CLINICAL STUDY PROTOCOL

This protocol has regard for the HRA guidance.

Full Study Title: Anterior Cruciate Ligament Stratified Accelerated Repair or Reconstruction Single blind randomised controlled trial for patients with proximal ACL injuries treatment with ACL repair v ACL reconstruction (ACL STARR-UK)

SHORT STUDY TITLE: Anterior Cruciate Ligament Stratified Accelerated Repair or Reconstruction

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Study website: https://sites.google.com/view/acl-starr/home

Contents

1 RESEARCH REFERENCE NUMBERS

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2 ORGANISATIONAL INFORMATION

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Sponsor: Joint	Cambridge University Hospitals NHS Foundation Trust and University of Cambridge Refer to the KEY STUDY CONTACTS section for contact details.
Clinical Trials Unit:	The study is managed by the Surgical Intervention Trials Unit (SITU) E-mail: situ@ndorms.ox.ac.uk Trial Manager: **Mr Nicholas Beale** Oxford Clinical Trials Research Unit (OCTRU) Botnar Research Centre, University of Oxford, Windmill Road, Headington, Oxford, OX3 7LF. E-mail: octrutrialshub@ndorms.ox.ac.uk
Funder:	The study is funded by National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme.
Co-applicants:	The following are co-applicants on the study grant and have contributed to the study design and development of the protocol: [Position held / Role in the study] **Professor David Beard** [Professor of Musculoskeletal and Surgical Science, NIHR Senior Investigator / Co-Investigator] Director of Surgical Intervention Trials Unit (SITU) University of Oxford ✉ david.beard@ndorms.ox.ac.uk **Professor Andrew Metcalfe** [Professor of Orthopaedics / Research Lead British Association for Surgery of the Knee] University of Warwick ✉ a.metcalfe@warwick.ac.uk **Professor Andrew McCaskie** [Professor of Orthopaedics / Co-Investigator, Data Interpretation] University of Cambridge ✉ awm41@cam.ac.uk

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	Miss Hayley Carter [Clinical Specialist Physiotherapist, NIHR Clinical Doctoral Research Fellow / Physiotherapy Lead] University Hospitals of Derby and Burton NHS Foundation Trust ✉ hayley.carter1@nhs.net **PATIENT AND PUBLIC CONTRIBUTORS** **Mrs Carrie Dunn** [PPI co-applicant / PPI Representative]
Conflict of Interest statement:	The following conflicts of interest have been declared by the co-applicants/protocol contributors: Andrew Metcalfe (AM) leads two studies (START:REACTS, about a shoulder device, and RACER-Knee, about robotic-assisted knee replacement) and is a co-investigator on another (RACER-Hip, about robotic-assisted hip replacement) that are funded by the UK National Institute for Health and Care Research (NIHR) but for which Stryker, an orthopaedic company, have funded treatment costs and some imaging and training costs. For all these studies, the full independence of AM and the study team are fully protected by legal agreements agreed between the parties and approved by NIHR. There is no link between these studies and the current study. Nicolas Nicolaou has received payment for educational events for both Arthrex and Smith and Nephew. Zimmer-Biomet fund the Child and Adolescent Knee Fellowship at Sheffield Children's Hospital. Not conflict but for awareness: both Stephen McDonnell and David Beard are co-applicants on a parallel (mirror) Australian NHMRC study for this research question (ACL STARR Aus) No other conflicts of interest have been declared by the co-applicants/ protocol contributors.
Confidentiality Statement:	In accordance with the NIHR Open Access policy, the protocol will be published and made freely and openly accessible to all.

3 KEY STUDY CONTACTS

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Trial Steering Committee (TSC) Chair:	Professor Hemant Pandit Institute Director (Head of School), School of Medicine, University of Leeds. Clinical Director (Chapel Allerton Hospital) ✉ H.Pandit@leeds.ac.uk Other members of the TSC are detailed within a study specific TSC charter.
Data and Safety Monitoring Committee (DSMC) Chair:	Ellen Lee Statistician - Research Fellow Clinical Trials Research Unit, Sheffield Centre for Health and Related Research (ScHARR), University of Sheffield ✉ e.lee@sheffield.ac.uk Other members of the DSMC are detailed within a study specific DSMC charter.

4 PROTOCOL APPROVAL/SIGNATORIES

This Protocol has been approved by the Funder, Sponsor, Chief Investigator and Lead Study Statistician. Approval of the Protocol is documented in accordance with OCTRU Standard Operating Procedures.

All parties confirm that findings of the study will be made publicly available through publication without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any important deviations and serious breaches of GCP from the study as planned in this Protocol will be explained.

The study is funded by the NIHR HTA Programme. Funding approval followed a two-stage application process, with external peer-review at each stage via the HTA Funding Committee.

5 LAY SUMMARY/PLAIN ENGLISH SUMMARY

The knee is the most injured joint. The Anterior Cruciate Ligament (ACL) is an important band of tissue that supports the knee. It is a strong structure in the centre of the knee which attaches the femur (thigh bone) to the tibia (shin bone). It is often injured during manual work or sports. Injury to the ACL can lead to the knee becoming unstable, giving way and a loss of confidence. An unstable knee can cause damage to other parts of the knee such as the cartilage or meniscus (shock absorbers), which can lead to osteoarthritis (OA) developing in later life.

There are different surgical options for people with an ACL injury. The most common is reconstruction, which uses tissue from other parts of the body, such as the hamstrings, to act as a replacement. This is a successful operation but does involve damage to bones from drilling holes, removal of tissue from elsewhere in the body, and does not keep any of the torn ligament which has potentially useful nerve endings. An alternative approach is to reattach the original ligament back from where it has torn in a "repair" rather than reconstruction. By preserving the ligament, avoiding tissue harvest and bone drilling, ACL repair could provide faster recovery, better medium to long term stability, and might reduce likelihood of OA in the future. Older versions of ACL repair techniques have not worked well enough, but newer techniques are available, and this may now make repair a viable option.

What do we want to find out?

Modern ACL repair (stitching) is relatively new and, despite clear potential, has not been fully evaluated. It remains unknown whether it confers any of the theoretical benefits. We aim to conduct a comparative study to find out which is the best technique, reconstructing the ligament or repairing it. The research question is: For patients with recent proximal ACL ruptures (where the ligament has pulled directly off the bone), is ACL repair superior to ACL reconstruction at 24 months post-surgery? This will be measured by a questionnaire relating to the knee called KOOS-4.

How are we going to do this?

A special type of study called a randomised controlled trial is needed to answer this question. This involves assigning participants to different treatments using a process called randomisation so the effects of each treatment can be compared fairly. People who have injured their ACL, who may be suitable for either operation, will be invited to join the study. Participants will be randomly allocated to one of the two types of ACL surgery.

ACL REPAIR: this group will have surgery to repair the ACL, with the ligament being stitched back onto the bone.

ACL RECONSTRUCTION: this group will have surgery to reconstruct the ACL. This will involve replacing the torn ACL with other tissue from their body to act as a replacement.

Participants will be asked to complete a pain score at 3 and 6 weeks after surgery. Then they will be asked to complete questionnaires relating to their knee at 6-, 12- and 24-months post-surgery. Participants will be able to complete questionnaires electronically or on paper according to their preference.

Patient & Public Involvement

Four patient focus groups contributed to the design of this study, emphasizing the importance of a quick return to sports and work, and the impact this injury can have on mental wellbeing. They all considered this study as important, particularly in relation to measuring pain following the different surgeries, and having an online platform to complete questionnaires, which we have included. We have a PPI partner as co-applicant, who will be involved in all aspects of the delivery of this study.

Dissemination

We will publish results in scientific journals and present at international and national meetings including knee special interest groups. We will prepare a summary to help the National Institute for Health and Care Excellence (NICE) make a recommendation on ACL repair for the NHS. We will disseminate findings on social media and patient websites to ensure results reach a relevant audience.

6 STUDY SYNOPSIS

Full Study Title:	Anterior Cruciate Ligament (ACL) Stratified Accelerated Repair or Reconstruction Single blind randomised controlled trial for patients with proximal ACL injuries treatment with ACL repair v ACL reconstruction (ACL STARR)
Short Title:	Anterior Cruciate Ligament Stratified Accelerated Repair or Reconstruction
Study Acronym:	ACL STARR-UK
Study Design:	The ACL STARR study is a multi-centre two arm, parallel design, superiority randomised controlled trial.
Study Aim/Primary Objective:	The primary aim of the study is to establish whether ACL repair provides more benefit than ACL reconstruction in patients with recent proximal ACL ruptures of the knee.
Study Participants/ Target Population:	The ACL STARR study will recruit adults and adolescents (aged 14 years and above) with a proximal tear of the Anterior Cruciate Ligament (ACL) diagnosed by Magnetic Resonance Imaging (MRI). Refer to section OBJECTIVES AND OUTCOME MEASURES of the main body of the protocol for full eligibility criteria.
No. of study arms:	Two
Intervention(s):	ACL Repair
Comparator:	ACL Reconstruction
Planned Sample Size:	214 participants Randomisation will be performed intra-operatively following eligibility and suitability assessment. We anticipate 25% of those who consent to be assessed as unsuitable for repair intra-operatively, we expect approximately 286 patients will need to be consented into the study to reach the sample size of 214 participants.
Target no. of research sites:	Approximately 20 UK NHS Hospitals
Countries of recruitment:	UK
Planned recruitment duration:	Recruitment is expected to continue for 30 months.

Duration of intervention:	Day surgery with post operative physiotherapy	
Follow-up duration:	Each participant will be followed up for twenty-four months from randomisation.	
Primary objective and outcome measure:	**Objective** To assess whether ACL repair provides a superior clinical outcome compared to ACL reconstruction in patients with recent proximal ACL ruptures.	**Outcome Measure** Knee injury and Osteoarthritis Outcome Score-4 (KOOS-4) at 24 months post-randomisation.
Additional objectives and outcome measures:	Refer to the OBJECTIVES AND OUTCOME MEASURES section of the main body of the protocol for full study objectives and outcome measures.	

7 ABBREVIATIONS

ACL	Anterior Cruciate Ligament
ACLD	ACLDeficiency
ACL SNNAP	ACL Surgery Necessity in Non-Acute Patients
AE	Adverse Event
A&E	Accident & Emergency
AROM	Active Range Of Motion
BASK	British Association of Surgeons of the Knee
BOSTTA	British Orthopaedic Sports Trauma and Arthroscopy Association
BSCOS	British Society for Children's Orthopaedic Surgery
BTB	Bone-Patellar Tendon-Bone
CHI	Community Health Index
CI	Chief Investigator
CONSORT	The Consolidated Standards of Reporting Trials
CRF	Case Report Form
CPMS	Central Portfolio Management System
CTU	Clinical Trials Unit
DSMC	Data and Safety Monitoring Committee
EDI	Equality Diversity & Inclusion
EQ-5D-5L	European Quality of Life- 5 Dimensions - 5 Level version
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HCRW	Health and Care Research Wales
HEAP	Health Economics Analysis Plan
HES	Hospital Episode Statistics
HRA	Health Research Authority
HTA	Health Technology Assessment
ICF	Informed Consent Form
INCLUDE	Innovations in Clinical Trial Design and Delivery for the Under-served
ICMJE	International Committee of Medical Journal Editors
IMD	Index of Multiple Deprivation
ITT	Intention-to-Treat
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
KOOS	Knee injury and Osteoarthritis Outcome Score
KQoL-26	Knee Quality of Life-26
LEP	Lateral Extra-Articular Procedure
LSI	Limb Symmetry Index
MCID	Minimal Clinically Important Difference
MDC	Minimal Detectable Changes
MIC	The Minimal Important Change
MRI	Magnetic Resonance Imaging
MSK	Musculoskeletal
NHMRC	National Health and Medical Research Council

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NLR	National Ligament Registry
NRS	Numerical Rating Scale
OA	Osteoarthritis
OCTRU	Oxford Clinical Trials Research Unit
PCRF	Physiotherapy Case Report Form
PI	Principal Investigator
PIS	Participant information sheet
PPI	Patient and Public Involvement
PROMs	Patient-Reported Outcome Measures
QA	Quality Assurance
QALY	Quality-adjusted Life Year
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SITU	Surgical Intervention Trials Unit
SLR	Straight Leg Raise
SOP	Standard Operating Procedure
STRIDE	SupporTing Recruitment and retention Improvements for Diverse Ethnicities
SWAT	A study within a trial
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
VAS	Visual Analogue Scale

8 BACKGROUND INFORMATION AND RATIONALE

The Anterior Cruciate Ligament (ACL) is one of the key ligaments in the knee. It provides joint stability, allows normal knee kinematics, and maintains knee function giving confidence to undertake everyday activities, manual work, and recreational sports. Traumatic injury to the ACL is common with an incidence of 1 in 3000 per year[1] and can be substantially disabling.

Historically, rupture of the ACL is treated with either surgery or rehabilitation. The surgery normally consists of reconstructing the ligament with an autograft (a piece of tissue from the same person's body). A recent NIHR study ACL SNNAP - HTA:14/140/63[2] showed that, providing the injury is longstanding, surgical reconstruction is superior to rehabilitation and more cost-effective for these patients. However, there is more controversy around which is the best surgical treatment if it is carried out close to when the injury occurred. Reconstruction has been proven and can be valuable[3, 4] but a newer approach of reattaching the torn ligament back (ACL repair) is an increasingly valuable option. Salvaging all the original ACL tissue and minimising any further joint damage associated with more invasive reconstruction procedures could provide advantages, especially in the longer term. This study directly compares the two surgical treatments in a randomised controlled trial.

ACL Repair: is a surgical technique to reattach the detached ligament from its footprint on the femur. It has been shown to be possible in specific patterns of tear where the length of the damaged ligament is preserved, the tear is close to the femoral attachment and the gross structure of the ligament has been maintained. These features can be assessed pre-operatively on MRI scan and may be present in up to 43% of tears[5]. Time to surgery has been determined as a key factor in the success of ACL repair. Ideally, surgery must be undertaken as soon as possible, to maintain healing potential after the repair[6]. ACL repair is used by some surgeons in the UK but is not yet widely accepted, as evidence for benefit and value remains limited. This study will allow ACL repair to be evaluated in a safe and robust fashion, as recommended by the IDEAL (Idea, Development, Exploration, Assessment, Long-term study) framework for the investigation of surgical procedures[7]. The study has the support of the orthopaedic surgical community, via the British Association of Surgery for the Knee (BASK), British Orthopaedic Sports Trauma and Arthroscopy Association (BOSTTA) and British Society for Children's Orthopaedic Surgery (BSCOS). ACL repair takes a similar amount of surgical skill and theatre time as ACL reconstruction.

