committee will review and approve recruitment materials, such as cards with eligibility criteria, posters that can be used at the sites. The Committee will also encourage each site to do a presentation related to MLKIs and the STaR Trial at the site's Grand Rounds. Additionally, should a site be

recruiting fewer subjects than recommended, the Recruitment Committee will evaluate the site and make recommendations to improve recruitment. If recruitment fails to improve, the Recruitment Committee will make a recommendation to the Executive Committee to terminate the site.

5.3.5 Subject Payment

Individuals will be compensated for participation in the study. The participating clinical sites will be responsible for payment of subjects enrolled by the site. All participant payments will be processed by each site.

5.3.5.1 Pro-Rated Payments for Subjects Recruited at Civilian Research Site

If individuals participate and complete all research-related activities, they will receive up to $400. Payment for partial participation in the study will be pro-rated as follows:

- Participants will be paid by the site at which they were enrolled $50 for informed consent and $55 for completion of the baseline patient-reported forms;

The Coordinating Center at the University of Pittsburgh will assume responsibility for collecting all patient-reported outcomes data. Participant payment for completion of follow-up patient-reported outcomes data will be prorated as follows:

- Completion of 6-month return to activity & patient-reported outcome measures - $35;
- Completion of 12 month return to activity & patient-reported outcome measures - $35;
- Completion of 24 month return to activity & patient-reported outcome measures - $35;
- Participant assessment of rehabilitation activities at post-operative months 1, 3 and 6 - $10/month up to $30;
- Participant completion of brief return to activity measure at post-operative months 7, 8, 9, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 - $10/month up to $160

5.3.5.2 Payment of Participant from Military Treatment Centers

No payments will be provided to active military personnel that are recruited to participate in this study. Dependents of active military personnel and retired military personnel will be paid for participation in the study as described above for civilians.

5.3.6 Efforts to Maximize Subject Retention

5.3.6.1 Research Follow-ups

For US Sites, all research follow-ups starting 6 months after randomization will be initiated by the Coordinating Center at the University of Pittsburgh utilizing text and/or e-mail messages. Contact information, including the participant's primary and secondary e-mail accounts and home and cell phone numbers will be obtained at the time of enrollment in the study. Individuals will also indicate their preferred method for communicating with the study investigators (i.e. e-mail, text messaging, phone). Additionally, we will ask participants to identify and provide contact information for two family members or close friends that do not live with the participant but know and will most likely always know how to contact the participant. Access to identifiable information will be limited to the site local research team and to research team at the Coordinating Center.

Canadian sites will enter de-identified clinical data including screening, baseline clinical examination, surgical findings and procedures and information from all clinical follow-up visits into the University of Pittsburgh electronic data capture system (REDCap). Contact information for each participant (email and/or phone number) is needed for the research follow-ups; however due to Canadian privacy laws that information for Canadian participants cannot be maintained on the University of Pittsburgh servers. Therefore, a copy of the REDCap project structure for the surveys involving patient reported outcomes will be sent to each Canadian site so that they can create their own survey project in the REDCap instance at their institution. Once the surveys have been administered, each Canadian site will be responsible for regularly exporting de-identified survey data and sending it to the STaR Trial DCC. The DCC will send reports back to

each Canadian site pertaining to missed follow-ups, potential adverse events and emotional health problems, and data quality.

Multiple attempts to contact non-responders will be utilized. Generally, participants will be contacted by their preferred method (either via e-mail or text messaging) one week prior to the follow-up due date, at the due date, and up to three times after the due date. If the participant does not respond to the third contact to their preferred contact, phone calls will be made by the Coordinating Center and/or by the site research staff.

5.3.6.2 Clinical Visit Follow-Ups

Standard of care clinical follow-up of participants will occur approximately 1 week and 1, 3, 6, and 9 to 12 months after surgery. This follow-up will make use of a standardized clinical examination and will be documented on the Clinical Visit Form. Sites will be paid upon completion and submission of the clinical forms. The electronic data capture system will generate regular reports of missing forms and missing data points. These reports will be shared with the site research coordinator for adjudication and resolution.

Should participants move or not attend follow up visits, efforts will be made by the research team to access the electronic health records to collect data from the follow-up clinical visits to complete the Clinical Follow-Up Visit form. The collection and use of clinical information from the medical record for research purposes is included in the IRB protocol and study participants agree to this in the informed consent process.

5.4 Treatment Assignment Procedures

To address Aim 1, 392 individuals with a MLKI that present within 6 weeks of injury will be randomized to early (within 6 weeks of injury) or delayed (12 to 16 weeks after injury) surgery and early (WB as tolerated and unrestricted ROM exercises starting first week after surgery) vs. delayed (non-WB and limited ROM exercises for the first four post-op weeks) rehabilitation. To address Aim 2, 298 individuals with a MLKI that present greater than 6 weeks after injury, have an injury that precludes randomization to early or

delayed surgery as well as those that refuse randomization to surgery will be eligible to participate in the trial that randomizes only early vs. delayed rehabilitation.

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 rehabilitation in the two-arm trial (Aim 2). Therefore, participants will have an equal chance of being randomized to one of four groups in the trial that randomizes timing of surgery and timing of post-operative rehabilitation and to one of two groups for the trial that randomizes only timing of post-operative rehabilitation.

For those enrolled in the trial for Specific Aim 1, randomization to early versus delayed surgery will occur after the informed consent process in individuals who are eligible for randomization to early surgery and agree to be randomized. To prevent the allocated rehabilitation intervention from influencing the surgical intervention, allocation to early vs. delayed rehabilitation will not be disclosed to the participant until after surgery. Randomization for the rehabilitation only trial (Aim 2) will remain pending until the participant has undergone surgery and eligibility criteria are re-confirmed. The allocated rehabilitation protocol will be communicated to the physical therapist by the surgeon and/or research coordinator at the time when the subject is referred to physical therapy one week after surgery.

5.4.1 Randomization Procedures

Randomization will occur at the subject level. The randomization schedule will be created by the Data Coordinating Center (DCC) statisticians using permuted blocks with random block sizes stratified by site and injury pattern (KD I, KD II-KDIV, KD-V). The randomization lists will be created using SAS version 9.4 using a random number generator and fixed seed. The lists will be uploaded into the REDCap randomization module. This module permits allocation concealment such that the allocation to the treatment arm is only viewed once all eligibility criteria are entered and confirmed to be met. 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 subject.

The SAS program used to generate the randomization schedule will be stored in the DCC STaR network folder which is only accessible by DCC staff.

5.4.2 Masking Procedures

These are unblinded trials as the participants and care providers will know when they are receiving surgery and when they are receiving rehabilitation. Both interventions being tested (early versus delayed surgery, early versus delayed rehabilitation) cannot be masked to the site coordinators because of these individuals are responsible for scheduling (or assisting with scheduling). The rehabilitation assignment will only be communicated to the surgeon after the surgery so as not to influence surgery. The dates of the surgery and rehabilitation are collected as part of the standard of care and will be available to the surgeons during follow-up. The primary outcome and most of the secondary outcomes are patient self-report, therefore, the health providers and research team have no influence on the response. Given that our interventions are either early or delayed surgery and/or rehabilitation, it is difficult for us to estimate the direction of potential bias (if any) that could come from the unblinded nature of this study.

5.4.3 Subject Withdrawal

Subjects may withdraw, at any time, their consent for participation in this research study. Any identifiable research or medical information recorded for, or resulting from, their participation in this research study prior to the date that they formally withdraw their consent may continue to be used and disclosed by the investigators for the purposes of the research study.

To formally withdraw consent for participation in this research study each subject should inform their decision the research team at the contact information provided on the first page of the informed consent document.

A subject's decision to withdraw their consent for participation in this research study will have no effect on their current or future relationship with the institution at which they were recruited. Their decision to withdraw their consent for participation in this research study will have no effect on their current or future medical care at the institution or with an affiliated health care provider.

It is possible that subject's may also be removed from the research study by the researchers. Subjects may be withdrawn if they do not comply with study procedures.

5.4.4 Reasons for Withdrawal

Patients will be discontinued from the study if, for example, they are unable to be compliant with the study follow-up procedures. The following is a list of examples of reasons for withdrawal:

1. Participant is deemed ineligible after signing consent;
2. Participant is unable or unwilling to travel to study center;
3. Participant finds the frequency of full follow-up visits burdensome;
4. Investigator determination, specify: _____
5. Participant has withdrawn consent, not otherwise specified
6. Lost to follow-up
7. Participant Death __/__/____ (date of death)

   Other: (specify) _____

5.4.5 Handling of Subject Withdrawals or Subject Discontinuation of Study Intervention

As specified in the local Data and Safety Monitoring Plan, subject withdrawals and deviations from allocated interventions will be reviewed during regularly scheduled data and safety monitoring meetings. The local Data and Safety Monitoring Plan (DSMP) will be implemented by the site PI and Co-Investigators.

5.5 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Suspension or termination may be imposed by the Principal Investigators, Research Monitor, Data and Safety Monitoring Board, IRB and/or HRPO. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Drs. James Irrgang and Volker Musahl, the site principal investigators and Ms. Jessica Clement, the DoD Scientific Officer. If the study is prematurely terminated or suspended, the principal investigator will promptly inform and provide the reason(s) for termination or suspension to the IRB and the DoD HRPO.

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

1. Determination of unexpected, significant, or unacceptable risk to subjects;
2. Failure to meet recruitment targets;
3. Insufficient adherence to protocol requirements;
4. Data that are not sufficiently complete and/or evaluable;
5. Determination of futility;
6. Non-compliance with the terms and conditions of the award from the DoD.

6 STUDY INTERVENTION

6.1 Description of Study Procedural Intervention(s)

6.1.1 Early vs. Delayed Surgery for MLKI

For the clinical trial that is performed for Specific Aim 1, we have operationally defined early definitive surgery to be surgery within 6 weeks of injury to repair and/or reconstruct the torn structures. Delayed surgery to has been operationally defined as repair and/or reconstruction of the torn structures 12 and 16 weeks after injury. Although early surgery is defined as within 6 weeks, every effort will be made to perform surgery as soon as possible, if randomized to early surgery. Staged surgery will not be considered an option for surgical treatment of MLKIs in this study and will render a potential participant ineligible.

All surgical findings and procedures will be documented on electronic surgical case report forms. As the QC for Surgery, Dr. Musahl will be available to answer any questions from surgeons regarding a subject's participation in the study.

Definitive surgical treatment of soft tissue injuries will follow a standardized algorithm (Figure 2) comprising primary repair and/or reconstruction. Surgery will be performed in accordance with the principles of anatomic repair and/or reconstruction of injured structures in a manner that will allow for early range of motion. Graft choice for reconstruction of injured tissues will be at the discretion of the operating surgeon and will not be standardized; however, graft choice will be recorded on the surgical case report form.

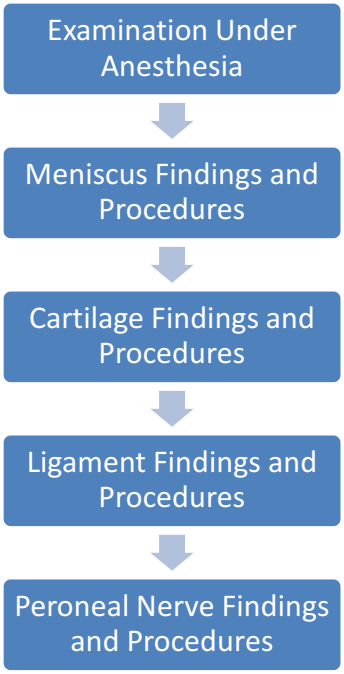

Figure 2. Surgical Algorithm

Examination Under Anesthesia – A complete assessment of knee function will be performed after anesthesia has been induced. The surgeon will assess

range of motion of the knee joint as well as the function of the cruciate ligaments, collateral ligaments, and the posterolateral corner.

Meniscus and Cartilage - The status of the menisci and cartilage will be assessed arthroscopically. Injuries to the menisci or cartilage may be left in situ, or surgery may be performed to repair or debride the tissue at the discretion of the operating surgeon. Meniscus and cartilage findings and procedures will be documented on form.

Cruciate Ligaments - Primary suture repair may be performed in cases of complete soft tissue avulsions or bony avulsions of either the ACL and/or posterior cruciate ligament (PCL). These injuries may also be reconstructed or augmented with an autograft or allograft. Anatomic single- or double-bundle reconstruction will be used for mid-substance disruptions of the ACL and/or PCL. Tunnels will be created in the footprints of the ACL and PCL on the femur and tibia using standard arthroscopic equipment, drill guides, and reamers. Grafts will be anchored either within the tunnels using interference screws or outside the tunnels using cortical suspensory buttons or suture post screws. For reconstruction of PCL injuries, PCL fixation will be performed with the tibia reduced at 90 degrees of knee flexion. Fixation of grafts for ACL reconstruction will be performed near extension.

Medial Injuries – Open approaches will be used for repair and/or reconstruction of the medial collateral ligament (MCL) and posteromedial corner. Soft tissue planes will be separated to facilitate layer-by-layer repair of the sartorius facia, superficial MCL and posterior oblique ligament (POL), as well as deep MCL and capsular structures. Suture anchors will be used as indicated for soft tissue or bony avulsions. Reconstruction of the medial structures will be performed as necessary depending on soft tissue quality and size of the zone of injury. Grafts will be placed into the MCL footprints on the femur and tibia. Fixation will be performed at 30° of knee flexion under varus stress following ACL and/or PCL fixation as described above.

Lateral Injuries – Open approaches will be used for repair and/or reconstruction of the lateral collateral ligament (LCL) and posterolateral corner structures [popliteus tendon and popliteofibular ligament (PFL)]. Injuries to the biceps femoris tendon or iliotibial

band will be addressed as necessary. Soft tissue planes will be separated to facilitate layer-by-layer repair of the iliotibial band (ITB) and biceps; LCL, PFL, and popliteus tendon; as well as the posterolateral and anterolateral capsule complex as indicated. Suture anchors will be used as indicated for soft tissue or bony avulsions. Reconstruction with grafts will be performed as necessary depending on soft tissue quality and size of the zone of injury. Grafts will be placed into the anatomic footprints of the LCL, PFL, and popliteus on femur/fibula, tibia/fibula, and femur/tibia, respectively. Fixation will be performed at 30° of knee flexion under valgus stress following ACL and/or PCL fixation as described above.

Peroneal Nerve Injury – During open lateral surgery, the peroneal nerve will be identified and protected from further injury. In cases of existing injury, the type of injury and any treatment provided will be documented.

Complications – Complications that occur during surgery will be documented. Intraoperative complications that are expected include nerve or vascular injury, loose hardware, and intraoperative fracture. Other unexpected complications that occur will also be documented.

At the conclusion of surgery, a hinged, long-leg brace will be placed on the participant's leg. This brace will be locked in extension (anatomic 0^{o}) until the first post-operative visit with the surgeon. The brace will be worn for a minimum of 6 weeks and will be unlocked based on the rehabilitation program to which the participant was randomized.

Medication for pain control, anti-coagulation/deep vein thrombosis prophylaxis, and antibiotics will be prescribed at the discretion of the operating surgeon. The decision to discharge the patient to home or to admit to the hospital for monitoring will also be made at this time. Each of these decisions will be documented at the first post-operative visit.

6.1.2 Early vs. Delayed Rehabilitation after Surgery for MLKI

We will investigate the effects of early vs. delayed post-operative rehabilitation after surgery for a MLKI in the randomized trials for Aims 1 and 2. Delayed rehabilitation will

be characterized by not allowing knee motion and use of a non-weight bearing gait for four weeks after surgery. Early rehabilitation will be characterized by weight bearing and unrestricted motion starting after the first post-operative visit with the orthopaedic surgeon.

After introduction of weight bearing and unrestricted ROM, all trial participants will follow the same criterion-based rehabilitation progression with three phases – Tissue Protection, Restoration of Motor Control, and Optimization of Function (Figure 3). The randomized intervention is nested inside of the Tissue Protection Phase; however, the Motor Control and Optimization of Function phases are the same for both groups.

