Study Title: The ACL SNNAP Trial: ACL Surgery Necessity in Non Acute Patients

Comparison of the clinical and cost effectiveness of two management strategies for non-acute Anterior Cruciate Ligament (ACL) injury: Rehabilitation versus surgical Reconstruction.

Internal Reference Number / Short title: ACL SNNAP

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Confidentiality Statement

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1. SYNOPSIS

Study Title	**The ACL SNNAP Trial: ACL Surgery Necessity in Non Acute Patients** **Comparison of the clinical and cost effectiveness of two management strategies for non-acute Anterior Cruciate Ligament (ACL) injury: Rehabilitation versus surgical Reconstruction.**	
Internal ref. no. / short title	**ACL SNNAP**	
Study Design	Multi-centre superiority randomised controlled trial, with internal recruitment pilot using a 2 arm parallel group design with 1:1 allocation ratio.	
Study Participants	Patients >18yrs with symptomatic ACL deficiency confirmed by clinical assessment and MRI scan. Excluded if: Less than 4 months since injury, previous knee surgery to study (index) knee (except diagnostic arthroscopy), meniscal pathology sufficiently symptomatic to require surgery i.e. locked knee, large bucket handle tear, knee joint status grade 3 or 4 KL scale [1], grade 3 MCL/LCL injury, PCL/PLC injury, inflammatory arthropathy.	
Planned Sample Size	320	
Planned Study Period	48 months	
	Objectives	**Outcome Measures**
Primary	The primary objective is to determine in patients with non-acute (greater than 4 months since injury) Anterior Cruciate Ligament Deficiency (ACLD) whether a strategy of non-surgical management [Rehabilitation] (with option for later ACL reconstruction only if required) is more clinically effective and cost effective than a strategy of surgical management [Reconstruction].	Knee Injury and Osteoarthritis Outcome Score (KOOS4) at 18 months [2].
Secondary	Secondary objectives are to compare the management strategies with regards to; 1. Return to activity / level of sports, 2. Generic quality of life, 3. Knee specific patient reported outcomes, 4. Intervention related complications, 5. Health economics, 6. Expectations, 7. Patient satisfaction.	1. Return to activity / level of sports , Modified Tegner [3]). 2. Generic quality of life measured using validated scale such as EQ-5D [4]. 3. KOOS (all subscales) [2], Anterior cruciate ligament quality of life score (ACL-QOL) [5] . 4. Intervention related complications. 5. Health economics – cost effectiveness, ability to work (e.g. sickness absences/return to work number of days off

		work and subjective working ability) resource use and costs. 6. Expectations of return to activity and confidence in relation to the knee, Anterior cruciate ligament quality of life score (ACL-QOL) [5]. 7. Patient satisfaction.
Qualitative sub study:	To assess the acceptability and adherence to the treatment interventions for trial participants and participating healthcare practitioners.	Semi structured interviews

2. ABBREVIATIONS

ACL	Anterior Cruciate Ligament
ACLD	Anterior Cruciate Ligament Deficiency
ACL-QOL	Anterior Cruciate Ligament Quality of Life Score
CI	Chief Investigator
CLRN	Comprehensive Local Research Network
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTRG	Clinical Trials & Research Governance, University of Oxford
GCP	Good Clinical Practice
GP	General Practitioner
HCPC	Health and Care Professions Council
HES	Hospital Episode Statistics
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
ICMJE	International Committee of Medical Journal Editors
KOOS	Knee Injury and Osteoarthritis Outcome Score
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NIHR HTA	National Institute of Health Research, Health Technology Assessment Programme
NDORMS	Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences.
NRES	National Research Ethics Service

OA	Osteoarthritis
OCTRU	Oxford Clinical Trials Research Unit
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
UKCRN	UK Clinical Research Network

3. BACKGROUND AND RATIONALE

Anterior Cruciate Ligament (ACL) rupture is a common injury, mainly affecting young, active individuals with estimated 200,000 injuries annually in the US [6]. ACL injury can have a profound effect on knee kinematics (knee movement and forces) with recurrent knee instability (giving way) as the main problem [7]. Furthermore, the injury can lead to poor quality of life, decreased activity [8] and increased risk of secondary osteoarthritis of the knee [9]. Some patients, once recovered from initial injury, are able to function well without their ACL (copers), usually after undergoing some formal rehabilitation [10]. Other patients continue with episodes of knee instability and it is thought surgery (ACL reconstruction using a graft) is necessary to stabilise the knee.

In the UK, a surgical management strategy has become the preferred treatment for ACL injured individuals. Our recent survey shows that the ratio of surgical intervention to non-surgical conservative intervention is 4:1. Our data suggests 80% of non-acute patients are now directly listed for surgery in the NHS. In England it is estimated that around 15,000 primary ACL reconstruction surgeries are performed each year [11]. However, this is a modest estimate based on HES data and the real figure for a UK population of 63 million may be closer to 50,000 pa (based on Swedish ACL registry data - incidence 71/100,000 pa) [12]. Based on the conservative estimate (n=15,000), the costs of ACL reconstruction to the NHS will be approximately £63 million for 2015.

Despite ACL reconstruction being common, current management for ACL injury is based on limited evidence [10, 13-15]. A 2009 Cochrane systematic review examined whether surgery or non-surgical (conservative) management was superior for ACL injury [16] and concluded no high quality evidence exists on which to base practice. This is supported by the NHS DUETS website which indicates uncertainty for treating ACL injured patients. It is unclear whether surgical stabilization of the knee joint is more beneficial than non-surgical intervention. The above Cochrane review is currently being updated by the study team [17]. Early findings suggest the evidence has not improved.

The unsupported preference for surgical management of the ACL deficient knee has recently been questioned further by evidence obtained in a Scandinavian trial [18]. The benefit of surgery, for all injured patients, was shown to be uncertain with an operation being unnecessary in many cases. Frobell et al showed that a period of prior rehabilitation before considering operation can reduce ACL surgery by

up to 50%. The clinical implication is that a period of rehabilitation should always be offered prior to surgical reconstruction. However, whilst this clinical decision making evidence is valid for acutely injured individuals, it is not applicable to those more typically seen in the NHS. Patients seen in the NHS are usually non-acute having sustained ACL injury more than 4 months previously. By the time NHS patients are diagnosed and begin dedicated ACL injury management, 4-12 months can have passed since initial injury [19].

The mixed acknowledgement and uptake of this evidence, and the uncertainty over the applicability to a less acute UK population has resulted in a highly varied approach to managing ACL injury in the NHS [20-22]. There may be an overuse of surgical management in the non-acute population, yet conversely there may be an argument to bypass any formal rehabilitation and undergo immediate reconstructive surgery. It remains unknown which strategy is the most clinically and cost effective. As surgery is expensive and may also have greater complications [11, 23] it is even more important to generate evidence for default ACL reconstruction [24]. Likewise, the routine prescription of formal rehabilitation, if not beneficial, is considered wasteful. There is a need to identify the most appropriate treatment strategy.

