BMJ Open

Study protocol for double-blind, randomised placebo-controlled trial evaluating semitendinosus function and morbidity following tendon harvesting for anterior cruciate ligament reconstruction augmented by platelet-rich plasma

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To cite: du Moulin W, Kositsky A, Bourne MN, *et al*. Study protocol for double-blind, randomised placebo-controlled trial evaluating semitendinosus function and morbidity following tendon harvesting for anterior cruciate ligament reconstruction augmented by platelet-rich plasma. *BMJ Open* 2022;**12**:e061701. doi:10.1136/bmjopen-2022-061701

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-061701).

Received 02 February 2022
Accepted 28 August 2022

Check for updates

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ABSTRACT

Introduction Anterior cruciate ligament (ACL) rupture is debilitating, often requiring surgical reconstruction. An ACL reconstruction (ACLR) using a tendon autograft harvested from the semitendinosus results in substantial injury to the donor muscle. Following ACLR, patients rarely return to their preinjury level of physical activity, are at elevated risk of secondary lower limb injuries and early onset knee osteoarthritis. To date, no randomised controlled trial has evaluated the efficacy of platelet-rich plasma (PRP) in aiding knee function and semitendinosus morphology of following ALCR.

Methods and analysis This is a multicentre double-blind randomised placebo-controlled trial. Fifty-four ACLR patients aged 18–50 years will be randomised to receive either a single application of PRP (ACLR+) or placebo saline (ACLR) into the semitendinosus harvest zone at the time of surgery. All patients will undergo normal postoperative rehabilitation recommended by the attending orthopaedic surgeon or physiotherapist. The primary outcome measure is between-limb difference (ACLR compared with intact contralateral) in isometric knee flexor strength at 60° knee flexion, collected 10–12 months postsurgery. This primary outcome measure will be statistically compared between groups (ACLR+ and standard ACLR). Secondary outcome measures include bilateral assessments of hamstring muscle morphology via MRI, biomechanical and electromyographic parameters during an anticipated 45° running side-step cut and multidirectional hopping task and patient-reported outcomes questionaries. Additionally, patient-reported outcomes questionaries will be collected before (baseline) as well as immediately after surgery, and at 2–6 weeks, 3–4 months, 10–12 months and 22–24 months postsurgery 10–12 months following surgery.

Ethics and dissemination Ethics approval has been granted by Griffith University Human Research Ethics Committee, Greenslopes Research and Ethics Committee, and Royal Brisbane & Women's Hospital Human Research Ethics Committee. Results will be submitted for publication in a peer-reviewed medical journal.

Trial registration number ACTRN12618000762257p.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Double-blind randomised placebo-controlled trial design is a rigorous design to address the research question.
⇒ In-depth functional and morphology analyses at multiple time points following anterior cruciate ligament reconstruction.
⇒ No haematological analysis will be conducted to verify concentration of platelet-rich plasma serum provided to each participant in experimental arm of study.

INTRODUCTION

Rupture of the anterior cruciate ligament (ACL) is a debilitating intra-articular knee injury endemic to field and court sports. To restore stability to the ACL deficient knee, ACL reconstruction (ACLR) is typically recommended.[1] In Australia, ~90% of ACLR are performed using a tendon autograft harvested from the semitendinosus (and potentially the gracilis).[2 3] The semitendinosus and/or gracilis tendons do not regenerate in ~30% of ACLR patients.[4] Moreover, ACLR patients often have long-term deficits in knee flexor and internal rotator strength,[5–7] as well as altered knee biomechanics,[8–10] muscle activation patterns[11–13] and knee function (patient-reported outcomes measure, PROM).[14 15] These chronic deficits in knee function are thought due, in part, to

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postoperative morbidity of the muscle harvested for the autograft,[6 16] and may contribute to increased risk of ACL rerupture,[17–19] primary hamstring strain injury[20 21] and early onset of knee osteoarthritis in ACLR patients.[22 23] Novel orthobiological therapeutics, such as autologous platelet-rich plasma (PRP), may promote hamstring tendon regrowth following ACLR. If so, they may improve levels of postoperative knee pain and function, while reducing secondary injury risk.[24–27]