The goals of the criterion-based rehabilitation progression are to return individuals to:

1. Normal activities of daily living, and
2. Work, military duty, and sports activities at the same level of participation as prior to injury.

6.1.2.1 Tissue Protection Phase

The Tissue Protection Phase begins immediately after surgery with a focus on restoring function while not disrupting the tissues addressed during surgery. The study rehabilitation interventions are nested in the Tissue Protection Phase; therefore, each group will have a different experience during this phase. Both groups will be managed identically between surgery and the first post-operative visit with the surgeon.

Generally, the Tissue Protection Phase ends when the participant meets the criteria to discharge all post-operative assistive devices for ambulation. In cases where hamstrings exercise must be limited, the Tissue Protection Phase ends when the participant meets the criteria to initiate non-resisted hamstrings exercise.

6.1.2.2 Immediate Post-Operative Rehabilitation

The brace will be locked in extension for the first week after surgery and participants will be non-weight bearing. Until the first post-operative appointment with the surgeon, all

participants will be instructed to perform isometric quadriceps exercises (quad sets, straight leg raises) and self-patellar mobilization.

During the first post-operative office appointment with the surgeon, the participant will be informed of the rehabilitation program to which he or she was randomized. The participant will be referred for standard of care physical therapy, with the instructions for WB and ROM as randomized. The physical therapist will be provided with the criterion-based protocol to advance gait and exercise activity as indicated by performance.

6.1.2.3 Delayed Rehabilitation Intervention

Participants randomized to the delayed rehabilitation treatment arm will be instructed not to bear any weight on the surgical limb for 4 weeks after surgery. For ambulation, the brace will be locked in extension. Participants will keep the brace locked in extension for four weeks and will continue the exercise program described in Section 6.1.2.2. After four weeks, the brace will be unlocked per the rehabilitation guidelines for gait and exercise. At this time, participants will also transition to a weight bearing as tolerated (WBAT) gait for ambulation. Four weeks after surgery, the participant's exercise and ambulation will be advanced based on the tissue response to treatment in a fashion that is identical to the progression of participants in the early rehabilitation treatment group.

6.1.2.4 Early Rehabilitation Intervention

Participants randomized to the early rehabilitation treatment group will be instructed to bear weight on the surgical limb as tolerated in the post-operative rehabilitation brace beginning one-week after surgery at the first post-operative visit with the orthopaedic surgeon. Participants will be able to perform unrestricted ROM exercise in the post-operative brace both in rehabilitation and at home.

The early rehabilitation intervention will not be confused with "accelerated" rehabilitation after anterior cruciate ligament reconstruction, in which range of motion is targeted aggressively after surgery and is generally the current standard of care. [28,71] The post-operative rehabilitation for the early rehabilitation group was developed to promote

gradual recovery of motion an weight bearing based on participant tolerance – no end range stretching or over-pressure is used and painful weight bearing is to be avoided.

6.1.2.5 Tissue-Specific Considerations During Tissue Protection Phase

The variety of injury patterns and surgical interventions to treat those injuries contribute to the variety of rehabilitation recommendations after MLKI. During the tissue protection phase, some tissues need significant protection to prevent disruption of the surgical repair or reconstruction. These protections are described in Table 2.

Table 2 Tissue Specific Considerations

Tissue Involved	Rehabilitation Modifications
ACL	Prevent resisted NWB knee extension between 10° and 60°
PCL	Prevent posterior translation of the tibia for 6 weeks No active or resisted hamstrings contraction
PLC/LCL	Range of knee extension limited to 0º (no hyperextension) Prevent posterior translation of the tibia for 6 weeks Avoid excessive varus forces on knee joint No active or resisted hamstrings contractions
MCL	ROM exercises with foot internally rotated Avoid excessive valgus forces on knee joint
Meniscus Repair (root or body repair)	Brace locked in extension for 4 weeks for ambulation, WBAT (if randomized to early rehabilitation) Avoid WB flexion in any range Flexion ROM limited to 90 degrees for 4 weeks (perform in non-weight bearing only)
	No active or resisted hamstrings contractions

6.1.2.6 Activity Progression during the Tissue Protection Phase

Progression of Weight Bearing

For this study, we have operationally defined “weight bearing as tolerated” as the amount of weight bearing that the participant can tolerate without evidence of increased inflammation of the knee (i.e. without pain, warmth, redness or effusion).

The time for initiation of weight bearing on the surgical knee will be based on the allocated rehabilitation group (early – starting at the first post-operative appointment with the physician; delayed – starting 4 weeks after surgery).

When initiating weight bearing, participants will be instructed to bear weight on their surgical limb as tolerated. Tolerance is defined as the amount of weight bearing that does not appreciably increase knee joint pain, effusion, or warmth.

Initially, weight bearing will be performed with an assistive device in a locked, double upright knee brace to prevent excessive sagittal or frontal plane motion. When participants can bear full weight on the leg without signs of increased inflammation and can demonstrate appropriate control of the knee when walking with the brace unlocked, gait training with a less restrictive assistive device (i.e. single crutch or cane) and with the brace unlocked brace will be initiated, and progressed as safely tolerated.

Progression of Exercise Activities

The immediate goal of exercise is to restore quadriceps activity and increase and/or maintain range of motion within the post-operative guidelines. Exercises progress from non-weight bearing quadriceps exercise through bilateral and unilateral weight bearing exercises. Weight bearing exercise recommendations and gait activity recommendations follow similar trajectories and complement each other.

All participants will begin exercises to restore quadriceps function immediately after surgery (e.g. quadriceps sets, straight leg raises).

All exercise recommendations are based on achievement of criteria as outlined in Figure 3. The criteria are identical between rehabilitation groups with the exception of time after surgery.

In the delayed rehabilitation intervention, non-weight bearing exercise, basic weight bearing exercise on two legs (e.g. squats and wall sits to 45^{O}), and simple unilateral exercises (e.g. step ups and single leg balance) may begin no sooner than four weeks after surgery.

In the early rehabilitation intervention, non-weight bearing exercise and basic weight bearing exercise on two legs (e.g. squats and wall sits to 45^{O}) may begin within two weeks of surgery. Simple unilateral exercises (e.g. step ups and single leg balance) may begin no sooner than three weeks after surgery.

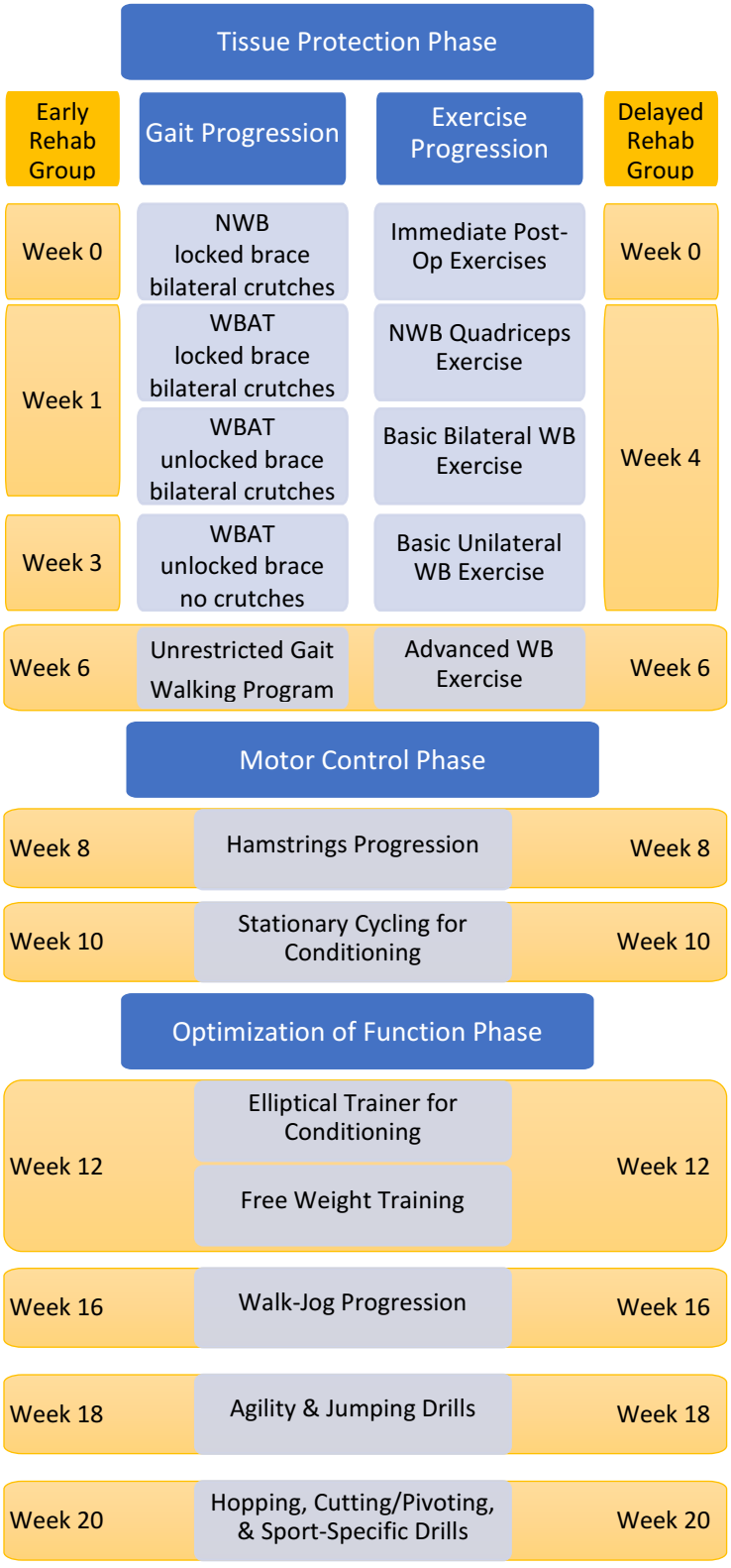

Figure 3. Rehabilitation Schema

Advanced weight bearing exercise (e.g. squats up to 90º, step down exercises) may begin no sooner than six weeks after surgery in either group.

6.1.2.7 Motor Control Phase

In the case of a PCL, PLC, or meniscus repair, hamstrings exercises are prohibited for 8 weeks and protected for 12 weeks. After 8 weeks, active contraction of the hamstrings without external resistance may begin. After 12 weeks, resistive exercises for the hamstrings may be initiated.

Because of the relatively long period of low-intensity cardiovascular training that allows the tissues to recover, conditioning exercises are important to initiate when safe cycling for aerobic conditioning can be initiated – 10 weeks after surgery, and when the individual has the necessary range of motion and control of the lower extremity to initiate and safely stop cycling. This is a direct progression from cycling for range of motion.

6.1.2.8 Optimization of Function Phase

Advanced training for general conditioning, lower extremity strength, and military, work and/or athletic movements is progressed from as early as 12 weeks after surgery through discharge from physical therapy. Progression is based on time from surgery, the inflammatory response of the knee joint, and mastery of more basic skills (e.g. the patient must master jumping on two legs before beginning hopping on one leg). This progression follows standard approaches after anterior cruciate ligament reconstruction.

6.2 Procedures for Training of Clinicians on Procedural Intervention

6.2.1 Procedures for Training Surgeons on Surgical Intervention

6.2.1.1 Investigator's Study Kickoff Meeting – February 10, 2018

To review study procedures, discuss preliminary recruitment issues, and re-orient the site investigators to the study, we hosted a Study Kickoff Meeting in Pittsburgh, PA in

February 2018. Discussion topics included study organization, clinical equipoise, inclusion and exclusion criteria, study design, assessment of safety, data management and quality control. The audio recording of the meeting and annotated meeting minutes are available in a shared folder with the investigators and research coordinators in the STaR Trial Meeting Repository.

6.2.1.2 Informational Investigator's Conference Calls

Informational conference calls with the study investigators are held on a monthly basis. The purpose of these calls is to relay important, study related information to site PI's and Co-I's. The calls are conducted via Skype for Business and are preceded by an electronic meeting invitation and updated with an agenda. Skype for Business allows for screen sharing capabilities and recording of the conference call. There is potential for attendee participation via both audio and text-based interaction. All audio and screen presentations of the calls will be recorded and archived. Annotated meeting minutes and recordings will be made available via a public web folder through the University of Pittsburgh for individuals who cannot attend the live meeting. No patient-specific or identifiable information will be discussed during a conference call.

6.2.2 Procedures for Training Physical Therapists on Rehabilitation Interventions

6.2.2.1 Rehabilitation Protocol and Written Guidelines

Because of the multi-centered nature of this project, as well as the participant's choice of physical therapist for their standard of care post-operative rehabilitation, we have established procedures to standardize and minimize variability in the allocated post-operative rehabilitation program. The Rehabilitation Committee created the standardized rehabilitation program for the early and delayed rehabilitation groups with clearly specified time- and criterion-based standards for progression of activity and exercise for each group. To standardize implementation of the rehabilitation program, we have also developed group-specific (early and delayed rehabilitation) written guidelines describing the post-operative rehabilitation program that will be provided to

the participant and the participant's physical therapist. These include Executive Summary Reference Sheets for the Physical Therapist.

6.2.2.2 Training Webinars via MedBridgeEducation.com

We have recorded training webinars that describe the following topics:

- Study Introduction, Overview, and Purpose
- Overview of Rehabilitation Program; Early and Delayed Rehabilitation Programs; Tissue Specific Protections
- Criterion-Based Activity Progression
- Potential Poor Outcomes and Indications for Contacting the Surgeon
- Your role as a physical therapist treating a patient in this study

The instructional videos will be made available to all physical therapists who provide post-operative rehabilitation to participants enrolled in the study. We have partnered with a third-party rehabilitation education company, Medbridge Education, to host the training videos. Medbridge will make the videos available to any physical therapist that treats a study participant, free of charge. We will include the information about the training videos in the introductory letter to the physical therapist from the surgeon-investigator. Medbridge will collect basic demographic data about the physical therapist when the physical therapist registers with the Medbridge system. This demographic information will allow us to identify the therapists and learn about their experiences. Additionally, Medbridge will be able to tell us how many of the physical therapists accessed and completed the videos.

6.2.2.3 On-going Interaction

As the Qualified Collaborator for Rehabilitation, Dr. Lynch will be available at all times to answer any questions from physical therapists regarding an individual's participation in the study.

6.3 Assessment of Clinician and/or Subject Compliance with Study Procedural Intervention

6.3.1 Assessment of Surgeon Adherence to Timing of Surgery as Randomized

To determine whether the surgery was performed as randomized, the date of surgery will be compared to the date of injury. In cases where the surgery was performed outside of the time window that corresponds with randomization, a protocol deviation will be filed, and the case will be flagged as non-adherent to timing of surgery.

All surgeons will follow the same general procedures for anatomic repair or reconstruction of torn structures; however, due to the variability of injury patterns in MLKIs, it is not possible to strictly standardize the surgical protocol for all participants. Rather, we will use surgical CRFs to thoroughly document the surgical findings and procedures.

6.3.2 Assessment of Participant Adherence with Rehabilitation as Randomized in the first Month after Surgery

To determine whether the participant was adherent to the allocated rehabilitation program, we will utilize a three-part monitoring process in the first month after surgery. We will consider participant self-report and the opinions and conclusions of the orthopedic surgeon and physical therapist. (See Figure 4) At the one-month post-operative clinical visit with the surgeon, the participant will complete a brief survey (Patient Reported Rehabilitation Activities Form) asking about his/her activity over the last month. Items include an estimate of how much weight the participant put on their

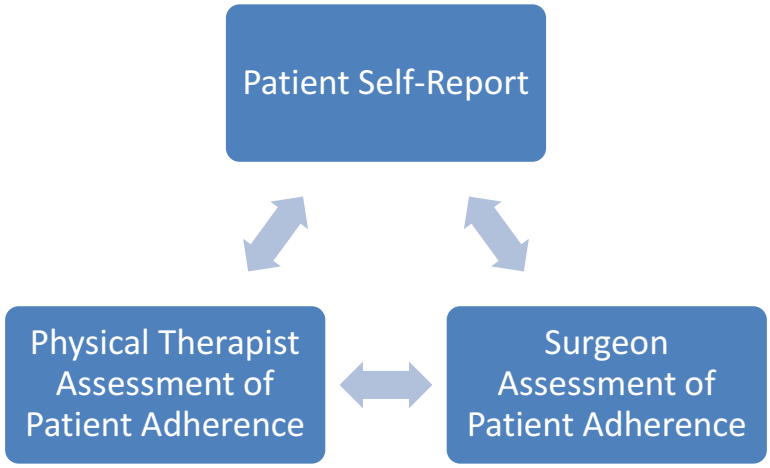

Figure 4. Triangulation of Adherence to Rehabilitation as Randomized

lower extremity on a regular basis and how restrictive the participant was with knee joint motion. To improve reporting, we have implemented a picture-based reporting mechanism to accompany written descriptions.

