

BMJ Open Single versus double hamstring tendon graft in anterior cruciate ligament reconstruction in the paediatric patient: a single-blind randomised controlled trial study protocol

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ABSTRACT

Introduction There is currently no clear indication in the literature regarding a single or double hamstring tendon (single bundle) autograft for anterior cruciate ligament (ACL) reconstruction in the paediatric patient. The primary aim of this single blind randomised controlled trial is to determine whether a single or double hamstring tendon graft ACLR leads to superior clinical outcomes postsurgery in paediatric patients with ACL injury.

Methods and analysis Single site, prospective, single blind, randomised controlled trial with two parallel treatment arms. 100 patients aged 10–18 years who present with an isolated ACL tear±meniscal injury, verified on MRI, will be randomly allocated to one of the two surgical groups. The primary outcomes will be side-to-side difference in anterior tibial translation and graft failure incidence 12 months postsurgery. Primary and secondary outcomes will also be assessed at 2-year and 5-year postsurgery.

Ethics and dissemination Results will be presented in peer-reviewed journals and at international conferences and disseminated to participants and healthcare professionals via newsletters and hospital presentations. This study is approved by the Children's Health Queensland Hospital and Health Service Human Research Ethics committee.

Trial registration number ACTRN12620001170910p; Australian New Zealand Clinical Trials Registry.

BACKGROUND

The diagnosis of anterior cruciate ligament (ACL) injury and reconstruction (ACLR) in skeletally immature patients is climbing at a rate significantly higher than adults.¹ The increased incidence has been attributed to several factors including a rise in competitive sport participation, decreased incidental activity, increased clinical awareness of a potential for ACL tear in this population, more comprehensive diagnosis and evaluation with MRI and a shift in clinical practice

STRENGTH AND LIMITATION OF THIS STUDY

- ⇒ This is the first study to compare these two anterior cruciate ligament reconstruction techniques in a randomised control trial in the paediatric patient assessing multiple outcome parameters.
- ⇒ Comprehensive evaluation of knee joint laxity, growth disturbance, lower limb function, muscle and graft morphology, patient-reported outcome measures and cost-utility in the paediatric patient.
- ⇒ One limitation is that follow-up at present is set for 5 years postoperatively—longer (up to 10 years) has been suggested in the literature.
- ⇒ A second limitation is that we are comparing surgical techniques and using only one type of autograft; it could be beneficial, given the acceptance of alternative graft choices in adults, to compare different graft choices in the paediatric population—however not the scope of this study.
- ⇒ A third limitation is the difference in tibial graft fixation between the two surgical techniques, which is necessary because the single hamstring tendon technique will result in a shorter graft compared with the double hamstring tendon technique

to provide early intervention.^{2–5} Most ACL injuries are non-contact with the mechanism and/or consequence of injury a combination of tibiofemoral joint external rotation and valgus.⁶ Historically, conservative management of ACL tears was the preferred clinical method in skeletally immature patients with bracing and modification of activities until skeletal maturity when ACLR could be safely performed.^{3,7} The weight of available evidence now supports reconstruction over conservative management with minimal complications^{8–12} and there is a growing body of evidence indicating that delayed ACL reconstruction increases the

risk of secondary articular injuries including irreparable meniscal tears, meniscal tears and chondral injuries in paediatric patients.^{13 14} Nonetheless, evidence regarding the ideal surgical technique for the skeletally immature patient is still lacking. Indeed, ACLR techniques that aim to reproduce the native ACL morphology with emphasis on graft placement within the native femoral footprint is well supported in the adult literature;¹⁵ however, the risk in the skeletally immature patient is the potential for growth disturbance.^{2 9 16}

Restoration of native anatomical laxity is a fundamental principle in ACLR. Indeed, suboptimal postoperative laxity may alter knee loading and have long-term consequences for the patient (ie, development of osteoarthritis). In studies of adults, positive rotational laxity results have been reported for double-bundle techniques, which use two smaller grafts to replicate the morphology of the native ACL.^{17–19} Nonetheless, a combined physeal-sparing, double-bundle method has led to less promising mid-term results in skeletally immature patients.²⁰ Regarding graft selection, there are a number of options including allografts, quadriceps tendon autografts, hamstrings tendon autografts, patellar tendon autografts and iliotibial band autografts. Nonetheless, there remains a lack of evidence surrounding the optimal graft selection when considering functional outcomes, failure rates and patient satisfaction for paediatric ACLR.²¹

At our institution, single bundle hamstring autografts are preferred for the skeletally immature patient using a single (semitendinosus tendon) or double (semitendinosus plus gracilis tendon) hamstring tendon graft. We acknowledge that hamstring tendon harvest is not without limitation or comparison (ie, quadriceps tendon, iliotibial band, various soft tissue allografts). In studies of adults, harvest of the semitendinosus and gracilis tendons has led to postoperative donor muscle atrophy as well as proximal retraction of the musculotendinous junction.^{22–24} This retraction is believed to occur until the regenerated tendon reaches an attachment site,²⁵ which may take longer than 2 years,²³ or it may not occur at all.^{22 26} These changes in donor muscle-tendon properties and impaired capacity to transmit force to the skeleton after medial hamstring harvest might be expected to contribute to the knee muscle weakness that has been reported in flexion^{23 27–30} and internal tibial rotation^{31 32} at up to 2 years after surgery. In a study of muscle and tendon morphology of 20 adult patients who underwent ACLR with hamstring autograft, Konrath *et al*³³ found only 35% of patients showed regeneration of both the semitendinosus and gracilis tendons. Furthermore, combined hamstring muscle volumes on the surgical side were reduced by 12%, although 7% larger volume was observed in the surgical limb for the biceps femoris muscle. The difference in volume, peak cross-sectional area (CSA) and length of the semitendinosus and gracilis correlated significantly with the deficit in knee flexion strength. To the authors' knowledge, no previous research has assessed muscle morphology in donor site muscles

or compared functional outcomes between single and double hamstring tendon graft methods following ACLR in paediatric patients.

Aims and hypotheses

There is currently no clear indication in the literature regarding a single or double hamstring tendon (single bundle) autograft for ACLR in the paediatric patient. The primary aim of this single blind randomised controlled trial is to determine whether a single tendon, single bundle ACLR or a double tendon, single bundle ACLR leads to superior clinical outcomes postsurgery in paediatric patients with ACL injury. Primary outcome measures will include graft failure and side to side difference in graft laxity.³⁴ Secondary outcome measures will investigate growth disturbance rates, passive and dynamic knee joint function (range, strength), lower limb function (power, agility, stability), muscle and ligament morphology and patient-reported outcomes. The primary timepoint will be 1-year postsurgery and secondary timepoints will be 2-year and 5-year postsurgery. We hypothesise that compared with double hamstring tendon graft ACLR, patients who receive a single hamstring tendon graft ACLR will have reduced rerupture rates and smaller side-to-side laxity deficits.

