Northern Care Alliance
NHS Foundation Trust

Study Title:	The Jewel ACL Study: Feasibility Randomised Controlled Trial Comparing the Outcomes of the Auto graft ACL Reconstruction (Using Hamstring Tendon) to a Hybrid Artificial (JewelACL) and autograft ACL Reconstruction
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Sponsor:	Northern Care Alliance NHS Foundation Trust
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Contents

SYNOPSIS

Study Title	JewelACL Study: Feasibility Randomised Controlled Trial Comparing the Outcomes of the Auto graft ACL Reconstruction (Using Hamstring Tendon) to an Artificial Hybrid ACL Reconstruction using synthetic and autograft (JewelACL)	
Study Design	Feasibility RCT	
Study Participants	Adults aged 18 years and over with a diagnosis of ACL rupture requiring surgical reconstruction	
Planned Sample Size	50 patients	
Planned Study Period	18-month recruitment with 2-year follow up	
	Objectives	**Endpoints**
Primary	Patient reported outcome measures and performance data using IKDC Score, Marx Activity Scale and ACL (RSI) scale.	Identify any differences in score between the 2 groups at 2, 6, 12, 26, 39 weeks; and at 1 year, 18 months, and 2 years post-surgery. IKDC, Marx activity scale and ACL RSI will only be used from 12 weeks
Secondary	Patient reported outcomes of pain, re-rupture rates and return to their pre-injury level of sport. Combination of subjective and objective functional data will be collected. Performance data on gait analysis and muscle strength will be collected	Identify any differences in pain between the 2 groups at 2, 6, 12, 26, 39 weeks; and at 1 year, 18 months and 2 years post-surgery. Also identify any differences in re-rupture rates and return to pre-injury level

LIST OF ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CI	Chief investigator
GCP	Good clinical practice
NICE	National Institute for Health and Care Excellence
PI	Principal investigator
PIS	Patient Information Sheet
REC	Research ethics committee
SAE	Serious adverse event
SAR	Serious adverse reaction
UoS	University of Salford

The JewelACL Study: Feasibility Randomised Controlled Trial Comparing the Outcomes of the Auto graft ACL Reconstruction (Using Hamstring Tendon) to an Artificial Hybrid ACL Reconstruction (JewelACL)

Background

Reconstruction of the anterior cruciate ligament (ACL) is one of the most common orthopaedic knee procedures performed. The main indication for this surgery is knee instability after a ligament injury/tear. Typically, this is performed using an autograft involving either the patient's patellar tendon or hamstring tendons in a young and active population keen to resume a high level of physical activity and recreation/sport. Both methods of autograft are associated with a significant incidence of donor site morbidity with associated pain and dysfunction after the surgery. An artificial graft has the potential to avoid such donor site morbidity and also be biomechanically superior. However, previous problems with graft/host incompatibility and tissue reactions to material used to construct an artificial graft have led to previous poor results and increased levels of complication [1].

Xiros Limited have designed a biomechanically strong range of artificial ligaments that have excellent biocompatibility with low documented complications [2,3].

The main potential benefits of artificial grafts centres around the avoidance of donor site morbidity and trying to improve and develop the biocompatibility of artificial grafts for the future. The artificial graft does not have to go through a ligamentisation process, which could potentially help patients return to their pre-injury level of recreation/sport earlier than expected. In addition to this, a major surgical advantage of using an artificial graft is less surgical time of approximately 10-15 mins (10% of the total surgical time).

Study Device

The JewelACL is a tissue graft-sparing device for the reconstruction of the ACL. It has been designed for use in partial or total tissue sparing ACL reconstruction with hamstring tendons. In a partial tissue graft sparing reconstruction procedure the JewelACL may be used in conjunction with the gracilis tendon.

The JewelACL is specifically designed for implantation with approaches that are familiar to most surgeons. Thus, bone tunnels may be prepared with appropriate standard instrumentation in current use. Also, the JewelACL (in combination with the gracilis hamstring tendon) may be secured to the bone with approved cortical suspension, cross pin fixation devices.

Method of Use

Standard ACL surgical reconstructive techniques but instead of using only patient autograft, an artificial ligament would be used in conjunction with the smaller gracilis autograft tendon. This hybrid graft is a recognised technique but has low level evidence in the literature regarding clinical outcomes. The surgery involves standard drill tunnels through both the proximal tibia and distal femur. This is the standard fixation technique used for hamstring autograft surgery.