Animal and preclinical research support use of orthobiological therapies to augment ACLR.[28 29] Many studies have examined PRP or autologous conditioned plasma (ACP), which is an autologous concentration of human platelets in a small volume of plasma produced by centrifuging a patient's blood.[25 27 30] Platelets contain a milieu of growth factors and mediators in their alpha granules, such as transforming growth factor-b1, platelet-derived growth factor, basic fibroblast growth factor, vascular endothelial growth factor, epidermal growth factor, and insulin-like growth factor-1, all of which are concentrated by the centrifugation process.[31] A concentration of platelets surrounding an injury site (eg, tendon donor site for ACLR) would enhance recruitment, proliferation, and differentiation of growth factors and mediators involved in tissue healing.[32] Indeed, both tendons and muscles heal through a dynamic process, with stages of inflammation, cellular proliferation and subsequent tissue remodelling. Many growth factors found in PRP/ACP are also involved in the healing process.[33–36] For patients undergoing ACLR, it is currently unknown if PRP/ACP has therapeutic effects on regeneration of the semitendinosus and its distal tendon. If so, it may limit the functional and neuromuscular deficits reported over the short-term and long-term following ACLR,[28] which would improve the current standard of care

To date, no randomised controlled trial has evaluated the efficacy of PRP/ACP in augmenting the recovery of the donor semitendinosus muscle following ALCR.[37] The primary aim of this trial is to determine whether post-operative isometric knee flexion strength in those receiving ACLR augmented by PRP/ACP is closer to the intact contralateral knee compared with standard ACLR. The secondary aims are to evaluate between-group differences in bilateral three-dimensional structural morphology of the hamstring muscles, lower limb biomechanics and electromyographical activity during functional tasks, and patient-reported outcomes of pain and function at several time points during rehabilitation following ACLR. It is hypothesised that the patients randomly allocated to the PRP/ACP intervention group will have smaller bilateral differences in isometric knee flexion strength, muscle morphology, lower limb biomechanics and electromyographical activity when compared with the control group. Improvement of short-term functional, morphology and PROMs may also protect knee from long-term structural degeneration.

OBJECTIVES

Primary objective

To determine if an intraoperative injection of PRP/ACP into the harvest zone of the distal semitendinosus tendon following an ACLR results in greater isometric knee flexion strength at 60° of knee flexion 10–12 months postsurgery compared with the uninjured contralateral limb and the control group. Note: the strength measure is bilateral difference expressed as a percentage (ie, [affected limb – unaffected]/affected × 100%), and this difference is compared statistically between the ACLR+ and ACLR groups.

Secondary objectives

To determine if, in comparison to standard ACLR, an intra-operative injection of PRP/ACP into the harvest zone of the semitendinosus tendon during ACLR will improve:

- Bilateral difference in isometric knee flexion isometric strength at 15°, 45° and 90° of knee flexion, 10–12 months postsurgery.
- Bilateral difference in hamstring muscle morphometry (ie, volume, peak anatomical cross-sectional area and length) 10–12 months postsurgery.
- Bilateral biomechanical difference in knee rotations (ie, abduction, internal rotation, flexion) and generalised loads (triplanar knee torques), and tibiofemoral contact forces during (1) an anticipated sidestep cutting manoeuvre and (2) a multidirectional hop.
- Bilateral differences in activation patterns of the hamstring muscles when performing (1) and/or (2).
- Patient-reported outcomes of knee function, hamstring function, quality of life, kinesiophobia and pain.

METHODS AND ANALYSIS

Study design

A prospective, multicentre double-blind randomised placebo-controlled trial will evaluate the clinical efficacy of PRP/ACP in ACLR in terms of bilateral differences in knee flexion strength. Fifty-four participants will be randomised to receive PRP/ACP or saline injection intraoperatively during an ACLR surgical procedure. The summary of this trial is outlined in figure 1.