METHODS AND ANALYSES

Study design and setting

We will conduct a single-site, prospective, single blind, randomised controlled trial with two parallel treatment arms. The study will be conducted in the Queensland Children's Hospital (QCH), the only paediatric focused quaternary hospital covering a population of 5 million people. We will offer recruitment to patients enrolled in the Australian Paediatric ACL Injury Registry at the QCH site. Inclusion will start in July 2021 and is expected to finalise in July 2023, which will allow for read-out of the primary endpoint in July 2024. The proposed flow of patients thought the trial is displayed in figure 1.

Recruitment strategy

All consecutive patients between the age of 10 and 18 who present to the orthopaedic outpatient's clinic at the QCH with an isolated ACL±meniscal injury will be provided with a recruitment package during their outpatient appointment. A follow-up phone call will be made to ensure that potential participants received the study information.

Inclusion and exclusion criteria

Potential participants will be excluded if they have:

1. Concomitant posterior cruciate ligament injury.
2. Collateral ligament instabilities of grade I or greater (2–5 mm).
3. Bilateral ACL deficiency.
4. Combined knee surgery with high tibial osteotomy or medial patellofemoral ligament.

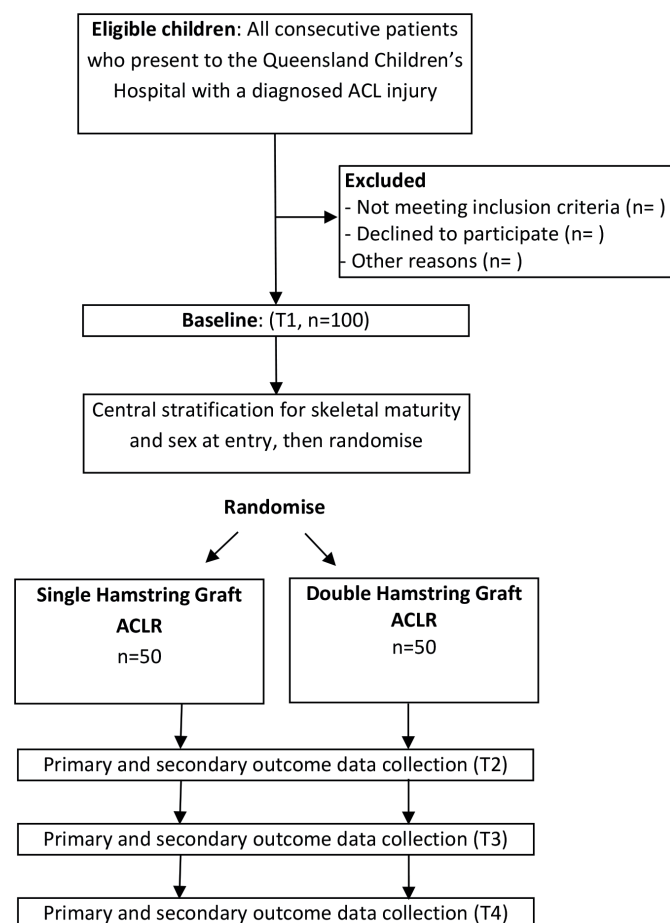


Figure 1 Experimental design flowchart according to the Consolidated Standards Of Reporting Trials (CONSORT) statement guidelines. ACL, anterior cruciate ligament; ACLR, ACL reconstruction.

5. Evidence of early knee osteoarthritis on MRI.
6. Previous knee surgery on the affected side.
7. Chronic musculoskeletal conditions.
8. BMI > 35.
9. Surgeon recommendation for an extraphyseal technique for ACLR.

Study procedure

Potential participants will first be screened against the inclusion criteria in the orthopaedic outpatient clinic at the QCH. Following baseline testing (T1 MRI), eligible participants will be randomised into one of the two surgical groups. The surgeons performing the surgeries will be well versed in both ACLR techniques and will be advised of the patient's randomised surgical technique just prior to the surgery and will proceed accordingly.

Patient and public involvement

Patients were not involved

- In the development of the research question.
- In the decision of the outcome measures.
- In the study design.
- In the recruitment to and conduct of the study.
- In how the results will be disseminated.

- In patient burden assessment.

Surgical techniques

Two senior surgeons will perform all the randomised ACLR surgeries as detailed below. Both have been allowed a surgical learning curve of 20 cases (minimum) before the start of the trial. So that there is no variability among equipment used, Smith & Nephew (S&N) will be used for the two techniques: single hamstring graft technique will use UltraButton+round ExtendoButton; double hamstring graft technique will use Endobutton+Biosure Regenesorb screw.^{35 36} Patients who exhibit a pivot-shift of grade 2 or greater following ACLR will be considered for an additional lateral-tenodesis.³⁷

Tendon harvest and graft preparation

The semitendinosus hamstring tendon alone will be harvested for the single graft technique and the semitendinosus +gracilis hamstring tendons will be harvested for the double graft technique. A tendon stripper will be used to release the tendons from their proximal attachment via a standard push technique to an appropriate length.

Graft preparation for the single hamstring technique will involve tripling the single semitendinosus tendon over two S&N UltraButton loops (with a round ExtendoButton being attached to the tibial UltraButton). Graft preparation for the double hamstring technique will involve doubling the semitendinosus+gracilis tendons over one S&N Endobutton loop. For both methods, the ends of the tendon complex are sutured via a whip-stitch technique using a #1 Ethibond suture on a J-needle. The prepared tendon complex will be set aside and soaked in a Vancomycin laden Raytec sponge and placed into the soft tissue tunnel where the hamstring tendons were harvested.

Once prepared, the graft is measured for both length (to ensure that the graft will adequately span the knee joint and sufficiently pass through both tunnels) and diameter (to determine the required femoral and tibial tunnel diameters for reaming).

Knee arthroscopy

The knee arthroscopy is performed using standard lateral and medial portal sites. All compartments of the knee are identified and examined for any additional pathology (chondral injuries, meniscal tears, etc), the notch is identified, and femoral and tibial attachments are identified. The pathological ACL is identified, and its stump or scarred remnant is debrided sufficiently. As much of the tibial stump/footprint is left to allow for optimal tibial tunnel placement and to aid in revascularisation of the graft,^{38 39} however, enough is debrided away, so that it does not interfere with passing of the graft or cause impingement. The lateral wall of the notch is cleared with either a shaver or via radiofrequency ablation and prepped with a curette. The fat pad is debrided to allow for adequate visualisation. If any meniscal pathology is identified, it is addressed prior to the ACLR.

Tunnel drilling

The femoral tunnel is drilled first. Once the notch has been cleared, the optimal position is determined—this is usually 30° lateral from the roof of the notch (11 o'clock in the right knee, 1 o'clock in the left knee) at the point 5 mm anterior to the posterior cortex of the notch.³⁶ The patient's knee is positioned into full flexion (normally 120°) to allow for adequate placement of the guide pin at the desired position. The pin is drilled through the femur and pushed through the soft tissues and skin of the anterolateral thigh. The desired position is achieved using an Acuflex offset drill guide and is reviewed on scope. In skeletally mature patients, the pin should be directed approximately 30° anteriorly and 30° laterally, with respect to the femoral long axis, however, in the younger patient with open physes the pin is directed as vertical as possible to ensure that the physis and subsequent growth is disrupted as little as possible.⁴⁰ With the knee still in full flexion, the femoral tunnel is drilled first with a 4.5 mm drill through the lateral femoral cortex, this tunnel is measured to determine tunnel length, then the preliminary tunnel is reamed to desired diameter as determined by graft measurement.