Manufacture and supply

The JewelACL is manufactured by Xiros Limited, Leeds. The JewelACL will be supplied by Xiros Limited.

Study Design

We intend to undertake a feasibility randomised controlled trial comparing outcomes of the hamstring auto graft ACL reconstruction and the artificial hybrid JewelACL reconstruction. This will help us decide on the feasibility and potential outcome measures to use in a larger trial. This study will help power a future study correctly. This will be an equivalency study comparing the two techniques. We hypothesise that there will be no significant differences in outcomes between the two groups.

Study objectives

Primary objective

1. To compare the patient reported outcomes using IKDC, Marx Activity Scale and ACL RSI Scores following a hamstring tendon ACL reconstruction versus the artificial hybrid JewelACL reconstruction.

Secondary objectives

1. To compare surgical operative data (including surgical time).
2. To compare patient reported pain levels.
3. Compare re-rupture rates and return to pre-injury recreation/sport level.
4. To compare objective measures of laxity and performance of quadriceps and hamstrings muscles.
5. To compare biomechanical movement patterns at 3, 6, 9, and 12 months in the individuals.

Participants

All patients listed for ACL reconstruction under the care of Mr Neil Jain at the Northern Care Alliance NHS Foundation Trust will be screened to participate in the study. All ineligible patients will be excluded, and the reasons will be documented under the exclusion criteria below.

Inclusion Criteria

1. Patient presents with persistent unilateral knee instability after ACL rupture that merits surgical intervention and ligament reconstruction.
2. Patients listed at Northern Care Alliance for routine unilateral ACL reconstruction.
3. Patients aged 18 years and over.

Exclusion Criteria

1. Declined to participate.
2. Inability to provide informed consent.
3. Inability to answer questionnaires for cognitive reasons.
4. Morbidly obese (BMI >40).
5. Patient is unable to attend rehabilitation and clinic appointments at the hospital or the University of Salford (UoS).
6. Revision ACL surgery.
7. Previous hamstrings injury or harvest procedure.

Trial procedures

Recruitment

We aim to recruit a total of 50 patients over an 18-month period. An increasing number of ACL reconstructions have been undertaken by Mr Jain in recent years, with over 50 procedures undertaken in 2018. Allowing for potentially ineligible patients and refusal to participate, we are confident that the target of 50 patients over an 18-month period is a feasible one. There will be 25 patients in each group. This will be produced by a randomisation procedure following the randomisation plan (www.randomization.com). The reason for choosing 25 patients in each arm is to assess feasibility of the protocol for a larger trial. Previous literature has recommended a sample size of 50 patients in total for pilot and feasibility studies[5].

Screening

Mr Jain will only recruit patients within NHS orthopaedic clinics. All patients listed for ACL reconstruction under the care of Mr Jain will be screened based on the eligibility criteria above. Mr Jain and Fraser Goodwin will inform the patients of the study whilst discussing the surgical options with potentially eligible patients at the time of listing for surgery. Eligible patients will then be given a patient information sheet (PIS). Patients will then be given the opportunity to discuss the study with family and friends before deciding to take part.

They will then attend a second clinic to be consented for the trial if willing to participate. This is an extra visit than routine care within the NHS. This is to allow the patient time to think about questions and discuss the trial. We cannot attend preoperative assessment clinics and we cannot consent on the day of surgery as the patient will need to visit the UoS for functional assessment.

Informed Consent

All ACL reconstruction patients will be consented by Mr Jain during the second orthopaedic clinic. They will have been given the PIS at the previous clinic visit. The patient will then have the opportunity to discuss any questions with the surgeon at this clinic or book into another clinic to discuss the procedure further if in any doubt. Patients being consented will be given a time earlier than the official clinic starts or at the end of clinic, so it does not affect other patients care within the NHS.

If a patient would like to discuss the study with someone who works in Orthopaedics but is not directly involved with the study, they will be advised to contact Tim Holland (contact details on PIS).

Written informed consent will be taken in accordance with GCP with the original copy retained for the trial site file, 1 copy for the participant, and a further copy to be kept in medical notes.

Withdrawal of Consent

Participation in the study is voluntary and participants are free to withdraw from the study at any time and this will not impact on the care that they receive. In the unlikely event that a participant loses capacity during the study, they will be withdrawn. Data collected for participants who are withdrawn will be retained and included in the study analysis, but no further data will be collected, or research activity carried out on or in relation to the participant. The consent documentation will be retained in the Investigator Site File.

Assessment times

Please refer to the schedule of events (Table 1).