In the one-month Clinical Visit Form and one-month Physical Therapy Case Report Form, the surgeon and physical therapist, respectively will be asked to comment on the participant's WB and ROM status. By obtaining information from the participant, surgeon, and physical therapist, we will be able to determine with reasonable certainty the participant's adherence with the allocated rehabilitation program.

In cases of agreement among all three data sources, there is a clear indication of adherence. In cases of discord between the three parties, the general rule is to take the opinion of the majority (i.e. 2 of 3 reports results in determination of adherence). However, if the participant self-reports that he/she was not adherent to recommendations, we will designate the participant as non-adherent.

6.3.3 Assessment of Patient Reported Adherence to Rehabilitation as Prescribed after the First Month after Surgery

Using the 3-month and 6-month Patient Reported Rehabilitation Activities Forms, we will determine how participants progressed through rehabilitation activities after surgery. We will compare this to the suggested beginning times for activities in the rehabilitation protocol. Specifically, we want to know how often participants begin impact activities (e.g. running, jumping, or cutting/pivoting) and advanced training prior to 3 months after surgery. The rehabilitation program delays initiation of these activities in an effort to promote appropriate healing of surgical procedures, however, the impact of these activities on healing and outcome is unknown.

We will also identify participants that have demonstrated poor progression of activity and have not initiated advanced training by 6 months after surgery. We will assess for predictors of individuals who have not returned to advanced training to identify those who may need more intensive rehabilitation or closer monitoring.

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

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

serve as the baseline outcome measures for those enrolled in the trial that randomizes only post-operative rehabilitation (Aim 2). The pre-operative patient-reported outcome measures for those in the trial for Aim 1 will not replace the baseline outcome measures that were collected at the time of enrollment in the study and will be used only for descriptive purposes.

At the time of surgery, the surgeon will perform a standard of care examination under anesthesia and diagnostic arthroscopy and will perform surgery in accordance with the principles of anatomic repair or reconstruction of all injuries in the knee. During or immediately after completion of surgery, all surgical findings and procedures will be documented on the following forms as outlined in Section 8.

For both trials, the research coordinator will only inform the surgeon and participant of individual's group assignment for post-operative rehabilitation after the surgery has been completed.

7.5 Standard of Care Clinical Follow-Up Visits

Clinical visits with the surgeon-investigator and his/her clinical staff will be performed as part of the standard of care after knee surgery. The clinical follow-up visits will occur approximately 1 week and 1-, 3-, 6- and 9 to 12 months **after surgery**. The results of the clinical follow-up visits will be documented on the Clinical Visit, Additional Surgeries – Clinical, Concomitant Medications, and Complication Reporting forms. Patient-reported rehabilitation activities will also be collected at each of the clinical follow-up visits. Sites will not be compensated for these standard of care clinical visits, however they will receive $75 per participant for their effort to complete the case report forms to summarize these clinical visits.

If participants have other standard of care clinical visits, the results of these clinical visits will be recorded as Interim Visits into REDCap.

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.

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-

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>

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.

Sensation to pain (pin prick) distal to the knee will be recorded as normal, diminished or absent. Distal motor function of the tibialis posterior, tibialis anterior, peroneus longus and extensor halluces longus will be recorded as strong/symmetrical to the contralateral leg, diminished or absent.

- Plan Pre-Operative Management

A standard of care pre-operative plan will be developed by the surgeon-investigator with recommendations to participants. Pre-operative recommendations will be at the surgeon-investigator's discretion and can include aspiration of the knee, protected weightbearing, bracing, ROM restrictions, prescription of a home exercise program, application of an external fixator for less than 10 days or referral of the participant for physical therapy. Each recommendation will be recorded by the research team.

8.1.3 Baseline Visit

After the screening procedures and final determination of eligibility, participants will be asked to complete patient-reported outcomes measures including the Multi-Ligament Quality of Life Questionnaire, International Knee Documentation Committee (IKDC) Subjective Knee Form, PROMIS Physical Function scale and PROMIS Global 10. The participant will also complete other patient-reported measures that are expected to be associated with the study outcome including the Patient Acceptable Symptom State (PASS), Global Rating of Change, Tampa Scale for Kinesiophobia, and the Brief Resilience Scale. The site coordinator will review the participant's medical record to complete the Concomitant Medications form in the electronic database (REDCap). Each of these patient-reported outcomes and other measures are described in Section 8.1.8.

8.1.4 Study Interventions

8.1.4.1 Early vs. Delayed Surgery for MLKI

For the clinical trial that is performed for Specific Aim 1, we have operationally defined early definitive surgery to be surgery within 6 weeks of injury to repair and/or reconstruct the torn structures. Delayed surgery to has been operationally defined as repair and/or reconstruction of the torn structures 12 and 16 weeks after injury. Although early surgery is defined as within 6 weeks, every effort will be made to perform surgery as soon as possible, if randomized to early surgery. Staged surgery will not be considered an option for surgical treatment of MLKIs in this study.

In all cases, surgery will be performed in accordance with the principles of anatomic repair/reconstruction of injured structures in a manner that will allow for early range of motion. Surgical reconstruction with allograft or autograft will be planned for mid-substance tears of the ACL and/or posterior cruciate ligament (PCL), as previous studies have demonstrated suboptimal outcomes with primary repair.[77,78] Repair/reconstruction will also be planned for injury to the medial collateral ligament (MCL) and the posterolateral corner (PLC) structures (fibular collateral ligament, popliteus tendon, and popliteofibular ligament). Injuries to the biceps femoris tendon or iliotibial band will be addressed as necessary. Medial and lateral meniscus tears will be repaired or debrided at the time of surgery. Neuropraxic nerve injuries will not necessitate early intervention; however, if a neurotmesis injury is discovered on MRI, then early intervention for primary repair, grafting or benign neglect may be warranted.

All surgical findings and procedures will be documented on electronic surgical case report forms. As the Qualified Clinical Investigator for Surgery, Dr. Musahl will be available to answer any questions from surgeons regarding a subject's participation in the study.

Definitive surgical treatment of soft tissue injuries will follow a standardized algorithm comprising primary repair and/or graft reconstruction. Surgery will be performed in accordance with the principles of anatomic repair and/or reconstruction of injured structures in a manner that will allow for early range of motion. Graft choice for

reconstruction of injured tissues will be at the discretion of the operating surgeon and will not be standardized; however, graft choice will be recorded on the surgical case report form.

8.1.4.2 Early vs. Delayed Post-Operative Rehabilitation

Two post-op rehabilitation protocols have been created, differing only in the time to begin WB and ROM exercises. After surgery, all individuals will be placed in a hinged brace that is locked in extension.

Individuals randomized to early rehabilitation will begin WBAT with the brace locked in full extension and unrestricted ROM within 1 week after surgery. Individuals in this group will be allowed to unlock the brace for ROM exercises but will keep the brace locked at all other times until the criteria to unlock the brace are met. Weightbearing will be gradually progressed to full WB no earlier than 3 weeks after surgery pending achievement of the criteria for doing so.

Participants allocated to delayed rehabilitation will be non-WB and with no knee motion for four weeks after which time they will progress to WBAT and perform unrestricted ROM exercises.

Immediately after surgery both groups will begin isometric quadriceps exercises with the knee in full extension (quad sets, straight leg raises) and high intensity neuromuscular electrical stimulation (NMES) for the quadriceps will be utilized. Use of the post-operative brace will be discontinued no earlier than 6 weeks after surgery pending achievement of the criteria to do so.

In the Motor Control and Functional Optimization phases of rehabilitation, progression to increasingly demanding activities will be time- and criterion-based to ensure that the individual is advanced safely, reducing the risk for further injury.

8.1.5 Post-Operative Clinical Visits

Follow-up standard of care clinical visits will be performed at the discretion of the surgeon-investigator, which typically occur 1 week and 1, 3, 6 and 9 to 12 months from surgery.

The findings from the clinical examination performed by the surgeon-investigator will be documented on a Clinical Follow-up Visit Form and will serve to provide additional secondary outcomes related to post-operative recovery. The information that will be collected on the Clinical Follow-Up Visit form includes pain, pain medication usage, joint effusion, wound and neurovascular status, ROM, WB status, use of a post-operative rehabilitation brace, adherence to the allocated post-operative rehabilitation program, imaging and/or laboratory tests ordered and completed, complications, additional surgeries, changes in medications and recommendations for return to military duty, work and sports status. Knee laxity will also be assessed during clinical follow-ups at the discretion of the surgeon-investigator.

- Pain, Active and Passive ROM, and Neurovascular Status

Pain, active and passive ROM, and neurovascular status 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).

- Pain Medication Usage

At each clinical follow-up visit we will record current pain medication usage. We will specify the name of the medication, dose, frequency of use and indication.

- Joint Effusion

We will utilize the modified stroke test to assess and quantify effusion of the knee joint. To perform this test, the subject will lie in the supine position with the knee relaxed in full extension. Starting at the medial joint line, the examiner will stoke upwards two to three times towards the suprapatellar pouch to move the joint effusion from the tibiofemoral joint into the suprapatellar pouch. The examiner will then stroke downward on the distal lateral thigh from just superior to the suprapatellar pouch towards the lateral joint line

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).

- 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.

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.

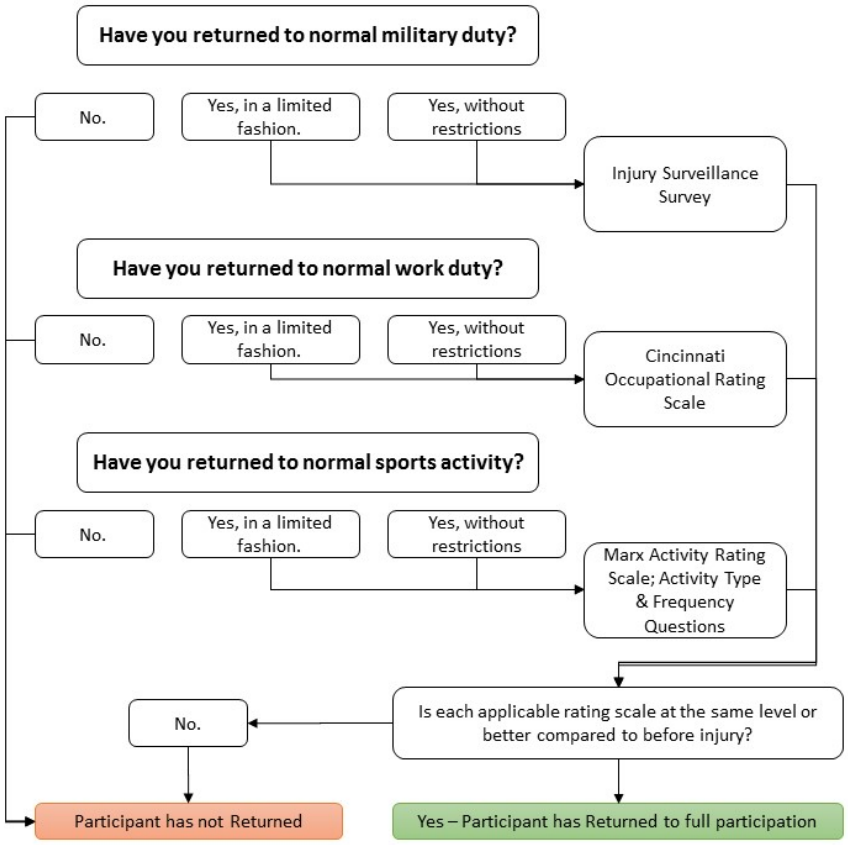

Figure 5. Determination of Return to Pre-Injury Activities

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].

- **Activity Limitation Scale of the Multi-Ligament Quality of Life (MLQoL) Questionnaire**

The MLQoL Questionnaire [60] is a condition-specific patient-reported outcome measure for individuals that have sustained a MKLI. Qualitative research involving individuals with a MLKI has demonstrated that existing knee-specific or generic patient-reported outcome measures lack items that represent the full spectrum of symptoms and activity limitations associated with vascular and neurological injuries. Additionally, existing knee-specific patient-reported outcome measures focus on sports activity and participation with few items related to participation in social roles and the profound emotional effect that MLKIs have on individuals.[60] The MLQoL Questionnaire was developed with stakeholder input from patients with a MLKI and clinicians that treat those patients to address the limitations of existing knee-specific and generic 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). Items representing impairments are phrased in terms of frequency and activity limitations and social involvement are worded in terms of degree of difficulty or extent of limitation. The item responses are based on a five-point Likert scale. Separate scores are calculated for each domain by summing the item response scores within each domain and dividing the sum by the total possible score for the domain then multiplying by 100 to provide a score that ranges from 0 to 100 with lower scores representing better outcomes (less impairment or limitations).

Interviews with patients that have a MLKI reveal that the content of the items is relevant to individuals with a MLKI. We selected the Activity Limitations scale of the MLQoL Questionnaire as a secondary primary outcome measure 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 Limitations scale in individuals with MLKI found no floor and ceiling effects and acceptable levels of internal

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).

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

enrollment/post-injury. The GRC is used to identify individuals who made a substantial improvement due to the treatment that was received (REF).

8.1.8 Other Patient-Reported Measures

Measures of kinesiophobia, resiliency and comorbidities will be collected because these constructs may impact return to military duty, work and sports. These measures will be collected only at the time of enrollment in the study.

- **Tampa Scale for Kinesiophobia**

Several studies have shown that fear of re-injury was the major and most common reason cited by individuals for not returning to sports or for returning to a lower level of sports participation after ACL reconstruction.[83-87] For individuals that sustain a MLKI there is no evidence on how fear of re-injury affects return to military duty, work or sports, however given the magnitude of the injury we expect that return to activity and participation following a MLKI will be associated with fear of re-injury. Therefore, to account for this potentially confounding variable we will utilize the shortened version of the Tampa Scale for Kinesiophobia (TSK) to assess fear of re-injury. The TSK aims to quantify fear of re-injury due to movement and physical activity for patients with musculoskeletal pain. The shortened version of the TKS consists of 11 statements related to an individual's perception of their experience of injury and physical activity. Each statement is provided with a four-point Likert scale that ranges from "strongly agree" to "strongly disagree". The TSK item scores are summed to create a score that ranges from 11 to 44, with a higher score indicating more fear. This scale has been found to have acceptable internal consistency (Cronbach's alpha 0.77 to 0.81) and the validity of the TSK was acceptable in patients with acute and musculoskeletal pain. [88-91] The presence of fear as measured by the TSK is related to physical function after ACL injury and reconstruction,[92] but it also can change over time.[93] Therefore we will administer the TSK at the time of enrollment in the study as well as at the 6, 12 and 24 month follow-ups after randomization.

- **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 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).

9.1.2 Adverse Events

An adverse event (AE) is any untoward medical occurrence during a subject's participation in the research study. The occurrence of adverse events will be monitored for each subject on an ongoing basis throughout the study at all sites. All AEs, regardless of its relatedness to the study intervention, it will be recorded on the electronic AE form. Standard medical terminology from the Common Terminology Criteria for Adverse Events (CTCAE) (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf) will be used when recording AEs. This standardization will allow sorting and grouping of like events, which will facilitate calculation of the incidence of AEs and reporting. In addition, this standardization will promote consistent documentation across all 23 sites.