The tibial tunnel is positioned using an S&N ACUFEXTM drill guide. The tip of the guide is passed through the anteromedial portal and positioned to create a tunnel that enters the joint through the posteromedial portion of the ACL footprint.^{13 41} In the skeletally immature patient, the length and angle of the tunnel may be more variable as the surgeon will target the drill tunnel perpendicular to the growth plate to minimise the likelihood of growth disturbance. A 2.4 mm drill-tipped guide wire is used to establish the line of the tibial tunnel using the jig. Using the positioned guidewire, this tunnel is reamed to desired diameter as determined by graft measurement earlier. The tunnel is again measured.

Both femoral and tibial tunnels are smoothed cleared of any debris using a shaver to allow for smooth graft passage in the subsequent steps. The graft is marked at either end using a sterile marking pen factoring in tunnel lengths and desired graft length spanning the knee joint. A nylon suture is threaded into the slot of a passing pin. The loop end of the suture is held externally, the passing pin is drawn into the joint and out through the femur, drawing the free ends of the suture out through the lateral thigh.^{35 36}

Single tendon, single bundle, graft passing and fixation

The nylon suture is pulled through the tibial tunnel, so that the loop end is exiting out of the tibial tunnel. The graft is orientated and the Ethibond sutures are placed through the nylon loop. The Ethibond sutures are passed through the tibial and femoral tunnels and out of the skin of the anterolateral thigh. The arthroscope is placed into the knee joint and the Ultrabutton loop and graft are pulled into the femoral tunnel under vision to the line drawn on the graft from previous measurements. The Ultrabutton is toggled and flipped on the femoral

side. The graft is held taught and the Femoral UltraLoop is reduced pulling the graft into the femoral tunnel to its desired length (~20 mm). The knee is then brought out to 30–40° flexion, and the tibial UltraLoop is reduced to pull the graft into the tibial tunnel. Final tensioning of the graft is done with knee extended to 0° flexion the ExtendoButton is secured down to the tibia.³⁵

Double tendon, single bundle, graft passing and fixation

As above, however, in this case, an Endobutton loop is used as opposed to the Ultrabutton loop. The graft is held taught with the Ethibond suture tails on the tibial side of the graft and, the knee is cycled through flexion/extension a number of times and the knee is then brought out to 20–30° flexion, the assistant is asked to secure the foot as well as place anterior directed force the distal femur. A wire is inserted behind the graft in the tibial tunnel and a Biosure Regenesorb screw is fully advanced and secured to fix the graft into the tibial tunnel.³⁶

Postoperative care and rehabilitation

The knee is placed in a Richard splint in full extension. In-patient (oral analgesia with option for intramuscular opioid injection) and discharge medication (oral analgesia only) doses as per individual patient requirements. The patient is seen by the physiotherapist day 1 postoperatively for assessment and treatment as per the Children's Health Queensland ACL Post-operative Rehabilitation Guidelines (online supplemental file 1).

In cases where meniscal repair was concomitantly performed weight-bearing and range of motion (ROM) restrictions are surgeon dependent based on extent and location of repair, but the majority will be non-weight bearing and have ROM restricted for 6 weeks postoperatively. These patients will all be discharged in an ROM brace with increasing ROM allowed over the 6-week period as per surgeon advice. Following 6 weeks, the brace is removed and patients can complete ROM and full weight bearing.

All patients will undergo rehabilitation as per the Children's Health Queensland ACL Reconstruction Rehabilitation Guidelines for Physiotherapists will be advised to completely abstain from full return to sports for at least 12 months and prior to return, they will be required to meet phase 5 criteria of the Rehabilitation Protocol (online supplemental file 1).

Standard medical imaging protocol

All patients enrolled into the randomised controlled trial obtain the following standardised imaging in accordance with current clinical practices at the QCH.

Preoperative medical imaging:

- ▶ Plain X-rays of the affected knee, in both coronal and sagittal projections
- ▶ Bilateral anterior–posterior lower limb weight-bearing X-rays to assess leg length and coronal plane alignment (ie, mechanical axis deviation, lateral distal femoral angle, medial proximal tibial angle).

- ▶ Wrist or elbow anterior–posterior and lateral X-rays for assessment of patient's bone age.
 - ▶ MRI to assess chondral status, menisci status, ACL or graft morphology, growth plate status.
- Day 1 postoperative medical imaging:
- ▶ Plain X-rays of the affected knee, in both coronal and sagittal projections
- 1, 2 and 5-year postoperative medical imaging:
- ▶ Plain X-rays of the affected knee, in both coronal and sagittal projections
 - ▶ Bilateral anterior–posterior lower limb weight-bearing X-rays to assess leg length and coronal plane alignment (ie, mechanical axis deviation, lateral distal femoral angle, medial proximal tibial angle).
 - ▶ MRI to assess chondral status, menisci status, ACL or graft morphology, growth plate disturbance, position of tunnels and hardware.

Study outcome measures

Primary outcomes

1. Passive anterior–posterior knee laxity: side-to-side difference in anterior tibial translation will be measured by a GNRB device attached to the patient's leg, measuring tibiofemoral displacement by performing an automated Lachman test and obtaining a force–displacement curve.^{42 43} Three measurements will be made on each knee, and the final value will be recorded as per the GNRB guidelines. Anterior–posterior tibiofemoral laxity will be categorised as a 'low' side-to-side difference (<3mm), a 'moderate' side-to-side difference (3 to 5mm) or a 'severe' side-to-side difference (>5mm or ruptured). The manual Lachman test and the pivot-shift test will also be graded according to International Knee Documentation Committee guidelines.⁴⁴
2. Graft failure incidence: the incidence of graft failures will be quantified at T2, T3 and T4. Failure in this study will be defined by a side-to-side difference in anterior–posterior knee laxity >6mm or a pivot shift ≥grade 2.
4. Muscle-tendon morphology and quality: in addition to the standardised imaging protocol for ACL patients at the QCH, additional medical imaging protocols will be performed at T1, T2, T3 and T4 to assess musculotendon volume, CSA and length of quadriceps and donor muscles in accordance with.^{33 33}
5. Graft morphology: a paediatric-trained radiologist consultant will be reviewing and reporting on the T2, T3 and T4 MRI scans. The three-dimensional graft structures will be segmented in Mimics Research 20.0 (Materialise, Belgium) from each participant's MRI scan. Graft structure and morphology will be assessed for CSA and integrity, both within the tunnels and spanning the knee joint.⁴⁶
6. Patient-reported outcome measures: patient-reported outcome measures will be collected at T1, T2, T3 and T4 and will include the Pedi-IKDC (paediatric international knee document committee),⁴⁷ HSS Pedi-FABS (hospital for special surgery paediatric functional activity brief scale)⁴⁸ and Paediatric KOOS (knee injury and osteoarthritis outcome score).⁴⁹
7. Physical/functional outcome measures will be collected at T2, T3 and T4 and will include: (1) Y-balance test, (2) forward step-down test, (3) double jump for distance, (4) vertical jump for height, (5) single hop for distance, (6) cross-over hop for distance.
8. Postoperative pain: the patient/family will be required to complete pain diaries and record medication usage for the first 2 weeks after the surgery.

