STABILITY 2: ACL Reconstruction +/- Lateral Tenodesis with Patellar vs. Quad Tendon

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Funding Agencies:

Canadian Institute of Health Research (CIHR)

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). All personnel involved in the conduct of this study have completed human subjects protection training.

PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale.

Version	Date	Description of Change	Brief Rationale
1.4	February 2, 2021	Administrative changes throughout.	Updated version dates, add amendment history, etc.
		Updated section 3.1 to clarify definition of clinical failure	To be consistent with section 4.1
		Updated section 4.1 with asymmetrical vs asymptomatic pivot shift	Incorrect word was used to describe clinical failure definition.
		Added IKDC Subjective Knee Form items related to giving way of the knee during daily activity and sports.	To further explore this relationship between instability and rotational laxity of the knee within the STABILITY 2 Trial we will administer the IKDC Subjective Knee Form items related to giving way of the knee during daily activity and sports. Furthermore, we will explore the number of individuals that meet the definition of ACL clinical failure that also have symptomatic knee instability as defined by the IKDC Subjective Knee Form items related to giving way of the knee.
1.3	November 17, 2020	Administrative changes throughout.	Updated version dates, add amendment history, etc.
		Collection of demographics on eligible, non-consenting participants.	Non-consenting, eligible patients will be asked if de-identified demographic data can be collected to accurately describe those that are eligible for participation in the study but otherwise do not consent for participation. This information will be useful to more accurately describe the representativeness of the sample that participated in the study relative to the population of interest.
		Added new baseline visit if outside 6-week window.	Collection of ROM and PROMs on day of surgery if baseline is outside of 6-week window. Collecting updated baseline information will allow us to more accurately describe the study participants' status at the time of surgery and randomization.
		Removed symptomatic instability from definition of clinical failure.	While instability of the knee is associated with ACL clinical failure, it is also associated with other conditions affecting the knee including pain, quadriceps weakness and patellofemoral pain. As such, the presence of symptomatic instability

			(patient's perception of knee giving way) it is not sufficient to make the determination of clinical failure. These changes in the operational definition of ACL clinical failure are consistent with the definition of ACL clinical failure reported in the STABILITY Study. Using the same definition of ACL clinical failure in the STABILITY 2 Trial as was use in the STABILITY Study will enable us to compare the effects of use of a quadriceps or patellar tendon graft with or without a lateral extra-articular tenodesis to the effects of use of a hamstring graft with or without a lateral extra-articular tenodesis, which is one of the planned comparisons in this project.
		Updated BTB femoral fixation.	BTB Femoral fixation will be with either an interference screw or suspensory fixation to accommodate surgeon practice.
		Added collection of range of motion during examination under anesthesia.	Prior to undergoing surgery, range of motion of the knee may be limited by pain and swelling. To more accurately determine passive range of motion of the knee at the time of surgery, passive range of motion will be visually assessed and recorded by the surgeon as part of the examination under anesthesia.
		Removed active knee extension from 12 and 24-month follow-ups	Limited active knee extension is indicative of poor quadriceps muscle performance that is most likely observed within the first 6 months after surgery. More than 6 months after surgery it is unlikely that individuals will have a knee extensor lag as indicated by limited active knee extension and thus the range of active knee extension will provide little useful information beyond the 6-month follow-up visit. Further, isometric strength of the quadriceps and hamstrings will be quantified with a crane gauge starting at 3 months after surgery. To measure isometric quadriceps and hamstring strength, we will utilize a crane gauge (also known as a crane scale) as opposed to a hand-held dynamometer. The crane gauge is a digital strain gauge that is rated to 300 kg, which far exceeds force output for the quadriceps and hamstrings. To measure isometric quadriceps and hamstring strength, one end of the crane gauge will be securely attached to the participant using a padded ankle strap and the other end will

			be attached to an unmovable object. As the participant straightens or bends the knee, the device will record maximal force output in kilograms. Use of the crane gauge will allow for enhanced stabilization during the test, which is necessary to reliably and accurately measure isometric quadriceps and hamstring strength. Additionally, purchase of a crane gauge will reduce the costs for purchase for the sites that do not already have an available method for quantifying isometric strength. Reference to use of the crane gauge to measure isometric quadriceps and hamstring strength is made on pages 31 to 32 and 59 of the revised Clinical Protocol. Additionally, the details for use of the crane gauge to measure isometric quadriceps and hamstring strength have been added to the Manual of Operations and Procedures.
		Added manual pivot shift test at 3m	Performance of the manual pivot shift test will provide early information regarding the primary outcome of ACL clinical failure.
		Added PIVOT App test at 3m visit.	Performance of the PIVOT App test will provide early information regarding the primary outcome of ACL clinical failure.
		Added PIVOT App test on the contralateral knee.	Comparison of the PIVOT App test results obtained from the contralateral knee while under anesthesia with the PIVOT App test results of the test on ACL reconstructed knee at the 3, 6, 12 and 24 month follow-up with the patient awake is not valid. As such both the ACLR and contralateral knees need to be quantified at each follow-up visit.
		Added isometric strength testing to the baseline visit.	Pre-operative strength testing has been added to improve our understanding of the changes in muscle function after injury in both the ACL injured and contralateral normal knee. Additionally, this will benefit participants, as pre-operative strength measures may be a better comparison than the contralateral limb for identifying post-operative strength deficits. This information can be used to guide rehabilitation.
		Added the measurement of muscle strength with a crane	To measure thigh muscle strength using a crane scale (i.e. a strain gauge) was added to reduce

		scale and removed handheld dynamometer.	costs for sites that did not already have an available method for quantifying strength. This is a reliable method, which is commonly used in clinical settings.
1.2	April 20, 2020	Administrative Changes throughout.	Fix spelling errors, version dates, add amendment history, TOC updates, etc.
		Updated list of abbreviations.	To include all abbreviations.
		Updated study title.	To be consistent throughout all study documents.
		Updated aims.	To clearly define study objectives.
		Defined failure in primary outcome as ACL Clinical Failure.	The primary outcome is ACL clinical failure which will be a composite of rotational laxity defined as mild asymptomatic pivot shift (grade1) detected at two or more follow-up visits or moderate or severe (grade 2 or 3) asymmetric pivot shift at any visit, or graft rupture.
		Updated Participating Study Sites.	Removed U of Missouri and added U of Michigan and U of Kentucky.
		Updated Screening and Baseline visits to Screening/Baseline Visit throughout.	The screening and baseline visit ideally occur at the same time.
		Added PIVOT App data collection.	The pivot shift will be further objectively assessed using an optical tracking software application validated to measure anterolateral subluxation during a standardized pivot shift test. The results of the Pivot App will be correlated with the blinded clinical examination findings. Test will be performed at Baseline/EUA, 6, 12 and 24 months post-op.
		Added data collection on isometric quadriceps and hamstring strength utilizing a handheld dynamometer for all sites.	Not all sites have access to an isokinetic dynamometer. Study funds will provide each site with a handheld dynamometer.
		Updated DVJ will be measured by using Microsoft Kinect V2 and ACL-Gold software to	Not all sites have access to a 3D optical marker based motion analysis system.

		measure frontal plane kinematics.	This technology has been shown to be a reliable method of calculating frontal plane moments and has been shown to have a very high correlation with 3D optical marker based motion analysis systems.
		Added Anterior Cruciate Ligament–Return to Sport after Injury (ACL-RSI) Scale as a PROM.	To measure psychological readiness for return to sport at 6, 12 and 24 months.
		Added End of Study definition.	End of study is defined when the last enrolled subject reaches the 24-month follow-up time point and close-out activities are complete.
		Added a definition for “competitive pivoting sport”	Defined as sports that include cutting and pivoting activities such as basketball, American football, soccer, lacrosse, volleyball, tennis/squash, handball, downhill skiing etc.);
		Added definition of partial ACL injury.	Defined as one bundle ACL tear requiring reconstruction/ augmentation of the torn bundle with no surgery required for the intact bundle.
		Added inflammatory arthropathy as an exclusion criteria.	Inflammatory joint disease is not all that common and negatively affect the outcome of the procedure.
		Added pregnancy as an exclusion criteria.	Pregnancy will be confirmed as part of the standard of care for having surgery. Pregnancy post-operatively will not exclude individuals from continuing this research study. A pregnancy test will not be completed for research purposes.
		Updated Stability 1 data.	Study is complete. Added published data.
		Added quarterly Participant Newsletter.	To enhance participant retention.
		Added the requirement for participants to wear a tubigrip on both knees.	To maintain blinding during the clinical examination and testing of range of motion, strength and performance-based functional tests.
		Added the requirement to take an arthroscopic picture of the tibial tunnel and upload into the	To confirm the anatomic nature of the tunnel.

		EmPower Data Management System.	
		Added the requirement to measure the length and width of the tibial footprint using a flexible ruler intra-operatively.	This is to assure individualized anatomic technique is being used, i.e. size of native ACL will be correlated to graft size retrospectively.
		Added: For patients randomized to harvest of the quadriceps tendon (QT), either a soft tissue only or bone block technique may be utilized as per surgeon preference.	There have been no differences observed between techniques in the literature.
		Added: Bone block technique.	To maintain consistency across all surgeons who elect to use the bone block technique.
		Updated soft tissue only technique to include: The graft will be dissected off the patella with or without a strip of periosteum.	Some people may take a strip of periosteum with the soft tissue graft to assist in the graft preparation. This has no consequences in terms of donor site issues.
		Defined unscheduled visit.	In the event of an unscheduled patient visit, the subject will undergo safety screening by completing the clinical assessment. Depending on the reason for the visit, the subject may be asked to have a radiograph or other standard of care tests. All adverse events reported by the subject or observed by the investigator will be documented and reported. Aside from adverse events, information gathered at these unscheduled visits will not be included in the statistical analysis.
		Added: Risk of falling and re-injury to the knee.	Risk of Falling and Re-Injury to the Knee: The performance-based measures of physical function may be associated with an increased risk of falling and/or re-injury to the ACL. However, these measures will not be performed until at least 6 months after the surgical procedure and these risks are not greater than the ones encountered with typical rehabilitation activities or with participation in sports.
		Updated reportable events flow.	NIAMS – one of our funding agencies requires to be notified within 48 hours of the PI becoming

			aware of a Serious Adverse Event or Unanticipated Problem.
		Added comprehension quiz to the consent process.	To determine the participant's comprehension of the information that was discussed and understands their commitment.
		Added reconsent process when a minor turns age of majority during the trial.	If the child turns 18 while enrolled in the study, they will sign the Consent for Continued Research Participation. This consent is an addendum form to the participant's original informed consent form.
		Updated name of External Adverse Events Adjudication Committee.	Removed the "Eligibility" from the committee name as this is not part of the committee's role.
		Updated Rehabilitation Committee member – Andrew Lynch to Andrew Sprague.	Andrew Lynch has a new position outside of the University of Pittsburgh and Andrew Sprague is his replacement.
		Sample size updated from 1200 to 1236 patients.	To account for cluster effect.

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SIGNATURE PAGE

The signatures below constitute 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 Canadian and US federal regulations and ICH guidelines.

We 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.

"STABILITY 2: ACL Reconstruction +/- Lateral Tenodesis with Patellar vs. Quad Tendon"

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LIST OF ABBREVIATIONS

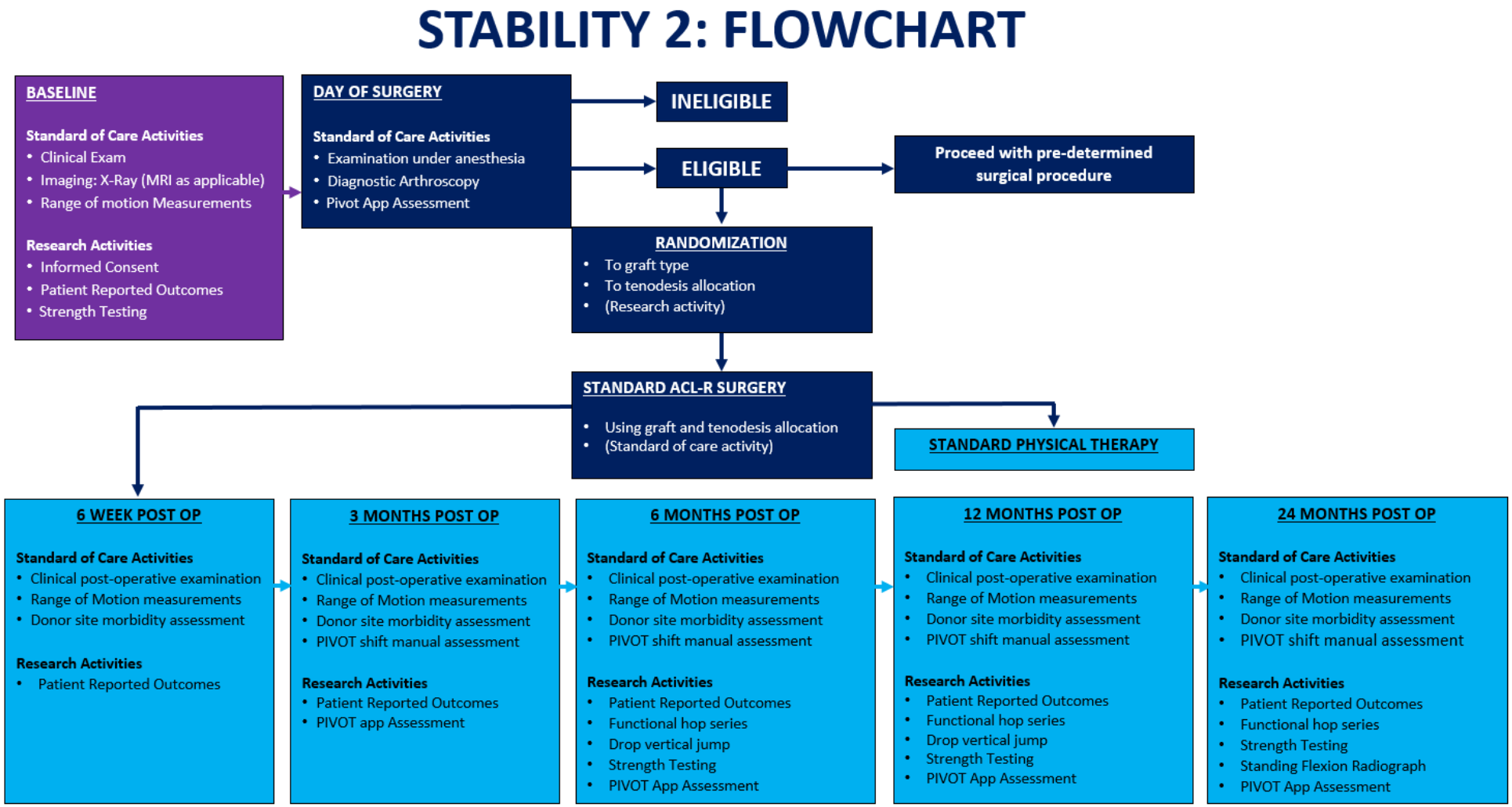
ACL	Anterior Cruciate Ligament
ACLR	Anterior Cruciate Ligament Reconstruction
ACL-QOL	Anterior Cruciate Ligament Quality of Life Questionnaire
AE	Adverse Event
ALC	Anterolateral Complex
ALL	Anterolateral Ligament
BPTB	Bone Patellar Tendon Bone
CCC	Clinical Coordinating Center
Co-I	Co-Investigator
Co-PI	Co-Principal Investigator
CRA	Clinical Research Assistant
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DSMB	Data Safety and Monitoring Board
DVJ	Drop Vertical Jump
EAEAC	External Adverse Event Adjudication Committee
eMonitor	Quality Control Clerk
ESC	Executive Steering Committee
EUA	Examination Under Anesthesia
FCL	Fibular Collateral Ligament
FCS	Full Conditional Specification
GCP	Good Clinical Practice
HT	Hamstrings Tendon
ICH	International Conference on Harmonization
ICMJE	International Committee of Medical Journal Editors
IKDC-SKF	International Knee Documentation Committee Subjective Knee Form
INB	Incremental Net Benefit
IRB	Institutional Review Board
ITB	Iliotibial Band
KOOS	Knee Osteoarthritis Outcome Survey
LET	Lateral Extra-articular Tenodesis
LSI	Limb Symmetry Index
MOOP	Manual of Operating Procedures

OA	Osteoarthritis
OHRP	Office for Human Research Protections
OR	Odds Ratio
PASC	Publications and Ancillary Studies Committee
PC	Project Coordinator
PD	Protocol Deviation
PI	Principal Investigator
PRO	Patient Reported Outcome
PTOA	Post-Traumatic Osteoarthritis
QC	Quality Control
QCL	Quality Control Lead
QALYS	Quality Adjusted Life Years
QOL	Quality of Life
QT	Quadriceps Tendon
RC	Research Coordinator
ROM	Range of Motion
RRR	Relative Risk Ratio
SAE	Serious Adverse Event
SSL	Scramble Word Format
UP	Unanticipated Problem

PROTOCOL SUMMARY

Title:	STABILITY 2: ACL Reconstruction +/- Lateral Tenodesis with Patellar vs. Quad Tendon
Précis:	STABILITY 2 is a 21-site multicenter, international, randomized clinical trial that will randomly assign 1236 individuals with an anterior cruciate ligament (ACL) deficient knee who are at high risk of re-injury to anatomic anterior cruciate ligament reconstruction (ACLR) using bone patellar tendon bone (BPTB) or quadriceps tendon (QT) autograft with or without a lateral extra-articular tenodesis (LET).
Objectives:	***Aim 1:*** Determine if graft type (QT, BPTB or HT) with or without a LET affects the rate of ACL clinical failure at 2 years after ACLR. ***Aim 2:*** Determine if graft type (QT, BPTB or HT) with or without a LET affects patient-reported symptoms, function & QOL, performance-based measures of function and return-to-sports 2 years after ACLR. ***Aim 3:*** Determine if graft type (QT, BPTB or HT) with or without LET affects the rates of intervention-related donor site morbidity, complications and adverse outcomes 2 years after ACLR. ***Aim 4:*** Determine if use of a particular graft type (QT, BTPT or HT) with or without addition of LET is a more cost-effective approach to ACLR.
Population:	The study population will consist of 1236 young, active individuals from the United States, Canada and Europe. Eligible patients will have an ACL deficient knee, be skeletally mature but ≤25 years of age, and meet ≥2 of the following criteria: participate in a competitive pivoting sport; have a pivot shift of grade 2 or greater; have generalized ligamentous laxity (Beighton score of ≥4) and/or genu recurvatum >10 degrees.
Phase:	III
Number of Sites:	21
Description of Intervention:	All patients will undergo an anatomic ACLR using BTBP or QT autograft with or without LET.
Study Duration:	60 months
Subject Participation Duration:	24 months
Estimated Time to Complete Enrollment:	30 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 Anterior Cruciate Ligament Injuries and Reconstruction

Anterior cruciate ligament (ACL) rupture is one of the most common musculoskeletal injuries in young individuals, particularly those that are active in sports. Age-specific patterns of ACL rupture differ in males and females, with a peak incidence (241.0 per 100,000 person-years) between 19 and 25 years in males and a peak incidence (227.6 per 100,000 person years) between 14 and 18 years in females.[1] However, relative to the number of individuals playing sport, the incidence of ACL injury is 2 to 4 times higher in females.[2-4] Epidemiological studies have shown that approximately 250,000 patients undergo ACL reconstruction (ACLR) annually in the USA.[5] Although surgery is recommended for those wishing to return to sport, several studies have demonstrated a significant reduction in quality of life (QOL) and subsequent socioeconomic burden as a result of ongoing knee instability,[6] failure of the reconstruction, revision surgery, and the development of post traumatic osteoarthritis (PTOA) in the long-term.[7]

Up to 30% of individuals under the age of 20 years suffer a re-injury to the ACL reconstructed knee.[8,9] Revision ACLR has been associated with degeneration of the articular cartilage and increased rates of meniscal tears, increasing the risk of PTOA, additional surgical procedures and reduced physical function and QOL.[10,11] As such, strategies to reduce ACLR failure, particularly in young active individuals, are critical to improving short and long-term outcomes after ACL rupture.