As dictated by the CTCAE, the data elements that will be recorded in the AE CRF are:

- Event term;
- Event severity: mild, moderate, severe/life-threatening/disabling or death;
- Start and end date of event;
- Relatedness to study procedures: unrelated, unlikely, possible, probable or definite;
- Action taken with study procedure: none, study procedure interrupted, discontinued or modified;
- Other action taken: none, treatment given (describe), discontinued from study or hospitalization;
- Status of Event: not recovered/not resolved, recovered/resolved, resolved with sequelae, recovering/resolving, fatal, unknown or lost to follow-up;
- Serious adverse event;

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

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.

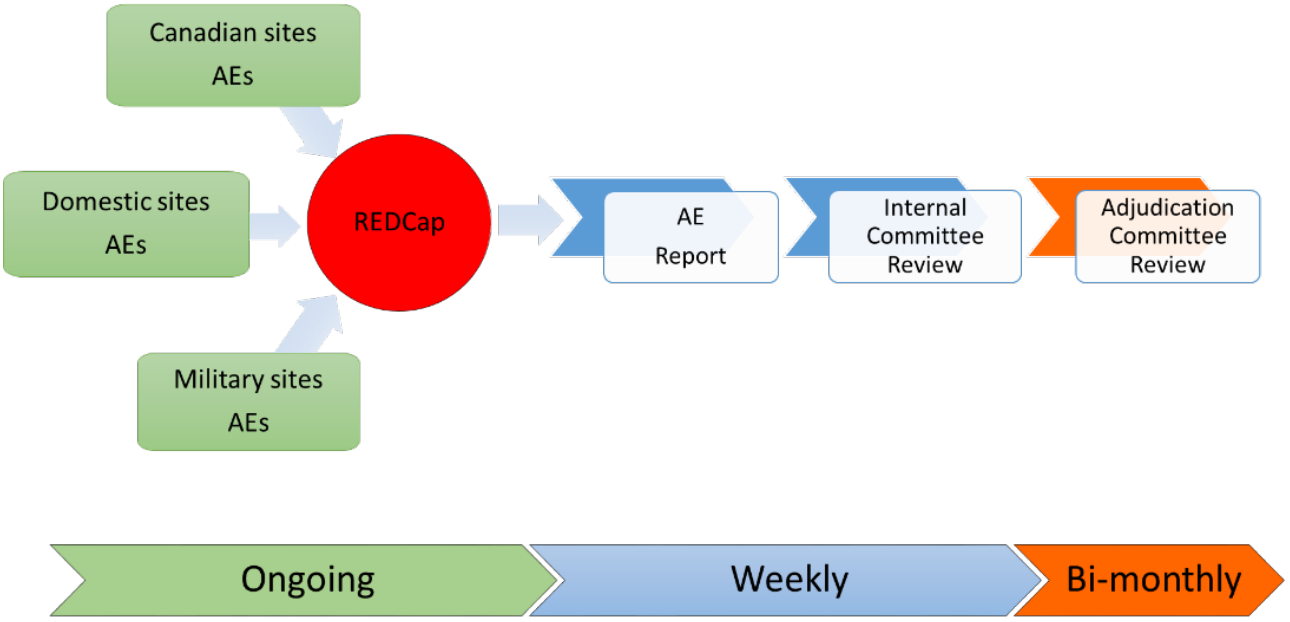

Figure 6 - AEs Internal and External Adjudication Flow Chart

9.5 Reporting Procedures

The RC, to whom the AE or SAE information is disclosed, will document the event in the REDCap system. Any event that poses risks to subjects or others will be submitted promptly to the US Army Medical Research and Material Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO).

9.5.1 Unanticipated Problem Reporting to IRB and HRPO

Incidents or events that meet the HRPO criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. The HRPO recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem to the IRB:

- Appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- A detailed description of the adverse event, incident, experience, or outcome;
- An explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an unanticipated problem;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

To satisfy the requirement for prompt reporting, unanticipated problems will be reported using the following timeline:

- Unanticipated problems that are serious adverse events will be reported to the IRB and to HRPO within 1 week of the investigator becoming aware of the event.
- Any other unanticipated problem will be reported to the IRB and to the HRPO within 2 weeks of the investigator becoming aware of the problem.

- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

9.5.2 Adverse Event and Serious Adverse Event Reporting to IRB and HRPO

Adverse events or SAEs that pose a risk to the study participant, or that are related to study procedures, will be reported as follows from the time the information is disclosed to research coordinator:

- For AEs that pose a risk to the study participant or are related to the study procedures, the RC will enter information related to the AE into the REDCap system and will report the AE to the site's IRB of record within timeframe specified by the IRB's policies, but no later than 5 business days. Additionally, the RC will report the AE directly to the site PI.

- All SAEs will be reported within 24 hours of learning of event. To do so the RC will enter the information into the REDCap system for SAEs. REDCap will automatically contact the study PIs (Drs. Irrgang and Musahl), the site PI, and the Independent Research Monitor. The site PI will notify the site IRB of record within 24 hours. Note that the study personnel may not know of SAEs that are not study related until the monthly follow-up. If such SAEs occur, they will be documented as above as soon as the study personnel are aware of the occurrence of the SAE.

9.6 Criteria for Intervention Discontinuation

Participants will be discontinued from the study intervention (early vs. late surgery and early vs. late rehabilitation) if a medical condition develops that, due to safety concerns, precludes the continuation of allocated intervention. In such events, the subject will continue to be followed per the study protocol and follow-up data will be obtained. The subject will remain in the group to which they were initially assigned to according to the intention-to-treat principle.

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

	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

	4420 Bayard Street, Suite 600 Pittsburgh, PA 15260	

10.2 Roles and Function of the DSMB

The University of Pittsburgh Clinical and Translational Science Institute (CTSI) will provide logistical management and support of the DSMB. The first meeting will take place before initiation of the trial to discuss the protocol, approve commencement of the trial, and to establish guidelines for monitoring of the study. Thereafter, the DSMB will meet every six months. An emergency meeting of the DSMB may be called at any time by the Chairperson should questions of patient safety arise.

The ongoing responsibilities of the DSMB are to:

1. Evaluate the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and other factors that can affect study outcome;
2. Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial;
3. Review clinical center performance, make recommendations and assist in the resolution of problems reported by the Principal Investigators;
4. Protect the safety of the study participants;
5. Report on the safety and progress of the trial;
6. Make recommendations to the Principal Investigators, and if necessary, to the HRPO concerning continuation, termination or other modifications of the trial based on the observed beneficial or adverse effects of the treatment under study;
7. Monitor confidentiality of the trial data;
8. Assist the Principal Investigators by commenting on any problems with study conduct, enrollment, sample size and/or data collection.

The DSMB will review SAEs and AEs at least twice annually and will be alerted by the research team to any interim concerns. At least twice annually, the DSMB will review enrollment to assure that enrollment targets are being met. The DSMB Chair will write a report after each meeting, summarizing the study status and outlining any concerns. A copy of this report will be provided to the DoD Program Officer.

Tables (Appendix C) for the open DSMB reports will include information on prescreening, screening, screen failures, randomized, demographics, study status, protocol deviations, AEs and SAEs. The open reports will be stratified by trial, but not by study arm.

Closed reports, if requested by the DSMB, will be stratified by study arm.

10.3 Independent Research Monitor

The funding agency (DoD) requires research determined as greater than minimal risk, that the IRB approve, by name, an independent research monitor with expertise consonant with the nature of risk(s) identified within the research protocol. The IRB has approved a written summary of the monitors' duties, authorities, and responsibilities.

The independent research monitor will perform oversight functions and report their observations and findings to the research team, the IRB, and DSMB.

The independent research –monitor functions include:

- Oversight of study interventions and interactions,
- Oversight of data collection, storage and analysis
- Reviewing monitoring plans and UPIRTSO reports,
- Consulting on individual cases as necessary and review and evaluate adverse event reports,

- Discussing the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research and will promptly report any discrepancies or problems to the IRB;

- Having the authority to stop research protocol in progress, if necessary, remove individual subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can make an assessment;

- Shall have the responsibility to promptly report the observations and findings to the IRB or other designated official and the HRPO.

Dr. John R. Fowler Jr., MD will serve as the independent research monitor for this study. Dr. Fowler is an Assistant Professor and Assistant Dean for Medical Student Research in the Department of Orthopaedic Surgery at the University of Pittsburgh. Dr. Fowler is a board certified orthopaedic surgeon with a certification of advanced qualifications in hand surgery. He has conducted extensive clinical research, including participation in several multicenter clinical trials. He is also a member of the University of Pittsburgh Institutional Review Board for Humans Subjects Research. Dr. Fowler's credentials to serve as the research monitor, as well as the duties, authorities and responsibilities of the research monitor have been reviewed and approved by the IRB.

10.4 Study Committees

This study is governed by an Executive Steering Committee and seven subcommittees. All committees consist of investigators or individuals associated with the STaR Trial, with the exception of the AE Adjudication Committee, which is comprised of individuals external to the study.

- Executive Steering Committee (ESC)

The role of the ESC is to provide oversight of the trial. The committee will define the vision and scientific goals of the STaR Trial. Additionally, the ESC will review and approve the final study protocol and any proposed future modifications.

Throughout the trial, the ESC will monitor the study progress including recruitment, retention, and site compliance with study procedures. During the study, the ESC will resolve any conflicts arise between investigators. The ESC will review and issue final approval or recommend modification for all subcommittee decisions. The ESC will meet monthly via conference call.

- Forms Committee

The Forms Committee drafted a set of forms that will be used in the study. During the study, the committee will review and approve all modifications to any forms used for data collection. The committee will regularly review and maintain the current set of approved forms. Additionally, the committee will be responsible for keeping a log of all form changes throughout the duration of the study.

- Publications and Ancillary Studies Committee (PASC)

The PASC has established policies and procedures for assigning writing groups and approving the STaR Trial-associated ancillary studies, secondary analysis of existing data and abstracts, presentations, and publications prior to their submission for dissemination. The PASC will also establish guidelines for authorship for investigators following the guidelines specified by the International Committee of Medical Journal Editors for authors who have contributed to the scientific design and merit of the study.

- Rehabilitation Committee

The Rehabilitation Committee has established the rehabilitation guidelines and protocols for subjects enrolled in the study. The committee will ensure the training and standardization of the rehabilitation procedures at all study sites through the development of training materials and learning modules. The committee will also create

materials for the home exercise programs for the study participants to use. Throughout the study, the Rehabilitation Committee will create procedures to monitor and maximize compliance with rehabilitation procedures at all sites.

- Quality Control Committee

The Quality Control Committee will review and affirm the quality of the conduct of the study including implementation of the surgical timing and rehabilitation interventions as randomized. The committee will oversee implementation of the study protocol and monitor the study data for completion of study procedures and for missing data. The committee will review the study on an ongoing basis to review loss to follow-up and protocol deviations in aggregate, and by individual site. Additionally, the Quality Control Committee will be responsible for the oversight of the site monitoring visit. Further information on site monitoring visits is described in Section 11.1.

- Recruitment Committee

The Recruitment Committee will establish a plan and monitor recruitment throughout the duration of the study. The committee will create recruitment materials to be used at all sites. Additionally, should a site be recruiting fewer subjects than recommended, the committee will evaluate the site and make recommendations to improve recruitment at the site.

- Adverse Events Adjudication Committee

The Adverse Events Adjudication Committee consists of three qualified surgical and rehabilitation professionals to provide an independent external review of all AEs that occur during the study. The committee will assign each AE a level of severity and will determine the relationship with the study intervention. Further information on the AE Adjudication process and committee is described in Section 9.4.

Table 5. Members of the Study Committees

Committee	Committee Members
Executive Steering Committee	James Irrgang, PT, PhD, ATC Volker Musahl, MD Andrew Lynch, PT, PhD Charity Patterson, PhD Travis Burns, MD Christopher Harner, MD Bruce Levy, MD Brett Owens, MD Robert Schenck, MD Daniel Whelan, MD
Forms Committee	Christopher Harner, MD - Chair Brett Owens, MD – Co-chair Lane Bailey, PhD, DPT, CSCS Jonathan Cooper, MD Andrew Lynch, PT, PhD Charity Patterson, PhD Ryan Khan, CCRP James Irrgang, PT, PhD, ATC – Ex Officio Volker Musahl, MD – Ex Officio
Publications and Ancillary Studies Committee	Robert Schenck, MD – Chair Matthew Matava, MD – Co-chair Kenneth Cameron, PhD, MPH, ATC Andrew Lynch, PT, PhD Charity Patterson, PhD Matthew Posner, MD Brett Owens, MD Michael Stuart, MD James Irrgang, PT, PhD, ATC – Ex Officio Volker Musahl, MD – Ex Officio
Rehabilitation Committee	Andrew Lynch, PT, PhD – Chair Michael Stuart, MD – Co-chair Lane Bailey, PhD, DPT, CSCS Cathy Coady, MD Jonathan Cooper, DO David Pezzullo, PT, MS, SCS, ATC Robert Schenck, MD Daniel Whelan, MD Johnny Owens, MPT Terrance Sgroi, DPT, SCS, MTC Terese Chmielewski, PT, PhD, SCS

	James Irrgang, PT, PhD, ATC – Ex Officio Volker Musahl, MD – Ex Officio
Quality Control Committee	Alexandra Gil, PT, PhD – Chair Charity Patterson, PhD – Co-chair Christopher Harner, MD Joseph Hart, MD Jeffrey Macalena, MD Matthew Matava, MD Bradley Nelson, MD James Irrgang, PT, PhD, ATC – Ex Officio Volker Musahl, MD – Ex Officio
Recruitment Committee	Mark Pallis, MD Cale Jacobs, PhD, ATC Timothy Mauntel, PhD, ATC Alan Getgood, MD Brian Waterman, MD James Irrgang, PT, PhD, ATC – Ex Officio Volker Musahl, MD – Ex Officio
Adverse Events Adjudication Committee	Kurt Spindler, MD G. Kelley Fitzgerald, PT, PhD Susan Spillane, RN, CCRP

11 CLINICAL SITE MONITORING PLAN

In addition to the PI's responsibility for oversight, study oversight will be under the direction of the Clinical Study Oversight Committee (CSOC). The PI and CSOC have developed the Clinical Monitoring Plan (CMP) that establishes guidelines for conducting monitoring visits and related tasks to monitor the STaR Trial. The Clinical Coordinating Center (CCC) at the University of Pittsburgh will be responsible for CMP under the leadership of Dr. Alexandra Gil, Co-Investigator and Quality Control Coordinator (QCC), Maria Beatriz Catelani, Project Coordinator, in collaboration with Drs. Irrgang (Principal Investigator), Musahl (Co-Principal Investigator and Qualified Clinical Investigator [QCI] for Surgery) and Lynch (Co-Investigator and QCI for Rehabilitation) as well as Dr. Charity Moore, (Co-Investigator and Director for the Data Coordinating Center [DCC]). Dr. Gil and Ms. Catelani will serve as the Clinical Trial Monitors.

The intent of the CMP is to ensure the rights of human subjects are protected; the study is implemented in accordance with the protocol; compliance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines, national and local regulations, and institutional policies across all sites; and that the quality and integrity of study data and data collection methods are maintained. The focus areas for the CMP include: 1) site assessment review and staff training; 2) human subjects' protection; 3) protocol compliance; 4) regulatory compliance; 5) quality assurance; 6) adverse event reporting; and 7) integrity of research data. Implementation of the CMP will include annual on-site monitoring visits and continuous remote monitoring that includes review of electronic records and regular communication with Research Coordinators (e.g. biweekly phone calls).

11.1 Clinical Monitoring Communication Plan

Communications for each monitoring visit will include a letter confirming the site monitoring visit, agenda for the monitoring visit, on-site post-monitoring visit debriefing, and a follow-up letter and/or visit report and Action Item Tracker. All documents will be sent via email to the study PI, QCIs for surgery and rehabilitation, Director of the DCC and site PI and Research Coordinator (RC).