Secondary outcomes

1. Growth disturbance incidence and type: in accordance with the previous assessments of growth disturbances, following ACLR, measurements will be recorded at T2, T3 and T4, and limb length will be assessed. A limb length discrepancy or angular malformation will be classified as a difference of 1cm and/or 3° between the operated and non-operated limbs, respectively.^{9 45}
2. Knee joint ROM: the flexion or extension deficit will be calculated at T1, T2, T3 and T4 by subtracting the respective degrees of the operative knee from those of the contralateral knee.
3. Isokinetic strength evaluation: an isokinetic dynamometer (Humac NORM, Massachusetts) will be used to evaluate knee flexion/extension concentric strength as well as internal/external tibial rotation concentric strength on both the surgical and contralateral lower limbs. For knee flexion strength measurements, participants will be seated with their pelvis, chest and thigh

stabilised using Velcro straps, their hip flexion angle set at 90 degrees and their ankle flail and held in place above the medial malleoli to the Humac NORM shank with a Velcro strap. At T1, flexion/extension isokinetic concentric strength tests will be performed at an angular velocity of 60 deg/s through the patient's available knee flexion ROM and isometrically at standardised angles within the patient available knee flexion ROM. At T2, T3 and T4, repeat T1 knee flexion/extension assessment at 60 and 180°/s and additionally perform knee internal/external rotation isokinetic concentric strength tests at 60 and 180°/s, across an ROM between each participant's maximum comfortable internal/external rotation limits. Testing will be performed on both the non-operative and operative limbs, with the order of limb tested randomised to negate any fatigue effects. In addition to individual peak strength measurements, agonist/antagonist strength ratios will be calculated using the peak strengths for flexion/extension and internal/external tibial rotation.

4. Muscle-tendon morphology and quality: in addition to the standardised imaging protocol for ACL patients at the QCH, additional medical imaging protocols will be performed at T1, T2, T3 and T4 to assess musculotendon volume, CSA and length of quadriceps and donor muscles in accordance with.^{33 33}
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7. Physical/functional outcome measures will be collected at T2, T3 and T4 and will include: (1) Y-balance test, (2) forward step-down test, (3) double jump for distance, (4) vertical jump for height, (5) single hop for distance, (6) cross-over hop for distance.
8. Postoperative pain: the patient/family will be required to complete pain diaries and record medication usage for the first 2 weeks after the surgery.

Sample size determination

Our sample size calculations are based on a three-level outcome variable comparing anterior–posterior tibiofemoral laxity in the reconstructed and unaffected knee ('low' side-to-side difference (<3mm), 'moderate' side-to-side difference (3 to 5mm) or 'severe' side-to-side difference (>5mm or ruptured) as differences of this magnitude were considered to be clinically important.^{44 50} Pilot data

from our hospitals' perspective ACL injury registry classified 74% as low, 7% as moderate and 19% as severe or rupture, and we assume that these percentages will hold in our single hamstring tendon graft ACLR group. We expect that in the experimental arm, the equivalent probabilities will be 93%, 2% and 5%. This is equivalent to specifying a proportional OR of 0.07. With $\alpha=0.05$ and power=80%, we are required to record outcome data on 43 participants in each group to detect a between-group difference of this size or greater. To increase the power of the study and allow the maximal tolerated level of dropout at T2, 100 patients will be randomised.

Randomisation

Participants will be randomly allocated by the Griffith University randomisation service to the single hamstring tendon graft ACLR group or the double hamstring tendon graft ACLR intervention group. Participants will be stratified according to skeletal maturity and sex to minimise confounding bias and a randomly varied block size will be used to ensure participants are more evenly allocated throughout the entire trial. The Griffith University randomisation service will conceal group allocation from the study investigators until the participant has been enrolled and baseline data have been collected.

Blinding

To minimise ascertainment-bias, this trial is single-blinded, where patients are blinded to surgical technique. External entry points for surgery are equivalent for both surgical techniques and, therefore, patients will not be able to guess group allocation. Due to the nature of the intervention, the treating surgeons cannot be blinded to group allocation. Furthermore, it is not feasible to blind the postoperative management team as surgical notes will be reviewed prior to follow-up appointments.

Data management

The percentage of eligible participants successfully recruited, and numbers of eligible who choose not to participate will be recorded along with their age and sex. Participant retention will be recorded throughout the trial period. Paper documents and files will be deidentified, labelled with a participant identification code and stored in a locked filing cabinet. Consent forms and demographic information will be kept separately, also in a locked filing cabinet. The list of patient identification codes and all other electronic data will be stored securely through a Research Electronic Data Capture database (<https://www.project-redcap.org/software/>) on a secured network accessible only to the registered members of study team.

Statistical analysis plan

Standard principles for RCTs will be followed, and primary analyses will be conducted using between-group comparisons on all participants on an intention-to-treat basis. There is a small risk that the surgeon may deem a harvested hamstring tendon inadequate for a single

tendon graft (see safety consideration below) and, therefore, need to break randomisation. To account for this potential, a secondary, per-protocol analysis will be used to assess the effect of treatment received and models will be adjusted for potentially confounding variables if necessary. The primary timepoint will be after 1 year, and the primary comparison will be the quantitative anterior-posterior laxity results between the two surgical techniques. Effect of surgical technique will be assessed using ordinal logistic regression with technique (single/double) included as the main effect. To determine between-group differences at 2 and 5 years postsurgery, we will employ mixed effects ordinal logistic regression models with patient included as a random effect, and time (1, 2 and 5 years) and surgical technique included as main effects and a time-by-technique interaction included as fixed effects. For continuous outcomes, comparison will be by linear regression models. Where continuous data do not meet linearity assumptions, as assessed by inspection of boxplots and the Shapiro-Wilk test, it will be assessed using non-parametric methods such as median regression. For dichotomous outcomes, comparison will be by logistic regression models. For count outcomes, comparison will be by Poisson regression models. Significance will be accepted at $p<0.05$. Sensitivity analyses to assess the effect of missing data will be undertaken on an outcome-by-outcome basis using MAR (multiple imputation) or NMAR (using pattern-mixture models) according to the pattern of the missing data.