Failure of ACLR is multifactorial, with four broad categories of factors associated with failure including traumatic re-injury, poor biological healing, insufficient rehabilitation (poor neuromuscular conditioning,[12] proprioception and no sport-specific training), and surgical technique.[13] The surgical method of reconstructing the injured ligamentous structures to re-establish knee stability can impact all of these risk factors and provides an opportunity to improve the likelihood of a favorable outcome.[14] Two surgical strategies that continue to be a significant topic of interest for surgeons trying to address

persistent rotational laxity and ACLR failure are the reconstruction of anterolateral complex and graft choice.

2.1.2 Importance of the Anterolateral Complex

The anterolateral complex (ALC) includes the iliotibial band (ITB), the anterolateral ligament (ALL) and the lateral meniscus.[15] Anterolateral reconstruction, such as lateral extra-articular tenodesis (LET), may provide greater rotational stability,[16] yet surgery-induced lateral compartment OA is a concern given the potential for over-constraint of the joint.[17] New evidence from the STABILITY 1 Study group members[18-20] and others[21-23] have suggested that the ALC plays a key role in controlling knee stability and that ACLR may not be adequate to control rotation alone. Both the University of Pittsburgh and Western University in Canada, have been instrumental in determining the importance of the anterolateral complex to knee stability, importantly recognizing that high-grade rotatory laxity is not the result of an isolated ACL injury.[24,25] Two anatomic studies from Western University[26] and University of Pittsburgh,[27] illustrated the characteristics of the anterolateral ligament and the iliotibial tract respectively. These studies were then followed by biomechanical studies in the respective laboratories. In a study at Western, Spencer et al.[21] were the first to show that LET was superior to ALL reconstruction in controlling the pivot shift. Rahnemai-Azar et al.[28] showed that the anterolateral capsule was not as important as the iliotibial tract for providing knee stability, with Guenther et al.[28] observing that the capsule acted more as a fibrous sheet than a distinct ligament. Further work at Western showed the importance of the other structures in the ALC in providing knee stability, including the lateral meniscus posterior root[19] and the capsule-osseous layer of the ITB.[21] This body of work demonstrates the importance of the ALC and the potential need for LET to aid in controlling pathologic rotatory laxity of the ACL reconstructed knee.

Additionally, a systematic review, published by the team at Western University in Canada, showed that augmentation of ACLR with LET reduces the risk of rotational laxity of the knee.[29] This review provided the basis for a 9-site randomized clinic trial lead by Co-PIs Getgood and Bryant that randomized 618 young patients (<25yrs) at

high risk of ACLR failure to compare hamstring tendon (HT) autograft ACLR with or without LET (STABILITY 1).[30] The results of this study suggest that the addition of LET to ACLR reduces rotational laxity (RRR=0.38, 95%CI 0.21 to 0.52, p<0.0001) and ACL graft failure (RRR=0.67, 95%CI 0.36 to 0.83, p<0.001).[31]

2.1.3 Importance of Graft Choice

Surgeons in North America moved away from performing a LET when one study suggested that a well performed ACLR with a bone patella tendon bone (BPTB) autograft negated the need for additional anterolateral surgery.[17] Unfortunately, this study was underpowered, poorly controlled, and a retrospective comparison. However, the idea that graft choice could overcome anterolateral biomechanical deficiencies has been the basis of significant study over the past 20 years. Numerous comparative studies and case series contributed to multiple meta-analyses comparing the results of different graft choices (see **Table 1** for comparison and **Figure 1** for graft choice of experts).[32-39] The majority of studies fail to demonstrate a difference in patient-reported outcomes (PROs) between HT and BPTB grafts. Although most agree that BPTB has lower failure rates, less laxity, and limited loss of knee flexion compared to HT grafts. In contrast, HT grafts are associated with less patellofemoral crepitance, kneeling pain, and loss of knee extension[33]. In a 2016 study, Mohtadi et al. observed that rotational laxity, as measured by a positive pivot shift, resulted in a 22% prevalence of persistent abnormal rotational laxity in HT grafts compared to 16% in BPTB grafts.[35] A randomized control trial by the same group comparing HT and BPTB autograft reconstructions[40] showed that HT grafts resulted in a higher rate of traumatic failure, with a greater number of patients presenting with persistent rotational laxity. Importantly, they found that patients under the age of 27 had a worse outcome in terms of failure and instability. However, with only 17 cumulative failures in the study, it was drastically underpowered.

Few studies have thoroughly compared the effects of BPTB and HT graft harvest on functional performance of individuals, prior to return to sport. Successful return to sport with low-risk of injury depends on successful neuromuscular re-training and should be

assessed by measuring quantity and quality of movement.[41] Quantity of movement includes muscle strength and hop test performance.[42] Quality of movement includes dynamic knee flexion and valgus when landing from a jump.[43,44] Quantity and quality of movement are modifiable and may predict ACL re-injury[45,46]; however, a systematic review by Engelen-van Melick et al., indicates that few high level studies comparing HT vs. BPTB evaluate both quantity and quality of movement.[47] Because only 63% of individuals after ACLR return to previous levels of activity,[48] and re-injury rates can be as high as 30%, assessment of functional performance should be an integral component of future studies evaluating the risk of failure after ACLR.

In addition to the paucity of information regarding functional performance with HT and BPTB grafts, quadriceps tendon grafts are becoming popular and there is some evidence supporting their use.[49] In a recent editorial in the Journal of Arthroscopy entitled, “Quadriceps Tendon Autograft Is the Least Utilized Choice for ACL Reconstruction, But Use Is Expected to Increase”, the editor-in-chief stated several reasons for this trend including, but not limited to the following: HT has a higher infection rate and risk of re-rupture is greater in small diameter grafts, allografts are prone to re-rupture in young, active individuals, and quadriceps tendon grafts are larger and stronger than BPTB grafts.[50]

Two comparative studies have recently been published investigating the merits of the QT graft. The first study by Cavaignac et al.[51] compared QT to HT autograft in 95 subjects undergoing ACLR. At two years follow-up there were no differences in terms PROs, although there were reduced rates of rotational laxity in the QT group. In a small, non-randomized prospective study,[52] Runer et al. compared QT to HT in 80 individuals after ACL rupture and reported no difference between the two groups in terms of PROs, stability, pain or function. Lastly, a recent meta-analysis of five retrospective studies comparing 452 BPTB grafts to 354 QT grafts demonstrated no differences in graft failure[53]; however, the small number of events (11 total) suggests this outcome was grossly underpowered. Stability rates and PROs were also similar, yet fewer patients with a QT graft complained of donor site issues.

Figure 1: Past and Current Trends in ACLR Autograft Selection, the International ACL Study Group

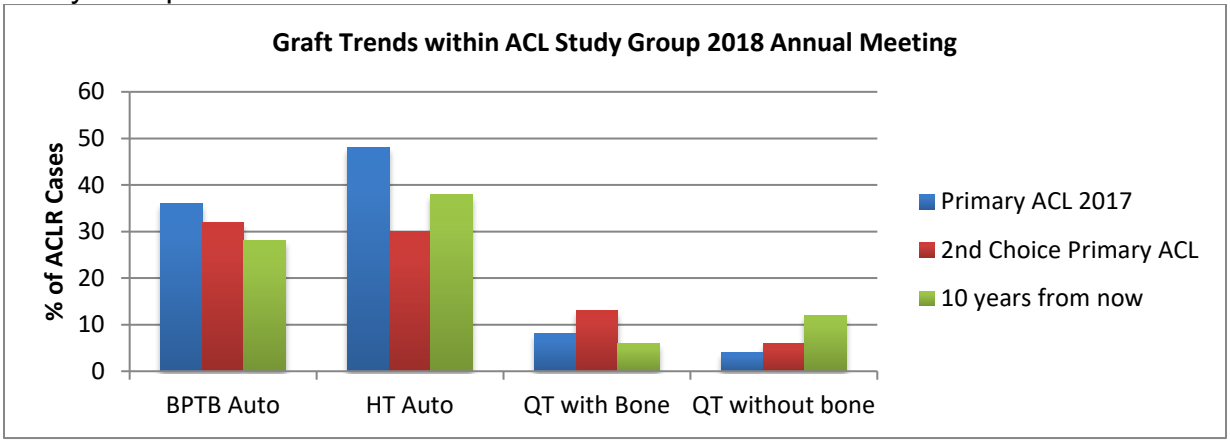


Table 1: Summary of Pros, Cons, Unknowns for Surgical Strategies for Treatment of ACL Rupture

Graft Type/Procedure	Pro	Con	Unknowns
Bone Patella Tendon Bone (BPTB) Autograft	▪ Strong, stiff graft ▪ Bone to bone healing ▪ Good stability rates[35] ▪ Lower rate of failure than HT[54]	▪ Donor site morbidity[35] • Anterior knee pain • Anterior knee numbness • Kneeling pain • Risk of patella fracture • Risk of patella tendon rupture • Patellofemoral osteoarthritis • Range of motion extension deficit	▪ No adequately powered study performed comparing BPTB to QT in young active patients at high risk of graft failure ▪ Not known if the addition of LET is required to lower failure rates in young active patients at high risk of graft failure
Quadriceps Tendon (QT) Autograft	▪ Strong, stiff graft ▪ Can harvest with or without bone from patella	▪ Donor site morbidity[53] • Risk of patella fracture if bone harvested • Quadriceps weakness	▪ Potential for reduced donor site issues compared to BPTB[55] ▪ Possible similar failure rates to BPTB with lower failure rates compared to HT[51] ▪ Potential for improved functional performance compared to BPTB and HT[51] ▪ Not known if the addition of LET is required to lower failure rates in young active patients at high risk of graft failure
Hamstring Tendon (HT) Autograft	▪ Simple, easy technique ▪ Satisfactory results in low demand patients	▪ Higher failure rates in young active individuals[54] ▪ Higher risk of infection than BPTB[56] ▪ Donor site morbidity[35] • Muscle cramping • Anterolateral shin numbness due to nerve injury • Persistent hamstring weakness	

Lateral Extra-articular Tenodesis (LET)	▪ Increased anterolateral stability[20] ▪ Reduced failure rates when combined with HT ACLR (Stability I) ▪ Reduced rotational laxity when combined with HT ACLR [29]	▪ Donor site morbidity[29] • Lateral knee pain • Hardware irritation • Haematoma	▪ Concerns of lateral compartment over constraint[57] and increased risk of OA (although this has not been shown to date)[58] ▪ Unknown if the addition of LET to BPTB or QT ACLR will result in reduced failure rates in young active patients at high risk of graft failure

2.2 Rationale

The scientific premise for the proposed STABILITY 2 multicenter randomized clinical trial is that the rates of rotational laxity and ACL graft failure can be reduced by determining the optimal autograft choice for ACLR as well as the need for a LET. Furthermore, if successful, the results of this study will inform the optimal treatment of ACL rupture in young athletes, and women specifically, who are at risk for persistent rotational laxity/instability and graft re-rupture. Reducing the risk for graft failure will reduce the need for revision ACLR and the associated decreased QOL and socioeconomic burden that occurs because of ongoing knee instability and the increased risk for PTOA.

3 OBJECTIVES

The overall primary objective of this 21-site international randomized trial is to determine if graft type (QT, BPTB or HT) with or without a LET will affect the rate of ACL clinical failure 2 years after surgery. Secondary objectives will determine the effects of graft type and LET on patient-reported outcomes, performance-based measures of function, return to sports, intervention-related donor site morbidity, complications and adverse outcomes and cost effectiveness. To achieve these objectives, we will randomize 1236 participants with an ACL tear who are at high risk of failure to undergo ACL reconstruction with a QT or BPTB with or without a LET. Study data will be combined with data from a prior trial that compared ACLR with HT grafts with or without a LET (STABILITY 1).

The specific aims for the study are:

3.1 Primary Specific Aim

Determine if graft type (QT, BPTB or HT) with or without a LET affects the rate of ACL clinical failure at 2 years after ACLR. ACL clinical failure will be defined by “a composite of rotational laxity defined as mild asymmetric pivot shift (grade1) detected at two or more follow-up visits OR moderate or severe (grade 2 or 3) asymmetric pivot shift at any visit, OR graft rupture.

3.2 Specific Aim 2

Determine if graft type (QT, BPTB or HT) with or without a LET affects patient-reported symptoms, function and quality of life, performance-based measures of function and return-to-sports 2 years after ACLR.

3.3 Specific Aim 3

Determine if graft type (QT, BPTB or HT) with or without a LET affects the rates of intervention-related donor site morbidity, complications and adverse outcomes 2 years after ACLR.

3.4 Specific Aim 4

Determine if the use of a particular graft type (QT, BPTB or HT) with or without LET is a more cost-effective approach to ACLR.

4 STUDY OUTCOME MEASURES

4.1 Primary Outcome

The primary outcome for this study is ACL clinical failure over the first two post-operative years. ACL clinical failure is operationally defined as a composite of rotational laxity defined as mild asymmetrical pivot shift (grade1) detected at two or more follow-up visits **OR** moderate or severe (grade 2 or 3) asymmetric pivot shift at any visit, **OR** graft rupture. The pivot shift test has been reported by Scholten et al. as the most specific of all clinical ACL tests (with a specificity of 0.97-0.99 and sensitivity of 0.18-0.48).[59] Graft rupture is defined as a tear of the graft confirmed either by MRI or arthroscopic examination. Though the surgeon who performs the ACLR is not blind to participant's group assignment, a second clinician, who is blinded, will conduct the physical examination and record the primary outcome.

The pivot shift will be further objectively assessed using an optical tracking software application validated to measure anterolateral subluxation during a standardized pivot shift test.[60,61] All patients will undergo pivot shift examination using the Pivot App on the provided tablets at the time of surgery under anesthesia and at 3, 6, 12 and 24 months post-operative **AFTER** the blinded assessment of the pivot shift. The results of the Pivot App will be correlated with the blinded clinical examination findings.

While Kocher et al (AJSM 32:629-634, 2004) did not find any significant relationships between patient-reported knee instability with anterior laxity of the knee (Lachman or KT-1000 tests), they did find significant relationships between knee instability defined as partial (p=0.01) or full giving way (p=0.01) of the knee with the pivot shift test. To further explore this relationship between instability and rotational laxity of the knee within the STABILITY 2 Trial we will administer the IKDC Subjective Knee Form items related to giving way of the knee during daily activity and sports (see below). Furthermore, we will explore the number of individuals that meet the definition of ACL clinical failure that also have symptomatic knee instability as defined by the IKDC Subjective Knee Form items related to giving way of the knee.

Over the past week, to what degree have your daily activities (around the home and at work) been affected by the following symptoms in your involved knee?

	I Did Not Have the Symptom	I Had the Symptom but it **Did Not Affect** my daily activity	Affected my daily activity **Slightly**	Affected my daily activity **Moderately**	Affected my daily activity **Severely**	**Prevented ALL** daily activity
Giving way, buckling, or shifting of your knee	☐	☐	☐	☐	☐	☐
Slipping or partial giving way of your knee	☐	☐	☐	☐	☐	☐

Over the past week, to what degree have your sports, athletic, recreational, or performance activities been affected by the following symptoms in your involved knee?

	I Did Not Have the Symptom	I Had the Symptom but it **Did Not Affect** my sport activity	Affected my sport activity **Slightly**	Affected my sport activity **Moderately**	Affected my sport activity **Severely**	**Prevented ALL** sport activity
Giving way, buckling, or shifting of your knee	☐	☐	☐	☐	☐	☐
Slipping or partial giving way of your knee	☐	☐	☐	☐	☐	☐

4.2 Secondary Outcomes

Secondary outcomes include PROs that assess symptoms, activity, participation and QOL, measures of impaired range of motion and muscle function (quadriceps &

hamstring strength), performance-based measures of physical function (hop tests, drop vertical jump), return to pre-injury sports, adverse outcomes, intervention-related donor site morbidity and complications. We will collect pre-operative data for all questionnaires, range of motion, muscle strength and the results of imaging procedures performed for clinical purposes (e.g. standing flexion radiographs and MRI results). Follow-up visits with the surgeon will occur at 6 weeks and 3, 6, 12 and 24 months after surgery, which is consistent with regular clinical practice patterns. Muscle strength and hop tests will be performed 6, 12, and 24 months post-operatively and the DVJ will be assessed 6 and 12 months post-operatively.

Patient-reported outcomes will include a combination of disease- and region-specific measures of symptoms, activity, participation and QOL as follows:

4.2.1 Disease-Specific Patient Reported Outcomes

The ACL Quality of Life Questionnaire (ACL-QOL)[62] assesses physical symptoms, occupational concerns, recreational activities, lifestyle, and social and emotional aspects of ACL injury. Each item has a 100 mm visual analogue scale (VAS) response option, with labeled anchors at 0 mm (e.g. extremely difficult) and 100 mm (e.g. not difficult at all). Scores are calculated by converting the average of each of the five domain scores to a total average score out of 100% where 100% represents the best possible score.

4.2.2 Knee-Specific Patient Reported Outcomes

The knee-specific PROs will include the International Knee Documentation Committee Subjective Knee Form (IKDC-SKF) and the Knee injury and Osteoarthritis Outcome Survey (KOOS).