ACL reconstruction: is the current gold standard treatment following an ACL injury, in which the old damaged/torn ACL is removed and replaced by a graft. The graft is usually the patient's own tissue that is excised and repurposed to reconstruct the damaged ligament, typically taken from the patient's hamstrings (semitendinosus and gracilis) or Patella Tendon in which a strip of bone and the central third of the patella tendon is used (BTB). Bone tunnels are drilled within the patient's femur and tibia to accommodate the graft that is threaded across the knee.

Theoretical benefits of repair over reconstruction

ACL repair preserves the native tissue and is a less invasive surgery than reconstruction. Surgical repair eliminates the need for the harvest of other graft tissues, which can cause pain, muscle weakness, altered mechanics and loss of strength for at least two years following surgery[8]. For these reasons, ACL repair has the potential for fewer surgical complications, and faster return to normal range of

movement (and activity) when compared to reconstruction[9]. In the case of failure (although not necessarily expected), revision surgery for primary repair would allow the subsequent operation to be similar to a primary reconstruction, whereas revision after ACL reconstruction is less optimal due to previous tissue harvest and drilling of bone tunnels[10].

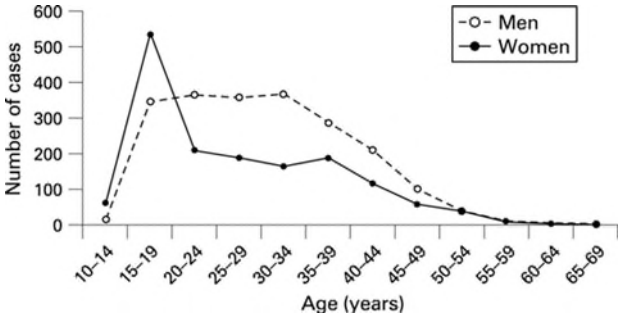
For child and adolescent ACL injuries, there may be potential benefits in maintaining the native ligament after rupture. ACL reconstruction in this age group is associated with both potential growth disturbance (from the drilling of tunnels) and high post reconstruction failure rates[11, 12]. Recent national guidelines on the management of paediatric soft tissue knee injuries recommended ACL repair should be carried out only as part of a prospective study, and existing weak evidence points to a role of this technique in management of proximal avulsions in children[13].

The benefits of ACL reconstruction, as the standard procedure in this population, are well evidenced and documented[14-16].

8.1 Evidence explaining why this research is needed now

While the recent re-emergence of primary research into ACL repair[17-21] demonstrates an encouraging step forward, there is a clear need for a robust RCT to inform treatment within the NHS and globally. The renewed interest from the surgical community is due to improvements in imaging and an enhanced ability to choose correct patient indications for the procedure, in addition to technical advancements. Past ACL repair techniques were tried before accurate MRI information was available to guide patient selection. There are several justifications for conducting this study now; including the repeated calls in the literature for further research[22, 23] and publications in support of early surgery of the ruptured ACL[18]. Research also shows that young active patients, who have early surgery, make a faster return to sport and take fewer days off work[24]. ACL repair is a typical innovative surgical procedure that may find its way into common practice without thorough evaluation. The study answers a research question about comparative effectiveness and cost effectiveness of a relatively new procedure prior to acceptance into mainstream practice. It has potential to show the optimum treatment for this condition, safeguards the uptake of ineffective or high-risk treatment and is in line with the current evaluation ethos at the Royal College of Surgeons (England). A request for additional evidence regarding repair in the BASK /BOSTAA “Best Practice Book for management of ACL injuries - 2021”[25] demonstrates this.

Following consultation with BSCOS, the study has been expanded to include paediatrics from the age of 14 years as the uncertainty between repair or reconstruction is a significant issue for the adolescent population (see Figure 1). This ensures that the study can be generalised to an entire population who may stand to benefit.



[1] **Figure 1: Demonstrating age distribution of ACL injuries[26]**

9 OBJECTIVES AND OUTCOME MEASURES

9.1 Aim

The primary aim of the study is to establish whether ACL repair provides more benefit than ACL reconstruction in patients with recent proximal ACL ruptures of the knee.

Research Question

Does acute ACL repair provide superior clinical outcomes (as measured by the Knee injury and Osteoarthritis Outcome Score (KOOS-4)) at 24 months, and is it cost effective compared to ACL reconstruction in patients with recent proximal ACL ruptures?

Primary and Secondary objectives/outcomes measures

The primary and secondary objectives are outlined below in Section 9.2. The primary outcome measure is the aggregated and averaged score of four of the five sub-scales of KOOS (KOOS-4): pain, symptoms, activities of daily living, and sport and recreation function, at 24 months post randomisation. The secondary outcomes are the five individual KOOS sub-scale scores (KOOS-5), repair/ graft re-rupture rate, re operation, health-related quality of life, time to return to work, time to return to sport, emotional functioning and cost effectiveness (including time away from paid employment and education). Measures include KOOS at 6 and 12 months post-randomisation and over the 24 months period, complications, graft failure, re-operation, EQ-5D-5L, emotional functioning questions taken from KQoL-26, post operative pain, and resource usage. A subjective measure will also be collected on the Surgery CRF to understand 'surgeon confidence' in the ACL surgery performed (recorded on a scale of 1-10).

Activity level will be assessed using the Tegner Scale, graded from 1 (low activity levels) to 10 (professional level). In addition, the Tegner has been modified as follows: three columns with the headings of (1) activity level before your injury, (2) current level of activity (today) and (3) level you expect to return to, were added to the baseline form. At 6, 12 and 24 months, the Tegner contains one answer column as follows: current level of activity (today).

9.2 Primary objective and outcome measure

Objective	Outcome measure	Time point(s) of evaluation of this outcome measure (if applicable)	Data required	Source data (including location)
To assess whether ACL repair provides a superior clinical outcome compared to ACL reconstruction in patients with recent proximal ACL ruptures	KOOS-4 Score: the aggregated and averaged score of four of the five sub-scales of KOOS (pain, symptoms, activities of daily living, and sport and recreation function).	24 months after randomisation	• KOOS-4 Questionnaire	Patient-reported outcome measure (questionnaire). Baseline completed by participant at site and entered by site team or by participant directly into REDCap. Follow-up questionnaires will be completed by participants either on paper or entered directly into REDCap.

9.3 Secondary objectives and outcome measures

Objective	Outcome measure	Time point(s) of evaluation of this outcome measure (if applicable)	Data required	Source data (including location)
Evaluate outcomes related to the knee and changes to scores over time	KOOS score (all five KOOS domains will be quantified at each time point)	6, 12 and 24 months after randomisation	• KOOS Questionnaire	Follow-up questionnaires. Completed by participants either on paper or entered directly into REDCap.
Determine the cost-effectiveness of ACL repair compared to	Resource use data (participant reported questionnaire and clinician reported i.e. surgery and rehabilitation data, complications/readmissio	6, 12 and 24 months after randomisation	• Health Economics Questionnaire • EQ-5DL & -VAS Questionnaire	Follow-up questionnaires. Completed by participants either on paper or entered

ACL reconstruction in patients with recent proximal ACL ruptures	ns, including length of procedure, complication rate; reoperation rate). EuroQol (EQ-5D-5L and EQ-VAS)		Case Report Forms: • Surgery • InPatient • Complications	directly into REDCap. Case Report Form (where the data is not recorded directly anywhere else first) Hospital records (from which data will be summarised into the CRF)
To assess patient emotional functioning following ACL repair or reconstruction surgery	Emotional functioning questions (6 item questionnaire taken from KQoL-26)	Baseline, 6, 12 and 24 months after randomisation	• Emotional Functioning Questionnaire	Follow-up questionnaires. Completed by participants either on paper or entered directly into REDCap.
To assess surgeon confidence in the ACL surgery performed	Surgeon confidence (a single question with the answer recorded on a scale of 1-10)	Day of Surgery	• Surgery Case Report Form	Case Report Form
To determine levels of post-operative pain at 3- and 6-weeks following ACL repair and reconstruction	Post operative pain score	3 and 6 weeks after randomisation	• Pain NRS	Follow-up questionnaires. Completed by participants either on paper or entered directly into REDCap.
To assess return to activity / level of sports following ACL repair or reconstruction surgery	Modified Tegner score Tegner score	Baseline 6, 12 and 24 months after randomisation	• Modified Tegner Questionnaire • Tegner Questionnaire	Follow-up questionnaires. Completed by participants either on paper or entered directly into REDCap.

Time to return to sport	1 question	12 and 24 months after randomisation	• Return to Sport Questionnaire	
To assess patient satisfaction with the outcome of treatment following ACL repair or reconstruction surgery	Patient satisfaction: 2 questions, Likert scale: 1. Would you have the treatment again if you could go back 2. Assessment of knee after versus before (is it better?)	12 and 24 months after randomisation	• Patient Satisfaction Questionnaire	Follow-up questionnaires. Completed by participants either on paper or entered directly into REDCap.
To assess the complication profile and rate for ACL repair and reconstruction in the management of recent proximal ACL tears.	Intervention related complications including re-operation	6, 12 and 24 months after randomisation Operative Postoperatively up to 24 months after randomisation Review at the 24-month time point.	• Health Economics Questionnaire • Case Report Form.	Case Report Form (where the data is not recorded directly anywhere else first) Hospital records (from which data will be summarised into the CRF)
	Objective evidence of graft/repair failure (defined on clinical assessment, imaging or operative assessment	Up to 24 months after randomisation	• Case Report Form.	Hospital records (from which data will be summarised into the CRF)

9.4 Choice of primary outcome/justification for the follow-up period

The primary outcome measure, KOOS-4, is a shortened version of the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire. The KOOS is a standardised assessment tool to evaluate outcomes related to knee injuries and osteoarthritis. The original KOOS questionnaire consists of five subscales that assess different aspects of knee health: pain, symptoms, function in daily living, function in sport and recreation, and knee-related quality of life. Each subscale contains a series of questions rated on a Likert scale to measure the severity and frequency of symptoms or limitations.

The KOOS-4 is a condensed version of the KOOS questionnaire, which includes only four subscales: pain, symptoms, function in daily living, and function in sport and recreation, and has been used extensively within ACL research. It is sensitive to change and can detect group differences in this population[2, 27].

The length of final follow-up for the study (primary endpoint) is 24 months post-randomisation. This gives sufficient time for patients to fully regain all potential function and a stable condition status for

their operated joint. The follow up gives patients' sufficient time to return to the level of sport they will return to and therefore provides a valid investigation time point for post intervention activity level outcomes. In an ideal situation follow up would continue beyond 24 months for longer term outcome and complication rate but the extra information gained (for this question) does not sufficiently offset the resources required within the study for longer term follow up. However, there may be availability of data from registries or NHS sources that allow a longer term (5-year post randomisation) evaluation. The opportunity for this will be reviewed during the duration of the study, and optional consent will be sought for collecting this subject to additional funding.

9.5 Use of core outcome sets (COS)

The outcomes reflect consensus opinion and the reference standard for evaluating ACL injury/reconstruction[28].

10 STUDY DESIGN AND SETTING

The ACL STARR study is a pragmatic multi-centre, two arm, parallel design, superiority, randomised controlled clinical study comparing ACL repair with reconstruction for proximal tears. An internal pilot will be conducted with clear progression criteria targeting recruitment.

The study sample size is 214 patients (107 in each of the two study arms) with acute proximal tears of the ACL. Patients will be identified and recruited following a routine pre-intervention MRI scan which identifies the proximal tear pattern. The research pathway will not differ greatly to routine care up until surgery. During the assessment phase, potential participants will receive standard acute knee injury care (such as advice and symptom management, or simple bracing if needed). This may be offered by surgeons or an appointment with a physiotherapist, according to routine care for the local site.

Surgery will be undertaken as soon as clinically appropriate and possible. Randomisation will be performed intra-operatively following eligibility and suitability assessment. Participants will be randomised to receive ACL repair or ACL reconstruction. We anticipate 25% of those who consent to be deemed unsuitable for repair intra-operatively, we expect approximately 286 patients will need to be consented into the study to reach the sample size of 214 participants. The patients will be recruited from approximately 20 sites in the UK.

A study flow chart is provided in APPENDIX 1 – STUDY FLOW CHART.

10.1 Recruiting sites/site types

Participants will be recruited from Accident and Emergency (A&E) departments, virtual fracture clinics and orthopaedic clinics from approximately 20 NHS secondary care hospitals who see patients with acute knee injuries with a probability of ACL tear.

Refer to Section 27 for information on identification and management of sites.

10.2 Collection of outcome data and follow-up assessments

The flow of the patients through the study and outcome collection timepoints is outlined in the flow diagram (Appendix 1). The patient self-reported questionnaire will include the outcomes indicated above and will be completed by participants at baseline, 6, 12 and 24 months (computer-based / e-mail /paper-based) depending on patient preference) post randomisation and collected by a web-

based platform (REDCap) developed and maintained by the CTU (OCTRU). Data on post operative pain will be collected at 3- and 6-weeks post randomisation via SMS message link /email link or post and recorded in REDCap.

Refer to Section 17 for full details of outcome data collection and follow-up assessments.

10.3 Countries of recruitment

Recruitment to this study will be within NHS secondary care hospitals the UK. It is not anticipated that this study will open in non-UK sites.

10.4 Duration of participant involvement

Participants will be in the study for approximately 24 months from randomisation to last data collection/follow-up questionnaire completion.

10.5 Post-study treatment/care and follow-up

After surgery, all participants will have physiotherapy to help with rehabilitation (as part of routine NHS care).

10.6 Central review procedures

Not applicable for this study.

10.7 Use of clinical registries and national datasets (e.g. NHS England)

Permission will be sought from all study participants for collection of long-term follow-up (up to five years from time of consent) using routinely collected NHS data (from relevant national datasets) to facilitate assessment of long-term outcomes. This is subject to the receipt of additional funding.

10.8 Expected recruitment rate

The anticipated monthly recruitment rate is 1 participant per month per site. We have factored in a lag of one month between consent and randomisation (recruitment) to allow for the waiting time for surgery. It is expected that all sites will be open within 18 months of starting recruitment.

10.9 Equality, diversity and inclusion (EDI) for study participants

Guidance from various sources were used, such as NIHR INCLUDE Ethnicity Framework, and recommendations from the STRIDE (SupporTing Recruitment and retention Improvements for Diverse Ethnicities) project, to inform our EDI strategy for this study. The team aim to embed inclusion within the lifecycle of the project by incorporating the following actions, which would be reviewed regularly throughout the project:

- The team has clearly defined the study population (Section 12) and explored inequalities which are relevant to research with this population. Data from the National Ligament Registry (NLR), previous cohort[29], RCTs (e.g. ACL SNNAP) and research on disparities on ACL injury management[30, 31] (although primarily USA based,) has been used to inform this. The collection of ethnicity data on this patient population is limited and has been highlighted as an area of focus in this study for data collection. Similar approaches to patient and site recruitment used in the recently completed ACL SNNAP will be utilised as data collected was seen to be reflective of the UK ACL injury population described in the literature.