Cost-utility analysis

Utility values will be obtained from the EQ-50 (with a 1-week recall) at baseline (T1), and 1-year, 2-year and 5-year postsurgery and will be transformed into Quality of life-adjusted years with means and variances. The health economic evaluation will be determined using the incremental cost-utility ratio. Resource utilisation will be determined from hospital finance reports related to the initial stay in hospital and using a patient (or parent) administered case report form that documents information on patient and caregiver demographics, educational and employment information, used of health resources (ie, visits to general practitioners, physiotherapists, emergency department, patient expenses related to medication and out-of-pocket transportation costs to receive additional medical care, patient or caregiver days off work) using a health resource utilisation questionnaire. Furthermore, the following health service utilisation data will be collected:

- Details of hospital admissions, outpatient episodes and emergency department presentations including episode, clinical, demographic and costing information (such as diagnosis, procedures, length of stay, cost of encounter, etc) for the duration of the study and 12 months prior to consenting—from routinely collected hospital and emergency department administrative data.

- Medicare Benefits Schedule claim details, costs and service provider information and Pharmaceutical Benefits Scheme item description, costs and prescribing details—from Services Australia.

Safety, adverse events and complications

Surgical treatment and clinical follow-up will be conducted in accordance with current clinical practices for the participating surgeons at the QCH. Intraoperatively, if a harvested hamstring tendon is deemed to be inadequate (ie, <6 mm in diameter and/or of poor quality) the decision may need to be made to convert from the single to the double hamstring graft technique. Presence of meniscus injuries, defined by the necessity to repair or partially resect tissue due to meniscus instability, will be determined during ACLR. Any adverse events occurring during preoperative and follow-up testing sessions will be recorded on an Excel spreadsheet. Minor adverse events are classified as muscle soreness, muscular fatigue or mild injuries that do not require medical attention. Major adverse events are conditions that require medical attention, such as a fracture, equipment failure or infection and would likely result in the child discontinuing the testing session. All adverse events, regardless of their severity, will be documented and reported to a senior study advisor and if serious, escalated to the ethics committee with information reported to the child's treating physician as necessary. Risk assessments, including strategies to minimise adverse events, will be completed prior to participation in the testing session. For all onsite testing, participants will be directly supervised by an investigator who is trained to deliver first aid and CPR. Postoperative complications (ie, thrombosis, infection, rupture) will be recorded. A data monitoring committee will convene every 6 months to monitor patient safety and treatment efficacy during the surgical stage of the trial. The DSMB membership comprising a Chair, Medical Monitor and Secretary, will be independent to the trial and will not participate as investigators of the trial or have any financial, scientific or other conflict of interest with the trial.

Ethics and dissemination

Full ethical approval for this study has been obtained by the Children's Health Queensland Human Research Ethics committee (HREC/21/QCHQ/73043, Protocol V.2.1 29072021). The study will be conducted in agreement with the Helsinki declaration. Written and informed parent/guardian consent will be obtained prior to study enrolment by the study investigator. Verbal assent will be obtained from children under the age of 12 years and written assent will be obtained from children who are 12 years and older. This trial is registered with the Australian New Zealand Clinical Trials Registry and the study protocol is reported according to the Standard Protocol Items: Recommendations for Intervention Trials statement⁵¹ (see Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist online supplemental file 2). Changes to the study protocol will

be communicated to the ethics committee and updated on the trial registry. The primary study results will be submitted for publication to an international, peer-reviewed journal and disseminated to participants and healthcare professionals via newsletters and conference presentations.

DISCUSSION

This study protocol describes a prospective randomised controlled trial design to determine whether a single or double hamstring tendon graft ACLR leads to superior clinical outcomes at 1, 2 and 5-year postsurgery in skeletally immature patients with ACL injury. The International Olympic Committee (IOC) has advocated for further research with regards to efficacy of graft choice and different surgical reconstruction techniques.¹³ We aim to add to the current knowledge putting to test these two reconstruction techniques with long-term clinical follow-up and imaging. To our knowledge, this will be the first RCT study to investigate two different randomised ACLR techniques in the skeletally immature patient with standardised rehabilitation protocols, clinical follow-up and postoperative imaging to track the patient's progress and assess graft and intra-articular integrity.

The surgical procedures have been selected based on commonly used reconstruction techniques using hamstring autograft for the skeletally immature patient. The difficulty is that within the literature or among surgeons that there is no true consensus for which has better long-term results with regard to both graft longevity and patient recovery postoperatively.⁴⁰ The literature supports other graft choices in adults such as quadriceps tendon or patella tendon,^{52 53} however, the paediatric literature remains scarce. At present, hamstring autograft is the most common technique used to reconstruct the ACL in the skeletally immature patient. As with all injuries, options exist for both operative and non-operative treatment of ACL injuries in the paediatric population; however, the literature supports early reconstruction to avoid the potential consequences of arthritis and consequent chondral and meniscal pathology.¹³

Primary outcome measures will include graft failure and graft laxity. Secondary outcome measures will investigate growth disturbance rates, passive and dynamic knee joint function (range, strength), lower limb function (power, agility, stability), muscle and ligament morphology and patient-reported outcomes at 1, 2 and 5-year postsurgery. Children with open or closed physes and children of differing sex are likely to respond differently to the intervention. For this reason, we will stratify randomisation enable equal distributions across intervention groups. Children with meniscal tears at baseline may be managed differently, and, for this reason, results may also be stratified on this basis.

A limitation of this study is that our follow-up at present is set for 5 years postoperatively—the IOC has suggested that follow-up goes as long as 10 years so that long-term

knee-health and quality of life can be captured.¹³ A second limitation is that we are comparing surgical techniques and using only one type of autograft; it could be beneficial, given the acceptance of alternative graft choices in adults, to compare different graft choices in the paediatric population.

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Guideline

ACL Reconstruction Rehabilitation Guidelines for Physiotherapists

Children's Health Queensland

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Executive sponsor	Executive Director of Allied Health			Effective date	17/10/2018
Author/custodian	Director of Physiotherapy			Review date	17/10/2022
Supersedes	New				
Applicable to	Physiotherapists treating adolescent ACL patients				
Authorisation	Executive Director Clinical Services (LCCH)				

Purpose

These rehabilitation recommendations are a guide for clinicians treating paediatric and adolescent patients who have undergone an anterior cruciate ligament (ACL) reconstruction.

Related documents

Procedures, Guidelines, Protocols

- [CHQ-WI-65671-Post-Operative Management and Patient Flow of Patients Following ACL Reconstruction](#)
- CHQ ACL Reconstruction Rehabilitation Guidelines for Patients

Guideline

Rates of ACL re-rupture are much higher in the paediatric population (Clare L Ardern et al., 2018), so additional caution is required in the management of this patient group. Ensure sound clinical reasoning is used and only progress your patient when you feel confident in their ability.

General Guidelines:

- Rehabilitation in this population is *slower* than in adults.
- Rehabilitation includes five phases and continues for 12 months following surgery.

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- Exercise bike can commence at three months.
- Swimming with a pool buoy can commence at four months and progress to kicking at five months.
- Swimming with flippers can commence at six months.
- Running in a straight line can commence at four-six months.
- Return to sport is not recommended before 12 months.