The IKDC-SKF is an 18-item questionnaire querying symptoms, function and sports activities.[63] The items are summed and transformed to a score that ranges from 0 to 100 with 100 representing no symptoms or limitations with function and sports activities.

The KOOS consists of 42 items in 5 domains that separately measure pain, other symptoms, function in daily living, function in sports/recreation and knee-related QOL.[64] Domain scores represent the sum of all items in the domain standardized to a score from 0 to 100 (worst to best).

Both the IKDC-SKF and KOOS are being used because each is more familiar in different parts of the world and thus, including both will broaden the interpretability of the results.

4.2.3 Measures of Impaired Range of Motion and Muscle Function

A blinded assessor will measure passive and active knee extension and active-assisted knee flexion with a goniometer. For passive knee extension, the patient will lie supine on the examination table with a bolster under the heels with the quadriceps and hamstrings relaxed to assure full passive extension of the knee. For active-assisted knee flexion, the patient will be seated on the examination table with both legs extended and instructed to perform active-assisted knee flexion by placing one hand under their thigh to initiate flexion and then clasp both hands just below the tibial tuberosity. The side to side difference in ROM will be determined and interpreted based on IKDC guidelines.[65]

To assess quadriceps and hamstring strength bilaterally we will use a computerized isokinetic dynamometer using methods previously shown to be reliable and valid.[66,67] Briefly, the patient will wear a tubigrip sleeve on the operative limb to conceal group allocation.[66] Isokinetic measurements will be performed at 90 degrees/sec because we are interested in peak torque and power measurements rather than endurance and fatigability. To assess strength, quadriceps and hamstring indices will be calculated as the ratio of peak torque of the ACL reconstructed knee to peak torque of the contralateral normal knee multiplied times 100. We will also calculate the hamstring to quadriceps ratio for the reconstructed and contralateral knees. We will present these ratios by group by visit but expect that early between-group differences will reflect issues related to donor site morbidity that will resolve by 24 months postoperatively.

Not all sites have access to an isokinetic dynamometer therefore we will also collect isometric quadriceps and hamstring strength utilizing a crane scale (i.e. strain gauge) that has been shown to provide a reliable measure of muscle strength after ACL reconstruction.[68] Additionally, isometric thigh strength will be collected prior to surgery on both the ACL-injured and contralateral normal knees. To measure isometric quadriceps and hamstring strength, one end of the crane gauge will be securely attached to the participant using a padded ankle strap and the other end will be attached to an unmovable object. As the participant straightens or bends the knee, the device will record maximal force output in kilograms. Use of the crane gauge will allow for enhanced stabilization during the test, which is necessary to reliably and accurately measure isometric quadriceps and hamstring strength.

4.2.4 Performance-Based Measures of Physical Function

Performance-based tests of the participant's physical function will include hop tests[69] and the drop vertical jump test to assess dynamic knee flexion and valgus. The series of four hop tests (single hop for distance, triple hop for distance, triple cross over hop and timed 10-meter hop) are proxies for neuromuscular control, strength, and confidence in the limb. The hop tests are one of the most common functional outcomes used in ACL research.[69-71] Participants will perform a series of four hop tests using methods previously shown to be reliable and valid following ACL reconstruction.[69] The hop tests will be conducted by a trained physical therapist, kinesiologist or research assistant who is blinded to the operative procedures via tubigrip worn over the participant's operative knee. For each hop test, we will present results as a limb symmetry index (LSI),[71] which expresses test performance of the operative limb as a percentage of the non-operative limb. A higher LSI indicates a higher level of function for the operative limb. LSI for each hop test as well as the average LSI of the four hop tests will be used for data analysis.

The DVJ test, which mimics the physical demands of competitive jumping sports like basketball or volleyball,[72,73] will be used to access dynamic valgus collapse of the knee that is associated with risk of ACL injury.[73-75] The test is particularly suitable for patients

who are preparing for return-to-sport after ACLR because it allows for a highly relevant evaluation of knee stability during sport specific movements. Recent studies have shown that measures of dynamic knee valgus during a DVJ test effectively demonstrates differences between healthy- and ACLR knees,[76] and knees reconstructed with HT vs. BPTB grafts.[41] The DVJ will be assessed on all participants using the Microsoft Kinect V2 and ACL-Gold software to measure frontal plane kinematics. Dynamic valgus of the lower extremity is operationally defined as the ratio of the distance between the knees to the distance between the ankles. This technology has been shown to be a reliable method of calculating frontal plane moments and has been shown to have a very high correlation with 3D optical marker based motion analysis systems.[77,78] To perform the DVJ, participants will stand on a box approximately 30 cm in height with the balls of each foot off the edge of the box. A Microsoft Kinect V2 sensor is placed 3.4 meters away from the box, mounted on a 1 meter high tripod. The Kinect sensor is connected to a Windows based computer with the ACL-Gold software. The participant drops off the box, landing on both feet and then performs a maximum vertical jump as quickly as possible, landing in the same spot as the initial landing. The participant then takes a few steps forward, which triggers the automated data collection. The results are then automatically populated in a results screen in the system. The participant will perform 3 DVJs with the average measurement of dynamic valgus of the lower extremity calculated.

4.2.5 Return to Activity Measures

The Marx Activity Rating Scale will be used to measure return to activity. It is a four-item scale[79] where individuals rate how often they are able to perform each activity (e.g. running, cutting, decelerating, and pivoting). One point is allocated for each response category to create a score that ranges from 4 to 16 points, with 16 representing the highest level of activity.

Psychological readiness for return to sport will be measured using the Anterior Cruciate Ligament–Return to Sport after Injury (ACL-RSI) scale.[80] The scale was developed to quantify psychological factors associated with return to sport (RTS). This scale includes

12 items measured on a 0 to 10 visual analogue scale (VAS) and was developed based on 3 components correlated to RTS in the literature: emotions, confidence in performance and risk appraisal. It has been shown to be a valid tool to assess psychological readiness for RTS, with studies showing that psychological and physical readiness are different constructs that may require different time frames for full recovery.[81]

We will also record the primary sport and level of participation prior to injury and postoperatively to determine whether participant returns to his/her previous level of activity, and if not, why not.

4.2.6 Donor Site and Adverse Events

We will assess donor site morbidity by determining the presence of anterior kneeling pain and sensory disturbance secondary to the graft site skin incision. Anterior kneeling pain will be assessed by asking the participants to rate their pain using an 11-point numeric rating scale while they kneel on a hard floor. Sensory disturbance will be assessed via light touch to regions around the graft skin incision and anterolateral tibia and will be rated as absent, mild, moderate or severe.

All complications (intra- and postoperative) will be recorded. Adverse events will be classified based on the standard medical terminology from the Common Terminology Criteria for Adverse Events. Plain standing flexion AP radiographs will be obtained prior to and 2 years after surgery and will be used to assess lateral compartment joint space narrowing by a central reader blind to group and scan order.

4.3 Cost-Effectiveness Measures

Quality-adjusted life years (QALYs) will be measured using the European Quality of Life Scale (Euro-QoL).[82] The EuroQoL comprises two sections, the EQ-5D index and the EQ-5D VAS. The EQ-5D index is a 5-item standardized generic measure of health-related QOL (HRQOL) that includes the domains of mobility, self-care, usual activities, pain and discomfort and anxiety and depression. Each item is scored using a 5-point

response scale and each combination of response choices describes a health state (3125 unique health states). Each health state can be converted to a utility value from 0 (worst) to 1.0 (best) using a scoring formula. The EQ-5D VAS is a 0 (worst) to 100 (best) scale that assesses patient-perceived health status. We are including the EQ-5D as a measure of QALYs for an economic cost effectiveness analysis.

5 STUDY DESIGN

The proposed study is a multicenter, international, randomized clinical trial that will include 21 sites across the USA, Canada, and Europe. Twelve hundred participants with an ACL deficient knee will be randomly assigned to ACLR with either quadriceps tendon (QT) or bone-patellar-tendon-bone (BPTB) autograft with or without lateral extra-articular tenodesis (+/- LET). Randomization will be stratified by surgeon, sex and meniscal status (normal/repaired vs. meniscectomy). Patients will follow a standardized rehabilitation protocol. Outcomes will be assessed over two years postoperatively by a blinded evaluator. The primary outcome is ACL clinical failure, as defined by either graft rupture requiring revision ACLR surgery or persistent rotational laxity as measured by an asymmetrical positive pivot shift compared to the contralateral side (see section 4.1). Secondary outcomes will include PROs that assess symptoms, activity, participation and QOL (ACL-QOL, IKDC-SKF, KOOS, EQ5D), measures of impaired range of motion and muscle function (quadriceps & hamstring strength), performance-based measures of physical function (hop tests, DVJ), and return to pre-injury sports. Complications, adverse events, intervention-related donor site morbidity, lateral joint space narrowing on plain AP standing flexion radiographs and costs will also be recorded. End of study is defined when the last enrolled subject reaches the 24-month follow-up time point and close-out activities are complete.

6 STUDY ENROLLMENT

6.1 Subject Inclusion Criteria

Subjects deemed eligible for the study will have an ACL deficient knee, be 14-25 years old, skeletally mature (i.e. closed epiphyseal growth plates will be confirmed on standard of care knee radiographs for all study subjects), and have two or more of the following factors that are associated with a high risk of graft failure: participate in a competitive pivoting sport *(defined as sports that include cutting and pivoting activities such as basketball, American football, soccer, lacrosse, volleyball, tennis/squash, handball, downhill skiing etc)*; or have a pivot shift of grade 2 or greater; generalized ligamentous laxity (Beighton score of ≥4) and/or genu recurvatum >10 degrees.

6.2 Subject Exclusion Criteria

Individuals will be excluded from the study if they have had previous ACLR on either knee, partial ACL injury (defined as one bundle ACL tear requiring reconstruction/ augmentation of the torn bundle with no surgery required for the intact bundle), multiple ligament injury (two or more ligaments requiring surgery), symptomatic articular cartilage defect requiring treatment other than debridement, >3 degrees of asymmetric varus, inflammatory arthropathy, pregnant or are unable to provide consent.

> *Please note that pregnancy post-operatively will not exclude individuals from continuing this research study. Pregnancy will be confirmed as part of the standard of care for having surgery. A pregnancy test will not be completed for research purposes.*

6.3 Strategies for Recruitment and Retention

6.3.1 Recruitment Process

All consecutive patients with an ACL deficient knee presenting to a surgeon-investigator will be screened for eligibility. Eligible patients will have the study explained to them and if interested, they will be presented with a regulatory review board approved consent form. All patients will have an opportunity to ask questions about the study and all of the

study procedures prior to providing informed consent. All eligible patients who wish to participate in the study will review and sign the approved consent form. Prior to signing the consent form, all questions will be answered to the satisfaction of the individual by the surgeon investigator and/or research staff.

Non-consenting, eligible patients will be asked if de-identified demographic data can be collected to accurately describe this population in our manuscript. We will collect age, sex, type and level of sport, pivot shift test grade and Beighton score or hyperextension >10 degrees. This information will be useful to more accurately describe the representativeness of the sample that participated in the study relative to the population of interest.

Since the surgeons are also investigators 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, individuals 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 study.

6.3.2 Efforts to Maximize and Monitor Subject Recruitment

Several strategies 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 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.

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 permitted to recruit additional subjects beyond their targeted enrollment. 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. 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.

6.3.3 Efforts to Maximize Subject Retention

As with any longitudinal study, participants that are lost to follow-up are a concern. We recognize that keeping participants enrolled and active in this research study is important to the success and validity of the study. In our sample size calculation, we accounted for an attrition rate of 15% at the 2-year follow-up; however, as described below, we will make concerted efforts to minimize loss to follow-up rates.

A total of 618 patients (297 males; 48%) with a mean age of 18.9 years (range, 14-25 years) were randomized as part of STABILITY 1. There were 18 patients lost to follow-up and 11 who withdrew (~5%), provides strong evidence that we are capable of successful retention in a study of this magnitude. In addition, the timing of follow-up assessments (6, 12 and 24 months postoperative) corresponds with regular standard of care visits to the surgeon following ACLR which will help minimize the attrition rate.STABILITY 2 will use the same measures used in STABILITY 1 to maximize completeness of follow-up. The following describe our data management and motivational strategies for the site and participant to maximizing retention.

1. The clinical research assistant (CRA) will collect complete contact information from the participant and two individuals who do not reside with the participant but are likely to maintain contact should the individual relocate. This information will be collected at the time of enrollment in the study. Additionally, participants will be asked to update their contact information at each follow-up visit.

2. The CRA will provide a regulatory institutional/ethics board approved consent form that details the purpose of the study, the importance of subject participation and attendance of follow-up visits. During the informed consent process, the surgeon and CRA will explain the time commitments required for participation,

and the participant will be given as much time as needed to read the consent form and ask questions, so that the participant fully understands their responsibility prior to signing the consent form.

3. The CCC will provide the site PI and CRA with a quarterly newsletter to distribute to all English-speaking participants, with a message from the PIs. Sites will be asked during the SIV of translation requirements.

4. The Project Coordinator (PC) and Quality Control Lead (QCL) at the data management company (EmPower Health Research) will proactively monitor participant retention using the web-based data management system. The EmPower data management software automatically generates reports of missing data. Missing data reports will be shared with the site CRA and principal investigator (PI) monthly for adjudication and resolution. In addition, site remuneration for data collection is dependent on complete and query-free CRFs per participant by visit. EmPower provides quarterly reports of visit completion and corresponding remuneration value to the site and to the lead institution responsible for issuing site payments.

5. The data management software offers a participant tracker report that the CRA at each site can generate. The report provides a list of each participant by row and each column represents a visit. Each cell provides the status of the visit as complete, incomplete, overdue or missed. Upcoming visits display the date the visit window opens and the date the visit window closes. The report can be limited to those with an overdue visit or with a visit coming up within a defined number of days as specified by the CRA. This feature assists the site with planning and tracking participant visits.

6. The EmPower data management software will send automatic email reminders to the CRA of an upcoming follow-up visit prior to the visit, on the date that the visit window opens, the ideal date, and a few days after the ideal date if the CRFs remain incomplete. The CRA and site PI are notified if the visit still remains

incomplete 7 days prior to the final visit window date. The PC and eMonitor are notified if the visit remains incomplete on the final day of the visit window. Since the analysis will use time as a random factor, visits that take place outside the specified window are not as problematic as when time is defined as a fixed factor.

7. The EmPower data management software will send an automatic email or text message to participants (who have opted into this feature) regarding upcoming and overdue appointments. Multiple attempts to contact non-responders will be utilized. Participants will be contacted via email 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 site RC until the participant completes the follow-up visit or withdraws their consent. Data collected up to the date of withdrawal will be retained for analysis.

8. Participants may opt to complete the PROs by directly logging into the online EmPower data management software. Each participant is provided a secure login and login information. The EmPower data management software records the date, time and user information in the audit log so that the electronic information can serve as a primary data source. The audit log also tracks initial data values, updated data values and reasons for changes made to updated data values. Providing this option allows the research team to collect patient reported data when participants cannot physically attend a follow-up (e.g. vacation).

9. Participants are remunerated $50 for completion of each of the screening/baseline, 6, 12, and 24-month postoperative visits and $20 for completion of each of the 6-week and 3-month postoperative visits. Participants that complete all study visits will also be provided with an additional $50 payment.

6.3.4 Randomization Procedures

Randomization will be stratified by surgeon, participant sex, and meniscal status (normal/repaired v meniscectomy) in permuted block sizes to ensure that any differences in outcome attributable to these factors are equally dispersed between treatment groups. Each site will either use traditional or expertise-based randomization. Expertise-based randomization means that a surgeon with a preference or expertise for one intervention over the other (BPTB vs. QT) is paired with a surgeon at the same site who has a preference or expertise for the opposing intervention. Eligible and consenting patients are then randomly assigned to one of the surgeons who will perform their preferred intervention, reducing expertise bias. In this study, all surgeons will have the requisite expertise to perform an LET. The potential for expertise bias exists with graft harvest and thus, for sites participating in expertise-based randomization, randomization to graft type will occur prior to surgery. Randomization to LET or no LET will take place in the operating room following diagnostic arthroscopy and final confirmation of eligibility criteria. At sites participating in traditional randomization, participants will be randomized to graft type and LET or no LET following diagnostic arthroscopy. All randomization will use the web-based application available through the EmPower data management center. This system requires entry of the patient's date of birth, database ID and responses to all stratification questions prior to group allocation to ensure concealment of allocation is enforced.

6.3.5 Masking Procedures

Participants and their care provider (i.e. surgeon-investigator performing the surgery) will not be blinded to group assignment. To account for this, a second blinded clinician will conduct the physical examination and record the primary outcome for the study. To maintain blinding, study participants will wear tubigrip on the surgical knee during the clinical examination and testing of range of motion, strength and performance-based functional tests.

7 STUDY INTERVENTION

7.1 Surgical Intervention

All patients will undergo an anatomic ACLR, which will be performed in a similar manner across sites. Surgeons will use a BPTB or QT autograft as randomized, located in an anatomic position within the femoral and tibial insertion sites, with consistent graft fixation.

All surgical findings and procedures will be documented on the Surgical Information CRF (see Appendix C). As the quality control (QC) coordinators for the surgical intervention, Drs. Getgood and Musahl will be available to answer any questions from surgeons regarding a subject's participation in the study. The surgical treatment will follow a standardized algorithm (Figure 2).

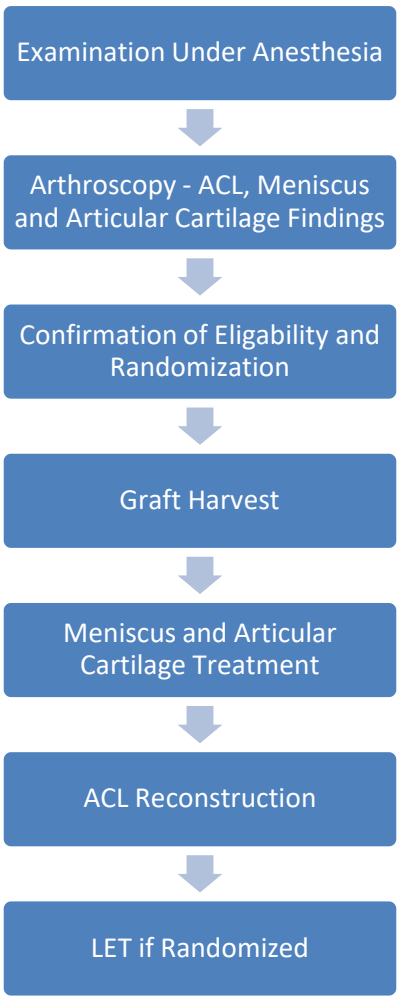


Figure 2. Surgical Algorithm

Examination Under Anesthesia – All patients will have standard of care surgery performed under general or spinal anesthesia as per the discretion of the operating team. The patient will be placed in a supine position on the operating table and the operative leg set up in an appropriate position to allow for deep flexion during femoral tunnel drilling. An examination under anesthesia will be performed allowing documentation of baseline findings including range of motion, presence of effusion, Lachman, anterior/posterior drawer, pivot shift tests and varus/valgus stability. A tourniquet may be placed on the operative limb and inflated either before or during the

procedure, or not at all as per the discretion of the operating surgeon. The limb will then be prepped and draped in a sterile manner.