Sample size

An a priori power analysis was performed using G*Power V.3.1 (Universität Düsseldorf, Düsseldorf, Germany). Effect size estimates (d=0.86) were based on Nomura *et al* who reported significant between-limb differences in isometric knee flexion strength at 60° knee flexion following semitendinosus autograft ACLR.[5] A sample size of 46, split into two groups of 23, with an effect size of *d*=0.86, an alpha of 0.05 and 80% power was deemed sufficient to test the two-tailed between-limb differences between two independent groups. To account for a potential participant withdrawal of 20% (n=8), in line

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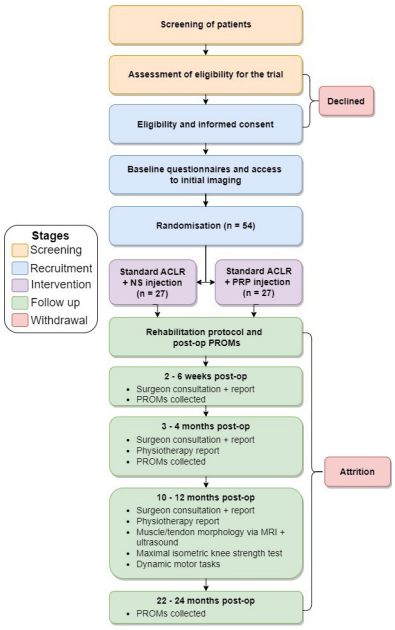


Figure 1 Study flow chart. ACLR, anterior cruciate ligament reconstruction; NS, normal saline; PRP, platelet-rich plasma; PROMs, patient-reported outcome measures.

with surgical randomised controlled trials,[38] a total of 54 participants will be recruited.

Patient and public involvement

The design of the current trial was based on a previous double blinded RCT[39] performed in ACLR patients. The study design and protocol were further refined and tailored to the investigation team conducting the trial. Patients were not involved in the design of the study, participant recruitment or in the determination of outcome measures in this trial. No public forum was organised to steer the design or management of the current trial. A summary of the trial outcome will be disseminated to trial participants on request.

Patients

Through diagnostic consultation with the treating orthopaedic surgeon(s), patients will be assessed according to standard practise, an injury history taken and appropriate MRI performed. Patients diagnosed with an ACL rupture, and who meet eligibility criteria will be contacted by the research team following orthopaedic consultation. Patients will be invited to provide their written informed consent to become participants within the trial. Those who agree to take part will complete baseline measures (ie, PROMS and access to primary care medical imaging) following consultation and will be randomly allocated to one of two treatment arms.

Inclusion criteria

- 18–50 years of age undergoing a unilateral primary ACLR.
- Patient can consent and participate fully in the intervention and follow-up testing.
- Patient is willing to follow the rehabilitation protocol established by the treating orthopaedic surgeon and referred physiotherapists.

Exclusion criteria

- Simultaneous multiligament repair/reconstruction or lateral extra-articular tenodesis.
- Utilisation of graft other than semitendinosus on injured limb (possible intraoperative exclusion).
- Any history of ACLR or major knee injury on either limb.
- The patient is unable to consent or participate fully in the intervention and follow-up testing.
- Any recent history of hamstring strain injury on either limb within 6 months of ACL rupture diagnosis.
- Pre-existing symptomatic knee osteoarthritis.
- Medically diagnosed platelet disorder or haematological related disorder.
- Any other medical conditions likely to interfere with testing (at discretion of recruiters).
- Concomitant meniscus repair of lesions >1.5 cm or requiring postoperative bracing.

Procedures

Baseline assessment

Baseline data will be collected following confirmation of eligibility and signed consent. Sociodemographic information will be collected, including age, sex, height, body mass, limb side of ACL rupture, limb dominance, activities of daily living, sport and recreational activities prior to injury, activity that led to ACL rupture and previous lower limb injury history. Patient-reported outcome measures (PROM) will be used to assess patient perceived pre-operative baseline knee function, hamstring function, quality of life, kinesiophobia and pain.[40–44]

Randomisation

There will be 1:1 randomisation to intervention and control arms. Participants will be enrolled sequentially as they become available and assigned a study identification number. Randomisation of participants will be achieved using a permuted block randomisation design. A block size of 4 will be used in conjunction with a random number sequence to create a master list for intervention allocation. The use of permutation blocks ensures the assignment of the intervention is balanced. Each study identification number will be randomly assigned a treatment allocation via this method. The participating hospitals will receive a set of *n* (2:1, Pindara to Robina allocation based on historical flow rates of participating surgeons) sequentially numbered and sealed envelopes which will contain the study identification number and treatment allocation. The site will open envelopes in consecutive order prior to in-theatre incision on the day of surgery to determine treatment allocation. If a patient withdraws from the study prior to surgery, the study identification number and corresponding envelope will be destroyed and will not to be used for any subsequent

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patient enrolled. The randomisation schedule will be kept securely on a password protected computer within a locked office at Griffith University by an unblinded associate investigator.