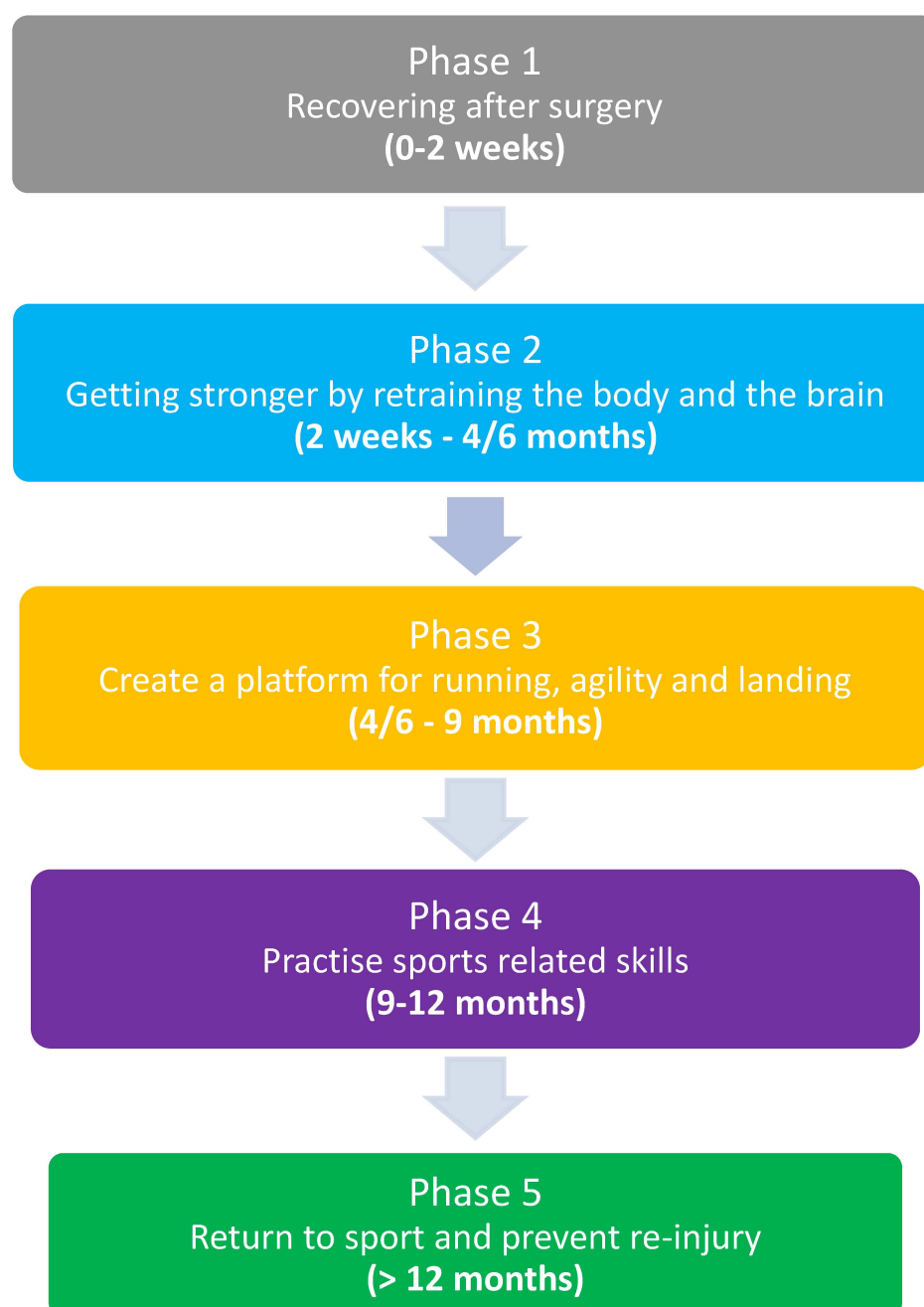
Do

- Ensure to individualise each patients program based on surgeon's recommendations.
 - Meniscal repairs will have period of Non-Weight Bearing (NWB) (generally six weeks post-op) and therefore be behind standard milestones.
 - Slow to progress or non-compliant patients should be encouraged but not progressed beyond where they are capable, irrespective of amount of time post-op.
 - Over-enthusiastic/impatient patients may require additional counselling to avoid them returning to dynamic activities and sports prematurely.
- Encourage swelling and pain management initially; this will impact the longer-term rehabilitation outcomes.
- Give patients and parents advanced knowledge of length and expectations of the rehabilitation; this should be part of the informed consent process.
- Aim to see the patient regularly in the first six months and at least monthly thereafter.
- Contact surgeon or LCCH Physiotherapy Department with any concerns, queries or difficulties

Don't

- Discharge the patient to progress on their own prior to 12 months. If you cannot provide this level of service, please refer back to CHQ.
- Progress the patient based purely on the protocol. If the knee is not stable or strong enough for an activity, utilise extra exercise/therapy to achieve this.
- Commence open chain weighted exercises.

The Five Phases of ACL Rehabilitation



Phase 1 Recovering after surgery (0-2 weeks)

- Knee extension/Richards splint to be worn at all times in these initial two weeks. Depending on surgeon preference the brace may be straight or bent to 30°, either way exercises are to be performed on top of the brace.
- Patient allowed to WBAT (if no meniscal repair) but advise crutch use until two-week post-op review.
- Dressings can be debulked Day 1 prior to discharge depending on wound ooze. Replace dressings with double layer Tubigrip®.

In this phase, the emphasis should be on swelling control and normalising gait with crutches.

Exercise suggestions

- static quads
- static hamstrings
- co-contractions quads/hamstrings
- glute squeezes
- heel slides

Outcome measures to guide progression to Phase 2

Patient outcomes at 2 weeks	Physiotherapist review at 2 weeks
• ↓↓swelling	• stroke test (Sturgill, Snyder-Mackler, Manal, & Axe, 2009) 0 - 1+
• straight knee	• knee extension = 0°
• knee flexion ≥ 90°	• knee flexion = 90-100°
	• quadriceps lag test = 0° to 5°

(Cooper, 2015)

Early Phase 2

Getting stronger by retraining the brain and the body (2- 6 weeks)

The graft is at its **weakest** 6-10 weeks post-op (C. L. Ardern, Webster, Taylor, & Feller, 2011). It is particularly important during this period that the patient adheres to recommended guidelines.