In terms of current research a review of the Clinical Trials Registry found one other study examining the clinical and cost effectiveness of two treatment strategies for ACL rupture [25]. This trial is being carried out in the Netherlands and has a sample size of 188 participants. As it also evaluates the newly injured (acute) patients it replicates the Scandinavian study setting and again cannot be directly applied to the typical NHS pathway.

In summary, at present there is no evidence-base management of non-acute ACL deficiency particularly in the NHS. Moreover, there is little consensus on the management of these patients. The proposed trial will address the gap in the evidence base regarding the clinical and cost effectiveness of these approaches and inform standards of care for ACL deficiency management.

4. OBJECTIVES AND OUTCOME MEASURES

4.1. Primary Objective

The primary objective is to determine in patients with non-acute (greater than 4 months since injury) Anterior Cruciate Ligament Deficiency (ACLD) whether a strategy of non-surgical management [Rehabilitation] (with option for later ACL reconstruction only if required) is more clinically effective and cost effective than a strategy of surgical management [reconstruction].

The primary outcome for the study is the Knee injury and Osteoarthritis Outcome Score (KOOS4) at 18 months post randomisation. This outcome measure is derived from 4 of 5 subscales; pain, symptoms, difficulty in sports and recreational activities, knee related quality of life [2, 26] with scores ranging from 0 – 100, a higher score indicating better health. KOOS is a validated patient reported outcome used in ACL research (including recent RCT of acute ACL patients [26, 27] and large scale databases i.e. National Ligament Registry [28, 29]). The KOOS4 is sensitive and specific for detecting functional deficits due to knee instability.

4.2. Secondary objectives

Secondary objectives are to compare the management strategies with regards to return to activity / level of sports, generic quality of life, knee specific patient reported outcomes, intervention related complications, health economics – cost effectiveness, ability to work (e.g. sickness absences/return to work number of days off work and subjective working ability) resource use and costs, expectations of return to activity and confidence in relation to the knee.

Return to activity/level of sport participation - Modified Tegner [3]: Activity level will be assessed using the Tegner scale, graded from 1 (low activity levels) to 10 (professional level).

Intervention related complications - Any complications associated with undergoing ACL deficiency treatment will be recorded. This includes; for surgery group; re-admission, delayed hospital discharge, infection, unexpected poor range of movement (stiffness), excess bleeding, continued swelling, episodes of giving way, continued feeling of instability. For non-surgical group; continued swelling, episodes of giving way.

Generic quality of life - The EuroQol EQ-5D is a validated, generic, self-reported outcome measure covering 5 health domains and used to facilitate the calculation of Quality Adjusted Life Years (QALYs) in health economic evaluations. The original EQ-5D questionnaire contained 3 response options within each of 5 health domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) [30]. More recently, the EQ-5D-5L has been developed to overcome problems with ceiling effects and to improve sensitivity [4]. The 5L version consists of the same five domains as the original but with 5 response options.

Knee specific patient reported outcomes - All 5 subscales of the KOOS [2] will be included (the fifth scale being activities of daily living).

Anterior Cruciate Ligament Quality of Life Score (ACL-QOL) [5] a validated 32 item, knee specific measure for chronic ACL deficiency, divided into 5 sub-scales which include symptoms and physical complaints, work-related concerns, physical activity and sports participation, lifestyle issues and social and emotional concerns. The overall scored is calculated (0-100) with higher scores indicating better outcome.

Resource-usage data: Detailed resource use data on initial treatments received (surgical reconstruction or rehabilitation) and on subsequent healthcare contacts including re-operations (surgery arm), subsequent surgical reconstructions (rehabilitation arm), surgery-related complications, further rehabilitation, and primary care and other secondary care contacts out to 18 months post-randomisation. In addition, data will be collected on ability to work (e.g. sickness absences/return to work number of days off work and subjective working ability).

Expectations of return to activity and confidence in relation to the knee: Patients will be questioned on their expected outcome in relation to return to activity, and how confident they feel about doing so, considering any limitation related to their injured knee. This will be assessed by the Anterior cruciate ligament quality of life score (ACL-QOL) [5].

Patient satisfaction: Simple Likert scale to assess satisfaction with the outcome of treatment.

The outcomes reflect consensus opinion and the reference standard for evaluating ACL injury/reconstruction [31]. A specially convened PPI focus group indicated that the KOOS score, despite

being the most valid tool available and having been used in most major ACL studies, did not reflect the entire scope of symptoms for ACLD patients. Additional secondary measurement instruments have therefore been added.

5. STUDY DESIGN

This study is a pragmatic multi-centre randomised controlled trial with two-arm parallel groups and 1:1 allocation ratio to compare non-surgical management (Rehabilitation) and surgical management (Reconstruction) options for patients with a symptomatic non-acute ACL deficient knee. An internal pilot will be conducted with clear progression criteria regarding recruitment.

Both interventions are routine NHS treatments. Intervention content is based on a minimal set of pre-established criteria in order to ensure the integrity of the comparison while allowing for varying in practice in delivering the interventions between both surgeons and physiotherapists (see section 8). This largely pragmatic approach will allow clinical management to reflect current practice and resource use within the NHS thus aiding generalisation.

Other than the allocated intervention, both groups will be followed-up in the same way to exclude bias (see Appendix A). Follow up for study purposes will be by patient self-reported questionnaire completed using an electronic data capture collection system (a postal option will also be available). The questionnaire will include the outcomes indicated in section 4 and will be completed by participants at baseline, 6, 12 and 18 months (timings of all assessments are detailed in Appendix B). Non-response will be minimised through use of multiple reminders such as web based, phone and text.

Neither participants nor health care practitioners (surgeons and physiotherapists) can be blinded to receipt of the intervention.

Internal pilot:

The main *a priori* threats to the successful completion of this study are threefold; 1. The treatment preference of the population under investigation, 2. The characteristics of the population, and 3. The equipoise and preference of the surgeon delivering the intervention. An awareness of these potential threats is critical for success of the trial.

1. Eligible patients for the study will be at least 4 months after their initial injury. Some patients will feel they have already tried conservative treatment during this 4 month period. These patients, who have the potential to be allocated to continued non-surgical treatment, are likely to have a stronger preference for surgery.
2. The ACL injured group tend to be a younger (18-40 yrs) population and therefore very geographically mobile. The pilot will check that such patients can be followed up consistently and any innovative methods used to follow up a young mobile population are successful i.e. web based questionnaires, phone and text.
3. On the clinical side, recruiting surgeons are often the primary management decision makers for this population (sometimes with input from therapists). There may be some issues of bias and preference for surgery in the recruitment process. The pilot will evaluate the safeguards established to counteract this potential bias.