Measurement of pivot shift using Pivot App – All patients will undergo pivot shift examination using the Pivot App on the provided tablets. Three yellow circular stickers will be placed on the lateral side of the knee. One is placed over the lateral epicondyle, a second on Gerdy's tubercle on the tibia, and a third placed 3 cm directly posterior to the second, in close proximity to the fibula head making a triangle on the lateral side of the knee (Figure 3). A standardized pivot shift will be performed on both the operative and contralateral non-operative limb measured using the tablet and Pivot App.

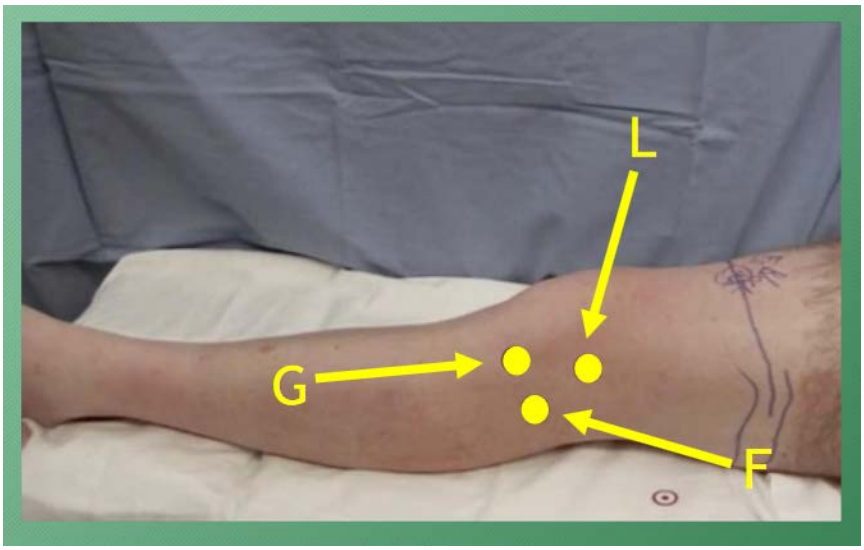


Figure 3: PIVOT App Subject Setup

Arthroscopic Examination of the ACL, Meniscus, and Articular Cartilage; Final Confirmation of Eligibility and Randomization - For patients at a site using traditional randomization, arthroscopy will be performed to confirm eligibility prior to randomization. Confirmation of eligibility prior to randomization reduces the risk of selection bias.

The arthroscopic examination will be done using the preferred portal placement of the operating surgeon that will facilitate anatomic graft placement via a transportal femoral tunnel drilling technique. The status of the menisci and cartilage will be assessed at this time. 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. Treatment other than debridement of articular cartilage injuries will result in the patient being excluded from participation. Meniscus and cartilage findings and procedures will be documented on the Surgical Information CRF. The findings during the diagnostic arthroscopy will serve as final confirmation of patient eligibility, i.e. the patient must not have a partial ACL rupture where an ACLR is not performed, an articular cartilage lesion that requires any other surgical treatment apart from debridement, or require multiple ligament surgery (repair or reconstruction). Partial ACL injury is defined as a case were a the fibers of a specific bundle (anteromedial or posterolateral) is reconstructed, maintaining the integrity of the other bundle. Conversely, if a tissue preservation/remnant preservation surgical technique is utilized, creating an anatomic reconstruction, then this would be included. Participants from a site using traditional randomization who are confirmed eligible following examination under anesthetic will be randomized to graft type with or without LET.

For patients in a site participating in expertise-based randomization, randomization to graft type (BPTB or QT) occurs prior to surgery. However, the operating surgeon will confirm eligibility by performing diagnostic arthroscopy. The criteria for determining eligibility is identical between the expertise-based and traditional randomization sites. Patients confirmed eligible will be randomized to the addition (or not) of a LET.

Intraoperative Complications that occur during surgery will be documented on the Adverse Events CRF. Intraoperative complications that are expected include nerve or vascular injury, loose hardware, and intraoperative fracture. Unexpected complications that occur will also be documented on the Adverse Events CRF.

7.1.1 Anterior Cruciate Ligament Reconstruction

A standardized transportal ACLR technique will be utilized for all patients. Specifically, following treatment of the meniscal lesions and chondral surfaces the femoral tunnel will be prepared. The femoral footprint will be debrided and the position of the tunnel marked in a slightly more anteromedial position within the footprint of the ACL.

Anatomic positioning of the femoral tunnel will be checked by viewing through the anteromedial portal, measurement of the femoral footprint and/or by fluoroscopic evaluation. With the knee in deep flexion, the guide pin will be drilled from the anteromedial portal following which the femoral tunnel socket will be prepared using an appropriately sized drill depending on the graft size. A passing suture will then be passed. An arthroscopic picture of the femoral tunnel will be taken from the medial portal to confirm the anatomic nature of the tunnel. This arthroscopic picture will be uploaded to Empower.

For the tibial tunnel, the position will be referenced off the tibial footprint of the ACL as well as the anterior root insertion of the lateral meniscus, aiming the guide pin position to be level with the posterior border of the anterior root of lateral meniscus, hugging the medial tibial spine. The length and width of the tibial footprint will be measured using a flexible ruler intra-operatively. A guide pin will be inserted from the anteromedial tibial cortex accessed via a separate skin incision using a 45-50 degree tibial guide depending upon graft length. Once the pin is in the desired location an arthroscopic picture of the tibial tunnel will be taken from the lateral portal to confirm anatomic nature of the tunnel. This picture will be uploaded to Empower. An appropriately sized tibial drill will then be utilized to create the tunnel. The passing suture will be retrieved from the knee and the graft will be ready to pass.

Graft passage will be performed from the tibial tunnel into the femoral tunnel. For the BPTB graft the bone block will be seated in the femoral tunnel and fixation will be with either interference screw or suspensory fixation. The knee will be cycled through the range of motion 15 times with tension applied to the graft. The knee will then be held at 10 degrees of flexion and the tibial end fixed with a 7x25 mm interference screw.

For the quadriceps tendon graft the femoral fixation will be similar to the BPTB graft if using a bone plug. For a soft tissue only graft, it will be advanced into the knee and pulled into the femoral tunnel. The suspensory fixation device will be flipped/deployed and the graft tensioned in a similar manner to that of the BPTB graft. The tibial fixation

will be performed using an interference screw 1 mm larger than the drill diameter with a screw post fixation utilized if cortical fixation is not achieved in instances where the graft is short.

7.1.2 Graft Harvest

The appropriate graft will be harvested as per randomization. A standardized technique will be followed for each graft type. Specifically, for patients randomized to bone patella tendon bone (BPTB) harvest, a longitudinal skin incision will be made over the patellar tendon. The subcutaneous tissues will be dissected sharply down to the paratenon, which will be split longitudinally. The central one third of the patella tendon (measuring approximately 10 mm) will be marked with a sterile skin marker pen. A bone block corresponding to the central third of the tendon will then be harvested from both the distal pole of the patella and the tibial tubercle. For the patella a 9 mm wide, 20 mm long bone block will be marked. A central 2 mm drill hole will be placed following which the block will be cut using a small oscillating saw. On removal of the block a high strength suture (#5 ethibond suture or equivalent) will be placed through the 2 mm hole. The tendinous part of the graft will then be incised in line of the tendon fibers down to the tibial tubercle. A 10mm wide, 25 mm long bone block will then be marked and cut using the small oscillating saw. Two 2 mm holes will be drilled to facilitate the passage of two high strength sutures (#5 ethibond suture or equivalent). At the end of the procedure the patellar defect will be bone grafted using the excess bone removed from the blocks and from the tibial tunnel drill.

For patients randomized to harvest of the quadriceps tendon (QT), either a soft tissue only or bone block technique may be utilized as per surgeon preference, as there have been no differences observed between techniques in the literature.[83]

Both techniques will utilize a longitudinal skin incision made over the proximal pole of the patella and quadriceps tendon insertion. The paratenon will be split in the midline allowing access to the quadriceps. A 10 mm wide strip of tendon will be marked closer to the midline, ensuring that there is enough tendon on the lateral border of vastus

medialis oblique. The tendon will be sharply dissected using a 15 blade and scissors. A minimum 5 mm thickness and 8 cm length of soft tissue graft will be harvested under direct visualization.

For the bone block technique, a 10 mm wide, 20 mm long bone block will be marked. A central 2 mm drill hole will be placed following which the block will be cut using a small oscillating saw. On removal of the block a high strength suture (#5 ethibond suture or equivalent) will be placed through the 2 mm hole. A high strength suture (#5 Fiberwire suture or equivalent) will then be whip stitched to the other end of the graft. At the end of the procedure the patella defect will be bone grafted from the excess bone removed from the block and from the tibial tunnel drill.

For the soft tissue only technique the graft will be dissected off the patella with or without a strip of periosteum. It will then be passed to the back table in the operating room where a suspensory fixation loop (endobutton or equivalent) will be attached by either splitting the graft or utilizing a strip of patella periosteum to wrap over the loop. The loop will be secured in place using a high strength suture (#2 Fiberwire suture or equivalent). A high strength suture (#5 Fiberwire suture or equivalent) will then be whip stitched to the other end of the graft.

For both techniques, the soft tissue graft diameter will be measured and recorded, looking to achieve between 8-9 mm of soft tissue.

Once the grafts (BPTB or QT) are prepared, they will be left soaking in a vancomycin-soaked sponge (5 mg/ml of saline) until implantation to reduce the risk of post-operative deep infection.

7.1.3 Lateral Extra-articular Tenodesis

In participants randomized to undergo the addition of a LET, the LET will be performed upon completion of the ACLR. Specifically, following final tensioning of the ACLR, a modified Lemaire procedure will be performed. A 6 cm curvilinear incision will be placed just posterior to the lateral femoral epicondyle. The posterior border of the ITB is

identified and freed of any fascial attachments to the level of Gerdy's tubercle. An 8cm long x 1cm wide strip of ITB is harvested from the posterior half of the ITB, ensuring that the most posterior fibers of the capsulo-osseous layer remain intact. The strip of ITB is left attached distally at Gerdy's tubercle, freed of any deep attachments to vastus lateralis, released proximally and a #1 vicryl whip stitch is placed in the free end of the graft. The fibular collateral ligament (FCL) is then identified. Small capsular incisions are made anterior and posterior to the proximal portion of the ligament and Metzenbaum scissors are placed deep to the FCL to bluntly dissect out a tract for graft passage. An attempt is made to remain extracapsular, while ensuring there is no iatrogenic damage to popliteus. The ITB graft is then passed beneath the FCL from distal to proximal. The lateral femoral supracondylar area is then cleared of the small fat pad found proximal to the lateral head of gastrocnemius using electrocautery to reduce risk of bleeding following damage to the lateral superior geniculate artery. The attachment site should be identified just anterior and proximal to the lateral gastrocnemius tendon. The periosteum is cleared using a cob on the metaphyseal flare of the lateral femoral condyle. Care is taken not to damage ACL femoral fixation as the suspensory loop button is often found close to this location. The graft is then held taught (<20 N) but not over tensioned, with the knee at 60-70 degrees flexion and the foot in neutral rotation to avoid lateral compartment over-constraint.

The graft is secured using a small Richards staple (Smith and Nephew Inc.) and then folded back distally and sutured to itself using the #1 vicryl whip stitch. The wound is irrigated, hemostasis is confirmed, and closure is performed in layers. The posterior aspect of the ITB where the graft was harvested is closed up to the level of the transverse ligament to avoid over constraint of the patellofemoral joint.

7.2 Rationale for Specific Surgical Intervention

Failure of ACLR is multifactorial, with four broad categories of factors associated with failure: traumatic re-injury, poor biological healing, insufficient rehabilitation (poor neuromuscular conditioning,[12] proprioception and no sport-specific training), and surgical technique.[13] The surgical method of reconstructing the injured ligamentous

structures to re-establish knee stability can impact all of these risk factors and provides an opportunity to improve the likelihood of a favorable outcome.[14] Two surgical strategies that continue to be a significant topic of interest for surgeons trying to address persistent rotational laxity and ACLR failure are the anterolateral complex and graft choice.

7.3 Alternative Treatments

Patients who do not wish to participate in the study may elect to undergo ACLR with one of the study interventions, BPTB or QT with or without LET as per their surgeon's expertise or preference. Patients may also choose to have ACLR with allograft tissue or hamstring autograft tissue.

7.4 Procedures for Training of Clinicians on Procedural Intervention

Surgeons will gather at an Investigators' Meeting prior to trial commencement at a central location at which time the interventions will be reviewed in detail. All surgeons participating in the trial are experienced at performing the aforementioned interventions. The purpose of this meeting will therefore be to ensure that all surgeons perform the interventions in a standardized fashion to limit the degree of variability within and across study centers. To standardize the procedures for ACLR, we will review and demonstrate the procedures for harvest of the patellar and quadriceps tendon graft, anatomic placement of the femoral and tibial tunnels and methods of graft fixation. To standardize the procedures for the LET, we will review the procedures for harvesting the ITB, location of the femoral placement of the graft and methods of fixation. To ensure competency in terms of performing a LET, all surgeons who have not completed at least 10 LETs will be required to complete at least 10 LET procedures prior to randomizing their first participant.

7.5 Monitoring Fidelity in Delivering the Intervention

Remote, electronic monitoring of the surgical interventions will be performed on 100% of the patients using the Surgical Information CRF (see Appendix C). The Surgical

Information CRF contains questions related to each procedure that alert the surgeon and the data monitoring team of protocol deviations(PD). The EmPower data management software automatically orders a PD CRF when a response is provided that signals that the surgical procedure did not follow the standardized plan. PDs are regularly reviewed by the Executive Steering Committee (ESC) and DSMB and, as needed, an action plan will be developed, documented and implemented to improved fidelity with the surgical interventions.

Remote, electronic monitoring of the fidelity of the rehabilitation intervention will be monitored for completeness for 100% of the participants using the Patients' Experiences with Rehabilitation CRF (see Appendix C).

7.6 Rehabilitation

Regardless of group allocation, all patients' physical therapists will be provided with the same postoperative rehabilitation protocol and a set of standardized instructions from the surgeon. Focus is placed upon early range of motion and weight bearing as tolerated.

The rehabilitation protocol will require the physiotherapists to exercise professional judgement to determine how to integrate the protocol into an appropriate treatment plan. All exercises will be dependent on the equipment available at each facility. Due to the variability in subject's progression, the protocol must be individualized for optimal return to activity. Variations may occur if limitations are imposed from additional associated injuries such as meniscal tears, articular cartilage trauma, bone bruises or other ligamentous injuries.

The span of the rehabilitation protocol is 12 months, and it includes three criterion-based phases.

7.6.1 Tissue Protection Phase

The rehabilitation focuses on general range of motion, control of swelling, quadriceps activation, and a return to basic activities of daily living and lasts anywhere for 4 to 8 weeks after surgery.

The suggested progressions in this phase are as follows:

- Patient education regarding:
    - Progressive increases in activity pending meeting criteria
    - Weight-bearing status and gently re-introducing loading to the knee;
    - Changes to rehab guidelines with concurrent pathologies (e.g. patellofemoral pain, meniscal repair, etc.)
- Decrease inflammation
    - Pain should be well controlled (e.g. no more than 4/10)
    - Swelling should be a 1+ or less on the sweep test prior to weight bearing exercise
- Increase range of motion & restore full extension* with the following goals:
    - Neutral Extension (0^o) to 90^o flexion by 2 weeks post-op
    - Hyperextension equal to the opposite limb to 120^o flexion by 4 weeks post-op
    - Full motion compared to the non-involved limb by 6 weeks post-op
- Quadriceps activation with the following goals:
    - Isolated quadriceps activation that produces a superior patellar glide by week 1 post-op
    - Straight leg raise with no quadriceps lag by 2 weeks post-op
- Maintain flexibility of hamstrings, calves
- Maintain cardiovascular fitness
    - Consider use of the upper body ergometer (arm bike)
    - Consider hydrotherapy when the incisions and portals have healed, and scabs have fallen off (~4 weeks)

- Normalize proprioception, balance, and neuromuscular control to normalize gait patterns, stair negotiation, and activities of daily living
    - Instruct in proper gait patterns with assistive devices
    - Progress to walking without assistive devices when the patient:
        - Has less than a 3^{o} quadriceps lag
        - Can stand on the surgical limb for 10 seconds with good balance
        - Can walk with a normal gait pattern including direction changes
    - Normal transitions from sitting to standing and standing to sitting (e.g. no weight shift away from the surgical leg)
    - Normal reciprocal stair ascent and descent

7.6.2 Motor Control Phase

This phase promotes strength, neuromuscular, and cardiovascular re-training to prepare the patient to return to impact activities and lasts until at least 16 weeks after surgery. The goals and treatment progression during this phase are:

- Range of Motion
    - Maintain full and pain free knee range of motion
    - Ensure normal hip joint motion (extension, rotation) and ankle joint motion
    - Address limitations in quadriceps, hamstrings, gastrocnemius flexibility
- Quadriceps and Hamstrings strength equal to 80% of the opposite limb
    - Perform electromechanical dynamometry or 1-Repetition Maximum (RM) testing at 12 weeks post-surgery.
    - Address documented strength deficits with non-weight bearing isotonic exercises
        - Heavy resistance from 45^{o}-95°
        - Light resistance from 90^{o} to 0^{o}
    - Isokinetic quadriceps strengthening should be performed from 90^{o} to 45^{o} at high and low velocity

**_only if_: ROM is full, no swelling, adequate muscle control, and no

meniscal or patellofemoral pathology

- Continue strengthening gluteal muscle groups, specifically through full range of motion
- Motor Control Phase ends when the patient meets all criteria to begin jogging:
    - Quadriceps Index of 80% or greater as measured with an electromechanical dynamometer or 1-RM knee extension test.
    - Able to walk 15 minutes at a fast pace without aberrant movements (limp), pain or swelling
    - Normal walking gait pattern has been achieved

7.6.3 Functional Optimization Phase

In the Functional Optimization Phase dynamic activities like running, jumping, agility training, and sport-specific training are introduced. The Functional Optimization Phase is the key to returning athletes to sport while minimizing the risk of injury. Athletes may be cleared to return to practice around 7 to 12 months after surgery, with full clearance as early as 9 months. The suggested progression during this phase is:

- Progressively return the athlete to normal dynamic loading patterns with good control to minimize injury risk.
- Implement evidence-based injury prevention techniques to reduce risk of second ACLR.
- Ensure optimal lower extremity strength and flexibility to promote return to full activity.
- Incorporate total body training to resume normal activity.
- Practice sport-specific conditioning, drills, and movements in a safe environment.
- Prepare the athlete to transition to training with coach, trainer, etc.