Blinding

The patient, surgeon, research personnel and individuals collecting all objective outcome measures will be blinded to the randomisation. Randomisation and patient assignments will be done through sequentially numbered opaque sealed envelopes opened by the circulating nurse, surgical assistant or anaesthetist in the operating room at the time of surgery. Randomisation information will be then recorded and placed into a sealed envelope with the patient's unique study identifier and deposited into a sealed study box. Unblinding of participant identity to the surgeon and research personnel will occur after the completion of the 12-month follow-up assessments.

Intervention

The two trial groups are:

- The PRP/ACP injection (intervention group): After successful ACLR, PRP/ACP is injected into the semitendinosus harvest site.
- Saline injection (control group): After the successful ACLR, saline is injected into the semitendinosus harvest site.

For both groups, ACLR will be performed using a quadruple bundle ipsilateral semitendinosus autograft[45] via an anteromedial portal technique.[46] Femoral and tibial sockets will be created using Arthrex GraftLink technology (Arthrex) or comparable drilling methods. The Arthrex TightRope (Arthrex) fixation implants will be adjusted to create optimal suspensory tibial and femoral graft fixation. Following successful reconstruction, the injection will be delivered by the surgeon while maintaining blinding to the treatment allocation. Both interventions will be delivered by the same technique. The PRP/ACP injection will be prepared directly in the operating room before or during the surgical intervention with an PRP/ACP separation kit and centrifuge system, as well as site application kit provided by industry partner Arthrex. Blood will be collected by the anaesthetist from a dedicated draw line applied to the antecubital site on the contralateral arm for both control and treatment patients.

Two vials of ~13.5 mL of raw blood will be withdrawn, mixed with approximately 1.5 mL citrate anticoagulant (~9:1) for centrifuging. The blood mixture will be centrifuged for 5 min at 1500 revolutions per minute. The purpose of this step is to separate the red blood cells from the PRP to a concentration approximately 1.7 times greater than baseline and with leucocyte depletion.[47] Two syringes of PRP (approximately 6–7 mL each) will be aspirated into the inner smaller-diameter syringe of the double-syringe system (Arthrex ACP Double-Syringe System, Arthrex) and set aside until ready for use. For the control group, two syringes of saline of 6–7 mL will be prepared in a similar fashion. The syringes will be opaque such that the surgeon cannot visually confirm if PRP/ACP or saline is used. The PRP/ACP or saline will then be applied to the semitendinosus proximal end of the harvest site using the Arthrex Knee Delivery Tubes (Arthrex,) fed via the harvest tract. Following application, the donor site is sealed and the remainder of the ACLR procedure is completed.

As this study requires a single treatment, adherence to the protocol consists of the participant receiving the allocated treatment. This will be monitored, and every instance of the participant not receiving the allocated treatment will be investigated. Unless the patient requests to withdraw from the study, these participants will be retained in the trial, to avoid missing data and for follow-up. However, if a participant is unable to receive an PRP/ACP injection for any technical reasons, they will receive the saline (control) injection, and this will be recorded. Each patient will be treated as per protocol on the intervention received (ie, PRP/ACP or saline) during surgery.

Rehabilitation program

All participants will be prescribed a standardised post-surgical rehabilitation programme, which consists of the following stages:

0–2 weeks: This early stage consists of gentle encouragement of knee flexion and extension movement within a range of motion (ROM) of 0°–90°, along with patella mobilisation.

2–6 weeks: To continue encouragement of ROM, flexion ROM will be done past 90°, with the aim to achieve of near or terminal extension. Proprioception and progressive controlled resistance training will also be introduced during this stage.

6–12 weeks: Improve lower limb strength, endurance, proprioception, and neuromuscular control, achievement of full pain free ROM of 0°–135° in terminal extension.