A two stage pilot study will be conducted to ensure recruitment and guarantee progression. For the first

stage, the trial will not progress without the recruitment of a minimum of 25 patients (from 8 centres) in the first 6 months of being open to recruit to the study. At this stage, a recruitment target for each centre will be at least 1 participant recruited or evidence provided through screening data of an active approach to recruitment. This will provide early evidence that centres are able to identify and recruit patients. A further review of progress will be made at one year from start of recruitment where 94 patients (from 12-18 sites) will comprise the progression criteria, with a target set for each centre open to recruitment to achieve an average of 1 participant per month. Recruitment and screening data will be monitored at individual sites and reasons for not meeting the targets explored. Where applicable and if necessary, the need to substitute sites that are unable to meet the target will be considered.

Frequent change in status to surgical management from non-surgical management is not considered a threat to study completion or a problem for analysis. The need for surgery, based on the firm standardised criteria outlined in section 7.4, would indicate failed management and will be an outcome measure in itself. Obviously, it will not be possible for patients to change from surgery to conservative management once surgery has been performed. However, it is possible that some patients may wish to change status immediately after randomisation after finding themselves allocated to a (self-perceived) inferior management group. Lessons learnt from recent qualitative work (CSAW study, Arthritis Research UK) [32] will be utilised to avoid this.

A qualitative study with a sub set of trial participants (approx. 30 - 40) and healthcare practitioners (approx. 10 -15) has also been incorporated. This nested study aims to assess the acceptability and adherence to the treatment interventions in the trial. This will facilitate evaluation of the interventions based on the experiences of healthcare practitioners and patients in delivering and receiving the intervention respectively; and will be used to inform the results of the main trial.

Recruitment of sites:

320 patients will be recruited from approximately 20 NHS orthopaedic units from across the UK including district general and teaching hospitals over a period of 2 years. Application to the UK Clinical Research Network (UKCRN) will be made to help facilitate recruitment and support the study.

The sites will be selected on the basis of having an established practice of ACL reconstruction and an experienced ACL reconstruction knee surgeon and physiotherapy team capable of providing contemporary care. All orthopaedic surgeons involved in performing the surgical intervention of the study will be designated as having expertise in soft tissue knee surgery as indicated in the Best Practice for Primary Isolated Anterior Cruciate Ligament Reconstruction guidelines (BOA, 2009), with a minimum experience of 50 procedures in their career. Non-surgical management (Rehabilitation) will be delivered (or closely overviewed) by senior physiotherapists (UK Health and Care Professions Council (HCPC) registered) with experience of ACL injury regimens.

Before including a site, evidence of patient through put will be reviewed. In addition, the protocol will be discussed with the clinical team to ensure that it would be feasible to run the study at the site. As the time interval between referral and treatment can be variable in the current care pathway, the time period between randomisation and intervention will be standardised (as much as possible) within the study. Only sites that can offer treatment (ACL surgery or rehabilitation) within the 18 week pathway, (in line with current NHS waiting time targets) will be recruited. In addition, as part of the site selection process, documentary evidence of the use of a rehabilitation protocol that reflects the guidelines set will

be required. Agreement to maintain consistency (adhere to the guidelines) with the aspects of the surgical intervention as laid out by the study protocol, will also be a requirement.

Regular contact and support will be maintained with study sites to help ensure that the protocol is carried out as planned.

6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

Patients referred to any of the participating sites with symptomatic knee problems consistent with an anterior cruciate ligament injury will be assessed for eligibility. Anterior cruciate ligament deficiency (ACLD) will be confirmed at the routine outpatient appointment through clinical assessment and MRI scan.

6.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Male or Female, aged 18 years or above.
- Symptomatic ACL deficiency (instability-episodes of frank giving way or feeling unstable) with ACL deficiency confirmed using clinical assessment and MRI scan.

6.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Patients will be excluded if they are; less than 4 months since injury,
- have had previous knee surgery (other than diagnostic arthroscopy) to index knee, concomitant severe injury to contra-lateral knee,
- Have meniscal pathology considered sufficiently symptomatic to require surgery i.e. locked knee, large bucket handle cartilage tear.
- have knee joint status of grade 3 or 4 on the Kellgren and Lawrence scale [1],
- have grade 3 MCL/LCL injury, associated PCL/PLC injury
- Have inflammatory arthropathy.
- Is pregnant. Pregnancy is checked for before receiving an MRI scan.

7. STUDY PROCEDURES

7.1. Identification and Recruitment

Patients referred to any of the participating sites with symptomatic knee problems consistent with an anterior cruciate ligament injury will be assessed for eligibility. The process of patient identification and recruitment will vary depending on the local treatment pathways at each participating site. The flowchart in Appendix A details the recruitment process.

As per routine practice anterior cruciate ligament deficiency (ACLD) will be confirmed at an outpatient appointment through clinical assessment and MRI scan.

The participating surgeon or member of the clinical team will initially approach potential participants who meet the eligibility criteria and inform them of the study. Patients who express a potential interest in participating would then be referred to a research nurse/physiotherapist for further details about the study and written information. Patients who wish to participate will complete an informed consent form and baseline questionnaire. If a patient would like more time to consider participation, the research team will agree an arrangement with the patient to confirm their decision.

There may be situations where a MRI scan is requested by the clinician prior to the confirmation of ACL deficiency. In these cases, information can be provided to the patient to inform them of the study and possible participation can be discussed once the diagnosis is confirmed.

The baseline questionnaire will include the following outcome measures: KOOS, EQ-5D, Modified Tegner and ACL-QOL, as detailed in section 4. Details of the baseline level of ACL injury and associated knee pathology from the MRI report will also be recorded.

7.2. Screening and Eligibility Assessment

Screening logs will be implemented at each of the recruiting sites in order to document the reasons for non-inclusion in the study (e.g. reason they were ineligible, or declined to participate). The central study office will use this to monitor recruitment at sites and to inform the CONSORT diagram.

7.3. Informed Consent

The patient must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the local site's Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site, a copy will be placed in the

patients' medical notes and another copy will be sent to the study co-ordinating team at Oxford for storage for central monitoring purposes.

The qualitative interviews will take place in a selected number of sites and with a small sample of participants. A separate information sheet and consent form will be used for the qualitative study. Written informed consent will be taken before the interview. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study office, Oxford.

7.4. Randomisation

Randomisation will be performed using a web based automated system. The allocation will be generated using permuted block randomisation with varying block sizes stratified by baseline KOOS score and site.

Patients will be allocated a study number and randomised on a 1:1 basis to receive one of two management options, non-surgical management (Rehabilitation) or surgery (Reconstruction). A standard letter will inform the admissions, care pathway co-ordinators, and GP (with patient consent) of allocation.