8 STUDY PROCEDURES AND MATERIALS

8.1 Consent Process

All patients with an ACL deficient knee will be assessed by a clinician to ensure they meet the eligibility criteria as specified on the Preoperative Screening Case Report Form (CRF). Eligible patients will have the study explained to them and informed consent will be obtained from those that are interested. All patients will have an opportunity to ask questions about the study and all of the study procedures prior to providing informed consent. All eligible patients who wish to participate in the study will review and sign a site-specific regulatory ethics board approved consent form. A detailed description of all possible randomization groups will be discussed with the patient during consent process.

Non-consenting, eligible patients will be asked if de-ideintifed demographic data can be collected to accurately describe this population in our manuscript. We will collect age, sex, type and level of sport, pivot shift test grade and Beighton score or hyperextension >10 degrees.

8.2 Screening

After signing the consent form, and before surgery, patients will be registered in the web-based EmPower data management software, and they will be assigned a unique identifier called a database ID number. At each site, a list of participant names and contact information matched to the database ID will be kept separate from the study data and will not be shared outside the participant’s health care team.

Once patients have been assigned a study ID, they will be asked to complete questionnaires on a tablet or on paper-based forms if requested. These questionnaires will ask about a patient's injury, pain, symptoms, activity level and quality of life regarding their ACL deficient knee. These questionnaires include the following:

- Demographics

- International Knee Documentation Committee Subjective Knee Evaluation Form (IKDC-SKF)
- Knee injury and Osteoarthritis Outcome Score (KOOS)
- Anterior Cruciate Ligament Quality of Life (ACL-QOL)
- EuroQol Visual Analog Scale (EQ5D VAS)
- EQ5D Index
- Marx Activity Rating Scale
- Sports Participation Questionnaire

Participants will be scheduled for surgery after signing the informed consent document and completing the standard of care pre-operative clinical examination (including imaging results) and isometric muscle strength testing.

All patients will undergo Anatomic ACLR. Following a complete diagnostic arthroscopy, it will be determined if the patient can continue in the study as per the study eligibility criteria (i.e. they must not have a partial ACL rupture where an ACLR is not performed, an articular cartilage lesion that requires any other surgical treatment apart from debridement, or need for a multiple ligament reconstruction). The menisci will also be assessed and the findings and any surgical procedures for the meniscus will be recorded. At this time, eligible participants will be randomized to BPTB or QT with or without LET.

8.3 Randomization and Surgery

Randomization to graft type with or without LET will take place in the operating room after evaluation under anesthesia (EUA) and diagnostic arthroscopy to confirm eligibility. Prior to surgery, the surgeon investigator will discuss surgical options should the participant be deemed ineligible following the EUA and arthroscopy. Patients found to be ineligible following the EUA and diagnostic arthroscopy will proceed with the procedure established by the surgeon and the patient during the pre-operative exam for this instance.

Possible randomization allocations (4) are as follows:

1. ACLR with Quad tendon
2. ACLR with Quad tendon and LET
3. ACLR with Bone-Patellar Tendon-Bone
4. ACLR with Bone-Patellar Tendon-Bone and LET

8.4 Rehabilitation

Regardless of group allocation, all patients' physical therapists will be provided with the same postoperative rehabilitation protocol and a set of standardized instructions from the surgeon. Focus is placed upon early range of motion and weight bearing as tolerated. Briefly, rehabilitation includes three criterion-based phases. In the Tissue Protection Phase, rehabilitation focuses on general range of motion, control of swelling, quadriceps activation, and a return to basic activities of daily living and lasts for 4 to 8 weeks after surgery. The Motor Control Phase promotes strength, neuromuscular, and cardiovascular re-training to prepare the patient to return to impact activities and lasts until at least 16 weeks after surgery. The Functional Optimization Phase introduces dynamic activities like running, jumping, agility training, and sport-specific training. The Functional Optimization Phase is the key to returning athletes to sport while minimizing the risk of injury. Athletes may be cleared to return to the practice around 7 to 12 months after surgery, with full clearance for return to sports as early as 9 months. See section 7.6 for additional details related to the standardized post-operative rehabilitation.

8.5 Clinical Follow-Up Appointments

After surgery, the subjects will participate in the following standard of care and research activities:

8.5.1 Standard of Care Clinical Follow-Up Appointments

- Participants will attend regular clinical post-operative appointments with their surgeons at 6 weeks and 3, 6, 12 and 24 months. Data from these clinical visits will be collected and recorded for research purposes, including range of motion measurements and results of manual assessment of rotatory laxity (i.e. pivot shift test). Range of motion measures: a blinded assessor will measure passive and

active knee extension and active-assisted knee flexion with a goniometer. For passive knee extension, the patient will lie supine on the examination table with a bolster under the heels with the quadriceps and hamstrings relaxed to assure full passive extension of the knee. For active-assisted knee flexion, the patient will be seated on the examination table with both legs extended and instructed to perform active-assisted knee flexion by placing one hand under their thigh to initiate flexion and then clasp both hands just below the tibial tuberosity. The side to side difference in ROM will be determined and interpreted based on IKDC guidelines.

- Pivot shift assessment: to perform this test, the examiner controls the patient's leg with his ipsilateral hand at the level of the heel. The examiner lifts the patient's leg off the table and gently abducts the hip. The leg is internally rotated with the ipsilateral hand. To control valgus stress, the examiners' contralateral hand is placed with the thumb up at just below the level of the proximal tibia-fibula joint. A gentle valgus stress is applied. Knee flexion is initiated with the both hands. Internal rotation- and valgus stress are maintained until around 20 degrees of knee flexion. The rotational stress of the ipsilateral hand is released, and the proximal tibia is allowed to rotate externally. The reduction movement is felt at around 20-40 degrees of knee flexion. The pivot shift is graded as per the International Knee Documentation Committee (IKDC) Knee Ligament Rating guidelines as either equal (grade 0), a + glide (grade 1), a ++ clunk (grade 2) or +++ gross reduction (grade 3).[84]

  The pivot shift assessment will be repeated at 3, 6, 12 and 24 months using the Pivot App. Three yellow circular stickers will be placed on the lateral side of the knee. One is placed over the lateral epicondyle, a second on Gerdy's tubercle on the tibia, and a third placed 3 cm directly posterior to the second, in close proximity to the fibula head making a triangle on the lateral side of the knee (Figure x). A standardized pivot shift will be performed on both the operative and contralateral non-operative limb measured using the tablet and Pivot App.
- Assessment of donor site morbidity: determined by the presence of anterior kneeling pain and sensory disturbance secondary to graft site skin incision. Anterior kneeling

pain will be assessed by asking the participant to rate his/her pain using an 11-point numeric rating scale while they kneel on a hard floor. Sensory disturbance will be assessed via light touch to regions around the graft skin incision and anterolateral tibia and will be rated as absent, mild, moderate or severe.

In the event of an unscheduled patient visit, the subject will undergo safety screening by completing the clinical assessment. Depending on the reason for the visit, the subject may be asked to have a radiograph or other standard of care tests. All adverse events reported by the subject or observed by the investigator will be documented and reported. Aside from adverse events, information gathered at these unscheduled visits will not be included in the statistical analysis.

8.5.2 Research Activities at Clinical Follow-Up Appointments

- Completion of Patient Reported Outcome Measures: At each standard post-operative clinical visit (6 weeks, 3, 6, 12, and 24 months), participants will complete the patient reported outcome measures as described in Section 4.
- Muscle strength: To assess quadriceps and hamstring strength (bilaterally) at 6, 12 and 24 months, we will use a computerized isokinetic dynamometer using methods previously shown to be reliable and valid. Briefly, the patient will wear a tubigrip sleeve on the operative limb to conceal group allocation. Isokinetic measurements will be performed at 90 degrees/sec. For sites without a computerized isokinetic dynamometer a crane scale will be used to measure isometric quadriceps and hamstring strength as described in section 4.2.3.
- Functional Hop Series: At the 6, 12- and 24-month time points, participants will complete for hop tests as a research activity. The four hop tests mimic the demands of high-level sports, focusing on hopping on one leg for maximal distance while completing a stable landing and a test for maximal speed. These tests have been used to classify patients after ACL injury and measure functional recovery and determine readiness for return to sport after ACL reconstruction. The contralateral limb will be used as a within subject control, with symmetrical performance identifying satisfactory management. The four hop tests include the: 1) single hop for

distance; 2) straight triple hop for distance; 3) triple cross-over hop for distance in which the subject crosses over a 15 cm wide strip with each successive hop and 4) timed hop in which the subjects hops 6 m as fast as possible. Each subject will first perform 2 practice trials followed by 2 trials which will be averaged to create the hop test score for that limb. For each test, the results for the ACL-reconstructed leg will be expressed as a percentage of the contralateral normal leg to represent the limb symmetry index. The hop tests will be administered by a trained tester (physical therapist, athletic trainer, kinesiologist, etc.) who is blind to the operative procedures via a tubigrip worn over the patient's operative knee.

- Drop Vertical Jump (DVJ): At the 6 and 12-month research visits, participants will complete a DVJ test as a research activity. The DVJ will be assessed on all participants using the Microsoft Kinect V2 and ACL-Gold software to measure frontal plane kinematics. Dynamic valgus of the lower extremity is operationally defined as the ratio of the distance between the knees to the distance between the ankles. To perform the DVJ, participants will stand on a box approximately 30 cm in height with the balls of each foot off the edge of the box. A Microsoft Kinect V2 sensor is placed 3.4 meter away from the box, mounted on a 1 meter high tripod. The Kinect sensor is connected to a Windows based computer with the ACL-Gold software. The participant drops off the box, landing on both feet and then performs a maximum vertical jump as quickly as possible, landing in the same spot as the initial landing. The participant then takes a few steps forward, which terminates the automated data collection. The results are then automatically populated in a results screen in the system. The participant will perform 3 DVJs with the average angular measurement of dynamic valgus of the lower extremity calculated.
- Standing Flexion Radiograph: Participants will undergo a standing flexion radiograph of the knee at 24 months to assess lateral compartment joint space narrowing by a central reader blind to surgical allocation. At the University of Pittsburgh, University of Virginia, University of British Columbia, McMaster University, PanAm Clinic, Oslo University Hospital, Sahlgrenska Institute and University Hospitals Coventry this is not standard of care radiograph and will therefore be considered a research

procedure. Female participants may be given a urine pregnancy test as per standard of care. Any determination of pregnancy will exclude the participant from this research activity.

8.6 Assessment of Outcomes

The primary outcome is ACL clinical failure which will be a composite of rotational laxity defined as mild asymptomatic pivot shift (grade1) detected at two or more follow-up visits **or** moderate or severe (grade 2 or 3) asymmetric pivot shift at any visit, **or** graft rupture. Individuals who experience a graft failure that results in revision ACLR will be asked to complete a healthcare utilization diary at the 2-year follow-up. The healthcare utilization diary will ask the participant to describe any direct costs (e.g. surgeries, number of rehabilitation sessions attended) and potential indirect costs (e.g. time missed from work).

Secondary outcome measures will include PROs that assess symptoms, activity, participation and QOL, measures of impaired range of motion and muscle function (quadriceps & hamstring strength), performance-based measures of physical function (hop tests, DVJ), return to pre-injury sports, adverse outcomes, intervention-related donor site morbidity and complications. Complications include adverse events, donor site morbidity (kneeling pain, graft harvest site sensory disturbance), and lateral compartment joint space narrowing on standing flexion AP radiographs.

8.7 Subject Payment

Subjects will be compensated for participation in this study. The participating clinical sites will be responsible for payment of subjects enrolled at their site. All subject payments will be processed by each site.

Subjects who complete all research related activities, including isokinetic testing, will receive up to $290.

Subject payment will be prorated as follows:

- $25 for providing informed consent and completion of screening procedures.

- $25 for completion of all screening/baseline data collection forms.
- $20 for completion of 6-week patient-reported outcome forms.
- $20 for completion of 12-week patient-reported outcome forms.
- $25 for completion of 6-month research visit that includes administration of PROs and performance of functional tests (hop tests and drop vertical jump tests).
- $25 for completion of 6-month isokinetic strength testing of the quadriceps and hamstrings.
- $25 for completion of 12-month research visit that includes administration of PROs and performance of functional tests (hop tests and drop vertical jump tests).
- $25 for completion of 12-month isokinetic strength testing of the quadriceps and hamstrings.
- $25 for completion of 24-month research visit that includes administration of PROs and performance of functional tests (hop tests and drop vertical jump tests).
- $25 for completion of 24-month isokinetic strength testing of the quadriceps and hamstrings.
- $50 incentive payment for completing the 6, 12 and 24-month research visits (all 3 visits must be completed to qualify for incentive payment).

9 POTENTIAL RISKS AND BENEFITS

Participants in this study will undergo ACL 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 associated with the study including the risks of surgery, radiation exposure and temporary pain are no greater what would be expected if the individual did not participate in the study because the surgery, radiographs and clinical tests like the pivot shift test and measurement of range of motion are part of routine care for patients undergoing an ACLR.

9.1 Potential Risks Associated with Study Interventions

- Risks of Surgery: All subjects who agree to participate in this study have already elected to undergo ACL reconstruction. The risks associated with this surgery include complications related to anesthesia and those related specifically to the operation. Risks associated with an anesthesia include cerebrovascular accident, cardiac arrest, and death, all of which are extremely rare and not increased by participating in this study.
- The expected effects after ACL reconstruction include temporary pain, swelling, limited range of motion, muscle atrophy and limited function. Adverse events related to ACL reconstruction include loss of motion/arthrofibrosis (5%), suture abscess, infection (<1%), nerve injury or paralysis (<0.5%), major vascular injury (<0.5%), deep vein thrombosis (<0.1%), pulmonary embolism (<0.1%) and graft failure (10-15%). Harvest of the bone block (BPTB or QT) may result in a patellar fracture; however, this risk is rare (less than 1 in 100 cases). Because all subjects would be undergoing surgery regardless of whether or not 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.
- Risk of Autograft Harvest with Bone Block: The risk of patellar fracture associated with autograft harvest is up to 1.8% for BPTB, and up to 8.8 % for QT. Previous reports indicate that for QT autograft, about 5% of the patellar fracture cases are symptomatic and require any intervention.

- Risk of Donor Site Morbidity: For each procedure, there is a risk of pain or complications associated with harvesting the required tissue. For a bone patellar tendon bone (BPTB) autograft, tissue is harvested from the tendon that attaches the patella to the tibial tubercle. Harvesting this tendon can cause anterior knee pain or kneeling pain (10%). For a quadriceps tendon (QT) autograft, tissue is taken from the quadriceps. Harvesting this tendon can cause discomfort at the insertion to the patella as well as risk of patella fracture if a bone block is harvested. For both grafts, a screw is used to attach the graft to the tibia, which can cause some local discomfort (10%). For the LET, tissue is taken from the iliotibial band (ITB). The ITB is an important lateral knee structure responsible for maintaining coronal plane and rotational stability when weight bearing, thus it is possible that the patient may experience some discomfort or tightness following graft harvest. For this procedure, the graft is left attached to the tibia at Gerdy's tubercle and reattached to the femur with a staple. Some patients complain of pain over the hardware used for the LET procedure (<5%).

9.2 Potential Risks Associated with Study Tests

- Risk of Radiation Exposure: Evidence of OA will be evaluated based on joint space narrowing on standing flexion AP radiographs obtained at screening/baseline and 2 years after surgery as per usual clinical care. For those sites at which 2-year radiographs are not standard of care, a research standing flexion AP radiographs will be obtained at the 24-month follow-up visit. The x-ray dose delivered as part of this study is well within recommended guidelines and poses very low risk to the subjects.

- Risk of Temporary Pain and/or Muscle Soreness: Some subjects may experience a temporary increase in pain during the pivot shift test to measure rotational laxity or during measurement of passive knee extension and active assisted knee flexion. However, this pain is expected to be short-lived, if it occurs at all. Further, the pivot shift test and measurement of range of motion are routinely performed as part of the standard of care for patients following ACLR. Therefore, the risks associated with

these measurements are no greater than what would be expected if the individual did not participate in the study.

- Risks Associated with Isokinetic Measures of Impaired Quadriceps and Hamstring Strength: Isokinetic measurement of quadriceps and hamstring strength may be associated with knee pain and swelling and muscle soreness for 24 to 48 hours after testing. This risk is no different than the risk of standard of care during rehabilitation treatment.

- Risk of Injury to the Lower Extremity: The performance-based measures of physical function include a series of hop tests and the drop vertical jump (DVJ) test. There is a rare (less than 1%) risk of a temporary increase in pain or injury to the knee or other region of the lower extremity during these activities. However, these activities are routinely performed as part of rehabilitation beginning 4 to 6 months after surgery. Additionally, based on this study's eligibility criteria, individuals included in this study will be accustomed to performing activities that require jumping and landing on one leg and are expected to be able to perform these activities after surgery and rehabilitation.

- Risk of Falling and Re-Injury to the Knee: The performance-based measures of physical function may be associated with an increased risk of falling and/or re-injury to the ACL. However, these measures will not be performed until at least 6 months after the surgical procedure and these risks are not greater than the ones encountered with typical rehabilitation activities or with participation in sports.

9.3 Potential Risks Associated with Privacy and Confidentiality

- Hard Copy Case Report Forms: This study will collect data from or about the participant using paper-based forms. These paper-based forms will only include a participant's unique database ID number. It will not include the participant's name. The file that links the participant's name with the unique database ID number is stored separate from the study data. All paper documents are kept in a locked filing cabinet in a locked room that is accessible only to individuals of the research team.