- Aim to include a diversity of voices in the research team, including patient voices with lived experience. The team plan to extend the diversity of our PPI group to reflect the population and expand the focus on PPI input e.g. inclusion of survey data in addition to focus groups to broaden the reach of views.
- Plan for a wide geographical spread of participating sites, utilising the growing community of research active sites (ACL SNNAP) but also identifying and supporting less research ready sites including utilising the Associate PI scheme.
- Collection of EDI data such as age, sex, ethnicity, an Index of Multiple Deprivation (IMD) score, as part of screening-eligibility data. These data will be used to help inform discussions around supporting inclusion of underrepresented groups during recruitment and for use in exploratory subgroup analyses alongside the main analysis e.g. sex, age.
- Development of patient facing recruitment, retention and dissemination materials will be supported by the PPI groups to ensure inclusivity e.g. considering language, creative means of communication [e.g. animation], and a range of approaches to retention such as paper and online to prevent digital exclusion.

10.10 End of study

The end of study is the point at which all Case Report Form (CRF) data relating to the study primary and secondary outcomes has been entered/received and all queries resolved. The study will stop randomising participants when the stated number of patients to be recruited is reached.

The Sponsor and the Chief Investigator reserve the right to terminate the study earlier at any time. In terminating the study, they must ensure that adequate consideration is given to the protection of the participants' best interests.

11 PARTICIPANT ELIGIBILITY CRITERIA

Participant eligibility will be confirmed by a suitably qualified and experienced individual who has been delegated to do so by the Principal Investigator. Potential patients will have undergone shared treatment decision making discussions with clinical personnel and have decided on pursuing a surgical intervention over conservative (non-surgical) treatment for their ACL injury.

11.1 Timing of eligibility assessment

In routine NHS practice, this patient group with acute knee injuries are initially reviewed in A&E. If significant injury is suspected, they are referred to a knee clinic and onward for MRI assessment. This may be a virtual review and is typically within 2 weeks of injury in an acute knee clinic. In this study, potential participants will be identified in A&E, virtual fracture clinics, or in the acute knee clinic. Following their MRI, if a proximal tear is confirmed, they will be deemed as potentially eligible. They will then be provided with verbal and written information. All clinical personnel assessing and managing ACL injured patients at participating sites will be aware of the study and potential for recruitment.

Final confirmation of eligibility will be made in theatre prior to randomisation. ACL surgery will begin with arthroscopy to assess the state of the ruptured ligament and determine if it is suitable for repair.

If it is “repairable” then patients will be randomised to either repair or reconstruction, and the procedure undertaken as allocated.

11.2 Overall description of study participants

The ACL STARR study will recruit adults and adolescents (aged 14 years and above) with a proximal tear of the ACL (Sherman classification Type 1 or Type 2[32]) diagnosed by routine MRI as part of clinical care. Acute knee injuries with a probability of ACL tear will be identified from A&E, virtual fracture clinics, and orthopaedic clinics at NHS hospitals.

Written informed consent must be obtained before any study specific procedures are performed. Participant eligibility will be confirmed by a suitably qualified and experienced individual who has been delegated to do so by the Principal Investigator (PI) based on the below criteria.

11.3 Inclusion Criteria

A patient will be eligible for inclusion in this study if **ALL** the following criteria apply:

- Patients aged 14 years and above
- Willing & able to provide informed consent and comply with study procedures
- Proximal ACL tear pattern diagnosed by MRI suitable for both repair or reconstruction*
- Willing to accept either study arm allocation

*A proximal tear will be diagnosed on review of the MRI scan, and eligibility will be confirmed intra-operatively on arthrospopic inspection, to confirm a Sherman Type 1 or Type 2 tear and acceptable tissue quality for repair (i.e. an intact synovial sheath surrounding the torn ACL as a single unit).

11.4 Exclusion Criteria

A patient with not be eligible for the study if **ANY** of the following apply:

- History of major knee surgery
    - Has had previous knee surgery (other than diagnostic arthroscopy or partial meniscectomy) to the index knee
- Concomitant severe injury to the contra-lateral knee
- High grade multi ligament injury
    - High grade injuries to other ligaments (i.e. medial collateral, lateral collateral, posterior cruciate) in the knee (Grade >2)

11.5 Rationale for inclusion and exclusion criteria

A paediatric population has been included within the study at the request of paediatric knee community and BSCOS, and their recommendations for an RCT in ACL repair[13]. Our lower age limit within this study is 14 years. Adolescent ACL injuries have a high associated re-rupture rate[33, 34] in comparison to the adult age group and evidence exists suggesting repair is an option for avulsion type ACL injuries. This cohort therefore has a high potential benefit from the results of the study. ACL injuries have a low frequency below the age of 14 years (as the bone typically fractures instead when younger). They will be managed within specialist centres who regularly manage adolescent patients.

It is at age 14 years upwards that paediatric knee surgeons would be in equipoise and happy to randomise for repair or reconstruction.

Upper age limit: We have not set an upper age limit to help ensure the study is inclusive and research findings will be applicable to the population. This will be left to a pragmatic decision of the treating surgeon based on clinical presentation.

11.6 Pre-study screening tests or investigations

There are no pre-study screening tests for inclusion in the study.

11.7 Protocol waivers to entry criteria

Protocol adherence is a fundamental part of the conduct of a randomised study. There will be no waivers regarding eligibility (i.e. each participant must satisfy all the eligibility criteria). Changes to the approved inclusion and exclusion may only be made by a substantial amendment to the protocol.

Before entering a patient onto the study, the principal investigator or designee will confirm eligibility. If unsure whether the potential participant satisfies all the entry criteria and to clarify matters of clinical discretion investigators should contact the ACL STARR central CTU study team, who will contact the Chief Investigator or designated clinicians as necessary. If in any doubt, the Chief Investigator must be consulted before recruiting the patient. Details of the query and outcome of the decision must be documented in the Investigator Site File (ISF) and Trial Master File (TMF).

11.8 Clinical queries and protocol clarifications

Contact the ACL STARR central CTU study team for clarification if any instructions seem ambiguous, contradictory or impractical. Clinical queries must also be directed to the central CTU study team. All clinical queries and clarification requests will be logged, assessed and a written response provided. Minor administrative corrections or clarifications will be communicated to all study investigators for information as necessary. For urgent safety measures or changes that require protocol amendment see Section 28.8.

12 SCREENING AND RECRUITMENT

12.1 Participant Identification

Participants with acute knee injuries with a probability of ACL tear will be identified from A&E, virtual fracture clinics, and orthopaedic clinics within NHS hospitals in the United Kingdom.

In normal NHS practice, patients are initially reviewed in A&E. If significant injury is suspected, they are referred to a knee clinic and undergo an MRI assessment. This is ideally within 2 weeks of injury in an acute knee pathway. A guidance note on the identification of proximal tears will be provided to site radiologists and orthopaedic teams. On confirmation of rupture, shared decision making can result in the patient undergoing physiotherapy, either as definitive treatment or as “prehab” before surgery. Patients will receive information on surgical and non-surgical management. Shared decision-making between patients and clinicians will result in a decision to proceed along the surgical or non-surgical pathway (physiotherapy). Should the non-surgical pathway be chosen, patients will continue with care as usual at that site. Should the surgical pathway be chosen, patients will be introduced to the study and consented should they wish to take part.

All clinical personnel assessing and managing ACL injured patients at participating sites will be aware of the study and potential for recruitment. The patients will have the appropriate diagnostic tests and clinic review within an acute knee pathway. As part of site feasibility assessments, we will explore with sites an accelerated patient pathway and confirm their capability and capacity to deliver the assigned interventions within 50 days post-injury (see Section 13.1).

MRI is the normal standard of care for acute knee injuries and most acute knee clinics have access to priority MRI slots (typically used for locked knees, for example). MRI will be used to make the diagnosis of a proximal ACL injury prior to recruitment into the study. Meniscal and cartilage injuries will be noted and managed appropriately. Following MRI, patients will be consented for inclusion in the study if they have a proximal tear that is considered repairable. All patients fulfilling the inclusion will be invited to participate, no patients or groups of patients will be excluded without justification. Written informed consent will be taken from those wishing to participate. Patients choosing not to be part of the study (or ineligible) will continue with routine care. Potentially eligible participants will be identified during routine clinic visits.

12.1.1 Identification of participants during routine clinic visits

Potentially eligible participants identified during clinic visits will be provided with a Participant Information Sheet (PIS) (electronic or paper) by a member of their care team (who may also be a member of the site research team) and asked to consider the study. Where the clinician is not a member of the site research team, any potential participants will be asked permission to pass name and contact details to the site research team who will make contact at a later time point (this may be in person in a clinic or via telephone or video call in accordance with local site practice) or during a further routine clinic visit. Alternatively, potential participants may be given the PIS and asked to call the number on it if they wish to find out more about the study. When a potential participant is approached for permission for their details to be passed onto the site research team – if this permission is given this should be recorded in their clinical notes.

12.2 Re-screening if a potential participant does not meet inclusion/exclusion criteria at first assessment

Not applicable for this study. Re-screening of ineligible patients is not permitted.

12.3 Use of screening logs

A screening log (within the REDCap data collection system) will be used to detail eligibility and acceptance to the study. This log will include any potential participants that are identified as ineligible, with the reason for being ineligible recorded; ii) all patients approached for a discussion about the trial, including reasons why eligible patients are not approached; iii) all patients accepting or declining participation including reasons for declining if given. For those identified as eligible, their ethnicity and gender will be recorded. Sites will also ask for their postcode (to calculate an IMD score – England only) but their postcode will not be recorded on the screening log. A screening number will be assigned to each patient screened.

13 STUDY INTERVENTION AND COMPARATOR

Once recruited and consented for the study participants will undergo the allocated ACL surgery which will be performed by a specialist soft tissue knee surgeon.

Lateral Extra-Articular Procedure (LEP)

A lateral extra articular procedure (LEP) will be an option for all participants in both groups. We will leave the decision to offer or perform a LEP to the treating surgeon, based on increased risk factors (age, participating in competitive pivoting sport, grade two, pivot shift or greater, generalised ligament laxity (Beighton score of four (4) or greater)). We expect the LEP to be balanced within both groups, and to be planned before randomisation. If LEP is planned (due to surgeon preference or a patient being considered at high risk of graft/repair failure) then this will be discussed and documented pre-operatively on the screening-eligibility form.

Prioritisation Score

We have engaged with the BASK Prioritisation Working Group to clarify ACL repairs. ACL repair has now been categorised by them as a "P2 procedure"[35]. This means that ideally, the procedure should ideally be undertaken within four weeks of listing for surgery (depending on local circumstances). However, we are aware of the pressures on NHS waiting lists and we take a pragmatic view that timing of surgery should align with local current practice for P2 waiting lists (but surgery must be undertaken no more than 50 days post-injury).

Both procedures will begin with arthroscopy to assess the state of the ruptured ligament and determine if it is suitable for repair. If it is "repairable" then patients will be randomised to either repair or reconstruction using a hamstring graft (primary intention, although the use of alternative grafts is acceptable in exceptional cases (i.e. graft failure during surgery)). Other damaged intra-articular structures, such as meniscal tears, will be dealt with by the treating surgeons in the normal way in both procedures. The study is pragmatic and allows for surgeons to perform the repair and reconstruction fixation using techniques for which they are most comfortable (see the ACL STARR Surgical Manual). This will reflect UK practice. Any devices used will be recorded on a surgery case report form (CRF).

13.1 ACL repair (intervention)

Participants randomised to ACL repair will have surgery to repair the ACL, with the ligament being stitched back onto the bone. This study specifies that surgery (for both repair and reconstruction), is undertaken no more than 50 days post injury (please see Section 28.7 for details of protocol deviations). This is a pragmatic approach, aligning with existing literature, which indicates that time to surgery is an important factor in primary repair outcomes (6), while also being mindful of the pressure on NHS waiting lists.

There are several techniques to re-attach the ACL to its footprint. Each technique may require different instruments and devices, but all have the same principle of re-attachment. The study is devoid of commercial interest with no single preferred technique or device. The techniques that can be used are well described within the literature, and included in the Surgical Manual. All surgeons will have the necessary skill set and experience to undertake the repair (peer review). We will not be allowing new

or innovative techniques to be undertaken within the study. Currently, only the two most common repair techniques are approved for use in ACL STARR. This decision was made following consensus consultation and to ensure consistency and external validity. The two options are: 1) suture anchors or 2) transosseous suture repair. The list (in the Surgical Manual) will be kept under review by the Trial Management Group (TMG) and discussed with the Trial Steering Committee (TSC) throughout to ensure the current list is representative of current practice.

Feedback from the surgeon co-applicants highlighted that repair can be a technically challenging procedure and, on occasion, can be abandoned midway through operation. We are aware of this potential crossover and have attempted mitigation in both patient selection criteria and analysis. Oversight of the potential for crossover will be maintained especially in the initial pilot phase.

13.2 ACL reconstruction (comparator)

Participants randomised to ACL reconstruction will have surgery to reconstruct the ACL. This will involve replacing the torn ACL with other tissue to act as a replacement.

For this study, we have specified the use of a hamstring as the graft choice (primary intention), although the use of alternative grafts is acceptable in exceptional cases (i.e. graft failure during surgery). Hamstring reconstructions make up the majority >80% of UK ACL reconstructions[36].

A similar approach will be taken for lateral extra articular tenodesis, if necessary. The adjunct procedure will not be restricted or guided but documented in the surgical case report form.

Post-operative Rehabilitation

A systematic review of post operative rehabilitation for ACL repair was undertaken ahead of the start of this study[37]. No evidence exists for an accelerated or different rehabilitation program to that for ACL reconstruction. Therefore, a similar pragmatic approach to post-operative rehabilitation will be undertaken in both groups, with the number of sessions recorded in a case report form (CRF) and captured in participant questionnaires.

Participants will be referred and undergo physiotherapy by a (or under supervision of) a senior physiotherapist with experience of ACL injury regimens. Routine rehabilitation protocols used at the participating site will be followed. Physiotherapists will also be blinded to the procedure undertaken for each patient. The post operative rehabilitation protocol will include the following components to achieve mandatory aims/goals:

1. Control of pain and swelling **2.** Regaining range of movement **3.** Improving neuromuscular control **4.** Regaining muscle strength **5.** Achieving normal gait pattern **6.** Returning to function/activity/sport with clearly identified progression milestones and return to sport criteria.

As there is little consensus in the literature over the most effective rehabilitation protocol, variation in specific exercises and use of adjuncts (such as cryotherapy) to reach these aims is permitted. Flexibility is permitted to adapt treatment to individual needs with no timelines specified for progression. Information about the number of sessions each individual attends, and the date of discharge from physiotherapy will be documented in the CRF (for on-site physiotherapy); the number of sessions attended will also be requested via participant questionnaires (to record the number of community-

based physiotherapy sessions). Rehabilitation guidance will be forwarded to site physiotherapists (see Appendix 2).