7.5. Subsequent Visits for treatment

Participants randomised to Rehabilitation will be referred to their nearest physiotherapy department and undergo standardised rehabilitation (to acceptable practice) delivered by physiotherapists with experience of ACL rehabilitation (as described in section 8). A physiotherapy case report form will be used to facilitate recording of the rehabilitation intervention and used to monitor compliance with the mandatory aims/goals of the rehabilitation intervention.

Participants randomised to Reconstruction will be placed on a waiting list to undergo ACL surgery. An operation case report form (OCRF) will be used to document the operation and monitor compliance with the intervention guidelines. As a period of post-operative rehabilitation forms part of standard treatment following ACL reconstruction, attendance (adherence) to rehabilitation and content will also be recorded for this group.

Follow up for study purposes will be by patient self-reported questionnaire completed using a web based data collection system. 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, Modified Tegner, ACL-QOL, patient satisfaction and will be sent out at 6, 12 and 18 months post randomisation to all participants. 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. The trial manager in Oxford 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.

The progress of patients who have been randomised to non-surgical management (Rehabilitation) will be monitored by their treating physiotherapist. If, after a minimum period of at least 3 months of rehabilitation, the participant continues to experience symptomatic knee instability the suggestion is that the non-surgical management has failed. Providing the patient meets the criteria listed below, a review appointment with the surgeon will be arranged. If following surgical assessment a decision is

made to proceed with ACL reconstruction surgery the participant will be listed for surgery, as per usual practice.

All other clinical follow up will occur as per routine practice at each participating site. The criteria for change in status (from non-surgical to surgical intervention) after a minimum of 3 months of rehabilitation were confirmed at a consensus meeting (surgeon/physiotherapist) 20th Jan 2016. The consensus group agreed that three months is considered the minimal time needed for the rehabilitation to provide any effect. The criteria for surgery include one or more of the following;

- Continued feeling of knee instability.
- At least two episodes of physical giving way of the knee.
- Unable to return to a Tegner activity level 2 points below pre-injury status.

The above criteria assume all patients will have undergone a comprehensive rehabilitation regime according to the study protocol – the physiotherapy case report form will provide evidence of completion and fidelity.

7.6. Qualitative sub-study

In addition to the main study, a qualitative sub study will also be conducted. This nested study aims to assess the acceptability and adherence to the treatment interventions in the trial. This will facilitate evaluation of the interventions based on the experiences of healthcare practitioners and patients in delivering and receiving the intervention respectively; and will be used to inform the results of the main trial.

After receiving the intervention, a small number of participants (approx. 30 – 40) who consented at trial entry to being contacted about the interview study, will be invited to participate in semi structured interviews. Healthcare practitioners (approx. 10 -15), delivering the trial interventions will also be contacted and invited to participate.

A separate information sheet and consent form will be used for the qualitative interviews. Interviews will be held at a convenient time and location for each participant. Ideally interviews will be undertaken face-to-face, however, given the geographical spread of participants, it may be more practical to perform some interviews by telephone or online (e.g. Skype). Participants may choose to have the interview within their own home in which case the researcher must adhere to the Oxford University and/ or Trust lone worker policy. It is predicted from previous experience that each interview will last between 30-45 mins.

Purposive sampling will be carried out to achieve a sample which includes; participants who were randomised to the surgical or rehabilitation intervention and those in the rehabilitation arm who subsequently decide to have surgery.

All interviews will be audio recorded, transcribed verbatim and analysed with the assistance of Nvivo qualitative data analysis software (QSR International Ltd, Melbourne, Australia). Field notes and memos will be recorded using a digital notepad. Participants will be offered the opportunity to check their transcript, providing an opportunity for them to remove anything with which they do not feel comfortable.

7.7. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- Withdrawal of Consent
- Loss to follow up

Participants will remain in the study unless they chose to withdraw consent or if they are unable to continue for a clinical reason. The reason for withdrawal will be recorded on the study change of status form. All other changes in status with the exception of formal withdrawal of consent will mean the participant is still followed up for all study outcomes wherever possible.

7.8. Definition of End of Study

The end of study is the date when all analysis is completed and the monograph is submitted to the funding body.

8. INTERVENTIONS

8.1. Health technologies being assessed:

The study compares two routine and well-established management strategies for patients with symptomatic non-acute ACL deficient knees; a) non-surgical management (Rehabilitation) and b) surgical management (Reconstruction).

Both interventions are routine NHS management strategies. The trial design is intentionally pragmatic with allowance for reasonable variation in intervention delivery between sites, physiotherapists and surgeons. Operations will be carried out according to the discretion of the participating surgeon. Two types of ACL reconstruction are commonplace and acceptable, one using a patella tendon graft, the other using a hamstrings graft. The rehabilitation content for the conservative arm will be based on standard care for the participating site. Minimal levels of quality and content have been set for both interventions (see below).

The description and standardisation of the interventions for the trial has been informed from several sources. These include; an overview of the best evidence to date, the results of a survey of ACL surgeons, synthesis of current practice guidelines/rehabilitation protocols from UK Trusts, and consensus meetings (surgeon/physiotherapist).

This pragmatic approach to the delivery of the intervention will allow the management approach to reflect current practice and outpatient resources within the NHS, yet include minimal levels of standardised quality and content for both interventions.

a) Non-Surgical Management (Rehabilitation)

Patients randomised to rehabilitation will be referred to their nearest physiotherapy department and undergo non-surgical management (Rehabilitation) delivered (or closely overviewed) by a senior physiotherapist with experience of ACL injury regimens. The routine rehabilitation protocol used at the participating site will be followed.

As part of the site selection process, documentary evidence of the use of or willingness to adopt a rehabilitation protocol that reflects the guidelines of the mandatory aims/goals set for the study rehabilitation intervention (see below) will be required. Part of the requirement will be for the site to be in a position to provide a minimum of six rehabilitation sessions delivered over at least a three month period.

The rehabilitation protocol will include the following components:

- Evidence of interventions aimed at achieving the 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.
- Clearly identified progression milestones.
- Return to sport criteria.
- Identification criteria for poor or non-progression.

Rehabilitation protocols commonly used in clinical practice consist of a progressive programme [33], designed to rebuild muscle strength, reestablish joint mobility and neuromuscular control, and enable patients to decrease the risk of re-injury and return to previous levels of activity [34].

As there is little consensus in the literature over the most effective rehabilitation protocol [35], variation in the specific exercises carried out and use of adjuncts (such as cryotherapy) to reach these aims is permitted. Examples of exercises used to reach the aims will be documented in a physiotherapy case report form (PCRF). Flexibility is permitted to adapt treatment to individual needs with no timelines specified for progression. Evidence of individual progression however will be documented in the PCRF. A physiotherapy case report form (PCRF) will be used to facilitate recording of the rehabilitation interventions to monitor for fidelity to these guidelines.

b) Surgical Management (Reconstruction)

Patients randomised to reconstructive surgery will be placed on a waiting list to undergo a standard ACL reconstruction procedure (ACLR). All surgical reconstructions will be patella tendon or hamstrings tendon depending on the surgeon's preference. All other care will be routine, including immediate post-operative care.