- Electronic data management: The study data is managed by a company called EmPower Health Research. All data is protected by a username and password. Data travels in a scrambled format (SSL) to an encrypted server that is secured by a professional company with extremely high standards of physical and virtual security. However, even with this high level of security, there is always a remote chance that study data could be accessed or "hacked". The collection of sensitive information from the subjects is limited to the amount necessary to achieve the aims of the research.

9.4 Potential Benefits

Participants in this study may benefit from being followed more closely than usual clinical practice in terms of the effort research personnel will put into ensuring that participants complete follow-up visits and with respect to the battery of tests that are not formally part of standard care (e.g. strength, hop and DVJ tests). This may mean more timely identification and treatment of any complications (e.g., graft failure, meniscal pathology or hardware-related discomfort) associated with ACLR or LET.

Because all subjects participating in this study would be undergoing surgery and standard of care follow-up regardless of whether they participate in this study, the associated risks of surgery, ACLR or rehabilitation are no greater than the risks had the subject not participated in this study.

It is possible that there will be benefits to the medical and research community as a result of this study. Specifically, the results of this study may lead to improved surgical treatment of an ACL rupture, resulting in a reduced risk for re-injury which would reduce the number of individuals undergoing revision ACLR and the associated decreased QOL and socioeconomic burden that occurs because of ongoing knee instability and the increased risk for post-traumatic knee osteoarthritis.

10 ASSESSMENT OF SAFETY

10.1 Definition of Adverse Events, Serious Adverse Events and Unanticipated Problems

An adverse event (AE) is any untoward medical occurrence during a subject's participation in the study that may or may not be related to the research procedures. Adverse events will include any new event not present during the pre-intervention period or events present during the pre-intervention period that have increased in severity.

A serious adverse event (SAE) is an event that results in death, is life-threatening, requires or prolongs hospitalization, results in persistent or significant disability, incapacity, congenital anomaly or birth defect. An important medical event that is not life-threatening, does not result in death or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the subject and require medical or surgical intervention to prevent one of the aforementioned outcomes.

The Office for Human Research Protections (OHRP) and the IRB of Record consider unanticipated problems (UPs) that involve risks to subjects or others to be any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given the research procedures that are described in the IRB-approved research protocol and informed consent document; and the characteristics of the patient population being studied;
- Related or possibly related to participation in the research (i.e., 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.

Based on the above definition, only a subset of AEs would be characterized as UPs involving risks to subjects or others. There are other types of incidents, experiences, and outcomes that are not considered AEs, but are characterized as UPs (e.g., breach of confidentiality or other incidents involving social or economic harm).

10.2 Reportable Events

The web-based data management software hosted by EmPower Health Research (Data Coordinating Center, DCC; www.secure.empowerhealthresearch.ca) will be responsible for the electronic monitoring of the quality of the data, generating missing data reports and creating queries to clarify nonsensical data.

The site Clinical Research Assistant (CRA) will document withdrawals and AEs, SAEs or UPs into the electronic database within 48 hours of learning of the event. To do so the site CRA will enter the information pertaining to the event into the EmPower data management system by completing AE Forms and follow-up CRFs (Figure 4).
When SAEs and UPs are reported, the DCC will automatically notify the site PI and CRA, KAI, and DCC/CCC Team by email notification. The Clinical Coordinating Center (CCC) will review the event report form and follow-up with the CRAs at each site to ensure queries are resolved in a timely fashion and determine whether the event should be reported to the IRB of Record. The CCC will notify KAI within 48 hours of the PI receiving notification of the event and KAI will notify NIAMS and the DSMB. The CCC will provide a report that includes a description of the event, as well as the investigator's assessment of expectedness, relatedness, and other relevant information. The CCC will report any actions taken.
. The timeline for reporting UPs to the IRB of Record is as follows:

- All UPs that are SAEs will be reported within 24 hours from the time when the study team member learns about the event.
- All UPs that are AEs will be reported within 5 working days from the time when the study team member learns about the event.
- All other UPs will be reported within 10 working days form the time when the study team member learns about the event.

As described in Figure 4, all AEs will be presented to the PIs during the weekly research team meetings unless noted that the AE is also an UP. The AEs will be reviewed internally by the study team at the CCC and DCC on a weekly basis.

A summary of AEs will be sent to members of the External Adverse Event Adjudication Committee (EAEAC) every 2 months, with a convened meeting twice annually. A summary of AEs will be included in the biannual report to the DSMB. The site PI will determine the severity of AEs, SAEs and UPs and their relatedness to the study intervention, which will then be confirmed by the EAEAC. The EAEAC will provide an independent, external and systematic review of all participants excluded at the time of surgery as well as all adverse events reported during the conduct of the trial. The EAEAC will independently review the documentation of AEs, SAEs and UPs in terms of their classification, severity and relatedness to study procedures. The members of the EAEAC will be blinded to treatment allocation to ensure the committee's recommendations are unbiased.

The EAEAC will convene for a meeting at least twice annually to discuss the reported events approximately two months prior to the planned DSMB Meetings or as frequently as every 2 months to resolve disagreements Study participants will be identified by a study identification number only in all event reports to ensure participant confidentiality. In addition to the EAEAC, the ESC will monitor AEs in a blinded manner on a monthly basis.

The PI will ensure participants' safety by complying with reportable event timelines described above to the IRB of Record, the NIAMS, and the Data and Safety Monitoring Board (DSMB).

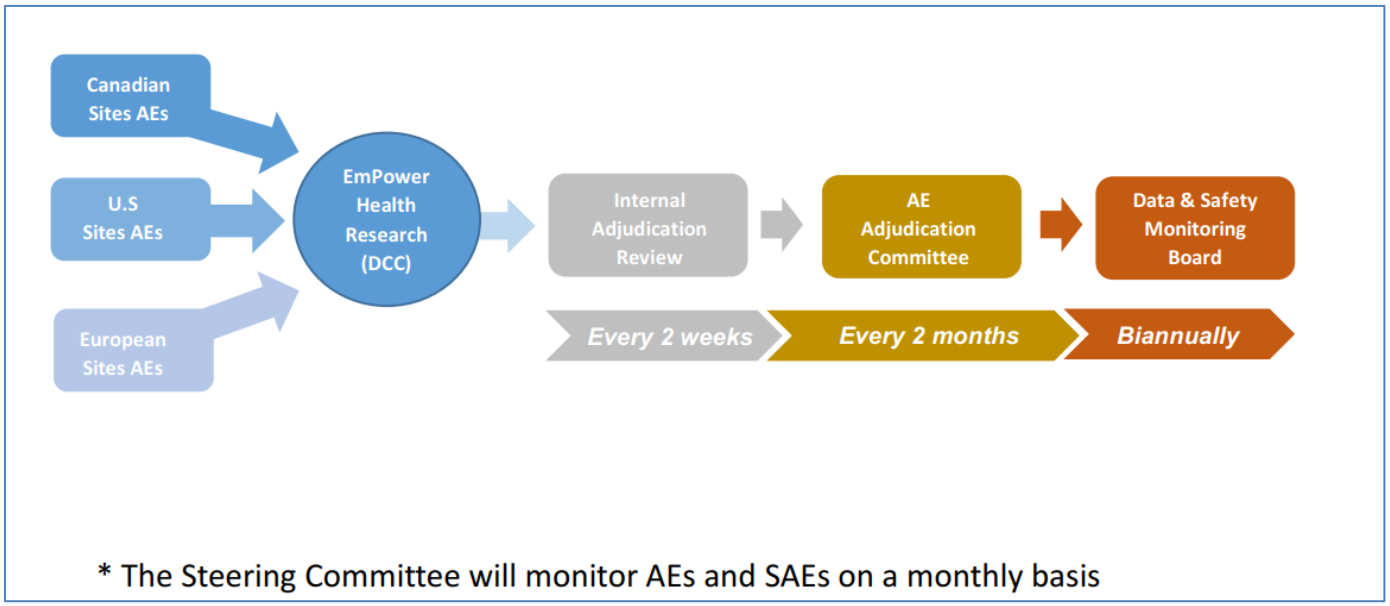
The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each clinical visit and through the electronic surveys, the research team will actively query participants on the occurrence of any potential health

related event since last contact. Events will be followed for outcome information until resolution or stabilization.

All AEs, regardless of their relatedness to the study intervention, will be recorded on the electronic AE form. *Hard* coded checkboxes will be used when recording and classifying AEs. This standardization will allow sorting and grouping of like events, which will facilitate consistent documentation across all 21 sites as well as the calculation of the incidence of each AE.

The data elements that will be recorded on the AE form include event term, event severity (mild, moderate, severe, life-threatening/disabling or death), start and end date, relatedness to study procedures (unrelated, unlikely, possible, probable or definite), action taken with study procedures (none, study procedure interrupted, discontinued or modified), other action taken (none, treatment given, discontinued from study or hospitalization), event status (recovered/resolved, resolved with sequelae, recovering/resolving, not recovered/resolved, fatal, unknown or lost to follow-up), and whether the event was an SAE.

Figure 4. Flow Chart of Internal and External Adjudication of AEs



11 ETHICS/PROTECTION OF HUMAN SUBJECTS

11.1 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.

11.2 Institutional/Ethics Review Board

The University of Pittsburgh Institutional Review Board (IRB) will serve as the IRB of Record for all clinical research sites in the US. To facilitate prompt IRB review and approval, the University of Pittsburgh will utilize the SMART IRB process to establish the reliance agreement with the other US clinical research sites. A similar process will take place for the Canadian sites, as sites under the same province will be submitted with one regulatory ethics board serving as the regulatory board of record (i.e. Clinical Trials Ontario will serve as the regulatory ethics board whose approval applies to any site located in Ontario, Canada). For the Canadian sites outside of Ontario, the study protocol will be submitted to local ethics review board/institution for review and approval, as per their institutional requirements, prior to initiation of any study procedures.

For the European sites, the study protocol will be submitted to local ethics review board/institution for review and approval, as per their institutional requirements, prior to initiation of any study procedures.

11.3 Informed Consent Process

For sites using traditional randomization, surgeons will describe the study to eligible patients including foreseeable risks. If interested, the CRA will provide the patient with the IRB approved consent form, further describe the study, including that randomization

to graft type and the possible addition of an LET will occur in the operating room, the required time commitments in terms of follow-up visits, and provide the opportunity for the patient to ask questions. If the patient is willing to participate in the study, prior to obtaining signature the CRA will quiz the participant by asking a series of comprehension questions to determine the participants comprehension of the information that was discussed. Once the participant understands their commitment s/he will sign and date the consent form prior to participating in any research-related activities. The consent form will also signed be and dated by the investigator or their delegate who is responsible for obtaining informed consent.

For sites using expertise-based randomization, patients referred to partnered surgeons will first meet with an independent clinician who will determine eligibility. Eligible patients will have the study described to them, including the random allocation to an expert surgeon and foreseeable risks of each procedure. If interested, the RC will provide the IRB approved consent form, further describe the study, that randomization to LET (or not) will occur in the operating room, the required time commitments in terms of follow-up visits, and provide the opportunity for the patient to ask questions. If the patient is willing to participate in the study, s/he will sign and date the consent form prior to participating in any research-related activities. The consent form will also be signed and dated by the investigator or their delegate who is responsible for obtaining informed consent.

For potential subjects that are younger than 18 years of age and depending on the legal age of consent as defined by the location of the site, the study will be explained to both the child and the child's parent or legal authorized representative. If the child is willing to participate in the study, permission from the child's parent or legal authorized 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. If the child turns 18 while enrolled in the study, they will sign the Consent for Continued Research Participation. This consent is an addendum form to the participant's original informed consent form.

All consent forms and study discussion will be presented in understandable language.

11.4 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.

Only 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 participant level information that is submitted for review to the DSMB, University of Pittsburgh Office of Research Conduct and Compliance, and the regulatory review boards, will be linked only to the participant's case number and not the personal identity of the subject.

12 STUDY OVERSIGHT

12.1 Composition of the Data and Safety Monitoring Board

The DSMB will be created to review and monitor the safety of the study and act in an advisory capacity to the NIAMS. Prior to the start of recruitment, the DSMB will review the research protocol, informed consent documents and plans for data and safety monitoring and, if acceptable, approve the study to initiate enrollment. Afterwards, the DSMB will meet at least twice annually to monitor and evaluate the progress of the trial; consider factors external to the study that may have an impact on the safety of the participants or the ethics of the trial; review clinical research site performance; protect safety of study participants; report on safety and progress of trial; consider risk-benefit ratios; monitor confidentiality of the trial data; and make recommendations to the Principal Investigators and the NIAMS regarding continuation, termination or other modifications of the trial. An emergency meeting of the DSMB may be called if there are any interim concerns. The DSMB Chair will write a report after each meeting, summarizing the study status and outlining any concerns. DSMB members will include experts in orthopaedic surgery, clinical epidemiology, and biostatistics.

12.2 Study Committees

The study will be governed by an ESC and five subcommittees. Each subcommittee will consist of investigators or individuals associated with the STABILITY 2 Trial, with the exception of the External Adverse Events Adjudication Committee. This external committee will consist of several qualified professionals who are not investigators or otherwise associated with STABILITY 2 Trial.

Executive Steering Committee (ESC)

The ESC will consist of James Irrgang (PI), Alan Getgood (co-PI), Volker Musahl (Co-PI), Dianne Bryant (Co-PI, Director of DCC), Trevor Birmingham (Co-I), Alexandra Gil (Co-I and QCL), plus three additional surgeons to represent US, Canadian and European sites. The role of the ESC is to provide oversight of the trial. The ESC will

define the vision and the scientific goals of the STABILITY 2 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. The ESC will resolve any conflicts that arise among investigators as well as have the ultimate responsibility for terminating the trial. The ESC will review and issue final approval or recommend modification for all subcommittee decisions. The ESC will meet monthly via conference call.

Publications and Ancillary Studies Committee (PASC)

The PASC will consist of Alan Getgood (Chair), Volker Musahl (Co-Chair), James Irrgang (Ex Officio), Dianne Bryant (Ex Officio), Jacquelyn Marsh (Co-I, health economist), plus three additional surgeons to represent US, Canadian and European sites. The PASC has established the policies and procedures for assigning working groups and approving STABILITY 2 Trial-associated ancillary studies, secondary analyses of existing data and abstracts, presentations, and publications prior to their submission for dissemination. The PASC has also established guidelines for authorship for investigators following the guidelines specified by the International Committee of Medical Journal Editors[85] for authors that have contributed to the scientific design and merit of the study. The investigators will pursue the publication of the results as soon as possible after the conclusion of the study. Each manuscript will include named authors and a study group name. Named authorship will be determined prior to writing the manuscript and will be based on the relative scientific contributions of the PIs and key personnel. All other participants will be listed under the group name, STABILITY 2 Study Group. The PI will attempt to resolve any conflicts or disagreements among authors regarding publication of the results. If they cannot reach a mutually agreeable resolution, the procedures for conflict resolution as described in the Multi-Principal Investigator Leadership Plan will be followed.

Rehabilitation Committee

The Rehabilitation Committee consists of several investigators and others rehabilitation professionals associated with the trial including James Irrgang (Chair), Trevor Birmingham (Co-Chair), Andrew Sprague (Co-I), Volker Musahl (Ex Officio), Alan Getgood (Ex Officio) plus additional three surgeons to represent US, Canadian and European sites. The Rehabilitation Committee has established the rehabilitation guidelines and protocols for subjects enrolled in the trial. 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 home exercise programs for participants. Throughout the trial, 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 include of Alexandra Gil (Chair, Co-I and QCL), Dianne Bryant (Co-Chair), James Irrgang (Ex Officio), Alan Getgood (Ex Officio), Volker Musahl (Ex Officio), Stacey Wanlin (PC), plus an additional three surgeons to represent US, Canadian and European sites. The Quality Control Committee will review and affirm the quality of the conduct of the trial including implementation of the surgical 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 trial on an ongoing basis to review loss to follow-up and PDs in aggregate as well as by individual site. Additionally, the Quality Control Committee will be responsible for the oversight of site monitoring visits.

Recruitment Committee

The Recruitment Committee will consist of Volker Musahl (Chair), Alan Getgood (Co-Chair), Dianne Bryant (Ex Officio), James Irrgang (Ex Officio) and at least three additional investigators representing the Canadian, US and European sites. The

Recruitment Committee will establish a plan and monitor recruitment throughout the duration of the trial. The committee will create recruitment materials to be used at the sites. Additionally, if a site struggles to meet recruitment targets, the committee will evaluate site factors and either provide recommendations to improve recruitment rates or terminate the site's participation in the study.

External Adverse Events Adjudication Committee (EAEAC)

The EAEAC will consist of several qualified orthopaedic surgeons who are not associated with the STABILITY 2 Trial. They will provide an independent external and systematic review of all participants excluded at the time of surgery as well as all adverse events reported during the conduct of the trial. In addition, the committee will assign each adverse event a level of severity and will determine the relationship to the study intervention. Use of a similar committee in a clinical trial involving spine surgery found that more than one-third of the adverse events were reclassified and the majority of reclassifications lead to an upgrade in the level of severity or greater relatedness to the surgery or device.[86] Therefore, we will assemble this committee to mitigate potential investigator bias and facilitate an accurate sampling and safety profile for the STABILITY 2 Trial.

13 CLINICAL SITE MONITORING PLAN

The purpose of this Clinical Monitoring Plan (CMP) is to establish guidelines for conducting monitoring visits and related tasks to oversee the conduct and safety of the STABILITY 2 Trial. The Clinical Coordinating Center (CCC) at the University of Pittsburgh in collaboration with Western University will be responsible for CMP under the co-leadership of Dr. Alexandra Gil and Stacey Wanlin, who will serve as Co-Investigator and Quality Control Lead (QCL) and Project Coordinator (PC) for this trial respectively. Drs. Irrgang (Principal Investigator), Getgood and Musahl (Co-Principal Investigators responsible for all aspects of surgery), Bryant (Co-Principal Investigator, Director of the Data Coordinating Center [DCC]) and the Project Coordinator from the Clinical Coordinating Center will also actively participate and contribute to the CMP. Dr. Gil and the Project Coordinators from the CCC and DCC will serve as the Clinical Trial Monitors.

The intent of the CMP is to ensure compliance with the research protocol, the International Conference on Harmonization (ICH) Good Clinical Practice Guidelines, national and local regulations, and institutional policies across all sites. The focus areas for the CMP include: 1) site assessment 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 regular communication with Clinical Research Assistants (CRA) (e.g. biweekly phone calls) as well as continuous year-round remote monitoring, such as review of electronic records using web-based software hosted by EmPower Health Research (*www.secure.empowerhealthresearch.ca*).