14 INFORMED CONSENT

14.1 Consent Procedure

Informed consent will be sought and will be collected by a member of the site research team listed on the delegation log from each participant before they undergo any study-related procedures or interventions related to the study. A member of the site research team will explain the details of the study, direct the participant to the explainer animation, in addition to the already presented Participant Information Sheet (PIS), ensuring that the potential participant has sufficient time to consider participating or not. A member of the site research team (authorised to do so on the delegation log) will answer any questions that the potential participant has concerning study participation.

The study will be open to patients from 14 years of age if they meet the inclusion criteria. Specific participant information and consent forms has been designed for young people. All consent and participant information has been carefully designed with the support of our PPI panel and team members, to ensure that those invited to take part will be well informed prior to providing consent.

For adolescents aged under 16 years, their parent/guardian will be provided with the Parent/Guardian PIS and asked to sign the Parent/Guardian Consent Form (on behalf of adolescents aged 14-15 years), and the adolescent will be provided with the 14-15 years PIS, and an assent form to sign. If any adolescent indicates dissent or indicates they do not want to take part, they will not be included in the study.

For adolescents aged 16 years and over and deemed to be competent to give consent to participate (based upon their capacity to understand the specific circumstances and details of the research being proposed), they will be provided with the adult PIS and asked to sign the adult Consent Form and give their own consent to participate.

Adolescents that consented when aged 14-15 years but reach 16 years during the study, will be contacted (via their Parent/Guardian) by sites and asked to consent to continue their participation by signing the Continuing Consent Form (for ages 16 years). Remote eConsent and paper options will be available. If the participant does not want to continue in the study, they will be withdrawn from the study following the process outlined in Section 17.6.

14.2 Time allowed to decide to take part

It is important that potential participants are under no pressure to decide whether they want to take part, so no time limit is applied, however, investigators should be mindful of the expedited nature of the pathway of this study.

14.3 Completion of the Informed Consent Form

The potential participant or parent/guardian (where applicable) and the Investigator (or authorised designee) must personally sign and date the current approved version of the informed consent form.

The Informed Consent Form will usually be offered to participants in clinic as an electronic form on a tablet device (with the consent form being filled in directly on REDCap), however, paper consent forms will also be made available for use in situations where electronic consent is not possible or suitable. Where it is not possible for a consent form to be completed in clinic (for example, if a participant has only had telephone appointments), remote electronic consent may also be used.

Where consent forms are completed electronically signatures will be either achieved by a finger tracing across a tablet device, using an electronic stylus on a tablet device or using a mouse dragging the cursor across the screen – all methods are to be used as if signing with a traditional pen.

A copy of the fully signed consent form will be given to the participant, and the central CTU study team (if the participant has agreed to either of the optional aspects of consent - see Section 14.4).

Where electronic consent (using REDCap) is used in clinic and the participant or parent/guardian has an email address, they are willing to provide, an electronic version of the signed ICF will be automatically emailed to them. If the participant does not have/does not provide an email address the site research team will be able to print a copy of the signed ICF and provide this to the participant. A downloaded copy of the electronic consent should be placed in the Investigator Site File and a copy in the participant's medical record.

Remote eConsent (using REDCap) will be obtained in accordance with OCTRU's standard operating procedure for obtaining consent. Where remote consent will be used, potential participants will be asked to provide an email address for receiving consent documents prior to obtaining written informed consent. Potential participants will receive a unique link via email to an electronic consent form which may then be completed remotely. Once completed this form will be countersigned by a member of the site research team authorised to do so and then sent, via email, to the participant as a PDF document. A member of the site research team will be required to countersign all consent forms completed remotely, in the same way as for paper forms, and verify the identity of the participant. Patients who do consent to study participation will receive a copy of the fully completed consent form via email once this has been countersigned.

For those that receive a link but decide not to take part, their email address will be deleted from the data collection system no later than four weeks after the form has been emailed.

14.4 Optional aspects of consent

The participant/parent/guardian may agree to be contacted (upto the time their child turns 16 for parents/guardians) about ethically approved research studies for which they may be suitable (for up to five years from the point after the study has finished). By agreeing to be contacted this would not oblige them to participate in any further studies. The participant may also agree to the retention of their NHS/CHI number for up to five years from entry into the study to enable long term follow up using routinely collected NHS national data.

Both are optional aspects of the consent process. Participation in these elements of the research is voluntary and refusal to participate will not affect their inclusion in the clinical study. Refusal to participate will involve no penalty or loss of benefits to which the individuals would otherwise be entitled or their standard management in any way.

14.5 Individuals lacking capacity to consent

Individuals lacking capacity to consent to study participation will not be eligible to enter the study.

14.6 Participants who lose capacity during the study

Participants who consent and are included in the study who lose capacity during the study will be withdrawn and have their data available for use up until the point when they lose capacity. After this point ongoing consent is not valid.

14.7 GP notification

Permission from the participant will also be obtained to inform their GP of their inclusion in the study. An approved GP letter will be sent by the ACL STARR central CTU study team together with study information to the participant's GP surgery informing them of their participation in the study for those that go on to be randomised.

14.8 Re-consenting

Should there be any subsequent amendment to the final protocol, that might affect a participant's participation in the study, continuing consent will be obtained using an amended consent form which will be signed by the participant.

Continuing consent will also be sought from those participants who reach their 16th birthday during the intervention period or during follow up, who were originally consented into the trial by their parent or guardian.

15 RANDOMISATION

15.1 Timing of randomisation

Randomisation will only be performed when informed consent has been obtained, once baseline questionnaires have been completed and final eligibility confirmed in theatre.

15.2 Randomisation procedure

Initial eligibility / final eligibility will be confirmed at the point of randomisation. Participants will be randomised by the site research team using REDCap.

Participants will be randomised to one of the following arms:

Arm	Treatment (or Description)
Arm 1 ACL Repair (intervention)	This group will have surgery to repair the ACL, with the ligament being stitched back onto the bone.
Arm 2 ACL Reconstruction (usual care/comparator/control arm)	This group will have surgery to reconstruct the ACL. This will involve replacing the torn ACL with other tissue i.e. hamstring to act as a replacement.

Upon randomisation of a participant, the ACL STARR central CTU study team and a member of the site research team will be notified by an automated email. Full details of the randomisation procedure will be stored in the Randomisation and Blinding Plan in the confidential statistical section of the TMF.

15.3 Randomisation methodology

Participants will be randomly allocated to one of two treatment options (1:1) via automated, secure (encrypted), web-based randomisation provided by the Oxford Clinical Trials Research Unit (OCTRU) using a REDCap platform.

Random allocation will be implemented using a minimisation algorithm with stratification factors: pre-injury Tegner score (2 groups (0-6, 7-10)), planned lateral extra-articular procedure (yes, no) and site. The minimisation algorithm will be seeded with several allocations and a non-deterministic probabilistic element will be introduced to prevent predictability of the treatment allocation.

Patients not randomised in theatre will be managed along the normal standard of care pathway.

15.3.1 Justification for stratification factors

Stratification by pre-injury Tegner score will ensure that the groups will have equal allocations of high (7-10) and low (0-6) pre-injury activity scores, where scores greater than 7 indicate participation in competitive sports.

Stratification by planned lateral extra-articular procedure (yes, no) will ensure that the groups will have equal allocations of an optional additional surgical procedure included at the surgeon's discretion. It is not known if this factor is a confounder.

Stratification of site will ensure that differences in caseload and site level care (pre, post operative) is balanced between treatment groups. This may also help with any differences in costs associated with either group at site level.

15.4 Back-up randomisation/registration procedure

Sites will call the Central CTU Study Team based in Oxford if REDCap is offline or not available. An emergency randomisation list prepared by the study statistician, and held securely by the Central Study Team, will be used.

16 SUB-STUDIES/TRANSLATIONAL STUDIES/MECHANISTIC STUDIES

No sub-studies (related to the study) are currently included.

17 STUDY ASSESSMENTS/PROCEDURES AND DATA COLLECTION

The study flow chart can be found in Appendix 1 of this protocol.

17.1 Overview

Table 1 shows scheduled assessments for the study.

Table 1: *Schedule of assessments*

Assessments	Screening	Baseline	Day of Surgery	3- & 6-weeks post randomisation	6 months post randomisation	12 months post randomisation	24 months post randomisation
Screening - Identification	*						
Screening - Eligibility	*						
Patient information given	*						
Consent		*					
Eligibility confirmation			*				
Randomisation			*				
Surgeon confidence in the ACL surgery performed (Surgery CRF)			*				
Demographics	*						
Post operative pain (pain NRS) via SMS message, email or post				*			
KOOS (Patient Questionnaire)		*			*	*	*
EuroQol-5D-5L / VAS (Patient questionnaire)		*			*	*	*
EuroQol-5D-5L / VAS | Retrospective Baseline - Pre-injury (Patient questionnaire)		*					
Emotional functioning (Patient questionnaire)		*			*	*	*
Tegner (Patient questionnaire)					*	*	*
Modified Tegner (Patient questionnaire)		*					
Patient satisfaction (Patient questionnaire)						*	*
Time to return to sport (Patient questionnaire)						*	*
Physio attendance (completed once the pt has been discharged from post-op physiotherapy, or at 24 months post-randomisation)						*	*
Resource use /Health economics (Patient questionnaire)					*	*	*
Intervention related complications including re-operation (Patient questionnaire -> Hospital records check -> Complications CRF)					*	*	*
+ Intra-operative complications (Surgery CRF) + Post-operative, pre-discharge complications (InPatient CRF)			* *				
Intervention related complications including re-operation (Hospital records check -> Complications CRF)							*
Safety data collection			*		*	*	*
Objective evidence of graft/repair failure (defined on clinical assessment, imaging or operative assessment) (Hospital records check) (if required)			*		*	*	*

17.2 Data Collection

17.2.1 Baseline

Baseline assessments may be completed in the outpatient clinic, pre-operative assessment clinic, designated research clinics or on the ward during admission for surgery. Patient demographics will be captured at baseline and in part used to describe the population included and assessed to evaluate equality, diversity, and inclusion of participants taking part. The KOOS, EuroQol EQ-5D-5L, emotional functioning questions taken from KQoL-26 and Modified Tegner, collated as a Baseline Questionnaire, will be collected prior to randomisation. Ideally, the Patient-Reported Outcome Measures (PROMs) will be completed in clinic but, if the participant requests to complete the PROMs outside of clinic (either on paper or electronically), this is permissible, but they will have to return the completed form to site staff prior to randomisation.

17.2.2 Follow-up assessments/subsequent visits

Follow up for study purposes will be by patient self-reported questionnaire completed using a web-based data collection system (REDCap). The option of being able to fill out the follow-up questionnaires in a hard copy and returning via post will also be available. The questionnaires will contain the following outcome measures: KOOS, EQ-5D-5L/VAS, emotional functioning questions taken from KQoL-26, Tegner, and will be sent out at 6-, 12- and 24-months post randomisation to all participants. Patient satisfaction and return to sport outcome measures will be added to the 12- and 24-month questionnaires. The questionnaires will also ask participants if they have returned to see a health care professional or been admitted to hospital in relation to complications with their study knee, and time away from paid employment and education. The central CTU study team will follow up any complications reported by participants with the research team at the participant's local hospital. Further details about the event will be collected and recorded on a complications form.

A final readmission checklist will be undertaken by the Research staff on hospital records at 24 months post randomisation to ensure that all complications data is collected from all participants (i.e. those who had not returned a questionnaire). Data from any readmission events identified will be recorded in a "Complications" CRF. The physiotherapy case report form (PCRF) will be used to record the number of post-operative rehabilitation physiotherapy sessions attended, and the date of discharge from physiotherapy. If a participant attends community-based physiotherapy, the number of sessions attended will be reported via the patient questionnaires.

Patients will also be asked to complete a pain numerical rating scale to report their post operative pain at 3- and 6-weeks post randomisation. A link to complete the score online will be sent by either SMS, email or post. Contact preferences will be recorded in REDCap after consent.

17.3 Study questionnaires

Participants will be emailed a link to complete their study questionnaires electronically where possible (participants will be asked at their baseline visit whether they wish to complete follow-up questionnaires electronically or on paper with postal return). Any links sent to a participant either by email or text to a questionnaire is unique to a participant and their timepoint/questionnaire in the study. Paper administered questionnaires may also be used if requested, where use of electronic

means is not possible or suitable. Where paper-based questionnaires are used, data will be entered into REDCap by the central CTU study team.

17.4 Communication with study participants by the CTU study team

Participants will be notified to complete study questionnaires by email, or where they have selected to receive postal questionnaires, these will be posted to the participant. Participants may be sent up to two reminder messages and/or where possible may be asked to complete questionnaires during a routine clinic visit. Participants that do not complete their study questionnaires, may be telephoned and/or texted to collect the data or request return of the questionnaire.

17.5 Qualitative assessments

No qualitative research will be performed as part of the study.

17.6 Withdrawal

Withdrawal of consent means that a participant (and/or their parent/guardian) has expressed a wish to withdraw from the study altogether or from certain aspects of the study only. The type of withdrawal will be collected on the CRF labelled 'Withdrawal'.

Participants may also be withdrawn from the study (or aspects of the study) by their clinician if they believe the participant needs to be withdrawn.

The Withdrawal CRF should be completed to document the reasons for withdrawal and state who the decision to withdraw was made by. Discussions and decisions regarding withdrawal should be documented in the participant's medical notes. Investigators should continue to follow up any SAEs and should continue to report any SAEs to resolution in the CRF in accordance with the safety reporting section.

Where a participant expresses a wish to withdraw from the study, the research team will determine which aspect(s) of the study the participant wishes to withdraw from.

The aspects of the study that the participant may request to withdraw from are as follows:

- No longer willing to have surgery
- No longer willing to complete study questionnaires
- No longer willing to attend study visits
- No longer willing to be contacted by the research team to obtain CRF/outcome data
- No longer willing to have routine data from the medical record provided to the study
- No longer willing for routine data from health data providers e.g. NHS England, to be provided to the study

Where a participant wishes to withdraw from all aspects of study participation detailed above this will be recorded on the Withdrawal CRF as full withdrawal.

In addition to participant self-withdrawal, an investigator may decide to withdraw a participant from study intervention for clinical reasons or other reasons such as non-compliance, eligibility. Participants and their parent/guardian will still be asked to participate in the collection of follow-up data. The reason for withdrawal will be recorded on the study withdrawal case report form.