For the purpose of this pragmatic trial the surgical ACL reconstruction will be performed according to standard local policy, provided there is consistency with the minimal quality and care components as described below.

All patients will undergo pre-operative evaluation to assess their clinical condition and co-morbidities. During the trial the operative intervention will take place adhering to their local trust policies for anaesthesia, DVT prophylaxis and antibiotic use.

Surgery will be performed or supervised in theatre by a specialised consultant knee surgeon with recognised expertise in ACLR (performed at least 50 previous ACL reconstructions). Patients will be placed supine on the operating table and setup for an arthroscopic knee procedure. Tourniquet use will be as per local protocols. The incisions (commonly anteromedial and anterolateral) will be placed at the surgeon's discretion. Under arthroscopic guidance the torn ligament will be removed and anatomical landmarks within the knee identified. The desired graft will be harvested from a separate incision. Using a combination of direct vision and instrumentation, tibial and femoral tunnels will be placed to receive the graft. The graft will be introduced into the pre-prepared tunnels and once in situ and under tension, the graft will be fixed in position. All incisions will be sutured and bandaged, as per local protocols.

Patients will be engaged in a post-operative rehabilitation programme as per standard care at the participating hospital. Note the initial content of post-operative physiotherapy is different to that for non-surgical management in that there are some aspects of graft protection and caution following ACL reconstruction.

An operation case report form (OCRF) will be used to document the operation and monitor compliance with the intervention guidelines. The content of and attendance (adherence) to the post-operative rehabilitation will also be recorded for this group.

No rapid changes are expected in the content or delivery of both management approaches in the near future.

9. SAFETY REPORTING

9.1. Safety concerns

Adverse event reporting will be undertaken in accordance with both the National Research Ethics Services (NRES) guidelines, Research Governance Framework and OCTRU Standard Operational Procedure guidelines for non CTIMP studies.

The study involves routine ACL reconstruction surgery and rehabilitation for the management of symptomatic ACL deficiency. There are no additional risks to patients. They will either undergo ACL reconstruction or rehabilitation as per standard management. Patients will be informed of the standard risks associated with anaesthetic and ACL reconstruction operations.

Possible (expected) complications and consequences are:

All ACL reconstruction procedures whether primary surgery or revision carry a risk of anaesthesia related problems which can include death, morbidity including would infection, bleeding intra and post operatively, PE, DVT, confirmed CVA, confirmed MI, and complications secondary to existing co-morbidity e.g. ischaemic heart disease, septicaemia, the need for blood transfusion and revision operation.

Specific complications following ACL reconstruction 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, lack of extension/fixed flexion deformity, stiffness, infection, graft failure and continued instability, delayed wound healing, continued or worsened pain, fracture, compartment syndrome, swelling, contralateral graft harvest and newly acquired meniscal pathology.

Specific complications following rehabilitation include: continued instability and subsequent newly acquired meniscal pathology, pain. These complications may result in the need for further surgery. Details of all complications will be collected and recorded as detailed in section 7.4. Only those complications which are serious, related and unexpected should be reported to the CTU on a SAE form.

9.2. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the 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.

9.3. Reporting Procedures for Serious Adverse Events

The reporting procedures for all study related adverse events are detailed in Appendix D and are in accordance with the guidance from the Health Research Authority (HRA).

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures.

When the SAE form is completed detailing any possible related and unexpected SAEs, the Chief Investigator (CI) or delegate will be notified. If in the opinion of the local PI and CI, the event is confirmed as being related (resulted from administration of any of the research procedures) and unexpected (i.e. not listed in section 9.1 as a possible expected occurrence), the CI will submit a report to the main REC and the study sponsors within 15 days of the CI becoming aware of it.

10. STATISTICS AND ANALYSIS

10.1. Description of Statistical Methods

All primary analyses will be based on the intention-to-treat principle, analyzing participants in the groups to which they are randomized. The principal analysis will be carried out once the 18 month time point has been reached by the last participant. Analyses will be pre-specified in a statistical analysis plan prior to unblinding of the data.

An independent Data Monitoring Committee (DMC) will meet early in the course of the trial to agree its terms of reference and will review confidential interim analyses of accumulating data (including the interim analysis of clustering).

10.2. The Number of Participants

320 participants will be recruited to the study. The Minimal Clinically Important Change (MIC) for the KOOS score is 8-10 points [36]. Estimates of the Minimal Detectable Change (MDC) for the two KOOS subscales most relevant for ACLD vary between 5 and 12 points (Symptoms 5-9, and Sport/Rec 6-12) [36]. Conservatively, a target difference of 8 points and standard deviation of 19 (the highest value observed in a trial of acute patients at baseline amongst the KOOS subscales) has been assumed. Given these assumptions, 120 participants per group are required (240 in total) to achieve 90% power at 2 sided 5% significance level in the absence of any clustering of outcome. However, in order to ensure sufficient power clustering (clsampsi Stata command [37]) has been allowed for by conservatively assuming an intracluster correlation (ICC) of 0.06 [38] and cluster size n, mean (SD) of 26, 5 (12) and 43, 3 (5) for ACL reconstruction and rehabilitation groups respectively. This leads to the larger number of 130 participants per group (260) which has just over 80% power. Given the conservative nature of the assumed values and the anticipated gain in precision from adjusting for the baseline scores and other randomisation factors, actual power is likely to be higher even in the presence of clustering. In order to allow for just over 15% missing data (response in a similar trial [26]), 320 participants will be needed. An interim analysis will be carried out to estimate the magnitude of clustering for the 6 months KOOS4 outcome once data is available for 100 participants. Based upon this a decision as to whether the sample size should be increased to allow for a greater level of clustering than anticipated will be made.

10.3. Analysis of Outcome Measures

The primary outcome measure (KOOS4 overall score) will be compared using a regression model with adjustment for the randomisations variables. Secondary outcomes will be analysed using generalised linear regression models with adjustment for randomisation and baseline variables as appropriate. Statistical significance will be at the 5% level with corresponding confidence intervals derived and analyses will be carried out in Stata 13.0 [39]. All participants will be analysed according to their allocated group (i.e. intention to treat). A single main analysis will be performed at the end of the trial once 18-months follow-up is available. Exploratory subgroup analyses will explore the possible treatment effect modification of clinically important baseline factors (age, gender, high versus moderate or light physical activity as measured by the modified Tegner score, and KOOS4 overall score), through the use of a treatment by factor interaction and will be interpreted cautiously. The impact of missing data and non-

compliance will be explored utilising a multiple imputation and complier average causal effect (CACE) approaches respectively. Clustering will be quantified as the ICC with associated 95% confidence interval calculated using a bootstrapping approach. Study analyses will follow a statistical analysis plan agreed in advance by the Trial Steering Committee.