Exercise suggestions

Range of motion <ul style="list-style-type: none"> heel slides prone assisted knee bend stretches prone knee hangs hamstring and calf stretches 	Manual therapy <ul style="list-style-type: none"> patello-femoral mobilisations
	Balance and proprioception <ul style="list-style-type: none"> balance: single leg stance → wobble board gluteus medius activation in standing
Cardiovascular exercises <ul style="list-style-type: none"> gentle hydrotherapy; exercise in the pool is optional once surgical wounds have healed. This may comprise of walking in water, mini squats, calf raises, lunges, and stretches. <p>DO NOT commence swimming</p>	Strength <ul style="list-style-type: none"> VMO activation co-contractions of quads/hamstrings in isolation and with weight bearing exercises bridging calf raises (bilateral progressing to unilateral) wall sits step ups hamstring wobbles hamstring curls (unresisted) mini squats → progressed as able mini lunges → progressed as able

(Cooper, 2015)

Outcome measures to guide progression to Later Phase 2

<ul style="list-style-type: none"> no knee joint effusion 	
<ul style="list-style-type: none"> knee flexion 	125+ degrees, still maintain full knee extension
<ul style="list-style-type: none"> calf raises 	10x minimal support, knee fully extended
<ul style="list-style-type: none"> balance testing 	Able to hold terminal knee extension during single leg stance

Later Phase 2

Getting even stronger by retraining the brain and the body (6 weeks – 4/6 months)

Exercise suggestions

<p>Strength</p> <p>6 weeks</p> <ul style="list-style-type: none"> • step ups/downs • seated knee curls with TheraBand® • squats and lunges with light weights • single leg squats • eccentric hamstring drills • core stability exercises <p>8 weeks (aim for full range of motion)</p> <ul style="list-style-type: none"> • increase depth squats/lunges • over edge of bed flicks and wobbles • chair bridging (bilateral) <p>10-12 weeks</p> <ul style="list-style-type: none"> • split squats • walking lunges and weight • lower limb stretches 	<p>Gym program</p> <ul style="list-style-type: none"> • leg press (avoid resisted knee extension exercises - this loads the graft) • incline leg press • seated hamstring curls → prone hamstring curls <p>Gym program guidelines (Lloyd et al., 2014)</p> <ul style="list-style-type: none"> • should be always supervised to ensure correct technique • remember equipment is designed for adult sizes and have weight increments that can be too large for younger adolescents. Free weights are preferable in this situation. • explosive and rapid lifting of weights is not recommended • strength-training for adolescents should begin with low-resistance exercises until proper technique is perfected. When 8 to 15 repetitions can be performed, it is reasonable to add weight in 10% increments. • for strength gains workouts need to be at least 20 to 30 minutes long, take place 2 to 3 times per week, and continue to add weight or repetitions as strength improves.
<p>Balance and proprioception</p> <ul style="list-style-type: none"> • Single Leg Stance (SLS), wobble board etc • flicks and wobbles • single leg rebounder balance 	
<p>Cardiovascular exercises</p> <ul style="list-style-type: none"> • exercise bike with increasing resistance (after 3months) • pool running with vest or flotation belt • CV training- intervals • rower • stepper/versa-climber (90' only, not meniscal repairs) 	

(Cooper, 2015)

Phase 3

Create a platform for running, agility and landings (4/6 - 9 months)

Outcome measures to guide progression to Phase 3	
• single leg bridge test (repetitions)	80% of other leg
• single leg calf raises on a step (repetitions)	80% of the other leg
• side bridge endurance test (side plank) (hold time)	80% of other leg
Functional alignment test • single leg squat test- 5x squats on 20cm step with crossed arms	Can be rated 'good', 'fair', 'poor'
Unipedal stance test • SLS with other leg raised and arms crossed	• Eyes open = 43 seconds • Eyes closed = 9 seconds

Returning to running is often one of the patient's greatest goals, however it embodies a high-risk. Rehabilitation must be thorough, and individualised to the child's physiological and psychological maturity to achieve successful outcomes. Emphasise exercises that facilitate dynamic lower limb alignment and biomechanically sound movement patterns and don't be afraid to slow children down if you do not think they are meeting milestones.

Exercise suggestions


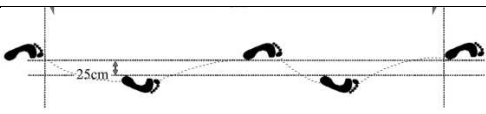
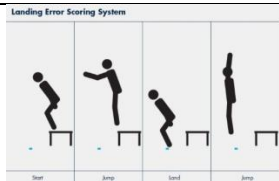
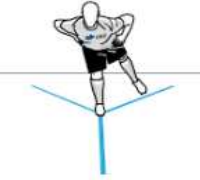
Continued from previous Continue with lower limb strengthening and core exercises: <ul style="list-style-type: none"> • walking lunges and weight • clock lunges • single leg squats, progress to weighted • hamstring curls (TheraBand or weights) • single leg bridging-on ball pluhamstring curls • forward and side planks 	Balance and proprioception <ul style="list-style-type: none"> • rebounder jogs and stops (two pillows at home)
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<p>Agility and plyometric exercises</p> <ul style="list-style-type: none"> • jumping on spot • jumping forwards/backwards • jumping side-to-side <p><i>Progress to</i></p> <ul style="list-style-type: none"> • 90 degree turns • hopping drills (jump-stop, hop-stop, from 10cm to 20cm etc) • obstacle hopping, grid hopping • step running • ladder running • box jumps <p><i>Progress to</i></p> <ul style="list-style-type: none"> • single leg landings with perturbations 	<p>Pool program</p> <ul style="list-style-type: none"> • can start freestyle with pool buoy at 3 months, kicking with freestyle at 4 months and then progress to kicking with flippers at 6 months <p>Cardiovascular exercises</p> <ul style="list-style-type: none"> • as before plus bike work with cleats can be introduced on a wind trainer
<p>Running type activities</p> <ul style="list-style-type: none"> • running on mini tramp <p><i>Progress to</i></p> <ul style="list-style-type: none"> • running in clinic towards mirror <p><i>Progress to</i></p> <ul style="list-style-type: none"> • treadmill running <p><i>Progress to</i></p> <ul style="list-style-type: none"> • field jogging in combination with walking (i.e. walk 30m, jog 30m) • gradually increase jog component once have confidence in straight line • progress speed • progress surface/incline • progress to shuttle runs 	

(Cooper, 2015)

Outcome measures to guide progression to Phase 4

<ul style="list-style-type: none"> • single leg bridge test (repetitions) 	90% of the opposite leg
<ul style="list-style-type: none"> • single leg calf raises on a step (repetitions) 	
<ul style="list-style-type: none"> • side bridge endurance test (side plank) (hold time) 	
<ul style="list-style-type: none"> • single leg press (if doing gym program) 1 Repetition-Maximum (1RM) 	
<p>Single hop test</p> <p>Subjects stand on one leg and hop as far as possible and land on the same leg. Two valid hops are performed. A limb symmetry index is calculated by dividing the mean distance in cms of the involved limb by the mean distance of the non- involved limb then multiplying by 100.</p> 	<p>90% of the opposite leg</p> <p>With adequate strategy and movement quality/fluidity.</p> <p><i>Focus on four factors:</i></p> <ol style="list-style-type: none"> 1. Hip rotational control 2. Knee flexor control 3. Postural stability 4. Frontal plane knee mechanics <p>(Reid, Birmingham, Stratford, Alcock and Giffin, 2007)</p>
<p>Triple cross over hop test</p> <p>The test is performed over a 15cm-wide and 6-metre-long marking strip on floor. Patients are required to hop three consecutive times on one foot, crossing the strip on each hop. The total distance is measured. Two valid hops are performed. A limb symmetry index is calculated by dividing the mean distance in cms of the involved limb by the mean distance of the non-involved limb then multiplying by 100.</p> 	
<p>Modified landing error score system (less)</p> <p>Subjects jump off a 30cm box onto the ground at a distance which is 50% of their height. They then immediately jump vertically as high as possible. The patient performs these multiple times until assessor has observed and marked all of the criteria.</p> 	<p>See Appendix 1 for scoring sheet</p> <p>(Padua et al., 2009)</p> <p>(Ithurburn, Paterno, Ford, Hewett, & Schmitt, 2015)</p>
<p>Y-balance test</p> <p>This is performed in anterior, posterolateral and posteromedial directions. The patient stands with one leg in the middle and hands on hips. A composite score for all 3 directions is obtained for each leg. A limb symmetry index is calculated by dividing the mean distance in cm of the involved limb by the mean distance of the non-involved limb and then multiplying by 100.</p> <p>(Gribble et al, 2012)</p> 	<p>95% of opposite leg</p> <p>(Gribble, Hertel, & Plisky, 2012)</p>