Completion of the Withdrawal CRF by the site research team will trigger a notification to the central CTU study team. Appropriate action will be taken by the study teams (centrally at the CTU and by the site research team at each participating site) to ensure compliance with the participant's withdrawal request. This may include marking future CRFs as not applicable and ensuring any relevant communications which the participant had consented to receive regarding their participation are no longer sent.

Data collected up to the point of withdrawal will be used/analysed as explained in the PIS, unless the participant specifically requests otherwise.

18 BLINDING AND CODE BREAKING

18.1 Blinding

Table 2 provides an overview of the blinding status of all individuals involved in the conduct and management of the study.

Table 2: *Blinding status of those involved in study conduct and management.*

Role in study	Blinding status	Additional information
Participants	Blinded	All participants will be blinded to treatment allocation. In-theatre randomisation precludes any potential for patients to be unmasked or biased from cues prior to the operation. Patients will have a blinded operation note within their hospital medical records with the detailed operation case report form kept within the study paperwork.
Site research staff including Principal Investigator (may need to be broken down further if different levels of blinding/unblinding with the team)	Not blinded: Surgeons Blinded: aftercare personnel (physiotherapy), patient follow up and research staff	It is not possible to blind the surgeons as to the procedure that they perform, but aftercare personnel (physiotherapy), patient follow up and research staff will be blinded to allocated intervention. Patient notes will refer to 'ACL surgery' not the treatment allocation. CRFs accessed by research staff will also not contain the treatment allocation. Following randomisation, an email will be sent to the PI (unblinded for participants they randomise only) and/or member of the site research team performing the randomisation (as delegated) confirming treatment allocation.
Chief Investigator	Blinded for those at sites other than their own, except for any SAE causality assessment	It is not possible to blind the Chief Investigator as they may be the primary clinician for those participants recruited at their site, however they will be blinded to allocations for participants at other sites. In instances where serious adverse events are reported, the CI will become unblinded to complete the full causality assessment.

Data collection system programmer	Not blinded	The programmer is responsible for the management of the randomisation system and the REDCap data collection system and will have access to all unblinded datasets within both systems.
ACL STARR Central CTU Study Team	Not blinded	Will not be blinded to the allocation. Serious Adverse Event reports will be handled by the central CTU study team.
Data Management	Not blinded	Data management staff will have access to the unblinded datasets within the study randomisation system and REDCap to ensure data quality and undertake central monitoring activities.
Study Statistician and Senior Study Statistician	Not blinded	The study statistician and senior study statisticians will have access to treatment allocations or data needed for generating the Data and Safety Monitoring Committee (DSMC) closed reports and the final analysis.
Health Economist	Not blinded	The study health economist will have access to treatment allocations or data needed for generating the final analysis.

18.2 Code break/ unblinding

The operating clinician and the central study team will not be blinded to the allocation, so no code break procedure for clinical care or safety reporting is needed. The central study team will discuss specifically with each site which techniques they will employ to ensure participant and staff blinding. In any case in which unblinding is needed, or in which it occurs accidentally, the study team will follow processes as per the OCTRU Standard Operating Procedures (SOPs).

19 SAMPLES

This study protocol does not involve any taking of new biological samples or any use of pre-existing samples.

20 IMAGING

MRI is a standard of care investigation for patients with acute soft tissue knee injury. An MRI scan will be used as part of the assessment for initial eligibility assessment (see Section 11.3).

No images additional to standard care will be taken/collected as part of the study.

21 SAFETY REPORTING

21.1 Safety reporting period

For safety reporting the intervention is defined as ACL repair or reconstruction surgery (and post operative rehabilitation).

Safety reporting for each participant will begin from surgery and will end when the participant has reached their final main follow-up time point, at 24 months post-randomisation.

21.2 Definitions

***Table 3**: Definitions of Adverse Events*

An adverse event (AE)	Any untoward occurrence in a clinical study participant. *Note: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporarily associated with the study procedures, whether considered related to the procedures.* For ACL STARR, AEs will only be collected if relevant to the knee, the surgery, the anaesthesia or the rehabilitation and will be captured as complication data. It will be recorded on a complication CRF.
Related Adverse Event	An event that resulted from administration of any of the research procedures
Serious Adverse Event (SAE)	An AE that: • results in death • is life-threatening[1] • requires hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect; or • is otherwise considered medically significant by the Investigator[2]
Unexpected Related Serious Adverse Event	A serious adverse event related to the study (i.e. resulted from administration of any of the research procedures) and is unexpected (not listed in the protocol as an expected occurrence).

[1] participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe

[2] Medical events that may jeopardise the participant or may require an intervention to prevent one of the above characteristics/consequences.

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined using the criteria above. Hence, a severe AE need not necessarily be serious.

21.3 Expected adverse events

The expected adverse events related to the procedures are outlined below, and will be collected as complication data on CRFs, separating intra-operative complications, post-operative pre-discharge complications, and post-discharge complications. All complications will be graded using a standard classification, 'The Clavien-Dindo Classification of Surgical Complications'[(38)]. Participants will be informed of the standard risks associated with the anaesthetic and the surgical procedure.

- All ACL repair or reconstruction procedures whether primary surgery or revision carry a risk of anaesthesia related problems which can include death, morbidity including wound infection, bleeding intra and post operatively, pulmonary embolism (PE), deep vein thrombosis (DVT), confirmed cerebrovascular accident (CVA), confirmed myocardial infarction (MI), and complications secondary to existing comorbidity e.g. ischaemic heart disease, septicaemia, the need for blood transfusion and revision operation.

- Specific complications following both ACL reconstruction and ACL repair procedures include: patella fracture, patella tendon avulsion, anterior knee pain, vascular injury and bleeding, femoral tunnel blowout, nerve damage (including numbness or weakness), complex regional pain syndrome, lack of extension/fixed flexion deformity, stiffness, infection, graft failure and continued instability, delayed wound healing, continued or worsened pain, fracture, compartment syndrome, swelling, additional contralateral graft harvest (reconstruction-only) and newly acquired meniscal pathology.

- Specific complications following rehabilitation include continued instability and subsequent newly acquired meniscal pathology causing pain. These complications may result in the need for further surgery.

21.4 Reportable AEs/SAEs

If participants experience any of the expected events listed in Section 21.3 and they also meet the definition of serious they would not be reportable to the REC. Only unexpected SAEs related to the study procedures are reportable to the REC.

As outlined above any expected adverse events related to the procedures will be collected as complication data on a CRF.

21.5 Procedure for collecting safety events from sites/participants

Details of all complications will be collected and recorded as detailed in Section 21.3. A final readmission checklist will be undertaken by the Research staff on hospital records at 24 months post randomisation to ensure that all complications data is collected from participants (i.e. those who had not returned a questionnaire). Data from readmission events identified will be recorded in the CRF.

21.6 Reporting of SAEs from sites to the CTU study team

Only serious adverse events considered by the site investigator to be related (possibly, probably, or definitely) to the study intervention/any of the research procedures will be reported immediately to the central CTU study team. Such events will be reported immediately to the study team as follows:

SAEs will be reported by the site research team using the SAE form within REDCap within 24 hours of becoming aware of the event. The CTU is automatically notified of the SAE report via REDCap. A paper SAE form should be used as a back-up if the SAE form is not available electronically. This should be emailed to central study e-mail (aclstarr@ndorms.ox.ac.uk) within 24 hours of becoming aware of the event. The central CTU study team will acknowledge receipt of any SAEs reported via email within one working day and provide the site with a unique SAE Log number.

Refer to Section 21.4 for events that do not require reporting.

21.7 Assessment of SAEs by the Principal Investigator (or delegate)

The Principal Investigator (or delegated individual) is responsible for assessing all reported serious adverse events for seriousness, causality and expectedness.

21.7.1 Relatedness/causality

The assessment of “relatedness” to the study intervention is the responsibility of the PI at site or an agreed designee according to the following definitions:

Relationship to intervention	Attribution (Causality)	Description
Unrelated	Unrelated	The AE is clearly NOT related to the intervention
	Unlikely	The AE is doubtfully related to the intervention
Related	Possible	The AE may be related to the intervention
	Probable	The AE is likely related to the intervention
	Definite	The AE is clearly related to the intervention

21.8 Review of SAEs by the Sponsor/CTU Nominated Person

An appropriately qualified person will review the SAE and raise any queries with the reporting site. If the site has not provided an assessment of causality and has not responded to the query, it will be assumed that the event reported is related to the study procedures/intervention. The site will be encouraged to respond and if a response is not provided the CI will be consulted by the CTU and the CTU will complete the Sponsor part of the SAE report.

21.9 Reporting of SAEs to the Research Ethics Committee (REC)

All intervention/study procedure related SAEs will be recorded and reported to the REC as part of the annual reports. All SAEs that are assessed as related and unexpected will be submitted to the REC within 15 days of the CTU/Sponsor becoming aware of the event.

21.10 Unblinding of SAEs for reporting to the REC

Any serious unexpected SAEs that require reporting to the REC will be unblinded for reporting purposes. Unblinding will be performed, documented and communicated in accordance with OCTRU Standard Operating Procedures.

21.11 Follow-up of Serious Adverse Events

If the SAE is an unexpected, related event then follow up information must be provided as requested by the central CTU study team. A follow-up report must be completed when the SAE resolves, is unlikely to change, or when additional information becomes available.

22 PREGNANCY

If a participant does become pregnant during their participation in the study, it does not need to be reported due to the nature of the intervention as concluded in the risk assessment of the study.

23 STATISTICAL CONSIDERATIONS

23.1 Statistical Analysis Plan (SAP)

The statistical aspects of the study are summarised here with details fully described in a statistical analysis plan (SAP) that will be drafted early in the study and finalised prior to the final analysis data lock, or any planned interim comparative analyses. The SAP will be written by the Study Statistician in accordance with the current OCTRU SOPs. The TSC and DSMC will review and, if necessary, provide input into the SAP.

23.2 Sample Size/Power Calculations

The sample size calculation was premised upon a 1:1 randomised parallel group trial design with an analysis of the primary outcome (KOOS-4) using mixed-effects linear model adjusted for randomisation variables and baseline KOOS-4. Standard nominal 2-sided 5% significance level was adopted, and the power for detecting a between group difference of 8 and 9 points in the KOOS-4, was assessed for a missing data allowance of 15%.

We considered a variety of scenarios varying the adjustment for baseline correlation and desired statistical power. (See Table 4 below for a selection)

Table 4 *– Sample size scenarios; all based upon 2-sided 5% significance level, 1:1 allocation continuous outcome, pooled SD of 20, and non-central-t distribution calculation [Stata power two means command]*

No.	Target difference	Statistical Power	Missing data allowance	Adjusted for baseline	Sample size required (overall)
1	8	80	15%	No	236
2	8	90	15%	No	314
3	9	80	15%	No	186
4	9	90	15%	No	248
5	**8**	**80**	**15%**	**Yes**	**204**
6	8	90	15%	Yes	272
7	9	80	15%	Yes	162
8	**9**	**90**	**15%**	**Yes**	**214**

An overall sample size of 236 and 186 is required for 80% power for a difference of 8 points and 9 points respectively given a pooled standard deviation (SD) of 20 points. Equivalent 90% power, required number of observations are 314 and 248 respectively.

However, the expected sample size required is lower given the planned adjustment for baseline KOOS-

4 score as the effective variability is reduced. Implementing this using the formula provided by Borm[39] using a correlation between baseline and follow-up score of 0.37 leads to requiring only 204 and 272 for 80% and 90% power for a target difference of 8 points or equivalently 162 and 214 (all other assumptions and inputs as before) for 9 points difference. Therefore, we have opted for a sample size of 214 (no. 8, table 2) randomised participants which allows for 15% missing data for a target difference of 9 points (at 90% power). This sample size also ensures more than 80% power for a target difference of 8 points (no. 5, Table 2).

We anticipate that 25% of those who consent to be assessed as unsuitable for repair intra-operatively, we expect approximately 286 will need to be consented. The intraoperative assessment at arthroscopy has been shown to be crucial to determine the repairability of the ligament and reduce failure rate[40].

Justification of sample size inputs

Target difference: The selected target difference was informed by a review of the relevant literature conducted for the ACL SNNAP study which was updated for this submission. The Minimal Important Change (MIC) for the KOOS score is 8-10 points. Estimates of the Minimal Detectable Changes (MDC) for the two KOOS subscales most relevant for ACL deficiency (ACLD) vary between 5 and 12 points (Symptoms= 5-8.5 and Sport/Rec=6-12)[41]. A more recent review of the literature specifically for studies assessing meaningful values in the KOOS and other candidate patient reported outcome score for ACL tears or traumatic meniscus injuries) did not indicate a different value for KOOS or that another outcome had better research on meaningful differences[42]. Study findings agree with a search in PubMed review conducted for the study funding proposal (13 June 2023) of studies assessing clinical important differences in the KOOS score. The recently published ACL-SNNAP demonstrated that a mean difference of 8 points is possible between interventions and that this magnitude of difference related to tangible differences in other knee specific patient reported outcome, generic measure of patient satisfaction (would you have the treatment again if you could go back, and assessment of knee after versus before). We note that while figures such as 0.2 or 0.3 SD are regularly quoted patient-reported quality of life measures do differ in their underlying properties, and estimates for important differences in the literature have varied[43]. It has been suggested that 0.5 SD is a more appropriate standard deviation (SD) for the minimally important difference for quality of life[44], which would equate to a target difference of around 10 points here if implemented (i.e. “Cohen’s effect size” distribution approach). We have used target difference values of 8 and 9 points when considering various sample size scenarios which the current evidence on important differences and responsiveness suggest are reasonable estimates of a minimal clinically important difference (MCID) for the KOOS-4 outcome.

Standard deviation: The (pooled) SD value of 20 was based upon the observed value in the ACL SNNAP study at 18 months (19.9 pooled SD). Given the target population in ACL STARR is more homogenous the SD may well be slightly lower.

Correlation between KOOS-4 24 month and baseline scores: This was based upon KOOS-4 data from the ACL SNNAP study. The 6-, 12- and 18-month KOOS-4 scores had similar Pearson correlation values to baseline (0.42, 0.41 and 0.37 respectively). We used the lowest of these values 0.37 in the corresponding sample size calculations.

Missing data: The selected sample size of 214 (randomised) incorporates an allowance of 15% missing data by 24 months. Based upon previous studies this seems a reasonable level. ACL SNNAP had 22% missing data at 18 months though the follow-up pathway for reconstruction/repair is different from rehabilitation. Additionally, we believe we have improved our retention process from this study and believe 15% is a realistic level.

Intraoperative suitability: Finally, the number needed to be randomised was inflated to allow for unsuitability for repair being identified intraoperatively. The required randomised number (214) was inflated by 25% to 286. This is due to the loss of integrity of the synovial sheath that surrounds the ACL. The figure of 25% unsuitability was based upon previous research. Ateschrang et al[40] show the importance of the synovial sheath in determining the repairability of the ligament, and subsequent outcomes.