11.2 Scheduling of Visits

The Quality Control Coordinator or her designee will work with the site PI and RC to schedule the monitoring visits. The study PI, QCIs, DoD Program Officer and Director of the DCC will be apprised of monitoring visit schedule. Prior to the visit, the site PI and RC will receive a visit confirmation letter and agenda. The site PI and RC will be expected to secure workspace for the Clinical Trial Monitor and to be available during the visit to facilitate monitoring activities. The Clinical Trial Monitor will be available at the conclusion of the monitoring visit to discuss findings and answer questions from the study staff. The site PI and RC are also expected to be available for a summary meeting at the conclusion of the visit. These expectations will be explained in the monitoring visit confirmation letter.

11.3 Types of Visits and Monitoring Activities

The CMP will include four types monitoring visits for this study including a Site Initiation Visit, Interim Visits, For-Cause Visits and Study Close-Out Visit.

11.3.1 Site Initiation Visit

The site initiation visit will take place prior to site activation once IRB and Human Research Protections Office (HRPO) approvals and all subcontracts and agreements are in place. Activities related to the site initiation visit will include:

- Confirming the preparedness of the site to execute the research protocol;
- Ensuring satisfactory facilities to support conduct of the study;
- Clarifying applicable regulations and requirements as they relate to the protocol;
- Reviewing the process for implementing the protocol at the site and
- Conducting any necessary training prior to initiating site enrollment.

Prior to the site initiation visit taking place the Quality Control Coordinator, Dr. Gil and the STaR Trial Project Coordinator, Beatriz Catelani, will develop the agenda, and follow the communication plan to ensure that all relevant parties are informed of the

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

- 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)	

• Facilities deemed acceptable	
5. Action Items from Site Initiation Visit Required for Site Activation Completed	
6. Study Specific Requirements Met	

11.3.2 Interim Visits

The first Interim Visit will be conducted remotely for each site after two or three subjects have been enrolled and followed for three to four months. Subsequent Interim Visits will be conducted annually and in-person. The objectives for the Interim Visits are to confirm:

- The subjects' rights are being protected;
- The study is being conducted according to the protocol and applicable regulations, including GCP;
- Accurate reporting of interventions, subject safety data and study endpoints.

In addition, to ensure accuracy and completeness of the data, the Clinical Trial Monitor will review and match surgical source documentation (paper or electronic) and clinical follow-up visits source documentation to the respective Case Report Forms (CRFs). After each visit, a debriefing meeting will be conducted with the site PI, RC and/or designee to review the findings and discuss key issues that may require follow up, and to share recommendations. This meeting will provide an opportunity for immediate dialogue, feedback, clarification, and education. These items will also be summarized as an Action Items Tracker attached to the monitoring visit documentation. At a mutually agreed upon time, or approximately two to four weeks after monitoring visit, whichever is earlier, the Quality Control Coordinator or designee and site research staff designee will meet via telephone conference to discuss resolved, in process, and pending action items. At this time the need for and frequency of subsequent meetings will be discussed. The follow-up letter, final monitoring visit report and Action Items Tracker will be sent within three weeks of the conclusion of the site visit.

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

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).

Assuming 10% lost to follow-up over two years, we expect to have 352 subjects (n=88 per cell).

We had no preliminary data on time to return to pre-injury military duty, work and sports, therefore we conservatively estimated power using the 24-month rate of return to full pre-injury activity and participation and a two-sample test of proportions. This sample size would provide 80%-92% power to detect a 15% absolute difference (α=0.05) in the rate of return to full pre-injury military duty, work and sports for the main effects (n=176 for each arm) for timing of surgery or timing of rehabilitation, assuming the delayed arm has a return rate of 30% to 70%. Power was calculated for a two-sided z test with pooled variance using PASS 13.[97] Additionally we would have 80% power to detect a 17% to 21% difference between the early surgery/early rehabilitation group (n=88) compared to any of the other 3 groups with rates from 30%-70%. With 176 subjects per main effect arm, we would have 82% power to detect a 15% difference in return to military duty, work and sports (hazard ratio=0.65, 35% improvement in the time to rate of return to duty, work and sports) using a log-rank test assuming two-year accrual, two-year follow-up for each participant, 10% dropout in each arm, and 5% crossover in each arm.

For the MLQoL Questionnaire Activity Limitations Scale, we would have 80% power to detect a 6.2 point difference at 24 months between early surgery and delayed surgery (or early rehabilitation and delayed rehabilitation) using a two-sided two-sample equal variance t-test (α=0.05, standard deviation=20.8) assuming a 10% attrition rate. This is equivalent to a small effect size of approximately 0.30. We would also have 80% power to detect a 10.2-point difference between the early surgery/early rehabilitation group and any of the other three groups using the same standard deviation and test (α=0.0167 adjustment for multiple comparisons).

After accounting for those included in the trial that randomizes surgery and rehabilitation and applying the exclusions described above we estimate that approximately 440 individuals with a MLKI will be eligible for participation in the trial for Aim 2 that randomizes only timing of post-op rehabilitation. If approximately 68% of the eligible

subjects agree to participate in the trial for Aim 2 that randomizes only timing of post-operative rehabilitation, this would provide a total sample size of 298 (n= 149 per cell). This total of subjects would provide 79% to 84% power to detect an absolute difference of 15% between the groups (α=0.05) assuming the delayed rehabilitation group has a return to military duty, work and sports rate of 65 to 70% and 10% attrition. Power was calculated for a two-sided z test with pooled variance using PASS 13.[97]

12.3 Safety Review

Adverse events and serious adverse events will be named and classified using the CTCAE. No formal rules have been established to halt enrollment for safety concerns. All tabulations and comparisons of rates of AEs and SAEs by treatment group will be shared with the DSMB at their regularly scheduled meetings. As required by *www.clinicaltrials.gov* and biomedical journals, all safety data will be reported by treatment group as part of the final dissemination of study results.

12.4 Final Analysis Plan

We will first compare the distribution of baseline characteristics and important prognostic factors (age, sex, pre-injury activity level, KD classification etc.) between the groups for each trial (surgery and rehabilitation, rehabilitation only). Continuous variables with fairly symmetric distributions will be summarized using means and standard deviations. Those with skewed distributions will be described using medians and inter-quartile ranges. Categorical data will be summarized using frequencies and percentages.

Because of the expected heterogeneity of pre-injury activity level of individuals that sustain a MLKI, we will combine return to 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 activity. See Section 3.2 for details.

12.4.1 Statistical Analysis for Specific Aim 1 (Randomization to Early vs. Delayed Surgery and Post-Operative Rehabilitation)

All analyses for the two by two factorial design trial will follow the principle of intention-to-treat. The primary outcome of return to military duty, work and sports will be assessed at monthly intervals via text message, email, or phone call from 6 to 24 months after randomization. This frequency of measurement will allow us to conduct more precise time to event analysis compared to having discrete time points several months apart. For those participants not returning to full activity and participation, the date of censoring for each participant will be the end of the two-year follow-up or last contact prior to 3 consecutive months of non-response/no data for this outcome. We will begin the analyses by estimating and comparing the time to event curves using Kaplan-Meier estimation and log-rank tests. We will begin the analyses by assessing the proportional hazards assumption for the four intervention groups using a plot of the log of the negative log of the estimated survival density vs. the log of time (for parallel lines) and by testing the group (4 levels) by time interaction in a Cox proportional hazards model (group*log(t)). If non-significant, we will assess using the collapsed main effects for surgery (early vs delayed) and post-operative rehabilitation (early vs delayed). We will also assess and test for non-proportional hazards by site and injury pattern (randomization stratification factors). If the proportional hazards assumption is not violated for the group effects, we will proceed using Cox proportional hazards model to test for intervention effects on time to return to military duty, work, and sports. Although we are not powered for detecting an interaction, we will test the interaction between timing of surgery and timing of rehabilitation using Cox proportional hazards model prior to looking at main effects. Assuming the interaction is not significant, we will compare the time to return to return to military duty, work and sports for both main effects, adjusting for site and KD injury pattern. We will present results using hazard ratios and 95% confidence intervals. If the proportional hazards assumption is violated, we will extend the Cox model to incorporate the group*log(t) term such that the hazards may vary over time across groups. If the proportional hazards assumption is violated for site or injury pattern, we will allow for this variability through stratification since the parameter estimates and testing for these two variables are not of interest.

We will use linear mixed models to compare and test the mean patient-reported physical function as measured by the MLQoL Activity Limitation Scale across the groups accounting for repeated measurements within patient. The fixed effects of surgery (early vs. delayed), rehabilitation (early vs. delayed), time (baseline, 6, 12, 24 months), the two-way interactions, and the three-way interaction will be placed in the model controlling for site and KD injury pattern. Assuming the 3-way interaction is not significant, we will proceed to test the two-way interactions for surgery*time and rehabilitation*time. If the two-way interaction is significant, we will test the separate treatment effects at 24 months (primary time point of interest) using contrasts. All treatment effects will be presented using adjusted mean differences and 95% confidence intervals. Using the linear mixed models is advantageous in the presence of data missing completely at random or missing at random as these models efficiently handle the observed data and correlations among the repeated measures to estimate treatment effects and standard errors.

With respect to missing outcome data, we will compare those patients missing follow up visits at 6, 12, and 24 on demographic and baseline clinical characteristics to assess the missing data mechanism. As a sensitivity analysis, if the proportion of patients lost to follow up exceeds 15% or any time point has more than 15% missingness, we will use pattern mixture models under non-ignorable missingness to test the impact on the inference of our trial results.

To determine if early surgery and early rehabilitation is better that the other combinations, we will specifically compare the early surgery/early rehabilitation group to each of the 3 other intervention arms using contrasts in the full models for both the time to event outcome and patient-reported physical function.

Secondary outcomes that are scales or continuous measurements will be analyzed similar to the methods used for physical function. Secondary outcome measures that are categorical will be analyzed using random effects logistic regression to control for repeated measures within person. The rates of complications and adverse events will

be compared using chi-square analysis (at the participant level) by type of complication, event term (>10% occurrence) and by organ system.

12.4.2 Statistical Analysis for Specific Aim 2 (Randomization to Only Early vs. Delayed Post-Operative Rehabilitation)

Analysis for the early versus delayed rehabilitation trial (Aim 2) will follow the principle of intention-to-treat. Baseline characteristics will be compared between the two groups to assess comparability. We will estimate the time to full return to activity and participation using Kaplan Meier curves and test between the two groups using log-rank testing. We will then test the curves adjusting for site and KD injury pattern using Cox proportional hazards model similar to the analysis for the surgery and rehabilitation trial. The approaches to assessing and testing the proportional hazards assumption will be the same. We will use linear mixed models to compare and test mean patient-reported physical function between the two groups over time accounting for the repeated measurements within patient. The fixed effects of early vs. delayed rehabilitation and time (baseline, 6, 12, and 24 months) and their two-way interaction will be tested adjusting for site and KD injury pattern. The approaches to investigating and handling missing data will be similar to those proposed in Specific Aim 1. All other secondary outcomes that are scales or continuous measures and will be analyzed similarly. Secondary outcome measures that are categorical will be analyzed using random effects logistic regression to control for repeated measures within person. The rates of complications and adverse events will be compared using chi-square analysis (at the participant level) by type of complication, event term (>10% occurrence) and by organ system.

13 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

All initial screening, baseline, inclusion/exclusion, pre-operative PROs and baseline clinical visit forms will be collected and stored in REDCap using the scheduling function. After randomization occurs, Standard of Care clinical visits and PROs will be completed remotely and managed through scheduled timepoints in REDCap

Medical record information that will be accessed for this study includes information related to surgical findings and procedures, radiographic findings and the clinical course of recovery following surgery including any complications that arise. Radiographs and MRI that are obtained as the standard of care will also be reviewed to determine the nature and extent of injury (and healing) to the ligaments, tendons, menisci, cartilage, nerves, blood vessels and bone. Study specific forms have been developed to collect this data and the information will be entered in REDCap.

Status of the data collection will be discussed at weekly clinical research meetings by Principal Investigator (Dr. James Irrgang) and Director of DCC and Biostatistician (Dr. Charity Moore Patterson) and members of the research team at the DCC. Each site study coordinator will review paper documents (i.e. signed consent forms) monthly and ensure the secure storage of the paper forms. All study questionnaires are designed to be completed out electronically, however if subjects elect to fill out paper forms, the data from the form will be entered by site staff and the paper form will be stored with their other paper documents.

Dr. Patterson will delegate management of the REDCap database to the research staff that she supervises, and they will reconcile with each site any data discrepancies through routine audits (quarterly) of the database.

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Study staff will permit authorized representatives of the DoD and regulatory agencies to examine (and when required by

applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

Table 8 lists the electronic forms that are collected in REDCap as well as the information that will be obtained from the medical records and from paper forms that will be utilized for the study (see Appendix B for study forms).

Table 8. List of forms and source of data collection.

REDCap	Medical Records	Paper Form
• Additional Surgeries – Patient Reported • Additional Surgeries – Clinical • Articular Cartilage Findings and Procedures • Baseline Injury Surveillance Survey/Military Activity • Brief Resilience Scale • Cincinnati Occupational Rating Scale • Clinical Visit Form • Complications Reporting • Concomitant Medications • Contact Information • Demographic & Participant Information • Examination Under Anesthesia • Functional Comorbidity Index • Global Rating of Change/PASS • ·IKDC Subjective Knee Evaluation	• Surgical findings and procedures • Radiographs/MRI findings • Clinical course of recovery • Surgical complications • Concomitant Medications	• Initial Screening Form • Contact Information • Demographic & Participant Information • Consent Forms • PRO's (as requested by participant)

• Initial Screening Form • Inclusion/Exclusion Form • Ligament Findings and Procedures • Marx Activity Rating Scale • Meniscus Findings and Procedures • Multi-Ligament Quality of Life Questionnaire • Patient Reported Rehabilitation • Peroneal Nerve Findings • Physical Therapy Case Report • Post-Operative Home Exercise Log • PROMIS Global 10 • PROMIS Physical Function • Return to Activity Monitoring Survey • Return to Military Activity • Return to Sports Activity • Return to Work Activity • Tampa Scale for Kinesiophobia		

14 QUALITY CONTROL AND QUALITY ASSURANCE

Quality Management in clinical research is the overall process of establishing and ensuring the quality of processes, data, and documentation associated with the clinical research activities. It encompasses both quality control (QC), and quality assurance (QA) activities. Quality control is comprised by a set of operational activities intended to ensure the quality requirements are being met. It continuously reviews data collection forms and other records for completeness and logic. Quality assurance is comprised of a set of activities intended to: 1) establish quality requirements and procedures; 2) ensure that those requirements are being met and procedures are being followed; and 3) verify that quality is being maintained. This includes creating procedural documents to guide quality activities and the review of documentation to assess adherence to written procedures, policies, and regulations.

14.1 Quality Management

Quality Management includes the QC and QA processes aimed at prevention of errors, as well as processes aimed at detection and correction of errors. Activities related to Quality Management (QM) prior to study initiation will primarily focus on the prevention of errors and will include:

- Reviewing consent documents to make sure that all proper elements are included and that the documents complies with all relevant regulations, local IRB requirements, and Good Clinical Practice, as appropriate
- Face-to-face kick-off Investigator's meeting to review study protocol
- Research Coordinators' conference calls and/or webinars for training on study protocol (e.g., screening, eligibility, clinical and research CRFs, adverse events, etc.). These conference calls will take place every 2 weeks until all sites are approved to initiate recruitment.
- Monthly Investigators' conference calls for training and discussion related to the logistics of implementation of the study at the site level.
- Executive Steering Committee conference calls will take place monthly.

- Development of the Reportable Events Policies by Site Standard Operating Procedures.
- Testing of the electronic data capture system (REDCap) functionality and data validation features (detailed description in Section 16).
- Training of research staff on case report forms (CRFs) for data collection, eCRFs in REDCap for data entry and overall utilization of the REDCap system for data collection.
- Site Initiation Visit which will have the goals of:
    - Orienting and training staff on the protocol and study related processes;
    - Confirming readiness for study implementation; and
    - Identifying additional requirements that must be satisfied prior to site activation and subject.

See Section 11 for detail list of activities.

Throughout the conduct of the study, processes to prevent errors, discuss any new or unforeseen issues and preserve expected level of training and knowledge of study protocol will be maintained by:

- Weekly STaR Trial research meeting at the Pittsburgh site;
- Monthly Research Coordinators conference calls;
- Annual Interim Site Visits;
- Monthly Investigators conference calls;
- Monthly Executive Steering Committee calls.