Routine Care for Patients:

Since using the Jewel ACL in complex cases Mr Jain has reviewed patients routinely at 2, 6, 12, 26, 39 weeks and 12 months to monitor outcomes. All research participants will have the same routine clinic follow up visits as above. At these clinic visits they will see the surgeon for clinical assessment and review by the physiotherapist, which is routine care also.

Research Care:

At each routine clinic visit the patient will also fill out the questionnaires for outcome data. There will only be one to maximum 2 patients within the trial per week in the NHS clinic.

Extra Research Visits:

All patients will be biomechanically assessed by Professor Richard Jones, Fraser Goodwin, two of the key investigators, and/or Samantha Rhodes at the UoS at pre-op., 3-, 6-, 9-, and 12-months post op. This will comprise a knee kinesiography assessment using the KneeKG (Emovi) which is the first solution to deliver diagnostic accuracy of knee motion in all three planes of movement. Laxity measures of the injured and contralateral limbs will be recorded on the Genourob machine also at the UoS at 3, 6, 9, and 12 months. These will be for research purposes only and will help provide difference in graft performance between the two groups. The laxity measures and biomechanical assessments will be performed on the same day. The patients will be reimbursed for travel costs to the institute. Xiros ltd. will fund the travel at £30 for all journeys. Laxity measurements with the Genourob machine will take 15-30 minutes, and the biomechanical assessment 2.5hours, including the KneeKG assessment (20-30 minutes in duration); the visits to the UoS will take ~3 hours.

Rehabilitation

All patients will follow the same 8-stage post-operative protocol guidelines as standard routine practice for ACL reconstruction at Fairfield General Hospital. This is routine care and will not be any different to the normal rehabilitation program. Patients will only progress on

to the next stage of rehabilitation when the clinical physiotherapist is satisfied that the patient has met the requirements documented in the routine rehabilitation protocol. The physiotherapy department will be under no further workload as they perform this protocol already.

Patients are routinely seen by an MSK physiotherapist on a 1:1 basis initially until they fulfil the criteria to progress to stage 2, from which point they will attend the ACL rehabilitation class until all 8 stages of rehabilitation are completed.

Due to the impact of donor site pain and dysfunction in the hamstring autograft tendon ACL reconstruction group, it is anticipated that the hybrid JewelACL patients may progress from stage 2 to the later stages of rehabilitation earlier than the hamstring group. All patients will follow the same 8 stages and the milestones of completing each stage will be documented.

Outcome Measures

Outcome measures are not routine practice for Mr Jain in the NHS. These will be performed for research purposes only by the patients. They will fill them out whilst waiting in clinic for their routine visits. It should not add any extra time for the patient.

Primary outcome

- Patient reported outcomes using the IKDC, Marx Activity Scale and ACL RSI Scale will be measured. These scores are validated for post knee surgery outcomes. They are very specific for showing patients who are not performing well after ACL reconstruction but not sensitive for showing who is ready to return to their previous injury level. For this reason, we will be using performance related data in the secondary outcomes section also.

Patient questionnaires

A combination of clinical outcome and activity scores will be used to provide a comprehensive outcome assessment for patients:

- The International Knee Documentation Committee 2000 subjective knee form (IKDC 2000) is a knee-specific outcome measure for assessing symptoms, function, and sports activity. The IKDC 2000 is frequently used to assess knee function in patients after ACL reconstruction and contains items highly relevant to individuals with a reconstructed ACL.
- ACL RSI Scale is a 12-item scale used specifically for patients following ACL injury attempting return to sport. It looks at fear of return to play and the psychological effect on outcomes from ACL surgery. We believe the JewelACL patient group may score better on this scale as they may feel more confident in the synthetic hybrid graft and may return to their pre-injury level quicker.
- The Marx Activity Scale will be used to compare pre-operative activity and post-operative activity progression at each review point. This is a scale which looks at four types of sporting movements, which will help show how far patients have progressed with the rehabilitation program.

Secondary outcomes

Patient reported pain will be collected using the Short-form McGill Pain Questionnaire (SF-MPQ) which includes visual analogue and verbal rating scales of pain intensity as well as 15 pain descriptors that are each rated on a four-point verbal scale; its reliability and validity are well established [4]. Performance related data as mentioned above will also be recorded to help decide on return to patient's pre-injury level of recreation or sport. The number of re-ruptures and when patients return to their previous level of sport/recreation will also be recorded here.