3–5 months: Progress lower limb strengthening, endurance and power training with an emphasis on single leg exercises, and the introduction of straight line running.

5–7 months: Progress and improve any sport-specific functional strengthening, plus graded introduction of sport-specific and plyometric drills.

Patient compliance to the prescribed rehabilitation programme and milestones will be recorded throughout the trial. This will be assessed by consultation report forms from the surgeon, physiotherapists and participants, gauging progress of rehabilitation during the follow-up window.

Measurement protocols

All enrolled participants will undertake strength and dynamic movement analysis testing within 1 week of the 10–12 months follow-up MRI at the Biomechanics and Gait Analysis Laboratory of Griffith University. The participants will first undergo strength assessment followed by

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the dynamic movement testing. The set up for both analyses including the fitting of electromyography sensors and reflective markers will provide a sufficient rest period (approximately 30 min) to prevent fatigue between the strength and dynamic movement assessments.

Biomechanical evaluation

Isometric knee flexion strength assessment

A motor driven isokinetic dynamometer (Biodex medical systems, New York, USA) will be used to bilaterally measure maximum isometric knee flexor strength. Participants will undergo a 5 min self-paced warm up on a bicycle ergometer (Monark, Rehab Technology, Australia). Participants will be positioned lying prone on a medical plinth with their hip at ~0° and their knee flexed from 0° to 90°. The knee joint axis of rotation will then be aligned with the rotary axis of the dynamometer by manual adjustment. The trunk and pelvis will be secured using Velcro straps, and the ankle will be fixed using an Aircast medical boot (DJO Global, Texas, USA) attached to the Biodex lever arm with a Velcro strap. Each participant will then perform one submaximal set of three isometric knee flexion contractions at knee angle of 60° flexion to warm-up the hamstrings and familiarise with the equipment. Subsequently, participants will be required to complete three sets of three maximal voluntary isometric isokinetic knee flexion strength tests at knee angles of 15°, 45°, 60° and 90° on both the surgically reconstructed and uninjured contralateral limb. The primary outcome measure of maximum isometric knee flexion torque (N.m) at 60° of knee flexion will be the first task performed following the participant warm up. The secondary outcome measures of maximum isometric torque (N.m) at 15°, 45° and 90° will be randomised in the order of their completion for each participant prior to maximal strength testing. Participants will then be instructed to perform three sets of three maximal voluntary isometric knee flexion repetitions. A trial will only be deemed acceptable if the torque trace plateaued after reaching a distinct peak, indicating the development of maximal volitional isometric force. For each trial, the maximum strength in torque (N.m) will be recorded. Participants will be given 20 s of rest between warm up sets, 1 min rest between test sets and 5 min rest between testing of each limb.

Dynamic movement and electromyography assessment

Participants will undergo motion analysis during an anticipated 45° running side-step cut and a multidirectional hopping task on both the surgically reconstructed and uninjured contralateral limb. The participants will be required to perform at least five successful repeated trials of each task. A trial will be deemed successful if the foot from the desired limb cleanly strikes on the centre of the force platform at the required speed, and the trial will be repeated if these conditions are not met. For all tasks, white masking tape will be placed along the ground to ensure participants move at the specified angle and to allow them to prepare for the movement. For the anticipated 45° running sidestep cut, participants will be instructed to run at a self-selected pace of 3–4.5 m/s.

Three-dimensional body motion capture, ground reaction forces, and electromyographical signals will be recorded synchronously during both tasks. A 12 camera Vicon motion capture system (Vicon, Oxford Metrics, UK) sampling at 200 Hz will be used to acquire three-dimensional motion data of participants wearing a full-body marker set consisting of 33 retroreflective markers (14 mm diameter) and eight marker clusters (3–4 markers each). Ground reaction forces will be acquired using two AMTI (Advanced Mechanical Technology Institute, Massachusetts, USA) force plates sampling at 2000 Hz. Participants will wear their own athletic footwear, while reflective markers will be secured with tape to bony landmarks on the lower limbs, pelvis, and trunk. Electromyographic activity will be recorded using bipolar Ag/AgCl surface electrodes (Duo-Trode, Myotronics, Washington, USA) placed on the muscle belly of interest, parallel to the presumed orientation of its fibres. Electromyograms will be acquired at 2000 Hz using wireless 16-channel acquisition system (Cometa, Bareggio, Italy). The muscles of interest include semimembranosus, semitendinosus, biceps femoris, rectus femoris, vastus lateralis, vastus medialis, medial gastrocnemius and lateral gastrocnemius. Electrode placement will be conducted in accordance with the surface electromyography for the non-invasive assessment of muscles guidelines[48] and confirmed via ultrasound (L12-5N60-A2, ArtUS, Telemed, Vilnius, Lithuania) to account for likely muscle tendon atrophy within the injured limb.