In addition, we will implement processes for detection of errors. Periodic reporting of key data elements to ensure protection of subjects' rights and data integrity will take place. See table 9 below:

Table 9. Reports of Records and Documents to be Periodically Monitored.			
Records and Documents To Be Monitored	**How?**	**Frequency?**	**Who?**
Site Human Subject Protection Training Records	• When a request for REDCap user access is submitted, permission is only granted when all training certifications are verified by STaR Trial Project Coordinator		Project Coordinator
IRB and HRPO Initial Approval and Annual Renewal Letters	• Electronic calendar system including dates of initial approval and due date for renewal will alert STaR Project Coordinator if a site is delinquent.		Project Coordinator
Signed Informed Consent Forms	• Signed IC forms will be scanned and uploaded into the REDCap system by each site's Research Coordinator.	Monthly	Project Coordinator
Eligibility Criteria	• REDCap SMART Eligibility Criteria form is auto-populated from Baseline Clinical Examination Form that is completed by the surgeon- investigators'	At form submission	

	answers and only those meeting all eligibility criteria will be permitted to be randomized.		
Surgical Source Documentation vs. CRFs	• Direct entry during surgery. Surgeon calls out data and research staff enters directly into REDCap. (REDCap is the source document)	Annually during site monitoring visits	Dr. Gil & STaR Project Coordinator
	• Surgical report written/dictated by surgeon and is included in the Electronic Health Record. (EHR).		
	• Documented on paper form and entered by research staff. In this case, comparison of paper CRF and REDCap will take place during the site monitoring visits.		
Clinical Follow-up Visits Source Documentation vs. CRFs	• Direct data entry during clinical visit. Surgeon and/or physician assistant will enter data directly into REDCap. (REDCap form is the source document)	Annually during site monitoring visits	Dr. Gil & STaR Project Coordinator

	• Examination and progress reports written/dictated by surgeon and in included in EHR.		
	• Documented on paper form and entered by RA. In this case, comparison of paper CRF and REDCap will take place.		
CRFs or Data Queries	• Direct data entry of PROs by subject using a tablet computer. (REDCap form is the source document)	Weekly	DCC
Process to Contact PTs when CRFs Were Not Submitted	• Research Assistants will log all attempts of communication in the Physical Therapy Data Center Portal/ Follow-up Dash Board.	Weekly	Research Assistants under supervision of Dr. Lynch
Missed Visits and Missing Data	• Interim Reports	Twice annually	DCC and DSMB
Documentation and Reporting of AEs, SAEs, Protocol Deviations Documentation	• Interim Reports • Email Alerts	Weekly	Internal Review
		Every 2 months	External Adjudication Review

		Twice annually	DSMB
Withdrawals and Dropouts Documentation	• Interim Reports	Every 6 months	DCC, QCC and DSMB
Site Regulatory Documents	• Verification at on-site Initiation and Interim Visits	Annually	
	• Verification remotely at Close-Out Visit	Event driven	

Corrective action plans to ensure QC and QA will be developed and implemented as necessary. Ongoing follow-up reports will enable the Clinical Coordinating Center to determine effectiveness of any corrective actions that are taken. Problems identified during the monitoring process may trigger additional training of site research staff. Continuing or serious protocol deviations discovered during the quality review process will be documented and reported to the site Principal Investigator, site RC and University of Pittsburgh IRB (see Assessment of Safety Section 9).

At the time of the site close-out visit, the following items will be verified to ensure that:

- All subjects have completed the final study-related visits;
- All final site-level Quality Management activities have been completed;
- All site data for all subjects have been entered in database;
- All queries from the DCC have been resolved/closed
- The Final Interim Monitoring Visit has been conducted as per approved Clinical Monitoring Plan;

- All action items identified during previous monitoring visits have been addressed and resolved;
- Notification is provided to the DoD to indicate that the site is approved for close-out visit.

For an orderly closure of study documents, at the time of study close-out we will ensure that:

- Appropriate source documentation is present for all subjects;
- All electronic CRFs have been completed and submitted to the DCC, as applicable;
- All electronic queries issued to date have been appropriately resolved, reviewed, and closed, where applicable;
- All CRF pages requiring signature have been electronically signed and dated by the investigator;
- All AEs, UAPs and SAEs have been captured, followed, and resolved per protocol, and reported to the appropriate parties according to protocol reporting requirements;
- All required follow-up documentation has been retrieved, communicated to appropriate parties, and is present in the study files;
- Signed consent forms are on file for all subjects;
- All required documents are present in the Trial Master File, including collection of all required documents from all Investigator Site Files, where appropriate;
- Reporting of study closure to the IRB and receipt/filing of confirmation of study closure in the investigator site files;
- If study was terminated early, confirmation of notification of study termination has been sent to all enrolled subjects as appropriate;

- All protocol deviations have been noted in source documentation and reported to the IRB as appropriate;
- All study logs, such as pre-screening, screening and enrollment, delegation of responsibilities, telephone and training log are complete.

The study close-out activities to ensure that data analysis, manuscripts and publications have been completed will include:

- Verification of final data analysis;
- Writing, review and approval of the primary manuscript(s) by the investigative team as specified in the Publications and Ancillary Studies policy;
- Submission of the results to PubMed and ClinicalTrial.gov

The quality management plan as described above has been developed to ensure ongoing review of data collection forms and other records for completeness and logic. In addition, it establishes processes to ensure quality requirements and procedures; and that those requirements are being met and procedures are being followed.

15 ETHICS/PROTECTION OF HUMAN SUBJECTS

15.1 Ethical Standard

The Principal Investigators will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6 or another country's ethical policy statement, whichever provides the most protection to human subjects.

15.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the University of Pittsburgh IRB for review and approval. Additionally, the protocol, informed consent forms, recruitment materials and all subject materials must be reviewed and approved for compliance with Department of Defense (DoD) human subjects' protection requirements and approved by the Office of Research Protections (ORP) Human Research Protection Office (HRPO). Approval from both the IRB and HRPO for the protocol and the consent forms must be obtained before any participants are enrolled. Amendments to the protocol will require review and approval by the both the IRB and HRPO before the changes are implemented in the study.

For this study, the University of Pittsburgh IRB will serve as the single IRB of record for all military and civilian sites in the US. Canadian sites will need to obtain local ethical board approval for the conduct of this study. The Pitt IRB will not act as IRB of Record for the Canadian sites.

A reliance agreement will need to be established between the relying sites and the University of Pittsburgh IRB to allow the relying institution to cede IRB responsibilities and oversight to the University of Pittsburgh.

15.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to and reviewed with the participant. Consent forms will be IRB- and HRPO-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study. The consent process will be documented in the clinical or research record.

Potentially eligible subjects will be informed of the study by the attending surgeon or a member of the surgeon's clinical team. If the patient expresses an interest in participating in the study, the physician will ask permission for the patient to be approached by the research staff. At that time, the patient will be introduced to the research coordinator responsible for study recruitment. The surgeon-investigator and research coordinator will inform the patient of the research study including the activities, expectations, risks and benefits, and rights as a research subject as related to participation in the study. All questions and concerns will be addressed before the participant signs the consent form. Investigators and coordinators will be available to answer questions about study participation throughout the duration of the clinical trial.

The informed consent discussion will occur after the clinical diagnosis of a multiple ligament knee injury, but prior to surgery and rehabilitation. The informed consent discussion will occur within the clinical practice of the treating physician, in the

outpatient office or within the hospital setting. Potential participants will be given time to review the study information and ask any questions about the study they may have. Potential subjects will be able to discuss participation in the study with family members and/or other health care providers. Once the potential participant is fully informed of the study and is voluntarily willing to take part in the study, the subject and the surgeon-investigator will sign informed consent form. Before agreeing to participate in this research study, or at any time during study participation, participants will be provided the opportunity to discuss the study with another doctor who is not associated with this research study.

For active duty military personnel, no individuals in the participant's chain of command will be involved in the recruitment process. Because the surgeon is also an investigator in the study, we recognize that the surgeon may be conflicted in their attempts to recruit the individual into the study. During the recruitment and consent process, subjects will be informed of this potential conflict and offered the opportunity to discuss their care with another surgeon that is not associated with the study. Once informed consent has been obtained, screening procedures will be performed to confirm final eligibility for participation in the trial for Aim 1 or 2. For potential participants that are between the 14 and 17 years of age, the study will be explained to both the child and the child's parent or legal guardian as required by state (or Canadian) law and institutional policy of each site. If the child is willing to participate in the study, permission from the child's parent or legal guardian will be sought and documented on the informed consent form. Additionally, the child will be required to provide written assent to participate in the study. The participant's physician will also be available to answer any questions that the subject has regarding his/her participation in the research study. If the individual agrees to participate in the study, the subject's surgeon will sign the informed consent form.

All subjects will be capable of providing direct informed consent for study participation. Participants with altered mental capacity due to traumatic brain injury or those unable to comply with study procedures will not be eligible to participate in the study. Individuals will not be approached to provide informed consent if they are under sedation,

anesthesia, or other medical treatment or substance that alters decision making abilities.

15.4 Subject Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover any study information related to the participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or data will be released to any unauthorized third party without prior written approval of the sponsor.

The study research monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study participants. The clinical study site will permit access to such records.

To ensure that the confidentiality of subject records is maintained, records associated with subject participation in this study will be indicated by a study identification number. Information linking these case numbers with subject identity will be accessible only to the investigators and their research team and will be stored in a locked file. Any data or subject level information that is submitted for review to the DSMB, HRPO, University of Pittsburgh Office of Research Conduct and Compliance, and the IRBs, will be linked only to the subject's case number and not the personal identity of the subject.

16 DATA HANDLING AND RECORD KEEPING

All study investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of all data that are collected and reported for this study. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.

16.1 Data Management Responsibilities

The purpose of the clinical data management plan (DMP) is to provide specific information regarding the study's data management practices including staff responsibilities, data collection, data standards and acquisition, data quality assurance, and dissemination. The DMP will be coordinated by the Physical Therapy Data Center in the Department of Physical Therapy at the University of Pittsburgh under the leadership of Dr. Charity (Moore) Patterson, DCC Director, in collaboration with Dr. Alexandra Gil, Quality Control Coordinator and Drs. Irrgang (Principal Investigator), Musahl (Co-Principal Investigator and Qualified Collaborator [QC]) for Surgery and Lynch (Co-Investigator and QC for Rehabilitation).

16.2 Data Capture Methods

The Research Electronic Data Capture (REDCap) system, hosted at the University of Pittsburgh, will be used as the web-based data collection and management system for this study.[98] REDCap is a secure, web-based application designed with the flexibility to support data capture for a variety of research projects. It provides:

- A mechanism for managing user-access to the data and the various system applications;
- A mechanism for validated data uploads from external sources;
- An intuitive user interface for validated data capture through the execution of real-time validation rules, such as univariate data type and range checks;

- An audit trail for tracking transactions within the system, such as study system setup and modifications, data imports, data entry and edits, and data exports and
- A mechanism for seamless data downloads to common data formats (SAS datasets will be the format of choice for this study).

16.3 Identifiers

Each study participant will be assigned a **Study Identification Number (SID)** determined by site, system generated enrollment number and patient initials. The patient names and contact information will be stored in a table in the REDCap project that is not in the same tables as the research data. Name and contact information will be available to the local site where the participant was enrolled and to the staff at the University of Pittsburgh where the centralized follow-up is conducted via surveys. Dates of birth, injury, clinical visits, and surgery will be entered into the system. Date of birth and date of injury are necessary to ensure eligibility based on calculated age at the time of screening. Dates of surgery and clinical visits are necessary to ensure and monitor protocol compliance. Subjects will not be identified by name in any publications of research results.

16.4 Confidentiality

All study subjects will be identified by the SID on all data collection instruments, documents, and files used in the statistical analysis and manuscript preparation. Only limited team members will have access to personal information needed for tracking and informed consent. No personal information concerning study participants will be released without their written consent. Authorized representatives of the U.S. Army Medical Research and Materiel Command (USAMRMC), which is the funding agency for this study, may review or obtain identifiable information (including subject SIDs) for monitoring the accuracy and completeness of the research data, for performing required scientific analyses of the research data, and as part of their responsibility to protect human research volunteers.

The DCC will work with the CCC to determine who will have access to the electronic data capture system and the type of access (i.e. data entry, data review, or analysis). The system is protected by a unique login and password. Once a research staff member has gone through data entry training and testing, the Systems Analyst or designee will permit access to the production system. A user access log will be maintained by the CCC and the DCC. We acknowledge that representatives of USAMRMC are eligible to review study records.

In unusual cases, the investigators may be required to release identifiable information related to subject participation in this research study in response to an order from a court of law. If the investigators learn that a subject or someone with whom the subject is involved with is in serious danger or potential harm, they will need to inform the appropriate agencies, in response to an order by a court of law.

16.5 Data Capture, Verification and Disposition

The Case Report Forms (CRFs) will serve as the basis for the structure of the REDCap database with the data entry screens being as visually similar to the CRFs as possible. Blank CRFs, Study Protocol, and the Manual of Procedures (MOP) will be available in the document sharing application in the REDCap system. The MOP will include the forms and detailed descriptions of how to enter each data element. Personnel at the DCC will be available to answer phone or e-mail questions during regular business hours. These include the DCC Director, the Systems Analyst, and Data Manager.

Each aspect of the REDCap system will be tested before actual study data is collected. Mock data will be entered onto CRFs by DCC personnel to be used in the User Acceptance Testing process. The University of Pittsburgh site project coordinator will serve as the User for acceptance testing, entering the mock data on the CRFs into each field of each data collection instrument and documenting the success or failure of a) the user interface for data entry, b) the on-line univariate and range data validation checks, and c) custom functions. The Systems Analyst or designee will verify the audit trail after the mock data are entered. The mock data will also be exported to SAS datasets by the

DCC Systems Analyst or Data Manager and the accuracy of the export will be verified by the DCC statistician.

Specific items to be included in the testing are described in below (Table 10).

Table 10 – List of items to be tested during REDCap development

Item	Details of Testing
1. Univariate and valid value checks	Confirm that checks have been properly built and documented.
2. Multivariate (two or more items on the same CRF) and cross-checks (two or more items on separate CRFs)	Confirm each check does and does not trigger appropriately.
3. Custom functions	Confirm each custom function behaves as intended.
4. Generation of subject numbers	Confirm that new subject IDs are generated as expected.
5. Data completion guidelines	Confirm that the completion guidelines are properly associated with each form/field.
6. Derived variable computation	Confirm variables are derived as expected.
7. Role assignment	Review system. Confirm using list of role functionality, have testers assigned to each role, and ensure that they are only able to do/see what they are entitled to per their assigned role.
8. Data Extracts	Confirm extracted data matches annotated CRF specifications.
9. Data Imports into REDCap	If applicable, create test data, import, and review imported data.
10. System Reports	Review system reports and ensure that they are functioning according to expectations. Run reports on test data.

The Case Report Forms (CRFs) will serve as the basis for the structure of the REDCap database, which will produce a data dictionary with labels for each data field captured and specific validation rules associated with each data field. Data values that violate these rules are identified at the time of data import or entry and require correction at the

entry source before they can be accepted into the database. The REDCap database structure will be designed and built by the Systems Analyst or designee and only these participants can modify the structure. User rights and access to all system data and applications will be assigned and managed by the Systems Analyst.

All screening, clinical, surgical, rehabilitation, and performance measures data will be single-entered from the CRFs or directly entered into the REDCap data-entry screens by the coordinator at each site. Patient reported outcomes will be obtained using surveys sent via SMS text messages or email directly to the participants or via direct entry when surveys are conducted by interview (telephone or in person). REDCap has the capability to send SMS text messages to survey subjects by using a third-party web service named Twilio. Using this service, a subject will be invited to complete the CRF by sending them an SMS message or by calling them on their phone. Using this service the data are collected in REDCap directly from the subject's phone without the need to use the webpage.