23.3 Description of Statistical Methods

The statistical analyses will be performed once the 24 months follow up has been reached by the last patient and sufficient time has been allowed for data collection and cleaning.

Results will be reported in line with the Consolidated Standards of Reporting Trials (CONSORT) statement and any appropriate extensions and will be described fully in a separate Statistical Analysis Plan. The SAP will be finalised prior to un-blinding of the data to clinical investigators and after consultation with investigators and other relevant stakeholders.

Nominal 2-sided 5% significance level will be used throughout. Subgroup analyses will be indicated as exploratory and non-planned analyses as “post-hoc”.

Intention-to-treat (ITT) will be the main analysis strategy and will be adopted for the primary and all secondary outcomes. In other words, the analysis will principally be focussed on a treatment policy estimand. As patients are randomised in theatre, following surgeon confirmation of suitability, non-compliance is expected to be minimised and intercurrent events more limited than in a typical NHS based surgical study (e.g. no post-randomisation timing of surgery mediation). However, some repairs may still be abandoned, perioperatively and post randomisation. Rates of compliance will be monitored throughout the study, including the pilot phase. Two secondary analysis populations will therefore be conducted on the primary outcome: a per-protocol analysis, that mirrors ITT but excludes patients with major protocol deviations, and an as-treated analysis, where patients are classified according to the treatment received. These secondary analyses will assess robustness of ITT analysis and any deviation from routine clinical practice. The handling of such events will be agreed in advance of conducting the analysis and detailed in the SAP.

The main analysis will be conducted using a complete case approach with no planned imputation for missing data. An independent Data and Safety Monitoring Committee (DSMC) will meet early in the study to agree its terms of references. They will review confidential interim analyses of the stop-go criteria and monitor within patient correlation of KOOS-4 scores between baseline and 24 months and compliance to randomised treatment.

It is anticipated that all statistical analysis will be undertaken using Stata (StataCorp LP, www.stata.com) or other validated statistical software.

23.3.1 Primary outcome

The primary outcome (KOOS-4 at 24 months) will be compared using a mixed-effects linear model to calculate the mean difference between treatment groups. Treatment, baseline KOOS-4 and planned lateral extra-articular procedure will be incorporated as fixed effects and recruiting site as a random effect. Results will be presented as estimates and 95% CIs whenever possible. A sensitivity analysis will be conducted that removes participants aged 20 years or younger at the time of completing baseline KOOS-4. Sensitivity to missing data will also be explored using informative missing to confirm tolerance to differential mechanisms (using a pattern-mixture model approach).

23.3.2 Secondary outcome(s)

Secondary outcomes will be analysed in a similar manner to the primary outcome. KOOS over 24 months, EQ-5D-5L and EQ-VAS, emotional functioning questions taken from KQoL-26, and postoperative pain will use mixed-effects linear regression, like that of the primary outcome, that also incorporates a time-by-treatment effect as a fixed effect and patient as a random effect. All five KOOS domains will be quantified at each time point. Pain-NRS at 3 and 6 weeks will be analysed using a simpler multiple linear regression model adjusted for site using robust variance. Modified Tegner will be compared at each time point in a similar manner. Graft failure and re-operation will be analysed using survival analysis methods: Kaplan-Meier curves, and Cox proportional hazards models (or log-rank test if insufficient events). The Cox model will be adjusted with mixed-effects, in line with the analysis approach for other outcomes, if there are enough events. If not, the model will be unadjusted[45]. Patient satisfaction questions will be analysed using logistic regression and adjusted for minimisation factors in line with other outcomes. Intervention-related complication (up to 24 months) will be presented using descriptive statistics, by type, frequency and treatment arm.

23.4 Inclusion in analysis

The principal analysis will be performed on the as-randomised ("intention to treat") population, analysing participants with available outcome data in their randomised groups, regardless of adherence. Secondary populations will also be analysed as defined in Section 23.3.

The study will be reported in line with CONSORT guidelines.

23.5 Subgroup analysis

Secondary subgroup analyses of the primary outcome will investigate visually, presenting using forest plots, whether treatment effects vary by the key clinical factors (baseline KOOS-4 level, and planned lateral extra-articular procedure, and age group (<20 years, 20 years and over).

23.6 Interim analyses

The main outcomes will be analysed as stated in the analysis plan once the study follow-up has been completed. No formal interim analyses of treatment effect are planned for any of the study outcomes.

23.6.1 Stopping rules

As no formal interim analyses are planned, no stopping rules have been incorporated into the study design. An independent Data and Safety Monitoring Committee* (DSMC) will review the accumulating

data at regular intervals and may recommend pausing or stopping the study in the event of safety concerns.

23.7 Level of Statistical Significance

All treatment comparisons will be reported with 95% confidence intervals and a significance level of 5% will be used to test statistical significance.

23.8 Procedure for accounting for missing data

The procedure for handling spurious or missing data will be described in the SAP. The study will attempt to collect data as completely as possible. The sample size calculation incorporated an inflation to account for potential loss to follow-up.

23.9 Procedures for reporting any deviation(s) from the original statistical analysis plan

Any deviation(s) from the original SAP will be described in the final statistical report.

23.10 Internal pilot/Decision Points

An internal pilot is planned that will progress seamlessly to the definitive study if all predefined progression criteria are reached. The embedded pilot phase will take place in UK sites with staggered initiation over a period of 10 months. Screening and recruitment to this study will occur in 2 phases. Patients will be identified and screened at A&E, virtual fracture clinics, and orthopaedic outpatient clinics and then will be invited to participate following confirmation of eligibility criteria. Randomisation will occur in theatre following a final eligibility check.

The recruitment rate will account for the time lag between patient consent and randomisation in theatre (therefore, no participants will be randomised in month 1), and for patients identified as not eligible in theatre and not randomised. Overall patient recruitment target for this internal pilot phase will be 28 randomised patients.

The internal pilot study will mirror the procedures and logistics undertaken in the main definitive study. It is intended that the study will progress seamlessly into the main phase.

Data from the internal pilot study will contribute to the final analysis. The purpose of the internal pilot is to assess the feasibility of site and test and refine the patient recruitment process. We will collect data on the number of patients screened, assessed for eligibility and randomised to determine the feasibility of the main trial. The decision to progress to the main trial will be made in collaboration with the TSC and NIHR HTA programme based on the pre-defined progression criteria. Progression to the main trial, will be informed using the traffic light system recommended by Avery[46] in terms of the decision-making process for stopping (red), amending the trial (amber) or proceeding (green) to a main trial. The internal pilot will also identify how well the sites are able to accommodate the delivery of our interventions within their existing pathways and workloads.

Stop-go criteria will be reviewed after 10 months of recruitment.

Stop-amend-go criteria for the pilot phase are given in Table 5 together with the definitions of how each will be measured.

Table 5: *Stop-amend-go criteria for internal pilot phase.*

Progression criteria	Red (Stop)	Amber (Amend)	Green (Go)
Total number of participants recruited (randomised)	<17	17-27	28
Study recruitment (randomisation)	<60%	60-99%	100%
Recruitment (randomisation) rate/site/month*	<0.5	0.5-0.75	>0.75
Number of sites opened	<5	5-8	9

NB: * Individual sites will vary, and indicative figures are means across all active sites

The Trial Management Group (TMG) will closely monitor the progression criteria during the internal pilot, and together with the Trial Steering Committee (TSC) and Data and Safety Monitoring Committee (DSMC) will perform a full review towards the end of the internal pilot. The TSC and funder would make the final decision to terminate the study.

24 HEALTH ECONOMICS

Cost Utility analysis

As with the statistical analysis, a detailed health economic analysis plan (HEAP) with full details of all analyses will be drafted early in the study and finalised prior to primary outcome analysis. The HEAP will be reviewed and will receive input from the Trial Steering Committee (TSC) and DSMC.

An economic evaluation will compare resource use, costs and health-related quality of life of ACL repair relative to ACL reconstruction following an intention-to-treat principle. The perspective of the analysis will be of the NHS and personal social care services. In sensitivity analysis, we will consider a societal perspective. The primary health economics outcome measure used in the study will be incremental cost per quality-adjusted life year (QALY). The health-related quality of life instrument EQ-5D-5L collected at baseline, 6-, 12- and 24-months follow-up will provide utility values for the calculation of QALYs. The valuation of EQ-5D-5L responses will follow the latest guidance from NICE's manual for health technology evaluations[47].

Direct treatment-related NHS resource use data including intervention (ACL repair and reconstruction), re-operations and re-admissions, physiotherapy sessions, adverse events, primary care and outpatient contacts will be identified and collected using patient questionnaires at 6-, 12- and 24-months follow-up complemented by hospital records, where appropriate. The questionnaires will build on the design, content and approach used in the ACL SNNAP study to enhance retention and response rates. The patient questionnaires will also collect information on lost earnings because of the knee injury, school or university absence due to knee injury and the use of private healthcare services. Resource use data will be costed using national average unit costs[48, 49].

Descriptive statistics (means, SD as minimum) will be reported for resource use, costs, and EQ-5D-5L utilities at each follow-up time point using complete data. Differences between study arms will be

estimated using mixed effects linear regression models to allow for multiple follow-ups clustered within participants. Missing data will be addressed following best practice in cost-effectiveness studies[50]. Mean imputation of baseline data and multiple imputation of follow-up costs and EQ-5D-5L values will be undertaken, if found to be appropriate after examining the patterns of missing data. Hence, we will use predictive mean matching to create a total number of imputed datasets as the proportion of data missing across all time periods.

Following multiple imputation, total costs and QALYs will be estimated for all participants in the study and discounted at the recommended 3.5% rate. On each imputed dataset, we will estimate incremental costs and QALYs using separate linear regression models controlling for treatment allocation and other variables. These estimates will be combined using Rubin's rule to produce the mean difference in costs and QALYs of ACL repair relative to ACL reconstruction. Incremental cost-effectiveness ratio (ICER) will be estimated by dividing the difference in costs by the difference in QALYs of the two treatments under analysis and will be depicted on the cost-effectiveness plane. This will be interpreted as the additional costs/savings associated with the additional QALY benefits from doing ACL repair compared with ACL reconstruction. The joint uncertainty around incremental costs and QALYs will be estimated using bootstrapping from each imputed dataset, running the estimation model and extracting the estimated treatment effects. From the bootstrap results, we will produce confidence intervals for the difference in costs and QALYs and estimate a cost-effectiveness acceptability curve informing the probability of the ACL repair being cost-effective at different maximum willingness to pay values, e.g. £20,000 to £30,000 per QALY gained.

Informed by the data from this study, we will also undertake a modelling exercise to explore the budget impact of promoting an accelerated pathway for ACL injuries, with early repair and reconstruction, compared to current practice as assessed in studies such as the ACL SNNAP study.

25 DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the study-specific Data Management Plan. See Section 29.3 for information on management of personal data.

25.1 Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no prior written or electronic record of data). Source data for the study is detailed in the tables within Section 9 and defined further within the study Data Management Plan.

25.2 Location of source data

The location of source data in the study is listed in the tables within the Section 9.

25.3 Case report forms (CRFs)

The Principal Investigator and study site staff will ensure that data collected on each participant is recorded in the CRF as accurately and completely as possible. Details of all protocol evaluations and investigations must be recorded in the participant's medical record for extraction onto the CRF.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

25.4 Non-CRF data

All study data will be recorded on the CRF. No additional data will be held outside of the CRF.

25.5 Access to Data

Members of the study team will only be able to access data that they need to, based on their roles and responsibilities within the study.

Direct access to source data/documents will be required for study-related monitoring and/or audit by the Sponsor, research team or NHS Trust or regulatory authorities as required.

To ensure compliance with regulations, direct access will be granted to authorised representatives from the Sponsor or permit study-related monitoring, audits and inspections. The data submitted by study participants directly in REDCap (i.e. electronic participant reported outcomes) will also be made available to the participating site that recruited the participant; this is detailed within the PIS so that participants are aware of who will have access to this data.

25.6 Data Recording and Record Keeping

The case report forms will be designed by members of the study management team which will include the Chief Investigator, study statistician(s) and study manager.

Data will, wherever possible, be collected in electronic format with direct entry into REDCap by site staff or participants. Electronic data collection has the major advantage of building “data logic” into forms, minimising missing data, data input errors and ensuring the completeness of consent and assent forms. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

All data entered will be encrypted in transit between the client and server. All electronic patient-identifiable information, including electronic consent forms, will be held on a server located in an access-controlled server room at the University of Oxford.

The data collection system and server are backed up to a secure location on a regular basis. Details of the data collected, where it is stored and who has access to it along with a fair processing statement will be available for the participants within the study participant information sheet.

Direct access to source data/documents will be required for study-related monitoring and/or audit by the Sponsor, research team or NHS Trust or regulatory authorities as required.

Data captured during phone calls to participants or from paper-based study questionnaires returned to the central CTU study team will be entered into REDCap by suitably trained study team staff. Full details of this process will be recorded in the Data Management Plan. Identifiable data will only be

accessible by members of the research team with a demonstrated need (managed via access controls within the application) and only used to communicate with the participant e.g. sending follow-up reminders for online form completion or telephone follow-up).

Refer to Section 29.5 for details about retention of participant identifiable data.

25.7 Electronic transfer of data

Any electronic transfer of data during the study will be strictly controlled in accordance with the Oxford Clinical Trial Research Unit's (OCTRU) Standard Operating Procedure for Secure Information/Data Transfer.

26 QUALITY ASSURANCE PROCEDURES

A rigorous programme of quality control will be implemented. The study management group will be responsible for ensuring adherence to the study protocols at the study sites. Quality assurance (QA) checks will be undertaken by OCTRU to ensure integrity of randomisation, study entry procedures and data collection. The OCTRU has a QA team who will monitor this study by conducting audits of the Trial Master File. Furthermore, the processes of obtaining consent, randomisation, registration, provision of information and provision of treatment will be monitored by the central CTU study team Additionally, the study may be monitored or audited by Sponsor or host sites in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

A study-specific data management and monitoring plan will be in place prior to the start of the study.

26.1 Risk Assessment

This protocol is designed to deliver a risk-adapted approach to conducting the research. A risk assessment has been conducted and a monitoring plan will be prepared before the study opens. The known and potential risks and benefits to participants have been assessed in comparison to those of standard of care. A risk management strategy is in place and will be reviewed and updated as necessary throughout the study or in response to outcomes from monitoring activities. Monitoring plans will be amended as appropriate.

26.2 Study monitoring

Monitoring will be performed by the central CTU study team according to a study-specific monitoring plan. Data will be evaluated for compliance with the protocol, completeness and accuracy. The investigator and institutions involved in the study will permit study-related monitoring and provide direct on-site access to all study records and facilities if required. They will provide adequate time and space for the completion of monitoring activities.