Performance data

This data is extra information for research purposes only and is not usually performed in the routine clinic setting. It will only add an extra 10 minutes onto each clinic visit.

Data will be collected on quadriceps and hamstrings strength using limb asymmetry index and the Genourob automatic dynamic laximetry machine arthrometer to assess differences between the two groups in the rehabilitation phase. The physiotherapy team will be comparing muscle mass with thigh measurements and comparing to the uninjured leg. They will perform single leg hop tests and compare distance covered. This data will help us pick up differences between the groups returning to their previous injury levels. This is part of their standard practice and will add no extra workload onto routine care.

Observer Evaluations

- Knee ROM
- Knee swelling
- Thigh circumference

Laxity Measure

We will use the Genourob laxity machine at the UoS to standardise laxity in the knee joint between the two groups. This is not used routinely in Mr Jain's practice. It will be for research purposes only. We will do this by comparing laxity directly to the contralateral leg. We do not expect any difference, but there is a theoretical possibility of increased laxity in the hamstring autograft group during the ligamentisation phase of graft healing. This usually occurs between 3 and 9 months when carrying out the rehab program.

Functional performance of the knee joint

This will be carried out at the Human Performance Lab at the UoS. Professor Jones, Fraser Goodwin and/or Samantha Rhodes, as key investigators, will assess the patients using three-dimensional gait analysis and knee kinesiography 6-weeks pre-operatively and at the 3-, 6-, 9-, and 12-month time point following surgery. The measures taken at the 6-month time-point are reflective of the time since surgery whereas the 12-month assessment is a typical return to sport biomechanical criteria used by the investigators. The assessment is as follows:

Pre-operative – the activities (like those listed below) will be as comprehensive as the patient allows.

3 Months:

- Bilateral squat
- Single leg small knee bend
- Walking
- Running (if able)
- Single leg step-down.

6 Months:

- Walking at a self-selected speed
- Running at a self-selected speed
- Small knee bend
- Single leg landing
- Hop for distance.

9 Months:

- Walking at a self-selected speed
- Running at a self-selected speed
- Small knee bend
- Single leg landing
- Hop for distance
- 90° directional change
- Isokinetic knee evaluation on the knee flexors and extensors

12 months:

Identical to the 9-month protocol.

All assessments will be performed at the Human Performance Lab at the UoS.

The outcome measures will be kinematic and kinetic patterns of the knee joint alongside strength aspects of the knee flexors and extensors.

Preadmission Clinic

Pre-operative assessment is routinely carried out around 6 weeks before surgery. Written informed consent will be obtained before carrying out baseline assessments. At this time the pre-operative Marx Activity Scale will be collected, and the functional performance of the knee will be assessed at the separate visit to the Human Performance Lab at the UoS. This will provide valuable data to compare to the post-operative data being collected as described above.

Inpatient Randomisation and Assessment

On the day of admission, the research team will ensure all questionnaires and assessments are completed. The patients will then be randomised into one of two groups. Randomisation will be computer generated as described earlier. Patients will be allocated to group A or Group B and the research team will inform the surgeon and theatre staff of the outcome of randomisation.

Group A will receive the auto graft ACL reconstruction using hamstring tendons.

Group B will receive the artificial Hybrid JewelACL along with gracilis tendon.

The following peri-operative and post-op data will be collected during the inpatient stay:

- Surgical time in minutes.
- Length of hospital stay.
- Patient demographic data, ACL injury data, and surgical operative data as recommended by the National Ligament Registry.

Patients will not be told which graft they have post-surgery to remove any bias towards one graft option during testing and questionnaire completion. Mr Jain will state this clearly to the patient preoperatively. They will be told once the study has finished in 2 years' time.

Follow-up Assessment after Surgery

Patients will attend routine outpatient assessments at approximately 2, 6, 12, 26, 39 weeks and 12 months post-op. These appointments are standard care in Mr Jain's practice following ACL reconstruction.

The patients will be assessed by the physiotherapists as routine care. They will record observer evaluations and assess performance (Table 1). Details of any complications or revision of the reconstruction (including date, indication, and cause of failure if known) will also be collected.

The relevant PROMS data at review will be undertaken by the medical team, which is extra information being gathered for research purposes only. Any patient who is unable to attend for a follow-up review will be either sent their questionnaires in the post or contacted by phone to complete as many of the follow-up questions as possible and to explain the importance of routine clinical review.