10.4. Cost-utility analysis

A health economic evaluation (more specifically a cost-utility analysis) will be designed as an integral part of the ACL SNNAP Trial and will be conducted from NHS and societal perspectives. Detailed resource use data will be collected for each trial participant on initial treatments received (surgical reconstruction or rehabilitation) and on subsequent healthcare contacts including re-operations (surgery arm), subsequent surgical reconstructions (non-surgical rehabilitation arm), surgery-related complications, further rehabilitation, and primary care and other secondary care contacts out to 18 months post-randomisation. Beyond the healthcare sector data will also be collected from each patient on contacts with private healthcare practitioners, unpaid informal care provided by relatives and/or friends, and time away from paid employment. Resource use data will be costed using national average unit costs from a variety of established sources [40-42].

Patients will complete the EuroQol EQ-5D-5L questionnaire at baseline, 6 months, 12 months, and 18 months, and responses will be converted into single index scores [4]. The UK value set to derive single scores from the EQ-5D-5L is currently under development but it is expected that it will be available before data analysis begins. These scores will be used along with patient survival data to facilitate the calculation of quality adjusted life years (QALYs) for each trial patient out to 18 months post-randomisation.

Resource use, costs, and QALYs to 18 months will be summarised using means and standard deviations for each trial arm. Mean differences and 95% confidence intervals for differences will be used when comparing between trial arms. Incremental analyses will be performed and, if appropriate, the incremental cost-effectiveness ratio (ICER) will be used to express results in terms of an additional cost per QALY gained. Sampling uncertainty around the ICER will be explored using non-parametric bootstrapping. Parameter uncertainty will be examined using sensitivity analysis. Cost-effectiveness acceptability curves will be used to estimate the probability of the interventions being cost-effective at a maximum willingness to pay of £20,000 to £30,000 per QALY gained.

Potential longer-term cost-effectiveness will be estimated by extrapolating costs and health outcomes beyond the time horizon of 18 months. Extrapolations will be based on a modelling of the rates of re-operations observed in the surgery arm of the trial and subsequent surgeries observed in the rehabilitation arm of the trial. A separate application may be made for these longer term data analyses.

11. DATA MANAGEMENT

11.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

11.2. Data Recording and Record Keeping

Data collection will be facilitated by a custom designed database created by Fr3dom, using the Fr3PROMS platform. A guide explaining how to use the ACL SNNAP electronic data collection system will be provided to every site.

The Chief Investigator will act as Data Custodian for the trial.

Data from the Web-based questionnaires will be captured automatically after the participant completes the online questionnaire. Data from any paper questionnaires will be entered manually into an electronic database by the local study team at participating sites or by the central study office in Oxford.

All electronic data will be captured via an xml schematic, encrypted and written down securely once a survey is <saved> on the device. Data is encrypted (proprietary 256 des) and stored on the device. Transfer happens securely over mobile, Wifi, or wired connection. The encrypted data is sent via a secured connection to the secure data centre. Industry standard protocols and processes are used to ensure the highest secure environment.

Data is transmitted in small packets, fully encrypted and once all data is received and parsed it is applied to the database by the FR3PROMS communication platform. Once all data is verified and saved the server issues a delete command and terminates the connection. This ensures that firstly no incomplete data sets can ever be applied to the database and secondly that the remote device does not control the communications termination, the server does. The system is designed this way to allow use in sensitive areas and to ensure data security.

Storage is in Fr3PROMS SSL access SQL cluster in a secure hosted environment. Access is monitored and dashboard access allows the download of unencrypted data but will not allow deletion of core data by users without prior written request from the commissioning party.

Access to data from the client is through an intelligent SSL fire wall and can only be accessed by authorised users.

A study specific participant number and/or code in any database will be used to identify the participants. The name and any other identifying detail will not be included in any study data electronic file. Any patient related data transferred between the main study office and participating sites will be identifiable only with the patients unique study number. If more identifiable information is required, secure measures such as registered post, courier, or nhs.net email accounts will be utilised. For quality control reasons, the main study team may initiate monitoring of site files and data collection forms.

12. QUALITY ASSURANCE PROCEDURES

The trial will be managed through the Surgical Intervention Trial Unit (SITU) and OCTRU, University of Oxford, and the research team's Trial Management Group (TMG). The Principal Investigators at the recruiting sites are responsible for the study conduct at their sites. SITU will provide day-to-day support for the sites and provide training through Investigator and research practitioners meetings, site initiation, phone calls and routine monitoring.

The study will be conducted according to the principles of GCP. A risk assessment will be conducted before the trial starts and a proportionate monitoring plan will be drawn up and used for the trial.

12.1 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be convened with independent statistician, clinician and chairperson to provide independent review. Its purpose is to monitor efficacy, safety and compliance data. The DMC will have access to unblinded study data. During the recruitment period, interim analysis will be supplied, in the strictest confidence, together with any other analyses that the committee may request.

12.2 Trial Steering Committee

A Trial Steering Committee with an independent chair will provide overall supervision of the trial. The TSC will meet every six months or more/less frequently if circumstances dictate during the trial. Its role is to monitor progress and supervise the trial to ensure it is conducted to high standards in accordance with the protocol, the principles of GCP, relevant regulations and guidelines with regard to participant safety.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Declaration of Helsinki

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

13.2. Guidelines for Good Clinical Practice

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

13.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

13.4. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

13.5. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database, with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

13.6. Expenses and Benefits

Any extra visits required for recruitment will be arranged at the patient's convenience. Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

13.7. Other Ethical Considerations

As the study is a comparison of two routine NHS management options for patients with non-acute ACLD knees, we do not anticipate any major ethical concerns with this study.

No treatment will be withheld. Patients requiring additional or subsequent treatment (i.e. non-surgical patients needing surgery) will be offered treatment according to clinical need.

14. FINANCE AND INSURANCE

14.1. Funding

The study is funded by the National Institute of Health Research, Health Technology Assessment Programme (Ref 14/140/63). The Nuffield Department of Orthopaedics, Rheumatology & Musculoskeletal Sciences at the University of Oxford will manage the finances and budget.

14.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

15. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the National Institute of Health Research, Health Technology Assessment Programme (Ref 14/140/63). Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

All investigators and co-ordinators who take part in the study will be members of the ACL SNNAP Study Group and will be publicly listed on the trial website. All ACL SNNAP publications will be published on

behalf of the ACL SNNAP Study Group, which means all trial group members can list these in their curriculum vitae. All members of the ACL SNNAP Study Group will be submitted to be listed and citable in PubMed.