Data processing will be performed using MATLAB (Mathworks, Massachusetts, USA). Marker trajectories and ground reaction forces will be low-pass filtered using a zero-lag, second order, Butterworth filter with a cut-off frequency of 15 Hz for cutting and hopping tasks. Electromyograms will be band-pass filtered (30–500 Hz), full wave rectified, and then low pass filtered with a cut-off frequency of 6 Hz to yield linear envelopes for each measured muscle, and subsequently normalised to their maximum value identified across all dynamic trials, functional tasks, and isokinetic maximum voluntary contractions. All biomechanical data will be normalised to 100% of stance for both sidestepping and the multidirectional hop. Gait analysis outcomes will include the spatiotemporal parameters, external hip, knee and ankle moments, hip, knee and ankle angles, ROM and lower limb joint contact forces, all calculated from the stance phase of the two tasks and analysed through OpenSim.[49] EMG-informed muscle-tendon and lower-limb joint contact forces will be determined using Calibrated EMG-Informed Neuromusculoskeletal Modelling Toolbox.[50]

MRI

A 3T MRI scanner (Ingenia, Phillips, Eindhoven, Netherlands) will be used to acquire images of both lower limbs in all participants. Participants will be instructed to lie supine atop the scanner bed, and images will be acquired from

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the level of the iliac crest to the ankle mortise. Coronal T_1 Dixon three-dimensional fast field echo sequences will be performed with a slice thickness of 1 mm with a 0 mm interslice gap. Voxel size will be 1×1×1 mm and the field of view will be 360×450×252 mm.[51] All MRI data will be processed and analysed using the Materialise Interactive Medical Image Control System software (Mimics, Materialise, V.21, Leuven, Belgium). The outer boundaries of the semitendinosus, semimembranosus, biceps femoris long head and biceps femoris short head muscles and tendons will be visualised and traced as separate objects in each axial slice in which they are visible. These traced margins will then be used to create a three-dimensional mesh model of each hamstring muscle using the tools within Mimics. A wrapping factor will be applied to each mesh model with a gap closing distance of 1.3 mm and smallest detail of 0.82 mm followed by a smoothing factor of 0.4. Following the generation of the three-dimensional mesh models, muscle morphology of each hamstring muscle in the surgically reconstructed and uninjured contralateral limb will be evaluated via measurements of musculotendon volume (cm^3), peak anatomical cross-sectional area (cm^2) and length (cm).[6 52] Distal tendon regeneration will be defined as having occurred if the neo-tendon is visible below the distal muscle-tendon junction and traced to the level of the femoral epicondyle.

Patient information and reported outcomes

Patient reported outcomes will be collected at baseline and all follow-up time points throughout the study. The following questionnaires will be used to assess patient perceived preinjury/postinjury knee function, hamstring function, quality of life, kinesiophobia, and pain[40–44]:

- Knee Injury and Osteoarthritis Outcome Score.[53]
- Functional Assessment Scale for Acute Hamstring Injuries (FASH).[41 42]
- International Knee Documentation Committee Score.[54]
- Tegner Lysholm Knee Scoring Scale.[44]
- EQ-5D-5L.[55]
- Anterior Cruciate Ligament Return to Sport After Injury Scale Short Form.[40]
- Short-Form McGill Pain Questionnaire.[43]

Data collection and management

PROMs, such as the FASH questionnaire, may be completed online by trial participants. Access to the data on the server will require the investigators to enter a confidential log-in and password on REDCap, a secure web application for managing online surveys and databases. The website staff will not have any access to the study data. Data will be downloaded from REDCap for analyses and be stored electronically in password-protected files on a secure Griffith University server. Access will be limited to the project researchers. All patient information and data will be deidentified to ensure confidentiality. Once data collection is complete, data will be permanently deleted from the external web-survey company's server.