Study sites will be monitored centrally by checking incoming data for compliance with the protocol, consistency, completeness and timing. The case report form data will be validated using appropriate set criteria, range and verification checks. The study site must resolve all data queries in a timely manner (within no more than 7 working days of the data query unless otherwise specified). All queries relating to key outcome and safety data and any requiring further clarification will be referred to the study site for resolution.

Study sites will also be monitored remotely and/or by site visit, as necessary, to ensure their proper conduct of the study. Central CTU study team staff will be in regular contact with site personnel to check on progress and deal with any queries that they may have. Any monitoring reports/data discrepancies will be sent to the site in accordance with OCTRU SOPs and the study monitoring plan. The Investigator is expected to action any points highlighted through monitoring and must ensure that corrective and preventative measures are put into place as necessary to achieve satisfactory compliance, within 28 days as a minimum, or sooner if the monitoring report requests.

26.3 Audit and regulatory inspection

All aspects of the study conduct may be subject to internal or external quality assurance audit to ensure compliance with the protocol, GCP requirements and other applicable regulation or standards. Such audits or inspections may occur at any time during or after the completion of the study. Investigators and their host Institution(s) should understand that it is necessary to allow auditors direct access to all relevant documents, study facilities and to allocate their time and the time of their staff to facilitate the audit visit. Anyone receiving notification of an audit that will (or is likely to) involve this study must inform the Central CTU study team without delay.

26.4 Study committees

26.4.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be established for the study and operate in accordance with a study-specific TMG charter. The TMG will manage the study, including the clinical and practical aspects and will meet approximately monthly to assess progress. Other specialities/ individuals will be invited as required for specific items/issues.

26.4.2 Data and Safety Monitoring Committee (DSMC)

An independent Data & Safety Monitoring Committee (DSMC) will be established for this study. The DSMC will adopt a DAMOCLES based charter, which defines its terms of reference and operation in relation to the oversight of the study. The DSMC will meet regularly throughout the study at time-points agreed by the Chair of the Committee and the Chief Investigator. At a minimum this will be on an annual basis. The DSMC will review the safety data generated, including all safety data and make recommendations as to whether the protocol should be amended to protect patient safety. Recommendations of the DSMC will be discussed between the CI, TSC, and the Sponsor.

26.4.3 Trial Steering Committee (TSC)

The TSC, which includes independent members, provides overall supervision of the study on behalf of the funder. The TSC will act in accordance with a TSC charter which will outline its roles and responsibilities. Full details including names will be included in the TSC charter. Meetings of the TSC will take place at least once a year during the recruitment period. An outline of the remit of the TSC is to:

- monitor and supervise the progress of the study towards its interim and overall objectives
- review at regular intervals relevant information from other sources
- consider the recommendations of the DSMC
- inform the funding body on the progress of the study

The TSC will consider, and act, as appropriate, upon the recommendations of the DSMC.

27 IDENTIFICATION AND MANAGEMENT OF PARTICIPATING SITES

27.1 Identification of recruitment sites

Recruitment sites will be selected based on suitability to conduct the study. Site feasibility meetings/ correspondence will be held and used by the Trial Management Group/Coordinating Centre to assess suitability of the site for the study; information will be recorded in a site feasibility questionnaire (SFQ), which will be completed centrally. The suitability assessment will primarily be based on the resources available at site and the feasibility of meeting recruitment targets.

27.2 Study site responsibilities

The Principal Investigator (the PI or lead clinician for the study site) has overall responsibility for the conduct of the study at each site but may delegate responsibility where appropriate to suitably experienced and trained members of the site research team. All members of the site research team must complete delegation log provided by the central CTU study team prior to undertaking any study duties. The PI must counter sign and date each entry in a timely manner, authorising staff to take on the delegated responsibilities.

27.3 Study site set up and activation

The Principal Investigator leading the participating study site is responsible for providing all required core documentation. Mandatory site training which is organised by the central CTU study team (see below) must be completed before the site can be activated. Training in the study processes will be administered at site initiation visits delivered either in person or online by the central CTU study team. The central CTU study team will check to confirm that the site has all the required study information/documentation and is ready to recruit. The site will then be notified once they are activated on the REDCap data collection system and are able to begin recruiting participants.

27.4 Training

Training in the study processes will be administered at site initiation visits (delivered face to face or online) by the central CTU study team.

A Surgical Manual has been developed, following surgeon consensus on acceptable repair techniques for this study. It is expected that all surgeons will be experienced soft tissue knee surgeons (peer reviewed by the CI at site feasibility meetings) and training in the study-eligible repair techniques will be part of their routine clinical practice.

Additional training (undertaken as part of routine clinical practice) will be available to sites via the technique providers.

27.5 Study documentation

The central CTU study team will provide an electronic Investigator Site File to each participating site containing the documents needed to conduct the study. The study team must review and approve any local changes made to any study documentation including patient information and consent forms prior

to use. Additional documentation generated during the study, including relevant communications must be retained in the site files as necessary to reconstruct the conduct of the study.

28 ETHICAL AND REGULATORY CONSIDERATIONS

28.1 Summary of study-specific considerations

28.2 Declaration of Helsinki

The Investigator will ensure that the study is conducted in accordance with the principles of the Declaration of Helsinki.

28.3 Guidelines for Good Clinical Practice

The Investigator will ensure that the study is conducted in accordance with relevant regulations and with the principles of Good Clinical Practice.

28.4 Ethical conduct of the study and ethical approvals

The protocol, patient information sheet, informed consent form and any other information that will be presented to potential study participants (e.g. advertisements or information that supports or supplements the informed consent process) will be reviewed and approved by an appropriately constituted, independent Research Ethics Committee (REC).

28.5 NHS Research Governance

Once Health Research Authority (HRA) & Health and Care Research Wales (HCRW) approval is in place for the study, sites will confirm capability and capacity to participate in the study.

28.6 Protocol amendments

All amendments will be generated and managed according to the central CTU study team standard operating procedures to ensure compliance with applicable regulation and other requirements. Written confirmation of all applicable REC and local approvals must be in place prior to implementation by Investigators as applicable for the amendment type. The only exceptions are for changes necessary to eliminate an immediate hazard to study participants (see below).

It is the Investigator's responsibility to update participants (or their authorised representatives, if applicable) whenever new information becomes available that might affect the participant's willingness to continue in the study. The Investigator must ensure this is documented in the participant's medical notes and the participant is re-consented if appropriate.

28.7 Protocol Compliance and Deviations

Protocol compliance is fundamental to GCP. Prospective, planned deviations or waivers to the protocol are not allowed. Changes to the approved protocol need prior approval unless for urgent safety reasons.

A study related deviation is a departure from the ethically approved study protocol or other study document or process or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Deviations from the protocol will be captured in REDCap using either using a protocol deviation form or via suitably designed fields within the CRF which will be extracted from REDCap and reviewed

regularly by the Trial Management Group (TMG). Deviations will be handled and reviewed in a timely manner in accordance with a study-specific Data Management and Monitoring Plan.

For ACL STARR, the acceptable time from injury to surgery has been defined as 50 days. If this is exceeded, it will be reported as a protocol deviation. This is a pragmatic approach, aligning with existing literature, which indicates that time to surgery is an important factor in primary repair outcomes[6], while also being mindful of the pressure on NHS waiting lists.

If the participant is randomised to repair surgery in theatre, and there is an unplanned intraoperative conversion to reconstruction surgery, e.g. if the ligament was thought to be repairable, but further surgical evaluation indicates the need for a reconstruction, the participant will be permitted to crossover to the reconstruction arm and will remain on the study.

The investigator must promptly report any important deviation from Good Clinical Practice or protocol to the central CTU study team. Examples of important deviations are those that might impact patient safety, primary/ secondary endpoint data integrity, or be a possible serious breach of GCP.

28.8 Urgent safety measures

The Sponsor or Investigator may take appropriate urgent safety measures to protect study participants from any immediate hazard to their health or safety. Urgent safety measures may be taken without prior authorisation. The study may continue with the urgent safety measures in place. **The Investigator must inform the central CTU study team IMMEDIATELY if the study site initiates an urgent safety measure:**

The notification must include:

- Date of the urgent safety measure;
- Who took the decision; and
- Why the action was taken.

The Investigator will provide any other information that may be required to enable the central CTU study team to report and manage the urgent safety measure in accordance with the current regulatory and ethical requirements for expedited reporting and close out. The central CTU study team will follow written procedures to implement the changes accordingly.

28.9 Temporary halt

The Sponsor and Investigators reserve the right to place recruitment to this protocol on hold for short periods **or** to declare a temporary halt. A temporary halt is defined as a formal decision to:

- interrupt the treatment of participants already in the study for safety reasons;
- stop recruitment on safety grounds; or
- stop recruitment for any other reason(s) considered to meet the substantial amendment criteria, including possible impact on the feasibility of completing the study in a timely manner.

The central CTU study team will report the temporary halt via an expedited substantial amendment procedure. The study may not restart after a temporary halt until a further substantial amendment to re-open is in place. If it is decided not to restart the study this will be reported as an early termination.

28.10 Serious Breaches

A "serious breach" is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) the safety or physical or mental integrity of the study subjects; or

(b) the scientific value of the research.

Investigators must notify the central CTU study team within one working day if any serious breach of GCP is suspected. central CTU study team will review the event and, if appropriate will report a serious breach to the REC and the NHS host organisation within 7 days of the central CTU study team becoming aware of the breach.

28.11 Study Reports

This protocol will comply with all current applicable Research Ethics Committee and Sponsor reporting requirements.

28.12 Transparency in Research

Prior to the recruitment of the first participant, the study will be registered on a publicly accessible database ISRCTN, which will be kept up to date during the study, and results will be uploaded to the registry within 12 months of the end of the study declaration. A Final Report will be submitted to the REC containing a lay summary of the study results which will be published on the HRA website.

The results of the study will be published and disseminated in accordance with the Section 34.

28.13 Use of social media

Social media (e.g. Twitter feeds) may be utilised to make general announcements about the study and acknowledge when milestones are met (e.g. sites open to recruitment, first recruitment at a site etc).

29 PARTICIPANT CONFIDENTIALITY

29.1 Collection and use of personal identifiable information

Contact details (email addresses/postal addresses/phone number/ parent/guardian contact details [where appropriate]) will be collected in this study for the following purposes, only with the specific consent of the participant:

- *Sending of follow-up questionnaires and any reminder messages*
- *Sending of responsive text messages*
- *Contact about future research*
- *Sending a copy of the completed consent form by email (for any participants that consent electronically and wish to receive a copy by email)*
- *Sending the GP letter*
- *Sending the gift voucher*

- *Collection of outcome data from NHS England (using only NHS number/CHI number)*

The patient information sheet explains what contact details will be collected and how these will be used.

Where remote eConsent is used, participants will be asked to give their permission verbally for a link to the consent documentation to be sent to their email address or an email address they provide.

29.2 Use of audio /visual recording devices

No audio/visual recording devices are being used in this study.

29.3 Storage and use of personal data

During the study personal data will be stored and used in accordance with the Oxford Clinical Trial Research Unit's (OCTRU) Standard Operating Procedure for confidentiality, protection and breach of personal data in relation to research subjects. This ensures that all personal data collected during the study is recorded, handled and stored in accordance with the requirements of the UK General Data Protection Regulation.

All electronic participant-identifiable information will be held on a secure, password-protected database accessible only to authorised personnel. Paper forms with patient-identifiable information will be held in secure, locked filing cabinets within a restricted area. The processing of the personal data of participants will be minimised wherever possible using a unique participant study number on study documents and any electronic systems.

Personal data on all documents will be regarded as confidential. The study staff will safeguard the privacy of participant's personal data.

The use of all personal data in the study will be documented in a study-specific data management and sharing plan which details what and where personal data will be held, who will have access to the data, when personal data will be de-identified and how and when it will be deleted.

The Investigator site will maintain the patient's anonymity in all communications and reports related to the research.

Data Breaches will be highlighted to the relevant site staff and reported as required by the UK GDPR and Data Protection Act 2018. This will also be deemed a protocol deviation.

29.4 Access to participants' personal identifiable data during the study

Access to participants personal identifiable data will be restricted to individuals authorised to have access. This includes a) members of the research team at participating study sites with delegated responsibility by the site Principal Investigator and b) members of the central CTU study team involved in the conduct/management of the study where this is necessary for their role.

Research staff that are not part of the potential participant's direct healthcare team will not have access to personal identifiable data until the individual has given their consent to take part in the study or the participant has indicated to their direct healthcare team that they wish to be contacted by a member of the site research team – permission for this will be recorded in the individual's medical notes.

The participant information sheet clearly describes who will have access to the participants personal identifiable data during the study and explicit consent is obtained from study participants for such access.

Participants will be asked to consent to relevant sections of their medical notes and data collected during the study being looked at by individuals from Cambridge University Hospitals NHS Foundation Trust, the Universities of Oxford and Cambridge, from regulatory authorities [and from the NHS Trust(s)], where it is relevant to their taking part in this study; only authorised individuals will be granted access where this is necessary for their role.

29.5 Destruction of personal identifiable data

Personal identifiable data will be destroyed as soon as it is no longer required – the time point for this destruction is detailed in the study data management plan and is in accordance with OCTRU standard operating procedures which comply with the UK GDPR.

Personal identifiable data may be retained longer than the duration of study – please refer to Section 35.1.1 for details.

29.6 Participant Identification Log

The site research team must keep a separate log of enrolled patients' personal identification details as necessary to enable them to be tracked. These documents must be retained securely, in strict confidence. They form part of the Investigator Site File and are not to be released externally.

30 PUBLIC AND PATIENT INVOLVEMENT

30.1 PPI in study design and protocol development

We have worked with patients and the public throughout the study development process to ensure that the study is fair and accessible to all who wish to participate. Our PPI partners include people who have had ACL reconstruction or repair, and members of the public with no history of ACL injury. This facilitates a discussion by people with a broad range of experiences and priorities. Training and support for our PPI partners will be provided throughout the study.

- Inclusion criteria have been kept deliberately broad to ensure that as many people with these injuries can take part as possible, regardless of demographics or location. The justification for the chosen age range can be found in Section 11.5. Similarly, the exclusion criteria are deliberately short to ensure that no person or group is excluded unnecessarily (see EDI Section 12).
- Patients have informed our choice of outcome measures. We have explored the information they think is most meaningful to collect, and they have given us feedback on our chosen scores.

30.2 PPI in development of participant information

Participant facing materials was developed with our PPI groups, to ensure the content was clear, age appropriate and easy to understand.

Following feedback from several members of the Cambridge University Hospitals PPI group, we changed some of the text to replace or explain medical terminology (e.g. words such as proximal and arthroscopy). We included references to research which has already been undertaken, and we changed the layout of the first page of the adult participant information sheet to make it easier to understand. The group found the diagrams aided their understanding of the study, and we are using pictures and diagrams in the participant information for 14–15-year-olds, to further support understanding.