13.1 Clinical Monitoring Communication Plan

Communications for each monitoring visit will include a letter confirming the date and time of the site monitoring visit, agenda for the monitoring visit, 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, Co-PIs for surgery, Co-PI and Director of the DCC, PC for the DCC, Co-I for rehabilitation as well as the site PI and CRA.

13.2 Scheduling of Visits

The Quality Control Lead or her designee will work with the site PI and CRA to schedule the remote monitoring visits. The study PI, Co-PIs for surgery, Co-PI and Director of the DCC, and PC for the DCC will be apprised of monitoring visits schedule. Prior to the visit, the site PI and CRA will receive a visit confirmation letter and agenda. The site PI and CRA will be expected to ensure they have the remote meeting software (Skype for Business, Go To Meeting or ZOOM) installed and determine that it is compatible with their computer system prior to the meeting time. 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 CRA are also expected to be available for a wrap-up meeting at the conclusion of the visit. These expectations will be explained in the monitoring visit confirmation letter.

13.3 Types of Visits and Monitoring Activities

The CMP will include four types of monitoring visits for this study including a Site Initiation Visit, Interim Visits, For-Cause Visits and Study Close-Out Visit. The CMP will also include ongoing monitoring of research records and documents. Site visits will be conducted remotely using Skype for Business, Go To Meeting or ZOOM.

13.3.1 Site Initiation Visit

The site initiation visit will take place prior to site activation once IRB approval 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, the QCL and PC will develop an agenda and follow the communication plan to ensure that all relevant parties are informed of the meeting date and time commitment in advance. The agenda will contain a list of topics in the order of 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 regulatory review board, and IRB of Record;
- All necessary site staff have been identified; and
- All staff have completed training on the use of the EmPower database.

The following list of activities will be used as a starting point for the agenda for the Site Initiation Visit:

- Protocol Overview
- Type of study
- Study objectives
- Enrollment goals
- Recruitment plans
- Informed consent discussion
- Key inclusion/exclusion criteria
- Completion of screening and eligibility scenarios
- Study visit schedule/schedule of events
- Study procedures
- Safety: Definitions, Collection, and Reporting, Review of AEs, SAEs, and 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 of procedures for data entry
- Review of action items for reportable events
- Discuss site-specific communication plan with participants, physical therapists, site PI, local regulatory review board and EmPower data management center.
- Clinical monitoring
    - Contacts
    - Site responsibilities
    - Frequency
    - Close out procedures
- Site Essential Documents File Review
- Structure of the study binder as well as essential documents to include:
    - Regulatory review board approved documents;
    - Protocol;
    - Patient handouts;
    - Advertisements;
    - Consent document
    - Document updates
- Summary/Review of Action Items

A site can be activated only after all of the requirements on the Site Activation Requirements Checklist have been met (Table 2).

Table 2. Site Activation Requirements Check List	
Item	Date
1. Regulatory Review Board 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 (MOOP), EmPower electronic data management system. (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).	
5. Action Items from Site Initiation Visit Required for Site Activation Completed	
6. Study Specific Requirements Met	

13.3.2 Interim Visits

The first interim visit will be conducted remotely for each site after two or three participants have been enrolled and followed for three to four months. Subsequent interim visits will be conducted remotely annually. The objectives of interim visits are to confirm that:

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

In addition, to ensure accuracy and completeness of the data, the QCL or her designee 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, CRA 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 in an Action Item Tracker attached to the monitoring visit documentation. At a mutually agreed upon time (no later than four weeks after the interim monitoring visit), the QCL or designee and site research staff designee will meet via telephone conference to discuss resolved, in process, and pending action items. The need for, and frequency of, subsequent meetings will also be discussed. The follow-up letter, final monitoring visit report and Action Item Tracker will be sent within three weeks of the conclusion of the site visit.

13.3.3 For-Cause Visits

For-Cause Visits will be conducted to address any unanticipated issues that arise that require training, remediation or other situations for which the site requires assistance. For-Cause Visits will be conducted remotely.

13.3.4 Close-Out Visit

The Close-Out Visit will be conducted to ensure that all study data and other documentation is complete and accurate, and that all study records have been reconciled. Study closure activities may require several remote visits that 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, DSMB NIAMS or ESC.

Study closeout procedures will begin when the last enrolled subject reaches the 24-month follow-up time point. Closeout procedures will include:

- Verification that study procedures have been completed and all data have been collected and entered into EmPower;
- Verification that all data queries have been resolved;
- Ongoing maintenance of study records consistent with local and University of Pittsburgh policy for retention of research records (whichever is more stringent);
- Maintenance of correspondence, study files and study participant files for future audits;
- Notification of the local IRB and IRB of Record that the study has been completed. Once subject enrollment and follow-up is complete, the IRB status will be changed to “ongoing for data analysis purposes only”;
- Preparation of a report summarizing the conduct of the study, which will be submitted to the IRB, DSMB and the NIAMS Program Officer;
- Notification of the participants that the study has been completed;
- Posting of final results on ClinicalTrials.gov website within one year of 2-year follow-up of the final enrolled participant.

13.4 Ongoing Site Monitoring and Documents to be Monitored

Remote monitoring of the site will also be done an ongoing basis. The documents needed to support ongoing remote monitoring of the site will be uploaded to the EmPower database. Participant-specific documents (e.g. consent forms, source documentation for comparison to CRFs) will be de-identified and entered into separate folders for each participant. Source documentation will be compared to the completed CRF of the first 10 patients enrolled in the study to identify any initial problems. Thereafter, the PCs will monitor research records and documents through remote visits,

interim reports or ongoing data verification at the frequency specified summarized in Table 3.

The ongoing monitoring process will be used to determine whether:

- Informed consent was obtained and documented in accordance with IRB regulations;
- Information recorded on EmPower forms is complete and accurate;
- There are omissions in specific data fields;
- Reasons for missing data are documented and;
- Participant disposition when withdrawing from the study is accurately documented.

A summary of the findings from the clinical monitoring process will be presented to the investigators at their monthly meetings. Corrective action plans will be developed, reviewed by PIs and study staff, and implemented as necessary. Ongoing monitoring will be performed to ensure resolution of any problems that are identified. Problems identified during the monitoring process may trigger a more thorough review, including scheduling of a for-cause visit, additional training, or review by the University of Pittsburgh Research Education and Compliance Office. PDs discovered in the quality review process will be documented and reported to the PIs, IRB, DSMB and the NIAMS Program Officer.

Table 3. Research Records and Documents to be Monitored			
Records and Documents to Be Monitored	**# Records**	**Type of Monitoring**	**Frequency**
Site Human Subject Protection Training Records	100%	Site Initiation Visit and Interim Visits	Annually
IRB Initial Approval and Annual Renewal Letters	100%	Site Initiation Visit and Interim Visits	Annually
Signed Informed Consent Forms	100%	Ongoing	Monthly
Eligibility Criteria	100%	Ongoing	Monthly
Surgical Source Documentation vs. CRFs	100%	Ongoing	Quarterly
Clinical Follow-up Visits Source Documentation vs. CRFs	10%	Ongoing	Quarterly
CRFs or Data Queries	10%	Ongoing	Weekly
Missed Visits and Missing Data	100%	Ongoing	Monthly
Documentation and Reporting of AEs, SAEs, PDs Documentation	100%	Ongoing	Weekly
Withdrawals and Dropouts Documentation	100%	Interim reports	Biannually
Site Regulatory Documents	100%	Site Initiation and Interim Visits	Annually
		Close-out Visits	Event Driven

14 STATISTICAL CONSIDERATIONS

14.1 Study Hypotheses

The overall primary objective of this 21-site international randomized trial is to determine if graft type (QT, BPTB or HT) with or without a LET will affect the rate of ACL clinical failure 2 years after surgery. Secondary objectives will determine the effects of graft type and LET on patient-reported outcomes, performance-based measures of function, return to sports, intervention-related donor site morbidity, complications and adverse outcomes and cost effectiveness.

To achieve these objectives, we will randomize 1236 participants with an ACL tear who are at high risk of failure to undergo ACL reconstruction with a QT or BPTB with or without a LET. Study data will be combined with data from a prior trial that compared ACLR with HT grafts with or without a LET (STABILITY 1).

Aim 1**:** Determine if graft type (QT, BPTB or HT) with or without a LET affects the rate of ACL clinical failure at 2 years after ACLR. ACL clinical failure will be defined by either graft rupture, symptomatic instability or persistent rotational laxity (asymmetrical positive pivot shift), at 2 years after ACLR.

Our hypotheses for Aim 1 are:

- The rate of clinical failure of ACLR performed with a QT, BPTB or HT graft will be reduced with the addition of a LET;
- ACLR with BPTB without LET will result in a lower rate of ACL clinical failure compared to ACLR with HT and LET;
- ACLR with QT without LET will result in a lower rate of ACL clinical failure compared to ACLR with HT and LET
- ACLR with QT and LET will result in a lower rate of ACL clinical failure compared to ACLR with BPTB and LET.

We also hypothesize that females who undergo ACLR and LET will have a lower ACL clinical failure rate.

Aim 2: Determine if graft type (QT, BPTB or HT) with or without a LET affects patient-reported symptoms, function and quality of life, performance-based measures of function and return-to-sports 2 years after ACLR.

Aim 3: Determine if graft type (QT, BPTB or HT) with or without a LET affects the rates of intervention-related donor site morbidity, complications and adverse outcomes 2 years after ACLR.

Aim 4: To determine if a particular graft type (QT, BTPT or HT) with or without addition of LET is a more cost-effective approach to ACLR.

14.2 Sample Size Considerations for Aim 1

The absolute risk of ACL clinical failure (as defined by either graft rupture/symptomatic instability requiring revision ACLR surgery or persistent rotational laxity as measured by an asymmetrical positive pivot shift compared to the contralateral side) is estimated to range from 25-35%.[40,87,88] We consider a relative reduction in ACL clinical failure rate of at least 40% by 24 months after surgery to merit a change in practice (i.e. of sufficient magnitude to warrant the additional costs of adding a LET). Since, our primary interest is in determining the main effect of graft choice and whether the effect of LET varies by graft choice, the focus will be on the following comparisons: 1) HT+LET versus HT (already shown by STABILITY 1), 2) BPTB+LET versus BPTB, 3) QT+LET versus QT, 4) BPTB versus HT+LET, 5) QT versus HT+LET, and 6) BPTP+LET versus QT+LET.

With 210 patients per group and a type I error rate of 1%, we would have 80% power to detect a hazard ratio of 0.56 (i.e. 44% clinical failure risk reduction when comparing the LET v no LET condition) assuming the clinical failure rate is 33% (the average rate of failure in STABILITY 1). A small type I error rate of 1% was used to reduce the risk of a type I error due to the multiple comparisons based on the Bonferroni method to achieve an overall type I error rate of 5%. Even if there is an intra-cluster/surgeon correlation coefficient (ICC) as large as 0.02, 1) the average number of surgeons per site is 3 given the number of surgeons at each site ranges from 1 to 4, and 2) the average number of patients per surgeon is 22, we will need 281 patients per group to account for the

clustering effect. To reduce the risk of losing precision from patients withdrawn and lost to follow-up, an additional 10% of patients will be recruited (attrition was 5% from STABILITY 1), for a total of 309 participants per group or 1236 patients total (or 1853 when STABILITY 1 and STABILITY 2 data are combined). To appreciate the greatest statistical efficiency, each surgeon in a traditional randomization site (17 sites, 49 surgeons) should recruit approximately 20 patients and each surgeon in an expertise-based randomization site (3 sites, 6 surgeons) should recruit approximately 36 patients (given the ICC for trials using expertise-based randomization is usually slightly larger than the ICC for trials using non-expertise based randomization).

14.2.1 For Sex-based Research Question

Preliminary results of STABILITY 1 suggested that HT+LET is superior to HT ACLR alone and is associated with an increased odds of failure compared to HT+LET for both males (odds ratio (OR) = 2.53, 95% confidence interval (CI) = 1.42, 4.51) and females (OR = 1.76, 95% CI = 1.05, 2.96).[31] Given these results, and because females tend to be quadriceps dominant in their landing biomechanics compared to males, and use of a HT graft is currently the most common method of ACLR, we need to understand whether harvesting the HT (which may further contribute to quadriceps dominance) should ever be a first-line option for females. Thus, STABILITY 2 will compare failure between HT+LET and other graft options (BPTB or QT) for males and females separately.

Among the 309 patients per group, we assume half will be female (51.5% of STABILITY 1 participants were female). Thus, we expect to have 159 females in each of the HT+LET, BPTB, and QT groups. Given the failure rate of 29% for females when treated with HT+LET (based on the result from STABILITY 1), the minimum detectable OR will be 2.1 with a power of 80% at the significance level of 0.05. Given the failure rate of 21% for males when treated with HT+LET (based on the result from STABILITY 1), we will be able to detect an OR of 2.4 with a power of 80% at the significance level of 0.05. According to the rule of thumb on magnitudes of effect sizes by Cohen,[89] an OR of 2.1 or 2.4 is considered to be as small (1.5) to medium (3.5) effect size, i.e. with the sample

size of 309 (159 females and 150 males) per group, we will have a power of 80% to detect a small to medium treatment effect for males and females separately at the significance level of 0.05.

14.3 Sample Size Considerations for Aim 2

All participants will complete data for the all PROs, ROM, hop and clinician-rated DVJ tests and Marx Activity Rating, however isokinetic testing can only be performed at 13 sites (approximately 780 patients for this study or 929 including STABILITY 1 patients).

The isokinetic tests are on a continuous metric and therefore do not require as large a sample size as the binary primary outcome. By recruiting consecutive patients at each site, we will maintain a representative sample. In keeping with the planned comparisons outlined for the primary outcome, we will have 80% power (type I error of 1%) to detect a standardized effect size of 0.28, which is considered small (0.2) to medium (0.5) effect size according to Cohen[89] for continuous outcomes measured for all participants (300 per treatment group), which include the hop test, Kinect V2 DVJ test, patient-reported measures of symptoms, physical function and quality of life, EQ5D, range of motion, and the Marx Activity Rating Scale. For the isokinetic strength test, we only require a sample size of 75 per treatment group to have a power of 80% (type I error of 1%) to detect a standardized effect of 0.56. Our expected sample size for the isokinetic test data is approximately 195 per treatment group (13 sites x 60 participants per site).

14.4 Sample Size Considerations for Aim 3

For the adverse outcomes associated with donor site morbidity (presence of anterior kneeling pain and sensory disturbance secondary to graft site skin incision), adverse events associated with surgery (intra- and postoperative complications, lateral compartment joint space narrowing) and knee re-injury or new injury (graft re-tear, contralateral tear, meniscal re-tear, meniscal tear), which are all binary data, and measured for every patient, we will have 80% power (type I error of 1%) to detect a medium effect size (OR = 3.5) assuming an outcome event rate in ACLR is as low as 10%.

14.5 Plan for Data Analysis

The data collected through this study will be pooled with the data from STABILITY 1 for analysis (n=1853). We will provide a descriptive summary of participants in each treatment group at each visit using means and standard deviations for normally distributed data, median and interquartile range for continuous but not normally distributed data, and count and percentage for categorical data.

14.5.1 Statistical Analysis for Aim 1

We will use a mixed-effects logistic regression using the primary composite outcome of failure measured over time as the dependent variable to estimate the effects for treatment group (HT+LET, HT, BPTB+LET, BPTB, QT+LET, and QT), time, and the time by treatment group interaction, with meniscal repair status, age, sex, surgeon (or surgeon pair for expertise-based sites) and tibial slope as time-independent covariates and contralateral injury, post ACLR meniscus tear/re-tear, ipsilateral limb exposure (in hours), time since returning to sport and time since discharge from physical therapy as time-dependent covariates and surgeon as a random effect. Time to return to sport and to discharge from physical therapy are considered as covariates in the model since we expect that participants who return to sport earlier or cease to attend physical therapy earlier are more likely to experience the outcome. Both contralateral injury (yes/no) and meniscus tear/re-tear (yes/no) collected at each study visit will be included in the model as a time-varying covariate since the occurrence of contralateral injury and meniscus tear will alter (i.e. eliminate or reduce) the risk of experiencing graft failure over the next few months while the patient recovers. Following sufficient recovery time, the patient will resume activities and again be at risk of suffering the primary outcome (graft failure). Exposure time will be defined as the total number of hours spent playing sports since the surgery. The greater the exposure the greater the risk of graft failure. Since graft failure will occur only once during the follow-up period, the outcome data will be treated as missing after the failure occurs. Given these data are not missing at random, we will use the maximum conditional likelihood approach proposed by Skrondal and Rabe-Hesketh[90] to provide an unbiased estimate of the treatment effect. Within the model, we

will calculate the odds ratio, 95% confidence intervals, and p values for the six prespecified intergroup contrasts and for change in rate of failure within each group over time.

As a second means to evaluate the primary outcome, we will conduct a time-to-event analysis to investigate the effects surgical procedures on the hazard of graft failure. The "survival" time is defined as the time from randomization to graft failure with data censored at the time of loss to follow-up or at the end of the study, whichever occurs first. We will use a multivariable Cox frailty model with random intercepts to account for site clustering, meniscal repair status, age, sex, surgeon as time-independent covariates, and contralateral injury, meniscus tear/re-tear, ipsilateral limb exposure, return to sport (yes/no), and discharge from physical therapy (yes/no) as time-dependent covariates. Within this model, we will calculate the hazard ratio, 95% confidence intervals, and p values for the six prespecified between-group contrasts.

To address the sex-based question, we will repeat the primary analysis for males and females separately and provide the odds of failure with a BPTB or QT graft compared to an HT+LET graft.

14.5.2 Statistical Analysis for Aims 2 and 3

For secondary outcomes like return-to-activity and donor site adverse events, we will conduct an analysis similar to that described for the primary research question, as both are binary outcomes measured at ≥3 time points. For each continuous secondary outcome that is measured at ≥3 time points (PROs, hop test, return to activity measured using the Marx Activity Rating Scale, EQ5D, range of motion, and strength), linear mixed-effects models for measures will be used to obtain the effects for the six prespecified intergroup contrasts and for change of the outcome measure over time, with adjustment of the same covariates and covariance matrix as in the primary analysis.

For the evaluation of lateral compartment joint space narrowing, which is a continuous outcome measure, we will conduct linear regression where the 24 month measurement will serve as the dependent variable, treatment group will serve as an independent variable, and adjustment for the lateral compartment joint space at screening/baseline, age, sex, meniscal repair status, surgeon, time between surgery and return to sport, and time between surgery and final rehabilitation visit as covariates.

For the Kinect V2 DVJ test, which is the secondary continuous outcome measured at 6 and 12 months after the surgery, we will run two separate linear regression models with treatment groups as the independent variable and adjustment for age, sex, meniscal repair status, surgeon, return to sport (yes/no), and discharge from physical therapy (yes/no).