Hardcopy survey data will be entered into a spreadsheet that will be stored electronically in password protected files on a secure Griffith University server, and access will be limited to the project researchers. Hardcopies of the questionnaires, consent forms, and any other relevant information will be stored in a locked filing cabinet in the researchers' office. The files will be then deleted from the digital recorders. All electronic and hard copy records will be stored for a minimum of 15 years.

An internal data and safety monitoring committee (DSMC) will be responsible for oversight of this clinical trial, including protocol adherence, recruitment, adverse events, severe adverse events, treatment side effects, and data analysis and data safety. The members of the DSMC will consist of the principal investigator and other investigators of the trial.

Statistical analysis

Descriptive statistics (such as means and SD for continuous variables and frequencies and proportions for categorical or binary variables) will be used to describe the baseline characteristics of the participants within the two study groups and will be evaluated with the appropriate analysis to establish group homogeneity. All outcome measures will be analysed using generalised linear models or appropriate statistical tests using SPSS V.25 (IBM). All comparative results will be presented as summary statistics with 95% CIs and reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.[56] A separately compiled statistical analysis plan will contain full details of all statistical analyses and will be prepared early in the trial, agreed on by the DSMC and finalised prior to the primary analysis database lock and before unblinding of the data.

ETHICS AND DISSEMINATION

This trial will be conducted in compliance with the Australian National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007), the ICH Guideline for Good Clinical Practice E6 (R2), and the conditions of the ethics approval granted by Griffith University Human Research Ethics Committee (GU Ref No: 2018/718), Greenslopes Research and Ethics Committee (18/30) and Royal Brisbane & Women's Hospital Human Research Ethics Committee (HREC/2021/QRBW/69253).

The trial will be reported in accordance with the SPIRIT statement and the Template for Intervention Description and Replication guidelines.[56 57] The results will be used as a component of a doctoral thesis, published in peer-reviewed medical literature, and may be presented at relevant national and international conferences.

Perspectives of the study

In many individuals, ACLR with a hamstring autograft results in significant deficits in knee flexor strength and

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function that persist long after successful rehabilitation and a return to sport. The primary aim of this trial is to investigate whether ACLR using a semitendinosus autograft augmented by PRP is more effective than standard ACLR in terms of restoring isometric knee flexion strength. The secondary aims of this trial are to evaluate between-group differences in three-dimensional structural morphology of the hamstring muscle complex, biomechanical and electromyography strategies used in functional tasks, and patient-reported outcomes. If an intraoperative PRP injection to the harvest zone limits or prevents post-ACLR musculotendon unit morbidity, it may provide evidence to support PRP injections in hamstring graft ACLR. Improved healing of the harvest zone following ACLR may enhance knee joint function and may also protect the knee from potential short-term lower-limb injury risk and long-term structural degeneration.

Trial status

The trial had an anticipated start date of 1 February 2021, with an allotment of 12 months for recruitment and an initial expected completion date of 1 February 2023. However, recruitment and trial progress has been suspended due to the ongoing movement restrictions and the continued burden on the local health network of the COVID-19 pandemic. The investigation team plans to recommence recruitment as soon as it is feasible within the participating hospitals.

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Contributors WdM was responsible for responsible for study design conceptualisation and manuscript development. AK contributed to study design and manuscript development. MB and LED contributed study design conceptualisation, study oversight and, to reviewing and editing of the manuscript. FT and CV contributed to study design conceptualisation, study oversight, listed as principal site investigator and, to reviewing and editing of the manuscript. DS contributed to study design conceptualisation, study oversight, listed as the chief coordinating investigator and, to reviewing and editing of the manuscript. All authors read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Funding This trial is being supported in collaboration with Arthrex on an Australian Research Council Industrial Training and Transformation Centre grant: Centre for Medical Implant Technology. Grant number: IC180100024.

Competing interests FT has given paid presentations for Smith & Nephew (Australia) and 3M Medical Solutions (Australia). CV: Director and Treasurer, Australian Orthopaedic Association. President of the Australian Knee Society.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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