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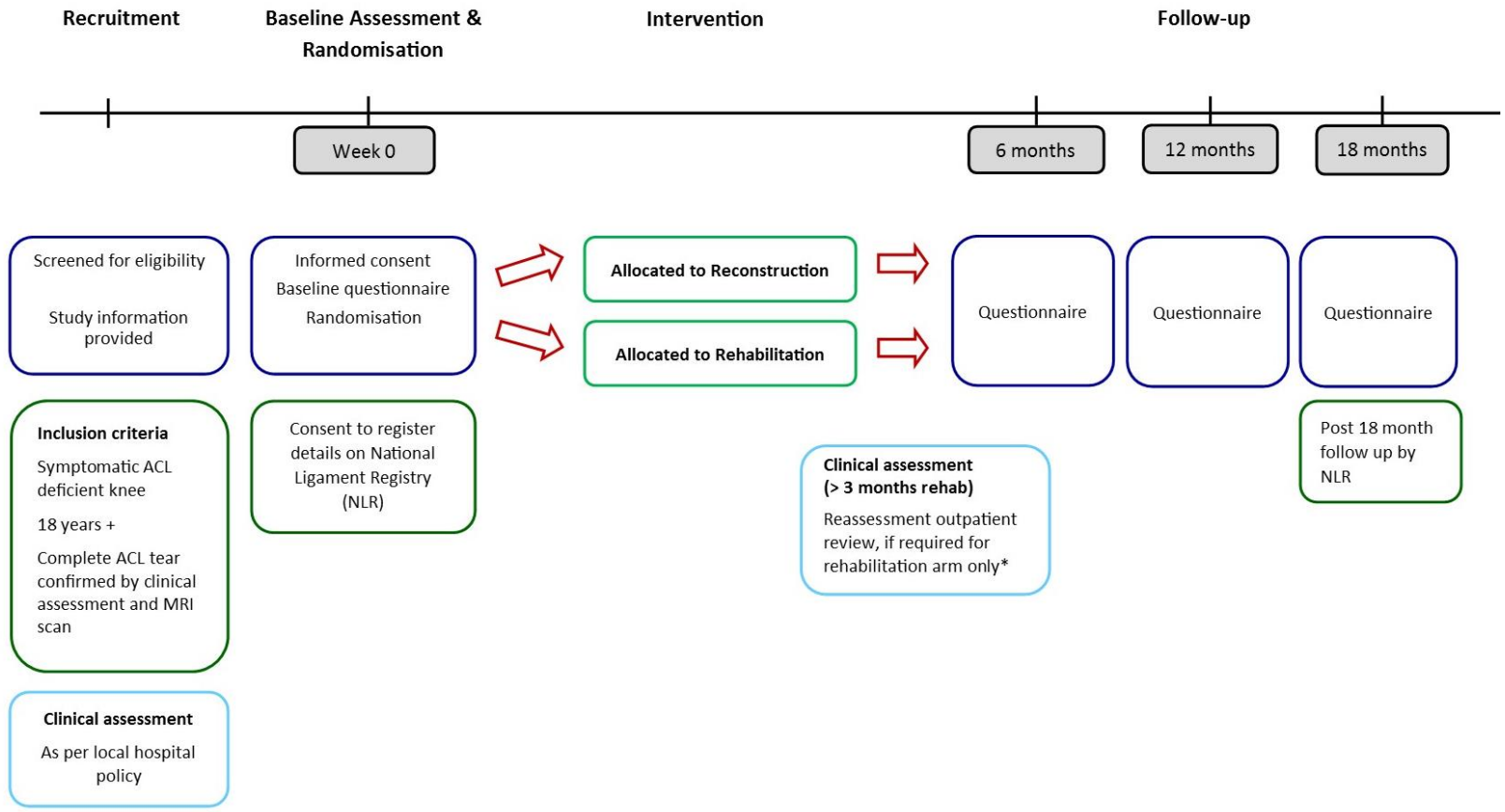
17. APPENDIX A: STUDY FLOW CHART



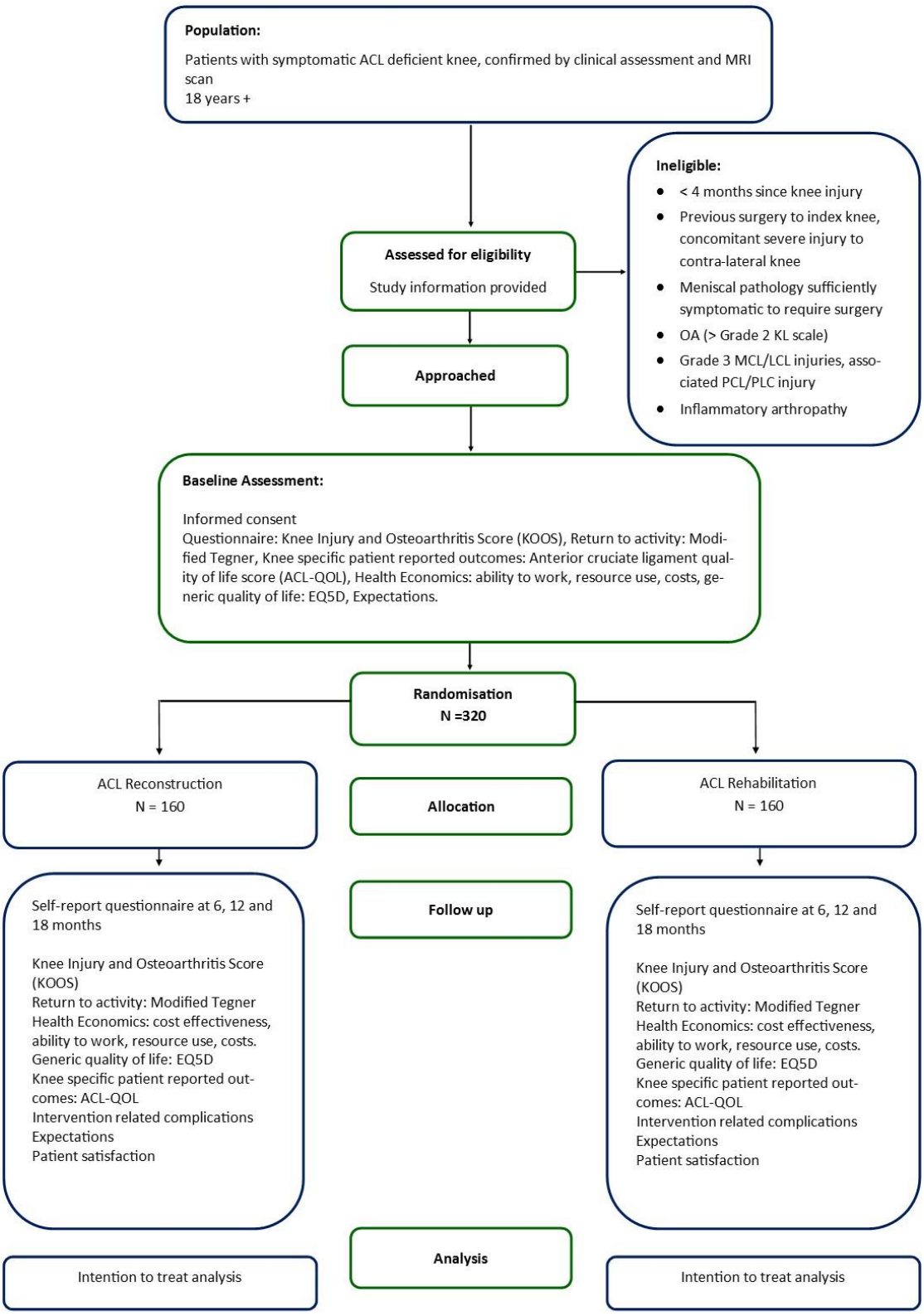
* Clinical assessment appointment for participants randomised to rehabilitation requiring reassessment due to continued problems with instability . See section 7.4

18. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

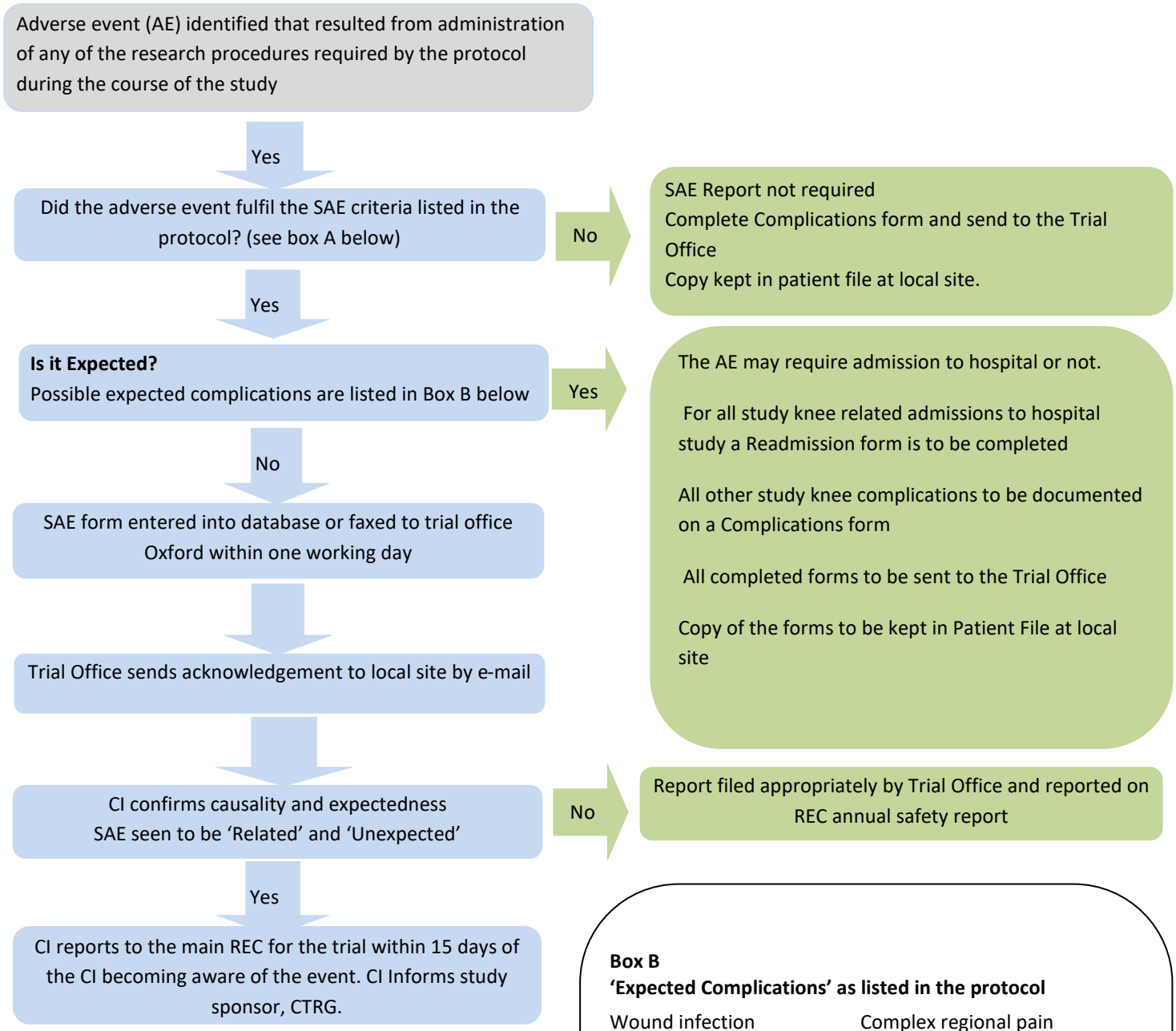
Procedures	Visits			Follow-up –postal/e-mail questionnaire		
	Screening	**Baseline**	Re-assessment*	**6 months**	**12 months**	**18 months**
Informed consent		X				
Demographics		X				
Medical history		X				
Physical examination			X*			
MRI (as part of routine practice)	X					
Eligibility assessment	X					
Randomisation		X				
Questionnaire:						
Knee Injury and Osteoarthritis Outcome Score (KOOS)		X		X	X	X
Return to activity/ level of sport participation - modified Tegner		X		X	X	X
Health economics – EQ5D		X		X	X	X
Complications				X	X	X
Knee specific patient reported outcomes, ACL-QOL				X	X	X
Patient satisfaction				X	X	X
Adverse event assessments				X	X	X

* Clinical assessment appointment for participants randomised to rehabilitation requiring reassessment due to continued problems with instability.

19. APPENDIX C: CONSORT FLOW DIAGRAM



20. APPENDIX D: ADVERSE EVENT REPORTING



Box A - SAE criteria

In this study a SAE is defined as any event resulting from a participant's reconstruction surgery or rehabilitation, that is

- Life threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity, or
- Other important medical events
- SAE forms will record all deaths for any cause during the course of the study

Box B

'Expected Complications' as listed in the protocol

Wound infection	Complex regional pain
Bleeding	Lack of extension/fixed flexion deformity
PE	Stiffness
DVT	Infection
Confirmed CVA	Graft failure
Confirmed MI	Delayed wound healing
Septicaemia	Continued or worsened pain
Blood transfusion	Fracture
Revision operation	Compartment syndrome
Patella fracture	Swelling
Patella tendon avulsion	Contralateral graft harvest
Anterior knee pain	Continued instability
Vascular injury and bleeding	Newly acquired meniscal pathology
Femoral tunnel blowout	Pain
Nerve damage (including numbness or weakness)	

21. APPENDIX E: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
001	2.0	07Mar2017	Professor David Beard	Randomisation method has changed. The new form involves stratification rather than minimisation. A small number of other changes were made in order to provide greater clarity; collection of MRI details at baseline; 'failure of intervention' collected and detailed as 'intervention related complications' and some typographical errors also corrected.