30.3 PPI during the study

We will engage with and involve PPI representatives throughout the course of the study.

The recruitment and retention processes are an important focus for ACL STARR. In building upon learning experiences from ACL SNNAP, our PPI groups are working with us to further refine our strategy, to ensure appropriate support is provided to participants to minimise drop-out and maintain a high response rate.

30.4 Dissemination of study results

Findings of the study will be made available to participants via the CTU website and social media.

We will work with our PPI groups to co-produce a plan for information sharing, engaging participants with study updates and disseminating study results.

31 EXPENSES/PAYMENTS TO PARTICIPANTS

All research activity is conducted during routine standard of care visits; no payments will be made to study participants to support these visits.

If, however, there is a reason a participant needs to attend a hospital appointment for other research purposes (e.g. a visit to speak further with a clinician about the study before signing a consent form), reasonable travel expenses will be reimbursed.

All participants will be given a £20 ‘thank you’ gift in the form of a voucher, at the end of their participation in the study, as a token of our appreciation for completing the follow-up questionnaires. This will be given to all participants, whether they complete all questionnaires or not.

32 SPONSORSHIP, FINANCE, AND INSURANCE

32.1 Sponsorship

Cambridge University Hospitals NHS Foundation Trust and University of Cambridge will provide written confirmation of Sponsorship.

32.2 Funding and support in kind

The table below provides a summary of all funding and support in kind for the study.

Funder(s)	Financial and non-financial support given
National Institute for Health and Care Research (NIHR) Health Technology Assessment Programme	Reference Number: NIHR157938

32.3 Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If participants are harmed whilst taking part in a clinical study because of negligence on the part of a member of the study team this liability cover would apply. The University of Cambridge meets UK Ethics requirements to provide an indemnity to pay non-fault damages or compensation to patients and volunteers who suffer bodily injury caused by their participation in a human research study or clinical trial.

Non-negligent harm is not covered by the NHS indemnity scheme. Cambridge University Hospitals NHS Foundation Trust, therefore, cannot agree in advance to pay compensation in these circumstances.

In exceptional circumstances an ex-gratia payment may be offered.

33 CONTRACTUAL ARRANGEMENTS

This study is subject to the Sponsor's policy requiring that written contracts/agreements are agreed formally by the participating bodies as appropriate.

34 PUBLICATION AND DISSEMINATION

The Sponsor will retain ownership of all data arising from the study.

Publication and dissemination of study results will be in accordance with OCTRU Standard Operating Procedures and irrespective of study findings.

The study protocol will be published in an open-access peer-reviewed journal in accordance with the Standard Protocol Items: Recommendations for Interventional Trials statement (SPIRIT, www.spirit-statement.org/). The study results will be published in an open-access journal, in accordance with the NIHR's policy on open-access research. The study will be reported following the CONSORT guideline including any applicable extensions to this. The Template for Intervention Description and Replication (TIDieR) statement will be used for reporting the intervention.

34.1 Study results

All data will be presented such that no individual participants can be identified.

34.2 Dissemination of study results to participants

A summary of the study results for study participants will be written collaboratively with clinicians and patient representatives and distributed accordingly. The PIS includes a link to the study website where participants will be advised that the results will be published. Newsletters, and social media e.g. Facebook, X, LinkedIn etc. will also be used to ensure the results of the study. are communicated to the wider community once they are available.

A Dissemination Plan will be developed for the UK study. Dissemination of results will include the following methods:

Conference: The results of this study will be disseminated to the clinical community via presentations at national and international meetings. Traditional conference dissemination will focus on presentations to include the key professional stakeholders. It is expected that findings from this study will be presented at national and international conferences such as British Association for Surgery of the Knee (BASK), British Society for Children's Orthopaedic Surgery (BSCOS), British Orthopaedic Sports Trauma and Arthroscopy Association (BOSTTA) and the American Academy of Orthopaedic Surgeons (AAOS).

Publications: Results will usually be published in peer-reviewed journals. Where possible, plain English summaries will be published alongside the full paper, along with links to other digital media on the study website to explain the study result in an accessible format – i.e. an explainer video and infographic.

Public Dissemination: To ensure a broad campaign we will target a range of social media outlets (this may include an explainer video and infographic). We will seek to engage the NHS Dissemination centre and seek to publish 'digital story' as part of the 'NIHR Signal'.

The wider public will be alerted via links with relevant organisations/charities, and the Research Media Offices. Engagement with the NIHR Dissemination Centre will also be sought, to ensure global awareness of study findings. Moreover, the Cambridge University Hospitals NHS Foundation Trust and University of Oxford have professional communication officers. It is anticipated that together these individuals, and NIHR equivalents, we will agree upon effective communication strategies including co-ordinated press releases, interviews etc.

34.3 Authorship

Authorship of any publications arising from the study will be determined in accordance with the ICMJE guidelines and any contributors acknowledged accordingly.

All publications arising from this study must acknowledge the contribution of participants, funder(s), OCTRU, Surgical Intervention Trials Unit (SITU) and the Sponsor.

35 ARCHIVING

35.1 Minimum Mandatory archiving period

It is the Cambridge University Hospitals NHS Foundation Trust's policy to store data for a minimum of 5 years following publication. Investigators may not archive or destroy study essential documents or samples without written instruction from the central CTU study team.

The minimum mandatory archiving period for essential study documents for this study is 5 years following publication.

At the end of the study the sponsor study team should archive securely all centrally held study related documentation for a minimum of 5 years. Arrangements for confidential destruction will then be made. It is the responsibility of PIs to ensure data and all essential documents relating to the study

held at site are retained securely for a minimum of 5 years after the end of the study, in accordance with national legislation.

(Essential documents are those which enable both the conduct of the study, and the quality of the data produced to be evaluated and show whether the site complied with the principles of GCP and all applicable regulatory requirements.)

The Sponsor team should notify the sites when study documentation held at sites may be archived. All archived documents must continue to be available for inspection by applicable authorities upon request.

35.1.1 Retention of documents/information beyond the mandatory archiving period

The following documents will be retained for up to five years from the point of entry into the study; explicit consent for this retention will be obtained from participants:

- Participant contact details forms, for the purpose of contacting participants about future research [1] and to enable long term follow up (NHS/CHI number only), and informed consent forms.

[1] *Participants will be given the option to be approached for future research; under GDPR, it is necessary to retain the consent form as the basis for retention of details and future approach. The contact details will be held securely, separately from the research data, and kept updated.*

35.2 Archiving responsibilities/procedure

During the study and after study closure the Investigator must maintain adequate and accurate records to enable the conduct of a clinical study and the quality of the research data to be evaluated and verified. All essential documents must be stored in such a way that ensures that they are readily available, upon request for the minimum period as specified above.

35.2.1 CTU Trial Master File

All paper and electronic data including the Trial Master File and study data collection system will be retained and archived in accordance with OCTRU's standard operating procedures which are compliant with the UK GDPR.

35.2.2 Investigator Site File and participant medical records

The Investigator Site Files will be archived at the participating site. The medical files of study participants must be retained for the mandatory archiving period stated above and in accordance with the maximum period permitted by the participating site. Sites should comply with the documentation retention specified in the clinical trial agreements (or equivalent) issued by the study Sponsor.

35.3 Retention of data sets

Study data and associated metadata electronically in a suitable format in a secure server area maintained and backed up to the required standard. Access will be restricted to the responsible Archivist and will be controlled by a formal access request. On completion of the mandatory archiving period the TMF and associated archived data sets will be destroyed or transferred as appropriate, according to any data sharing requirements.

36 DATA SHARING

The study statistician and health economist may retain copies of de-identified datasets for the purpose of data sharing in accordance with the study data sharing plan.

A parallel Australian study conducted to the same protocol (considering any country differences in healthcare delivery/pathway) will be led by co-applicant Professor David Beard and an Australian team of clinicians and methodologists (the ACL STARR-AUS study). The completion of two studies to the same protocol, will provide pooled data for potential future analyses, future secondary data analyses.

36.1 Retention of de-identified datasets

Upon completion of the study, de-identified research data may be shared with other organisations on request to the Chief Investigator and in accordance with the data sharing policies of OCTRU, the Sponsor and funder(s).

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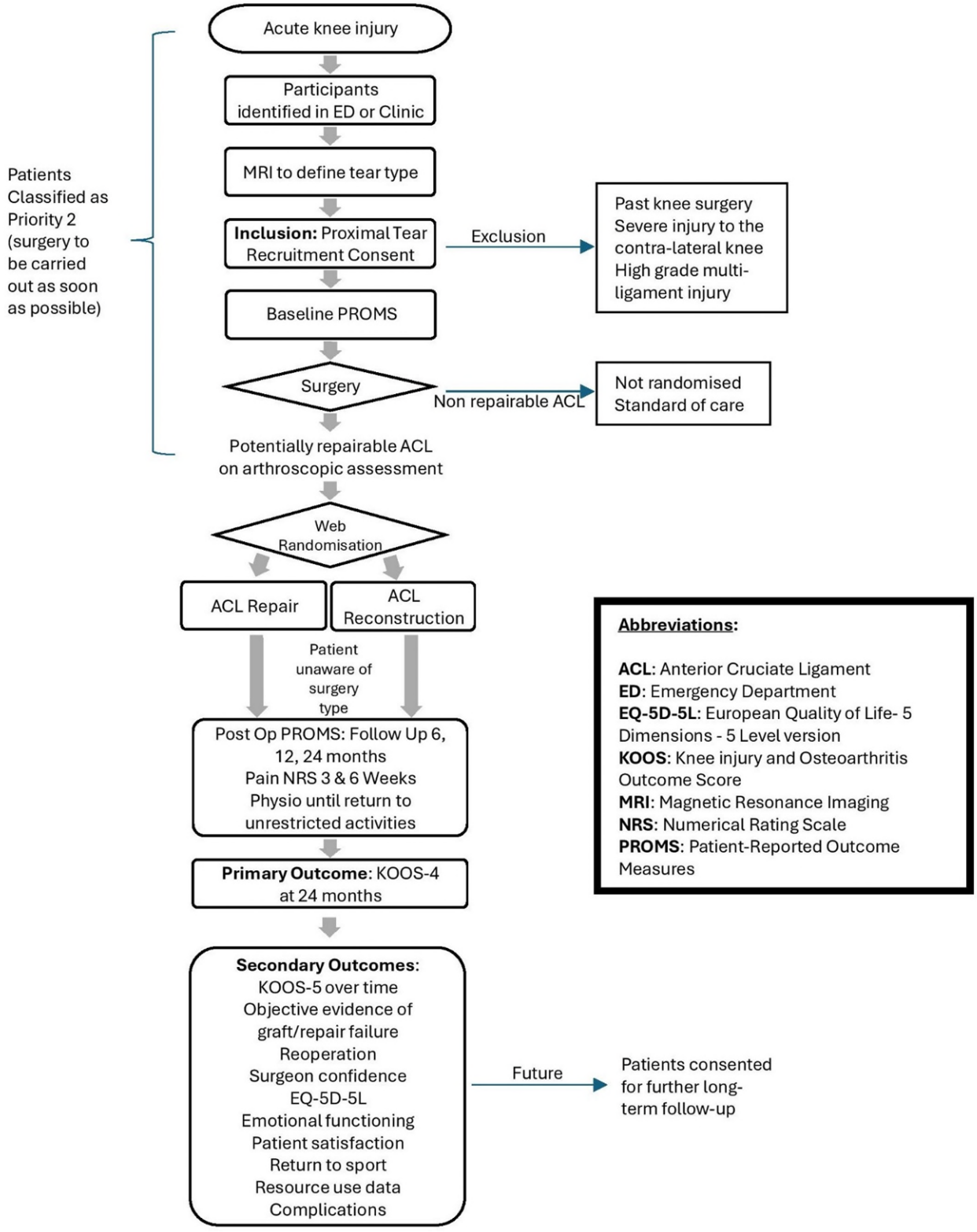
38 VERSION HISTORY

Previous versions of this protocol and a summary of the changes made are provided in the table below:

Protocol version no.	Protocol date	Summary of key changes from previous version
2.0	03Feb2025	Clarification of the consent/assent process for adolescents aged under 16 years.

APPENDIX 1 – STUDY FLOW CHART



APPENDIX 2 – POST-OPERATIVE ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION / REPAIR GUIDANCE

Evidence to support postoperative rehabilitation varies and there is considerable heterogeneity in the rehabilitation protocols available online and in the literature[1-3]. As there is no consensus for an optimal protocol for either ACL reconstruction or repair, with no evidence to suggest the protocols should differ[4], we propose the following guidance. This should be used in conjunction with local practice and the treating clinician's clinical discretion. We recommend progression based on objective criteria as progression against time-alone is no longer recommended in the literature[5].

Stage	Aims	Progression Criteria
Early	• Reduce swelling • Control pain • Achieve full active range-of-motion (AROM) • Mobilise fully weight bearing, unaided • Achieve a straight leg raise (SLR) with no lag • Return to work • Strengthening, proprioception and neuromuscular control	• Full AROM • Minimal effusion (e.g. patella circumference <1cm fluctuation – consider activity and 24-hour pattern) • Normal unaided gait • Weaned from brace (if used) • SLR, no lag • Tolerating graded muscle strengthening programme • Single leg balance >30s • Single leg squat x 5 (good technique and control, consider using quality scoring sheet, QASLS, or other objective measure) • Single leg calf raise repetitions >85% unoperated limb • Single leg bridge repetitions >85% unoperated limb
Mid	• Continue to build strength, proprioception and neuromuscular control • Return to running • Build tolerance to jumping, hopping and agility	• Minimal activity related swelling • Hop test (single leg, triple hop, triple crossover) >85% limb symmetry index (LSI) • Star excursion balance test >85% LSI • Squat 1 repetition max ≥1.8 x body-weight • Single leg sit to stand (90^0) > 22 repetitions
Late	• Continuation of strength, power, balance, landing and agility work • Return to sport specific training • Work towards returning to preinjury level of sport/activity	<u>Return to sport criteria</u>: • Full, pain-free AROM • No activity related swelling • Cardiovascular fitness at pre-injury level • Contralateral strength >90% • Hop test >90% LSI

		• Star excursion balance test >90% LSI • Consider patient readiness e.g. Anterior Cruciate Ligament Return to Sport After Injury (ACL-RSI), (Tampa Scale of Kinesiophobia) TSK-11

We further advise that clinicians:

- Do not allow a return to sport specific training sooner than 6 months
- Do not allow a return to unrestricted sporting activity sooner than 9 months
- Delay commencement of open kinetic chain exercises until at least 6 weeks post-surgery (90-40) unrestricted range from 12-weeks[6,7].
- Alter rehabilitation as appropriate for concomitant surgical procedures (align to local protocol)

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