Phase 4

Getting ready to return to sport; practise sports related skills (9-12 months)

Dynamic, multi-joint neuromuscular control is the primary focus of ACL rehabilitation in children and adolescents. Phase 4 is important to developing the necessary control and awareness for effective return to sport in stage 5 with appropriate and safe technique. This may mean allowing the child to return to training with specific guidelines, therefore maintaining the social benefits of remaining involved with the team. Providing modified restrictions to the coach or school teacher, ensuring the patient has excellent insight and recruiting the parent/guardian as an active participant can minimise the risks associated with this.

Exercise suggestions

- hopping and jump drills continue
- figure 8 running
- diagonal running
- change of direction drills
- slalom running
- sport specific drills and skills (from 26 weeks +) from restricted to unrestricted with game play
- sport specific cardiovascular training

(Cooper, 2015)

Outcome measures to guide progression to Phase 5

• hop tests (as previously described in Phase 3)	>90%
• muscle strength tests	90% symmetry
• performed gradual increase in sport-specific training without pain and swelling	
• confidence in knee function and psychological readiness to return to sport	>80%
• knowledge of high injury risk knee position and ability to maintain low-risk knee positioning in advanced sport specific actions.	

Phase 5

Return to sport and prevent re-injury (12 months and onwards)

At 12 months post-surgery the patient will be reviewed at LCCH orthopaedic by their surgeon and a physiotherapist. Final outcome measures will be taken and, all going well, return to sport clearance provided.

Data from international registries shows that children/adolescents are much more prone to secondary ACL rupture, including the contralateral leg. According to the [2018 Olympic Committee Paediatric ACL consensus Statement](#), a comprehensive injury prevention program, emphasising biomechanical alignment and landing/cutting technique should be integrated for all paediatric ACL patients post rehabilitation.

Prevention programs should

- incorporate plyometric, balance, strengthening exercises and education/feedback on proper technique.
- be performed more than once/week
- last greater than 6 weeks
- also include other items such fitness and warm up

Examples

- PEP program: 15-minute training session that replaces the traditional warm up in soccer players
- FIFA 11+ - Soccer
- Netball KNEE Program (Netball Australia)
- KIPP (Knee Injury Prevention Program) for high school basketball and soccer players
- Footy First: for AFL players (+18 years)

Links

- [PEP \(Prevent injury and Enhance Performance\) Program](#)
- [FIFA 11+](#)
- [Netball Knee Program](#)
- [KIPP \(Knee Injury Prevention Program\)](#)
- [Footy First \(AFL\)](#)

Consultation

Key stakeholders who reviewed this version:

- Linda Camilleri (Physiotherapist- Advanced, QCH)
- Dr David Bade (Director of Orthopaedics, QCH)
- Kylie Bradford (Orthopaedic Physiotherapy Clinical Lead, QCH)
- Natasha Weaver (Physiotherapist, QCH)

References and suggested reading

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5. Ithurburn, M. P., Paterno, M. V., Ford, K. R., Hewett, T. E., & Schmitt, L. C. (2015). Young Athletes With Quadriceps Femoris Strength Asymmetry at Return to Sport After Anterior Cruciate Ligament Reconstruction Demonstrate Asymmetric Single-Leg Drop-Landing Mechanics. *Am J Sports Med*, 43(11), 2727-2737. doi:10.1177/0363546515602016
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Audit/evaluation strategy

Level of risk	Low
Strategy	Audit Protocol Bi-yearly
Audit/review tool(s) attached	N/A
Audit/Review date	October 2020
Review responsibility	HP5 Advanced OPSC MSK Physiotherapist

Guideline revision and approval history

Version No.	Modified by	Amendments authorised by	Approved by
1.0	Advanced Physiotherapist	A/Divisional Director, Clinical Support	Executive Directors, Clinical Services (LCCH)

Keywords	Paediatric, ACL reconstruction, rehabilitation, physiotherapy, 65031
Accreditation references	NSQHS Standards (1-10): 1, 2, 6

Appendix 1 - Outcome Measures

- [Modified Landing Error Score System \(LESS\)](#)

Appendix 2 - Preventative Programs

- [PEP \(Prevent injury and Enhance Performance\) Program](#)
- [FIFA 11+](#)
- [Netball Knee Program](#)
- [KIPP \(Knee Injury Prevention Program\)](#)
- [Footy First \(AFL\)](#)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	<u>1</u>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<u>11</u>
	2b	All items from the World Health Organization Trial Registration Data Set	<u>Supplied with trial registration</u>
Protocol version	3	Date and version identifier	<u>11</u>
Funding	4	Sources and types of financial, material, and other support	<u>13</u>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<u>1</u>
	5b	Name and contact information for the trial sponsor	<u>13</u>
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	<u>13</u>
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	<u>10</u>

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	<u>2-3</u>
	6b	Explanation for choice of comparators	<u>3</u>
Objectives	7	Specific objectives or hypotheses	<u>3</u>
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	<u>4</u>

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	<u>4</u>
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	<u>4</u>
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	<u>4-7</u>
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	<u>10</u>
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	<u>8-10</u>
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	<u>10</u>
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	<u>7,8,10</u>
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	<u>4, Figure 1</u>

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	<u>8-9</u>
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	<u>8-9</u>

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	<u>9</u>
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	<u>9</u>
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	<u>9</u>
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	<u>9</u>
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	<u>N/A</u>

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	<u>6-7</u>
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	<u>9-10</u>

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	<u>9</u>
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	<u>9</u>
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<u>9</u>
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	<u>9</u>
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	<u>10</u>
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	<u>Details in DSMB ToR</u>
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	<u>Details in DSMB ToR</u>
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	<u>N/A</u>
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<u>11</u>
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	<u>11</u>

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<u>4</u>
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	<u>N/A</u>
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	<u>9</u>
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	<u>12</u>
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	<u>9-10</u>
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	<u>10</u>
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	<u>11</u>
	31b	Authorship eligibility guidelines and any intended use of professional writers	<u>N/A</u>
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	<u>N/A</u>
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	<u>Provided with PCIF</u>
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	<u>N/A</u>

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.