For all linear and linear mixed-model analyses, we will examine distributions of residuals and use transformations of the outcome variables to achieve normality when necessary.

14.5.3 Statistical Analysis for Aim 4

Healthcare Resource Use and Unit Costs:

We will assign the average procedure cost for an ACLR surgery at each participating institution with the additional cost of the lateral extra-articular tenodesis for those patients randomized to the LET group. The main driver in cost difference is expected to be failure of the reconstruction requiring revision. Therefore, in addition to capturing the cost of the revision procedure, patients who have a failed ACLR will also be asked to complete a healthcare resource use diary to capture additional direct and indirect healthcare resources from the time of failure to the end of the study period. This will include any emergency room visits, hospitalizations, family doctor, specialist, healthcare professional or outpatient clinic visits, tests, procedures, prescription or over-the-counter medications and any miscellaneous costs related to their knee. We will also record employment status and time-off paid employment, homemaking or volunteer activities, for both patients and their caregivers, if applicable.

Consistent with recommended guidelines,[91] we will incorporate multi-country costing and obtain unit cost prices that are jurisdiction specific to account for differences in relative or absolute price levels among participating centers. We will also report resource use separately from unit costs to increase the transparency of the analysis.

We will obtain unit costs for surgical procedures using outpatient facility (hospital-based or ambulatory surgery center) fees and jurisdiction-specific professional reimbursement schedules. Patients will self-report productivity losses, out-of-pocket costs and healthcare resource use not covered by government or privately funded healthcare plans during the study period. We will use each nation's average hourly wage to place a monetary figure on time off from paid employment, for both patients and their caregivers. We will use purchasing over power parity statistics to translate costs to a common currency ($USD). We will also report resource use separately from unit costs to increase the transparency of the analysis.

We will use quality-adjusted life years (QALY) as our effectiveness outcome two years after surgery. QALYs incorporate both length of life and quality of life into a single measure and are the product of a patient's utility score and the corresponding health state duration. Using each participants' prospectively collected EQ-5D scores, we will assign the corresponding utility value according to published valuation sets for each participating center's respective country.

For our base case analysis, we will estimate the cost-effectiveness of ACLR + LET compared to ACLR from a societal perspective that includes all direct and indirect costs. We will also conduct sensitivity analyses using a healthcare payer perspective incorporating only government funded costs to reflect the cost-effectiveness in publicly funded healthcare systems. Presenting our results from both perspectives will enable interpretation for knowledge users in both publicly funded and private healthcare systems.

We will report descriptive statistics to summarize country specific cost estimates (mean and standard deviation).

To analyze the cost-effectiveness data collected alongside multinational trials the recommended approach is hierarchical, multilevel modelling.[92] Bayesian hierarchical models that use both patient and country-level information facilitate between-country generalizability of the study findings and allow decision makers in each respective country to interpret the results in context. Using a random effects model, we will obtain more appropriate estimates of the population average incremental cost effectiveness and associated standard errors and location-specific cost-effectiveness estimates to explore the between-location variability of the results.[93]

We will calculate the incremental cost per QALY and estimate the incremental net benefit (INB) of ACLR + LET. To account for clustering among study sites as well as potential heterogeneity in costs and treatment effect across countries, we will use a random effects multilevel model where treatment group is a fixed effect and the treating institution and country are random effects. We will use Bayesian shrinkage estimation to derive a pooled, random effects estimate of incremental net benefit across all participating sites.[94] We will consider ACLR + LET cost-effective if our estimate of INB is greater than 0. We will adjust for patient and country-level covariates (sex, age, previous or current meniscal excision, time between surgery and return to sport, time between surgery and final rehabilitation visit) in our model. To characterize the statistical uncertainty around our estimate of INB, we will use an extension of the standard net benefit regression framework[95] using the hierarchical data to generate location-specific net benefit curves, and cost-effectiveness acceptability curves.[96] These curves represent the probability that the intervention is cost-effective for a given level of decision maker maximum willingness to pay for additional unit of outcome.

14.6 Handling Missing Data

For missing data, (missing secondary outcomes or time-dependent covariates), we will evaluate whether data are missing completely at random by comparing the available data (especially at baseline) for those with and without missing data at follow-up. Multiple imputation using full conditional specification method (FCS) (also called the multivariate imputation by chained equations), which is widely applied for the arbitrary

missing pattern, will be used for imputing the missing data. In particular, FCS logistic regression method will be used for imputing binary data and FCS regression method will be used for imputing continuous data. We will set the maximum number of iterations as 20 and generate 25 imputation datasets to ensure reliable inference.[97] Complete case analysis will also be conducted as a sensitivity analysis to assess the impact of missing data on the estimation of intervention effect. For the primary outcome (i.e. graft failure), since graft failure will occur only once during the follow-up period, the outcome data will be treated as missing after the failure occurs. Given the data are missing not at random, we will use the maximum conditional likelihood approach to handle it as described above in the analysis for the primary research question. We will also conduct the time-to-event analysis which does concern itself with data (either observed or missed) after the occurrence of graft failure. All the above analyses will be implemented using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

15 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 EmPower Health Research Inc. After randomization occurs, standard of care clinical visits and PROs will be completed remotely and managed through scheduled timepoints in EmPower.

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 ligament, 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 EmPower.

Each site CRA 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. Bryant will delegate management of the EmPower 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 and regulatory and institutional requirements for the protection of confidentiality of subjects. Study staff will permit authorized representatives of the regulatory funding 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.

16 DATA MANAGEMENT PLAN

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 Methods and Systems for Data Collection

EmPower Health Research Inc (www.empowerhealthresearch.ca) will be responsible for the electronic monitoring of the quality of the data. This software has demonstrated compliance with privacy and security standards. To assist the CRA, the database automatically sends instructions to participants who wish to enter data directly using their own username and password and sends an email to the participant to set up a password.

The EmPower data management software also generates several reports including Missing Data, Recruitment and Retention, Participant Tracker, AEs, Withdrawal, PD, Queries and Payout reports.

The Missing Data Report specifies the site, visit, CRF and data elements that are missing and can be limited to exclude data that has already been acknowledged as missing, where the site is unable to collect that data point.

The Recruitment and Retention Report provides a high-level report of the number of participants who are eligible and consenting, eligible after surgery, randomized, withdrawn and complete by site and overall.

The Participant Tracker Report provides a participant by visit classification of the status of each participant's visit. Participants are sorted by site; each participant is a row, each column is a visit. Cells provide each participant's visit status as complete (all required data fields within all forms required for that visit are complete and query free),

incomplete, overdue with the visit start and end date provided (a visit is overdue if the date falls after the ideal date according to the date of surgery), missed (if a Missed Assessment CRF has been submitted to indicate that the site is unable to collect that data), or withdrawn. This report is limited by site for research assistants but inclusive of all sites for data quality personnel. The report can also be limited to exclude withdrawn participants or missed participant or to only include participants whose visit window start and end date include today's date (date of query); features meant to add ease and efficiency to data management personnel at the site and DCC.

The Adverse Event Report lists all AEs by site, by surgeon, and by participant and includes the visit within which the event was reported, whether the event was resolved within the visit (or not), and the name of the event (e.g. graft rupture, deep infection, etc). This report can also be generated to present a tally of each event type across the study (e.g. number of graft ruptures, number of deep infections, etc.). The EmPower data management system can also produce a report that lists participants by row and details the original adverse event report and the data regarding any subsequent follow-ups for that specific adverse event.

The Withdrawal Report lists all participants by site, by surgeon and by participant and lists the visit within which the participant was withdrawn and the reason for withdrawal. This report can also be generated to present a tally of each reason for withdrawal across the study (e.g. number of participants whose surgeon withdrew them, who withdrew themselves, deaths, lost-to-follow-up, etc.).

The Protocol Deviation Report lists all participants by site and surgeon who have a PD. The report lists the visit where the deviation was reported and the description of the deviation.

The Queries Report provides the date, visit, database ID, details of any queries created by the data quality personnel, whether a response has been submitted by the site CRA, the status of the query (resolved vs. outstanding), and any additional communication between the data quality personnel at the DCC and the site CRA.

The Payout Report generates an amount owed to each site based on the quality of data for each participant visit. Each visit must be complete and query free for the site to be reimbursed. A draft of the report is sent to the site within two weeks of finalization to provide them with sufficient time to complete data entry and cleaning tasks prior to finalizing the payout report. Once finalized, the report is sent to the Coordinating Center to administer payment and the EmPower data management system marks these visits as paid in the next Payout Report, automatically beginning its assessment of the amount owed from where it last paid out.

The Monitoring Report provides an overall assessment of the status of each participant's visit according to whether the visit has been electronically monitored, source data verified, whether there are outstanding queries and whether or not the participant's file is locked. A participant's file can only be locked once the participant has reached the final study visit, been withdrawn or suffered the primary outcome, each form has been reviewed by the monitor, and there are no outstanding queries. Locking a subject file means that regular users can no longer edit that participant's data.

The system can generate several logs including an Audit, Access and Communications Log. The Audit Log presents the username, date and time (EST) of initial data entry and any changes made to data with the reason for the change. The Access Log provides a list of the date and time that users login and logout and any form that they edited. The Communication Log presents the date, time, user, subject line and content of any email or text message sent by the system.

Hard copy forms are available for participants who do not wish to enter data directly online, although with this age-group and our experience with STABILITY 1, the majority of participants are expected to enter their data online. The RC will enter data from paper-based case report forms directly into the online database the same day it is collected.

The EmPower data management software will facilitate the generation of clean datasets by guiding individuals through the data collection process by only displaying questions

and screens that are appropriate for the particular participant, using within and between CRF logic to reduce the possibility of nonsensical data entries and the need for extensive recoding and cleaning by the statistician.

The eMonitor in collaboration with the PC at the DCC will proactively monitor participant retention using the web-based EmPower data management system. Missing data reports will be shared with the site CRA and PI on a monthly basis for adjudication and resolution. In addition, site remuneration for data collection is dependent on complete and query-free CRFs per participant by visit. The eMonitor provides quarterly Payout Reports of visit completion and corresponding remuneration value to the site for verification. The verified quarterly reports summarizing the visit completion will be forwarded to the grants administrator at the University of Pittsburgh or Western University who will issue payments to the sites.

The EmPower data management software will send automatic email or text message reminders to the CRA of an upcoming follow-up visit prior to the visit, on the date that the visit window opens, the ideal date, and a few days after the ideal date if the CRFs remain incomplete. The CRA, and site PI are notified if the visit still remains incomplete 7 days prior to the final visit window date. The PC and eMonitor are notified if the visit remains incomplete on the final date of the visit window. Since the analysis will use time as a random factor, visits that take place outside the specified window are not as problematic as when time is defined as a fixed factor.

The EmPower data management software will send an automatic email or text messages to participants (who have opted into this feature) regarding upcoming and overdue appointments. Participants will have the option to login using their unique username and password to complete patient reported outcomes directly online or to wait to complete these CRFs at the clinic. When participants log in, they only have access to CRFs that are meant for participants and that fall within the visit window according to that day’s date.

To maximize participant compliance with the protocol's follow-up visit schedule, multiple attempts to contact non-responders will be utilized. Participants will be contacted via email 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 site CRA until the participant completes the follow-up visit or withdraws their consent for continued participation in the study. Data collected up to the date of withdrawal will be retained for analysis.

The PC and eMonitor will create reports for the investigators and the DSMB to chart progress of the study and identify potential problems with the data. The PC and eMonitor will generate reports for the DSMB on a semi-annual basis to allow for the early detection of problems.

When withdrawals or AEs are reported, the system automatically notifies the Principal Investigators, QCL and PC via email. The ESC will meet monthly via teleconference (more frequently during start-up or as needed). Agenda items for meetings will include topics such as reports that document compliance patterns and quantify reasons why subjects were not enrolled; compare actual with targeted enrollment; determine whether recruitment targets for minority and both sexes are being met; assess completed and missed follow-up visits and rates of missing and incomplete data at each visit; list adverse events associated with the protocol; and chart the frequency and character of PDs. Action plans to resolve any problem will be developed and implemented. Ongoing follow-up reports will enable us to determine the effectiveness of any corrective actions that are taken.

Data integrity and credibility of the study are dependent on strict adherence to the protocol, obtaining complete follow-up data from all participants and establishing and adhering to quality control measures to maintain high standards for data quality. The quality control procedures that have been developed and implemented for this study include following established procedures for the conduct of research and patient care at

the University of Pittsburgh, University of Pittsburgh Medical Center (UPMC) and respective study site as well as close monitoring of data and form completion.

All study staff will receive initial and ongoing training related to all study procedures to maximize adherence to the protocol and achieve high quality data. Additionally, all study investigators and staff will complete training on research integrity, human subjects research and good clinical practice.

16.2 Methods and Systems to Ensure Data Confidentiality and Subject Privacy

All research procedures will take place in the privacy of an examination room at all sites. Only the participant and research staff will be in the room during data collection and doors will be kept closed throughout the testing or intervention. During surgery, drapes and other barriers will be utilized, as is the standard of care, to prevent undue exposure of the participant. The collection of sensitive information from the subjects will be limited to the amount necessary to achieve the aims of the research.

Participant privacy and confidentiality will be maintained at all times. Consenting participants will be registered into the web-based EmPower Health Research data management software. EmPower has demonstrated compliance with privacy and security standards. To protect participant confidentiality, all participants will be assigned a unique database identification number. To ensure that the confidentiality of participant records is maintained, records associated with participation in this study will be indicated by only the case number. Information linking these case numbers with participant identity will be accessible only to the research team and will be stored in a locked file. Only the database ID number will be recorded on any paper forms or in electronic databases. Information collected for this study on any paper forms will be stored in a locked file cabinet and will be accessible only to the research staff involved in the study. Electronic data will be stored on a password protected secure network server. Access to computer-based files will only be made available to personnel involved in the study through the use of access permissions and passwords. Any data that is submitted for review to the DSMB, University of Pittsburgh Office of Research

Conduct and Compliance or the IRB will be linked only to the subject's database ID number. Participants will not be identified in any publications or presentation of the research results.

If a subject elects to withdraw from the study, any research data recorded for, or resulting from, participation in this research study prior to the date that he/she formally withdrew his/her data will continue to be used.

16.3 Data Sharing Agreement

After the last participant's final follow-up assessment at 24 months, the online database will be locked to create the full analyzable data set. A copy of the data used for the analysis will be frozen and the analytic code will be stored to allow for the replication of the results in the future.

The planned procedure on data access and sharing fulfills the requirements of the International Committee of Medical Journal Editors (ICMJE).[98] 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 DA 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 e-mail, ftp, or other mutually agreeable transmission method. The public-use version of the database will be made available two 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.

The 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 STABILITY 2 Trial will be registered with ClinicalTrials.gov prior to enrollment of the first participant. The STABILITY 2 Trial results will be placed on the ClinicalTrials.gov website within one year of the last enrolled participants final follow-up visit.

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APPENDICES

APPENDIX A: STUDY TIMELINE

Aim 1: Determine if graft type (QT, BPTB or HT) with or without a LET affects the rate of ACL clinical failure at 2 years after ACLR. ACL clinical failure will be defined by either graft rupture, symptomatic instability or persistent rotational laxity (asymmetrical positive pivot shift), at 2 years after ACLR.

Aim 2: Determine if graft type (QT, BPTB or HT) with or without a LET affects patient-reported symptoms, function and quality of life, performance-based measures of function and return-to-sports 2 years after ACLR.

Aim 3: Determine if graft type (QT, BPTB or HT) with or without a LET affects the rates of intervention-related donor site morbidity, complications and adverse outcomes 2 years after ACLR.

Aim 4: Determine if the use of a particular graft type (QT, BPTB or HT) with or without LET is a more cost-effective approach to ACLR.

Abbreviations: CCC = Clinical Coordinating Center; DCC = Data Coordinating Center; SS = Study Sites

		Year 1							Year 2	Year 3		Year 4	Year 5	
		Phase 1						Phase 2						
Major Tasks	**Sites involved**	1	2	3	4	5	6	7-12	13-24	25-30	31-36	37-48	49-57	58-60
Study Start-up	CCC, DCC, SS	X	X	X	X	X	X							
Subject Recruitment	CCC, DCC, SS						X	X	X	X				
Clinical Monitoring & Quality Control	CCC, DCC						X	X	X	X	X	X	X	X
Subject Follow-up	CCC, SS							X	X	X	X	X	X	X
Study Governance	CCC, DCC, SS							X	X	X	X	X	X	X
Analyze & Disseminate Results	CCC, DCC, SS													X

APPENDIX B: SCHEDULE OF EVENTS

	Baseline	Surgery	6 weeks	3 months	6 months	12 months	24 months	Unscheduled	PRN
Visit Windows	-6 weeks		+/- 2 weeks	+/- 1 month	+/- 1 month	+/- 1 month	+/- 3 months		
Consent	X								
Inclusion/Exclusion Criteria	X								
Demographics	X								
Operative Screening		X							
Group Allocation		X							
Surgery Forms		X							
PROs									
• ACL QOL	X*		X	X	X	X	X		
• KOOS	X*		X	X	X	X	X		
• IKDC-SKF	X*		X	X	X	X	X		
• Marx Activity	X*		X	X	X	X	X		
• EQ5D	X*		X	X	X	X	X		
• ACL - RSI					X	X	X		
• Sport Participation	X*								
• Return to Sport					X	X	X		
• Patient Experiences During Rehabilitation			X	X	X	X			
Clinical Assessment	X		X	X	X	X	X	X	
Pivot Shift Assessment (manual)	X	X		X	X	X	X	X	
Pivot Shift Assessment (App)		X		X	X	X	X	X	
Donor Site Adverse Events			X	X	X	X	X	X	
Radiographs- PA Standing Flexion	X						X		
Radiographs- Lateral view	X								
ROM & Muscle Function									
• Range of Motion (ROM)	X*		X	X	X	X	X		
• Strength Testing	X				X	X	X		
Performance Tests									
• Hop Test					X	X	X		
• Kinect V2 Drop Vertical Jump					X	X			
As Needed									
• Adverse Event									X
• Withdrawal Form									X
• Cost Forms for failed ACLs			X	X	X	X	X		

Estimated time duration per visit	**2 hr**	**5 hrs**	**30 mins**	**30 mins**	**1.5 hrs**	**1.5 hrs**	**1.5 hrs**	**.5 hrs**	

**Repeat if more than 6 weeks between baseline measurement and surgery.*

APPENDIX C: STUDY FORMS

APPENDIX D: DATA SAFETY AND MONITORING BOARD TABLES