The visits to the UoS are extra sessions pre-operatively and at 3-, 6-, 9-, and 12-months post-op. to provide valuable research information on biomechanics of the two surgical groups. The participants will be asked to attend the university for ~3 hours on each visit for assessment. The Human Performance Lab at the UoS is a separate centre to the NHS. They research the rehabilitation of patients following sports injuries. Professor Richard Jones is a world leading clinician in rehabilitation of patients following sports injuries. He analyses gait patterns and muscle strength. This data will be the first of its kind with regards to artificial grafts and having comparison between pre- and post-operative data. These visits will be funded privately by Xiros Ltd. Professor jones and Fraser Goodwin will analyse the data anonymously at the UoS and send the data to Mr Jain with the unique identifier number.

Table 1. Schedule of events

Procedure	Pre-op.	Inpatient	2 weeks	6 weeks	3 months	6 months	9 months	1 year	1.5 years	2 years

Screening	X									
Informed consent	X									
PROMS -IKDC -ACL RSI -Marx -SF-MPQ	X Marx	X SF-MPQ only	X SF-MPQ only	X SF-MPQ only	X	X	X	X post	X post	X post
Observer evaluations	X		X	X	X	X	X			
Surgical data/LOS		X								
Complications/ revisions		X	X	X	X	X	X	X post	X post	X post
Performance Data	X				X	X	X	X		
Genourob Arthrometer					X	X	X	X		

Reporting Procedures for Serious Adverse Events

We do not expect any serious adverse events resulting from the administration of any of the research procedures from this trial, but with surgery there are always complications despite being rare. Serious adverse events (SAEs) will be reported to the Chief Investigator in the first instance and to the Sponsor within 24 hours. The CI will then submit a report of the SAE

occurring to a participant to the REC that gave a favourable opinion of the study and the MRHA within 15 days. This will be in line with the NRES report form.

End of Trial

The trial will end when all participants recruited into the study reach a 2-year follow-up. The last year of follow up will be via questionnaire only. This will be via letter or email. The trial will be stopped prematurely if mandated by the Ethics Committee or the Sponsor. The REC that originally gave a favourable opinion of the trial will be notified in writing if the trial has been concluded or terminated early.

Stopping Rules:

- New information comes to light, which means that the aims of the study are futile.
- Safety issues come to light regarding the intervention.
- Resources to conduct the study are no longer available.

Statistical Analysis:

Statistical analysis will be planned and carried out in collaboration with a statistician based at the Centre for Biostatistics and Arthritis Research UK Centre for Epidemiology, University of Manchester. This study will be conducted and reported in accordance with the CONSORT 2010 statement: extension to randomised pilot and feasibility trials.

Patient demographics: Student t-tests and chi-square analysis will be used to compare patient demographics between groups for age, gender, BMI, side of operation, etc.

Primary outcomes: Patient reported outcomes (IKDC, Marx and ACL RSI Scales): Appropriate parametric or non-parametric statistical tests will be used to compare patient reported outcomes by subgroups based on the distribution of data. Missing data and non-compliance will be explored utilising a multiple imputation and complier average causal effect (CACE) approaches, respectively.

Secondary outcomes: Comparison of McGill pain scores between groups at day 1 post op, 2, 6, 12, 26 and 39 weeks will be analysed using general linear model (analysis of variance) tests, adjusting for confounding factors if identified from differences in basic patient demographics. Asymmetry index for each group will be compared during the rehab program. Biomechanical data on gait analysis and muscle strength will be compared also. The Genourob machine data will be compared to the contralateral leg to give differences for comparison. Complication and re-rupture rates will be given as simple percentages.

Research governance and regulatory approvals

The study will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and other applicable guidance. The study will not commence until all regulatory approvals are in place, which will include HRA Approval, REC approval and confirmation from the local R&I that the Trust has the Capacity and Capability to carry out the research.

Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be given a unique research ID number once consent has been gained. This will be used from then on for all data recording and any electronic database. All documents with personal data will be stored securely within the research folder and only accessible by study staff and authorised personnel. This folder will be locked away within the NHS clinic only. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

Funding

The Jewel ACL will be provided at free of charge by Xiros Ltd.

Xiros will also be funding patients visiting the Human Performance Lab at the UoS for pre-operative assessment and follow up at 3, 6, 9, and 12 months. Travel costs will be provided for all participants.

Research Team:

Contributorship:

The present research team wholeheartedly recognise and thank Mr Ricci Plastow for his significant contribution to initiating the project, especially proposing the study design and protocol, as well as completing all the relevant documentation. The results of this study remain in his best interests.

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