The CRFs are electronic forms completed by clinical site staff or study participants. Some forms will be completed during the participant's study visits, while others will be completed or verified using data extracted from the medical record (e.g. surgery dictation). The CRFs will be available in the REDCap file repository application and can also be obtained by emailing the Systems Analyst or Data Manager.

In addition to data capture through CRFs that will be specifically developed for this STaR Trial, the Patient Reported Outcome Measurement Information System (PROMIS) Physical Function Scale will be administered as a computer adaptive test (CAT) directly through the REDCap Shared Library.[98] All instruments kept in the REDCap Shared Library have been approved and reviewed for their importance to research, function and coding precision, and copyright related issues.

The web-based data submission software is REDCap ver. 7.4.7 built upon MySQL 5.5. The website is secured by HTTPS, individual usernames, and strong passwords. The database tables default engines are MyISAM and InnoDB. Non-secure ports of all servers are located behind the DCC network firewall and accessible only under the

following conditions: 1) a workstation physically present in the building and physically connected to the network 2) granted system access to the database server 3) a user name and password for that database server 4) a second username and password for database software 5) granted access to a data project 6) granted access to data items. All non-essential ports of the database server and web servers are closed. Only one secure (HTTPS) port on the website server is open outside of the firewall. All servers are physically located in a secured room which is accessible only by a key card; currently, only two system administrators, one financial administrator, and required IT maintenance and support staff have access to this room. In addition, the secured room is located in a secured suite which is also accessible only by key cards given to current University of Pittsburgh employees located in the suite. The building is locked and accessible only by University of Pittsburgh employees located in the building after business hours and on weekends. A network system administrator regularly monitors for occurrences of attempted access to the network by unauthorized users. There is a security administrator for the VM server where the application resides and a database administrator who monitors and authorizes appropriate use of REDCap and the MySQL database server. On-site backup of study data is performed nightly; off-site backups are taken twice weekly and stored at a secure University of Pittsburgh location, in a locked office in a secure suite.

All DCC statisticians use SAS version 9.4 for report and statistical analyses. SAS runs off individual computers. The SAS data files and programs used for monitoring, reporting, and analysis will be stored on the School of Health and Rehabilitation Sciences password protected server under this directory:

L:\\PT Data Center\Irrgang\STaR.

The real-time validation and regular quality monitoring by the DCC are intended to detect and correct errors as they occur. Therefore, minimal data cleaning should be needed near the closing of the study. Upon enrollment of the final participant, the DCC will begin the final cleaning process, assessing outstanding queries, missing items, missing forms, and range and value checks. In addition, all documentation concerning data validations, queries, resolutions, and participant locking will be reviewed for

completeness and consistency. The targeted date for locking participant data is 3 months after the final participant is off protocol for each study at which time the statistical analysis will begin. The full database lock will occur upon the approval of the Executive Steering Committee (ESC). Errors identified in the database after database lock will be documented. The correction process and database unlock will begin only with the approval of the ESC. This process will require documentation for the request for data change with justification, formal approval of the data change, the date of the change, and the future database lock date for the revised data.

16.6 Data Reporting

Table 11. List of Data Management Reports

Report Name	Description/Purpose	Frequency	Recipients/ Users	Methods for Provision
Query override report for REDCap	Lists all queries where the data entry user overrode the query with no change, includes the explanation for the change/DM review for acceptability of overrides.	Monthly	Data Managers and other DM staff	Automated SAS report stored on local network.
Executive Steering Committee (ESC) and Coordinator/Quality Control Committee reports	Screening and enrollment, attrition, missing data for primary and secondary outcomes, protocol deviations, SAEs, and unanticipated events	Monthly	Executive Steering Committee members, DoD program officer, and DCC team	SAS report stored on local network and delivered by email to the ESC members, CQCC members, and the DoD

				program officer.
Data and Safety Monitoring Board (DSMB)	Screening and enrollment, attrition, missing data for primary and secondary outcomes, protocol deviations, SAEs, and unanticipated events	Every 6 months or Annually (depending on meeting timeline established by DSMB)	Data and Safety Monitoring Board members, and Study PI	SAS report stored on local network and delivered by email to the DSMB and Study PI.
Adverse Events Adjudication Committee (AEAC)	Adverse Events and SAEs	Every 2 months	Adverse Events Adjudication Committee members	SAS report stored on local network and delivered by email to the AEAC.
Data queries	Lists all queries on multivariate checks (within the same form) and cross-checks (across different forms).	Bi-weekly then monthly after the first 5 participants are enrolled.	DCC Team and Site coordinators	Automated REDCap and SAS reports stored in REDCap or on local network and uploaded into REDCap system.
On-site monitoring	List of all participants enrolled, date of consent, patient information, serious adverse events, and protocol deviations.	As-needed.	On-site monitoring team	Automated SAS reports stored on local network and delivered by secure email.

16.7 Study Records Retention

The study database and all documentation will be maintained indefinitely at the DCC. A public-use version of the dataset will be constructed by the DCC with contents to be determined jointly by the study PIs and the DCC Director. Copies of the public-use version of the dataset will be housed at the DCC on the SHRS secure server along with suitable documentation of this dataset. The public-use version of the dataset will be exported by CRF in one or more files in simple, widely-accessible formats, e.g., .xls, .csv, and/or SAS datasets. Documentation will be in .pdf files. Outside investigators wishing to conduct analyses using the data will submit a request with objectives, methods, and analysis plan to the PI and the Director of the DCC. Once the request is approved, the public-use version of the dataset, with documentation, will be sent by secure email using e-mail, ftp, or other mutually agreeable transmission method. The public-use version of the database will be made 2 years after the study's main paper is published. Updates of the public-use version of the database will correct errors (if any) in the items included in earlier releases and will add new data items deemed to be locked since the previous version was released.

16.8 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the part of the subject, the investigator, or study staff. Protocol deviations will be captured on the Protocol Deviation Form and entered into the database. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly to remedy any problems. In addition, study staff will perform follow-up evaluations of actions taken, if necessary.

These practices are consistent with investigator and sponsor obligations in ICH E6:

- Compliance with Protocol, Sections 4.5.1, 4.5.2, 4.5.3, and 4.5.4.
- Quality Assurance and Quality Control, Section 5.1.1

- Noncompliance, Sections 5.20.1 and 5.20.2.

17 PUBLICATION/DATA SHARING POLICY

Publications and Ancillary Studies Committee (PASC) will consist of Robert Schenck (Chair), Matthew Matava (Co-Chair, site PI for Washington University), Kenneth Cameron (Co-I, Keller Army Hospital), Andrew Lynch, Charity Moore Patterson, Matthew Posner (site PI for Keller Army Hospital), Brett Owens, Michael Stuart (site Co-I for Mayo Clinic), James Irrgang (Ex Officio), Volker Musahl (Ex Officio). The PASC has policies and procedures for assigning working groups and approving STaR Trial-associated ancillary studies, secondary analyses of existing data and abstracts, presentations, and publications prior to their submission for dissemination. The PASC has guidelines for authorship for investigators following the guidelines specified by the International Committee of Medical Journal Editors (*http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html*) [99] for authors that have contributed to the scientific design and merit of the study. See the Manual of Operations for additional details related to publication of data from the STaR Trial.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as *ClinicalTrials.gov*, which is sponsored by the National Library of Medicine. As such, the STaR trial will be registered with *ClinicalTrials.gov* prior to enrollment of the first participant.

18 LITERATURE REFERENCES

Reference List

1. Medina O, Arom GA, Yeranosian MG, Petrigliano FA, McAllister DR. Vascular and nerve injury after knee dislocation: a systematic review. *Clin Orthop Relat Res.* 2014;472(9):2621-2629.
2. Niall DM, Nutton RW, Keating JF. Palsy of the common peroneal nerve after traumatic dislocation of the knee. *J Bone Joint Surg BR.* 2005;87(5):664-667.
3. Tzurbakis M, Diamantopoulos A, Xenakis T, Georgoulis A. Surgical treatment of multiple knee ligament injuries in 44 patients: 2-8 years follow-up results. *Knee Surg Sports Traumatol Arthrosc.* 2006;14(8):739-749.
4. Burrus MT, Werner BC, Griffin JW, Gwathmey FW, Miller MD. Diagnostic and Management Strategies for Multiligament Knee Injuries: A Critical Analysis Review. *JBJS reviews.* 2016;4(2).
5. Cook S, Ridley TJ, McCarthy MA, et al. Surgical treatment of multiligament knee injuries. *Knee Surg Sports Traumatol Arthrosc.* 2015;23(10):2983-2991.
6. Whelan DB, Dold AP, Trajkovski T, Chahal J. Risk factors for the development of heterotopic ossification after knee dislocation. *Clin Orthop Relat Res.* 2014;472(9):2698-2704.
7. Showery JE, Kusnezov NA, Dunn JC, Bader JO, Belmont PJ, Jr., Waterman BR. The Rising Incidence of Degenerative and Posttraumatic Osteoarthritis of the Knee in the United States Military. *J Arthroplasty.* 2016.
8. Engebretsen L, Risberg MA, Robertson B, Ludvigsen TC, Johansen S. Outcome after knee dislocations: a 2-9 years follow-up of 85 consecutive patients. *Knee Surg Sports Traumatol Arthrosc.* 2009;17(9):1013-1026.
9. Ross AE, Taylor KF, Kirk KL, Murphy KP. Functional outcome of multiligamentous knee injuries treated arthroscopically in active duty soldiers. *Mil Med.* 2009;174(10):1113-1117.
10. Peskun CJ, Whelan DB. Outcomes of operative and nonoperative treatment of multiligament knee injuries: an evidence-based review. *Sports Med Arthrosc.* 2011;19(2):167-173.
11. Arom GA, Yeranosian MG, Petrigliano FA, Terrell RD, McAllister DR. The changing demographics of knee dislocation: a retrospective database review. *Clin Orthop Relat Res.* 2014;472(9):2609-2614.
12. Owens BD, Mountcastle SB, Dunn WR, DeBerardino TM, Taylor DC. Incidence of anterior cruciate ligament injury among active duty U.S. military servicemen and servicewomen. *Mil Med.* 2007;172(1):90-91.
13. Barrow A, Sheean A, Burns T. Return to Duty Rates after Combat-Related Multiligamentous Knee Injury. *Arthroscopy.* 2016;31(6):e1-e2.
14. Denti M, Tornese D, Melegati G, Schonhuber H, Quaglia A, Volpi P. Combined chronic anterior cruciate ligament and posterior cruciate ligament reconstruction: functional and clinical results. *Knee Surg Sports Traumatol Arthrosc.* 2015;23(10):2853-2858.

15. Panigrahi R, Kumari Mahapatra A, Priyadarshi A, Singha Das D, Palo N, Ranjan Biswal M. Outcome of Simultaneous Arthroscopic Anterior Cruciate Ligament and Posterior Cruciate Ligament Reconstruction With Hamstring Tendon Autograft: A Multicenter Prospective Study. *Asian J Sports Med.* 2016;7(1):e29287.
16. Richter M, Bosch U, Wippermann B, Hofmann A, Krettek C. Comparison of surgical repair or reconstruction of the cruciate ligaments versus nonsurgical treatment in patients with traumatic knee dislocations. *Am J Sports Med.* 2002;30(5):718-727.
17. Stannard JP, Riley RS, Sheils TM, McGwin G, Jr., Volgas DA. Anatomic reconstruction of the posterior cruciate ligament after multiligament knee injuries. A combination of the tibial-inlay and two-femoral-tunnel techniques. *Am J Sports Med.* 2003;31(2):196-202.
18. Eranki V, Begg C, Wallace B. Outcomes of operatively treated acute knee dislocations. *Open Orthop J.* 2010;4:22-30.
19. Silverwood V, Blagojevic-Bucknall M, Jinks C, Jordan JL, Protheroe J, Jordan KP. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. *Osteoarthritis Cartilage.* 2015;23(4):507-515.
20. Cameron KL, Hsiao MS, Owens BD, Burks R, Svoboda SJ. Incidence of physician-diagnosed osteoarthritis among active duty United States military service members. *Arthritis Rheum.* 2011;63(10):2974-2982.
21. Rivera JC, Wenke JC, Buckwalter JA, Ficke JR, Johnson AE. Posttraumatic osteoarthritis caused by battlefield injuries: the primary source of disability in warriors. *J Am Acad Orthop Surg.* 2012;20 Suppl 1:S64-69.
22. Cross JD, Ficke JR, Hsu JR, Masini BD, Wenke JC. Battlefield orthopaedic injuries cause the majority of long-term disabilities. *J Am Acad Orthop Surg.* 2011;19 Suppl 1:S1-7.
23. Gabriel MT, Wong EK, Woo SL, Yagi M, Debski RE. Distribution of in situ forces in the anterior cruciate ligament in response to rotatory loads. *J Orthop Res.* 2004;22(1):85-89.
24. Levy BA, Dajani KA, Whelan DB, et al. Decision Making in the Multiligament-Injured Knee: An Evidence-Based Systematic Review. *Arthroscopy.* 2009;25(4):430-438.
25. Rios A, Villa A, Fahandezh H, de Jose C, Vaquero J. Results after treatment of traumatic knee dislocations: a report of 26 cases. *J Trauma.* 2003;55(3):489-494.
26. Wong CH, Tan JL, Chang HC, Khin LW, Low CO. Knee dislocations-a retrospective study comparing operative versus closed immobilization treatment outcomes. *Knee Surg Sports Traumatol Arthrosc.* 2004;12(6):540-544.
27. Dedmond BT, Almekinders LC. Operative versus nonoperative treatment of knee dislocations: a meta-analysis. *Am J Knee.Surg.* 2001;14(1):33-38.
28. Shelbourne KD, Nitz P. Accelerated rehabilitation after anterior cruciate ligament reconstruction. *Am J Sports Med.* 1990;18(3):292-299.

29. Kwok CS, Harrison T, Servant C. The optimal timing for anterior cruciate ligament reconstruction with respect to the risk of postoperative stiffness. *Arthroscopy.* 2013;29(3):556-565.
30. Decarlo MS, Shelbourne KD, McCarroll JR, Rettig AC. Traditional versus Accelerated Rehabilitation following ACL Reconstruction: A One-Year Follow-Up. *J Orthop Sports Phys Ther.* 1992;15(6):309-316.
31. Beynnon BD, Uh BS, Johnson RJ, et al. Rehabilitation after anterior cruciate ligament reconstruction: a prospective, randomized, double-blind comparison of programs administered over 2 different time intervals. *Am J Sports Med.* 2005;33(3):347-359.
32. Andersson D, Samuelsson K, Karlsson J. Treatment of anterior cruciate ligament injuries with special reference to surgical technique and rehabilitation: an assessment of randomized controlled trials. *Arthroscopy.* 2009;25(6):653-685.
33. Edson CJ, Fanelli GC, Beck JD. Rehabilitation after multiple-ligament reconstruction of the knee. *Sports Med Arthrosc.* 2011;19(2):162-166.
34. Irrgang JJ, Fitzgerald GK. Rehabilitation of the multiple-ligament-injured knee. *Clin Sports Med.* 2000;19(3):545-+.
35. Shelbourne KD, Wilckens JH, Mollabashy A, DeCarlo M. Arthrofibrosis in acute anterior cruciate ligament reconstruction. The effect of timing of reconstruction and rehabilitation. *Am J Sports Med.* 1991;19(4):332-336.
36. Jiang W, Yao J, He Y, Sun W, Huang Y, Kong D. The timing of surgical treatment of knee dislocations: a systematic review. *Knee Surg Sports Traumatol Arthrosc.* 2015;23(10):3108-3113.
37. Tay AK, MacDonald PB. Complications associated with treatment of multiple ligament injured (dislocated) knee. *Sports Med.Arthrosc.* 2011;19(2):153-161.
38. Tardy N, Boisrenoult P, Teissier P, Steltzlen C, Beaufils P, Pujol N. Clinical outcomes after multiligament injured knees: medial versus lateral reconstructions. *Knee Surg Sports Traumatol Arthrosc.* 2017; 25(2):524-531.
39. Fanelli GC, Giannotti BF, Edson CJ. Arthroscopically assisted combined posterior cruciate ligament/posterior lateral complex reconstruction. *Arthroscopy.* 1996;12(5):521-530.
40. Harner CD, Waltrip RL, Bennett CH, Francis KA, Cole B, Irrgang JJ. Surgical management of knee dislocations. *J Bone Joint Surg Am.* 2004;86-A(2):262-273.
41. Liow RY, McNicholas MJ, Keating JF, Nutton RW. Ligament repair and reconstruction in traumatic dislocation of the knee. *J Bone Joint Surg Br.* 2003;85(6):845-851.
42. Wascher DC, Becker JR, Dexter JG, Blevins FT. Reconstruction of the anterior and posterior cruciate ligaments after knee dislocation. Results using fresh-frozen nonirradiated allografts. *Am J Sports Med.* 1999;27(2):189-196.
43. Mook WR, Miller MD, Diduch DR, Hertel J, Boachie-Adjei Y, Hart JM. Multiple-ligament knee injuries: a systematic review of the timing of operative intervention and postoperative rehabilitation. *J Bone Joint Surg Am.* 2009;91(12):2946-2957.
44. Fanelli GC, Edson CJ, Reinheimer KN, Garofalo R. Posterior cruciate ligament and posterolateral corner reconstruction. *Sports Med Arthrosc.* 2007;15(4):168-175.

