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

1 KEY ROLES AND CONTACT INFORMATION

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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.

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.

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

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

- $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).

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

- 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

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,

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

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

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Co-PI: Volker Musahl, MD

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PI: Brian Waterman, MD

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PI: John Grant, MD

University of Kentucky
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Canadian Participating Sites

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Co-PI: Dianne Bryant

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Surrey, British Columbia, Canada
PI: Dory Boyer, MD

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.

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.

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

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.

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

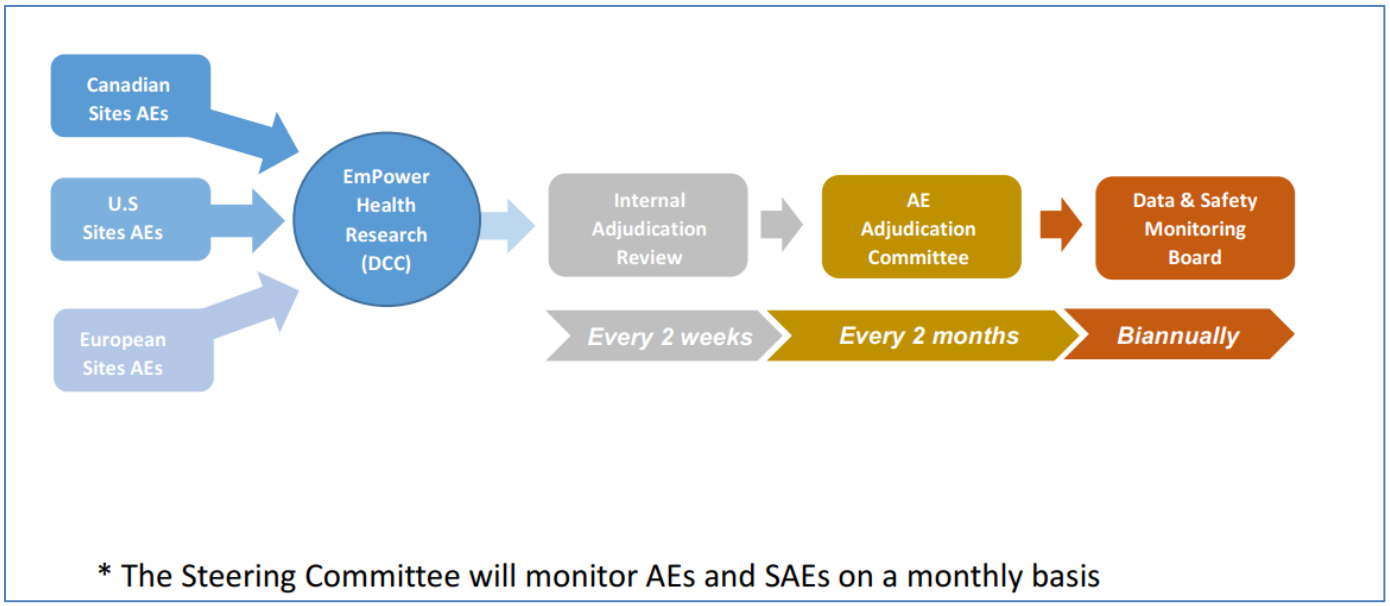
- Risks of Surgery: All subjects who agree to participate in this study have already elected to undergo ACL reconstruction. The risks associated with this surgery include complications related to anesthesia and those related specifically to the operation. Risks associated with an anesthesia include cerebrovascular 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.

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



- 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).

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.

APPENDIX D: DATA SAFETY AND MONITORING BOARD TABLES