45. Fanelli GC, Beck JD, Edson CJ. Combined PCL-ACL lateral and medial side injuries: treatment and results. *Sports Med Arthrosc.* 2011;19(2):120-130.
46. Fanelli GC, Fanelli DG. Management of Chronic Combined PCL Medial Posteromedial Instability of the Knee. *Sports Med Arthrosc.* 2015;23(2):96-103.
47. LaPrade RF, Johansen S, Agel J, Risberg MA, Moksnes H, Engebretsen L. Outcomes of an anatomic posterolateral knee reconstruction. *J Bone Joint Surg Am.* 2010;92(1):16-22.
48. Geeslin AG, LaPrade RF. Outcomes of treatment of acute grade-III isolated and combined posterolateral knee injuries: a prospective case series and surgical technique. *J Bone Joint Surg Am.* 2011;93(18):1672-1683.
49. Owens BD, Neault M, Benson E, Busconi BD. Primary repair of knee dislocations: results in 25 patients (28 knees) at a mean follow-up of four years. *J Orthop Trauma.* 2007;21(2):92-96.
50. Jenkins PJ, Clifton R, Gillespie GN, Will EM, Keating JF. Strength and function recovery after multiple-ligament reconstruction of the knee. *Injury.* 2011;42(12):1426-1429.
51. Gormeli G, Gormeli CA, Elmali N, Karakaplan M, Ertem K, Ersoy Y. Outcome of the treatment of chronic isolated and combined posterolateral corner knee injuries with 2- to 6-year follow-up. *Arch Orthop Trauma Surg.* 2015;135(10):1363-1368.
52. Camarda L, Condello V, Madonna V, Cortese F, D'Arienzo M, Zorzi C. Results of isolated posterolateral corner reconstruction. *J Orthop Traumatol.* 2010;11(2):73-79.
53. Stannard JP, Brown SL, Farris RC, McGwin G, Jr., Volgas DA. The posterolateral corner of the knee: repair versus reconstruction. *Am J Sports Med.* 2005;33(6):881-888.
54. Murphy KP, Helgeson MD, Lehman RA, Jr. Surgical treatment of acute lateral collateral ligament and posterolateral corner injuries. *Sports Med Arthrosc.* 2006;14(1):23-27.
55. Werner BC, Hadeed MM, Gwathmey FW, Jr., Gaskin CM, Hart JM, Miller MD. Medial injury in knee dislocations: what are the common injury patterns and surgical outcomes? *Clin Orthop Relat Res.* 2014;472(9):2658-2666.
56. Talbot M, Berry G, Fernandes J, Ranger P. Knee dislocations: experience at the Hopital du Sacre-Coeur de Montreal. *Can J Surg.* 2004;47(1):20-24.
57. Salter RB, Simmonds DF, Malcolm BW, Rumble EJ, MacMichael D, Clements ND. The biological effect of continuous passive motion on the healing of full-thickness defects in articular cartilage. An experimental investigation in the rabbit. *J Bone Joint Surg Am.* 1980;62(8):1232-1251.
58. Barber-Westin SD, Noyes FR, McCloskey JW. Rigorous statistical reliability, validity, and responsiveness testing of the CIncinnati Knee Rating System in 350 subjects with uninjured, injured, or anterior cruciate ligament-reconstructed knees. *Am J Sports Med.* 1999;27(4):402-416.
59. Marx RG, Stump TJ, Jones EC, Wickiewicz TL, Warren RF. Development and evaluation of an activity rating scale for disorders of the knee. *Am J Sports Med.* 2001;29(2):213-218.

60. Chahal J, Whelan DB, Jaglal SB, et al. The multiligament quality of life questionnaire: development and evaluation of test-retest reliability and validity in patients with multiligament knee injuries. *Am J Sports Med.* 2014;42(12):2906-2916.
61. Irrgang JJ, Anderson AF, Boland AL, et al. Development and validation of the International Knee Documentation Committee Subjective Knee Form. *Am J Sports Med.* 2001;29(5):600-613.
62. Irrgang JJ, Anderson AF, Boland AL, et al. Responsiveness of the International Knee Documentation Committee Subjective Knee Form. *Am J Sports Med.* 2006;34(10):1567-1573.
63. Greco NJ, Anderson AF, Mann BJ, et al. Responsiveness of the IKDC Subjective Knee Form in comparison to the WOMAC Osteoarthritis Index, Modified Cincinnati Knee Rating System and SF-36 in patients with focal articular cartilage defects. *Am J Sports Med.* 2010;38(5):891-902.
64. Anderson AF, Irrgang JJ, Kocher MS, Mann BJ, Harrast JJ, Committee MotIKD. International Knee Documentation Committee Subjective Knee Form: Normative Data. *Am J Sports Med.* 2006;34(1):128-135.
65. Muller B, Yabroudi MA, Lynch A, et al. Defining Thresholds for the Patient Acceptable Symptom State for the IKDC Subjective Knee Form and KOOS for Patients Who Underwent ACL Reconstruction. *Am J Sports Med.* 2016;44(11):2820-2826.
66. Hung M, Baumhauer JF, Latt LD, et al. Validation of PROMIS (R) Physical Function computerized adaptive tests for orthopaedic foot and ankle outcome research. *Clin Orthop Relat Res.* 2013;471(11):3466-3474.
67. Papuga MO, Beck CA, Kates SL, Schwarz EM, Maloney MD. Validation of GAITRite and PROMIS as high-throughput physical function outcome measures following ACL reconstruction. *J Orthop Res.* 2014;32(6):793-801.
68. Broderick JE, Schneider S, Junghaenel DU, Schwartz JE, Stone AA. Validity and reliability of patient-reported outcomes measurement information system instruments in osteoarthritis. *Arthritis Care Res.* 2013;65(10):1625-1633.
69. Driban JB, Morgan N, Price LL, Cook KF, Wang C. Patient-Reported Outcomes Measurement Information System (PROMIS) instruments among individuals with symptomatic knee osteoarthritis: a cross-sectional study of floor/ceiling effects and construct validity. *BMC Musculoskelet Disord.* 2015;16:253.
70. Hays RD, Bjorner JB, Revicki DA, Spritzer KL, Cella D. Development of physical and mental health summary scores from the patient-reported outcomes measurement information system (PROMIS) global items. *Qual Life Res.* 2009;18(7):873-880.
71. Shelbourne KD, Nitz P. Accelerated rehabilitation after anterior cruciate ligament reconstruction. *J Orthop Sports Phys Ther.* 1992;15(6):256-264.
72. Hollander IE, Bell NS. Physically demanding jobs and occupational injury and disability in the U.S. Army. *Mil Med.* 2010;175(10):705-712.
73. Rhon D. Personal Communication. 2016.

74. Abbott JH, Schmitt J. Minimum important differences for the patient-specific functional scale, 4 region-specific outcome measures, and the numeric pain rating scale. *J Orthop Sports Phys Ther.* 2014;44(8):560-564.
75. Hefti F, Müller W, Jakob RP, Stäubli H-U. Evaluation of knee ligament injuries with the IKDC form. *Knee Surgery Sports Traumatol Athroscopy.* 1993;1:226-234.
76. Watkins MA, Riddle DL, Lamb RL, Personius WJ. Reliability of goniometric measurements and visual estimates of knee range of motion obtained in a clinical setting. *Phys Ther.* 1991;71(2):90-96.
77. Kaplan N, Wickiewicz TL, Warren RF. Primary surgical treatment of anterior cruciate ligament ruptures. A long-term follow-up study. *Am J Sports Med.* 1990;18(4):354-358.
78. Miller MD, Harner CD, Koshiwagucht S. Acute posterior cruciate ligament injuries. In: Fu FH, Harner CD, Vince KG, eds. *Knee Surgery*. Baltimore: Williams and Wilkins; 1994:749-767.
79. Sturgill LP, Snyder-Mackler L, Manal TJ, Axe MJ. Interrater reliability of a clinical scale to assess knee joint effusion. *J Orthop.Sports Phys.Ther.* 2009;39(12):845-849.
80. Grindem H, Eitzen I, Snyder-Mackler L, Risberg MA. Online registration of monthly sports participation after anterior cruciate ligament injury: a reliability and validity study. *Br J Sports Med.* 2014;48(9):748-753.
81. Grindem H, Snyder-Mackler L, Moksnes H, Engebretsen L, Risberg MA. Simple decision rules can reduce reinjury risk by 84% after ACL reconstruction: the Delaware-Oslo ACL cohort study. *Br J Sports Med.* 2016;50(13):804-808.
82. Tanner SM, Dainty KN, Marx RG, Kirkley A. Knee-specific quality-of-life instruments: which ones measure symptoms and disabilities most important to patients? *Am J Sports Med.* 2007;35(9):1450-1458.
83. Kvist J, Ek A, Sporrstedt K, Good L. Fear of re-injury: a hindrance for returning to sports after anterior cruciate ligament reconstruction. *Knee Surg Sports Traumatol Arthrosc.* 2005;13(5):393-397.
84. Lee DY, Karim SA, Chang HC. Return to sports after anterior cruciate ligament reconstruction - a review of patients with minimum 5-year follow-up. *Ann Acad Med Singapore.* 2008;37(4):273-278.
85. Lentz TA, Zeppieri G, Jr., Tillman SM, et al. Return to preinjury sports participation following anterior cruciate ligament reconstruction: contributions of demographic, knee impairment, and self-report measures. *J Orthop Sports Phys Ther.* 2012;42(11):893-901.
86. McCullough KA, Phelps KD, Spindler KP, et al. Return to high school- and college-level football after anterior cruciate ligament reconstruction: a Multicenter Orthopaedic Outcomes Network (MOON) cohort study. *Am J Sports Med.* 2012;40(11):2523-2529.
87. te Wierike SC, van der Sluis A, van den Akker-Scheek I, Elferink-Gemser MT, Visscher C. Psychosocial factors influencing the recovery of athletes with anterior cruciate ligament injury: a systematic review. *Scand J Med Sci Sports.* 2013;23(5):527-540.

88. Woby SR, Roach NK, Urmston M, Watson PJ. Psychometric properties of the TSK-11: a shortened version of the Tampa Scale for Kinesiophobia. *Pain.* 2005;117(1-2):137-144.
89. Lunderg MK, Styf J, Carlsson, S.G. A psychometric evaluation of the Tampa Scale for Kinesiophobia from a psychotherapeutic perspective. *Physiother Theory Prac.* 2004;20.
90. Vlaeyen JW, Kole-Snijders AM, Boeren RG, van Eek H. Fear of movement/(re)injury in chronic low back pain and its relation to behavioral performance. *Pain.* 1995;62(3):363-372.
91. Vlaeyen JW, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain.* 2000;85(3):317-332.
92. Hartigan EH, Lynch AD, Logerstedt DS, Chmielewski TL, Snyder-Mackler L. Kinesiophobia after anterior cruciate ligament rupture and reconstruction: noncopers versus potential copers. *J Orthop Sports Phys Ther.* 2013;43(11):821-832.
93. Chmielewski TL, Zeppieri G, Jr., Lentz TA, et al. Longitudinal changes in psychosocial factors and their association with knee pain and function after anterior cruciate ligament reconstruction. *Phys Ther.* 2011;91(9):1355-1366.
94. Smith BW, Dalen J, Wiggins K, Tooley E, Christopher P, Bernard J. The brief resilience scale: assessing the ability to bounce back. *Int J Behav Med.* 2008;15(3):194-200.
95. Gabbe BJ, Harrison JE, Lyons RA, Edwards ER, Cameron PA, Victorian Orthopaedic Trauma Outcomes R. Comparison of measures of comorbidity for predicting disability 12-months post-injury. *BMC Health Serv Res.* 2013;13:30.
96. Groll DL, To T, Bombardier C, Wright JG. The development of a comorbidity index with physical function as the outcome. *J Clin Epidemiol.* 2005;58(6):595-602.
97. *PASS 13 Power Analysis and Sample Size Software (2014)* [computer program]. Kaysville, Utah, USA ness.com/software/pass: NCSS, LLC, ; 2014.
98. REDCap. (n.d.) Library - REDCap Shared Library Retrieved from https://projectredcap.org/resources/library/.
99. ICMJE. Internal Committee Medical Journal Editors. Defining the role of authors and contributors. (11/28/2016).

APPENDICES

APPENDIX A: STUDY TIMELINE

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.

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

Abbreviations: CCC = Clinical Coordinating Center; DCC = Data Coordinating Center; MS = Military Sites; USS = US Sites; CS = Canadian Sites

		Year 1												Year 2											
Major Tasks	**Sites involved**	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Study Start-up	CCC, DCC, MS, USS, CS	X	X	X																					
Subject Recruitment	CCC, DCC, MS, USS, CS			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Monitoring & Quality Control	CCC, DCC				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject Follow-up	CCC, MS, USS, CS					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Governance	CCC, DCC, MS, USS, CS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Analyze & Disseminate Results	CCC, DCC, MS, USS, CS																								

Major Tasks cont.:	**Sites involved**	**Year 3**												**Year 4**											
		25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
Study Start-up	CCC, DCC, MS, USS, CS																								
Subject Recruitment	CCC, DCC, MS, USS, CS																								
Clinical Monitoring & Quality Control	CCC, DCC	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject Follow-up	CCC, MS, USS, CS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Governance	CCC, DCC, MS, USS, CS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Analyze & Disseminate Results	CCC, DCC, MS, USS, CS																								X

APPENDIX B: SCHEDULE OF EVENTS

Forms	**Screening/ Baseline**	**Pre-Op/ Surgery**	**Clinical Follow-Up [1]**					**Research Follow-Up Visits**			
			1 wk	**1 m**	**3 m**	**6 m**	**9-12 m**	**6 m**	**12 m**	**24 m**	**Monthly 6-24 mo**
Contact Information	X										
Demographic and Participant Information	X										
Baseline Clinical Exam	X										
Baseline Injury Surveillance Survey (Military Only)	X										
Functional Comorbidity Index	X										
Inclusion Exclusion	X										
Randomization	X										
Cincinnati Occupational Rating Scale	X							X	X	X	X
Marx Activity Rating Scale	X							X	X	X	X
IKDC Subjective Knee Evaluation	X[2]	X[3]						X	X	X	
Multi-Ligament Quality of Life (MLQoL)	X[2]	X[3]						X	X	X	
PROMIS Physical Function	X	X[3]						X	X	X	
PROMIS Global 10	X							X	X	X	
PASS/Global Rating of Change	X	X[3]						X	X	X	
Tampa Scale for Kinesiophobia	X							X	X	X	
Brief Resilience Scale	X							X	X	X	
Concomitant Medications	X		X	X	X	X	X				
Pre-Op Clinical Visit form		X									
Examination Under Anesthesia		X									
Meniscus Findings and Procedures		X									

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

APPENDIX C: STUDY FORMS

APPENDIX D: DATA SAFETY AND MONITORING BOARD TABLES