Study Title:	The JewelACL Post Market Clinical Follow Up Study – Multicentre study of at least 5 years follow up, looking at clinical outcomes in patients treated with the JewelACL for ACL reconstruction
Investigational Device:	JewelACL (part number 102-6003)
Internal Reference No:	CRE 027 NCT04580290
Date:	14/04/2020
CIP No Version No:	Version 1.0
Investigators:	Refer to Principal Investigator signature page for CRE 027
Sponsor:	Xiros Ltd, Springfield House, White House Lane, Leeds LS19 7UE Anna LeMoine, Clinical Evidence Manager, Xiros, Springfield House, WhiteHouse Lane, Leeds, LS19 7UE : Anna.LeMoine@xiros.co.uk .

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, regulatory authorities, and members of the Research Ethics Committee.

Signature pages for clinical investigation plan

The approved protocol should be signed by author(s) and/or person(s) authorised to sign the protocol
I have read this protocol and confirm that to the best of my knowledge it accurately describes the conduct of the study.

Signed: Date: 22/04/2020

Print name: Jonathan Lorrison

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PRINCIPAL INVESTIAGTOR SIGNATURE PAGE

I have read and agree to adhere to the clinical investigation plan and all regulatory requirements applicable in conducting this clinical investigation

Principal Investigator

Printed Name:
Signature:
Date:

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1. AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

2. SYNOPSIS

Study Title	The JewelACL Post Market Clinical Follow Up Study – Multicentre study of at least 5 years follow up, looking at clinical outcomes in patients treated with the JewelACL for ACL reconstruction
Internal ref. no.	CRE 027
Type of study	Post Market Clinical Follow Up
Study Design	Retrospective data collection with at least 5 years follow up and telephone call to collect patient reported outcomes.
Study Participants	Patients treated with the JewelACL for ACL Reconstruction
Planned Sample Size	120 subjects
Follow-up duration	5 Years Follow Up
Planned Study Period	9 Months
Primary Objective	The primary objective is to assess, at least 5 year re-rupture rate from subjects who were implanted with the JewelACL device for ACL reconstruction.
Secondary Objectives	To report on all recorded adverse events To assess whether fixation type and autograft use have an effect on failure rates. To review patient reported outcome scores at a minimum of 5 year follow up and assess change from baseline, if baseline scores are available.
Primary Endpoint	Reconstruction Failure
Secondary Endpoints	IKDC score at 5 years minimum (compared to baseline, if available) Lysholm score at 5 years minimum (compared to baseline, if available) Tegner Activity score at 5 years minimum (compared to baseline, if available) Assessment of adverse events at 5 years minimum
Device Name	JewelACL
Manufacturer Name	Xiros Ltd
Principal intended use	The JewelACL is intended to be used for reconstruction of the anterior cruciate ligament.

3. INTRODUCTION

This document is a clinical investigation plan (CIP) for the JewelACL Post Market Clinical Follow-Up (PMCF) study. The objective of the study is to assess re-rupture rates and patient outcomes from subjects with at least 5 year follow up, treated with the JewelACL device for ACL reconstruction. The impact of fixation type and autograft augmentation will also be assessed. All adverse events related to the JewelACL device will be recorded. This study is Sponsored by Xiros.

This PMCF study will be conducted in accordance with this CIP. All parties involved in the conduct of the study will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

4. DEVICE DESCRIPTION

The JewelACL is a polyester scaffold for anterior cruciate ligament (ACL) reconstruction. It is matched in tensile strength to the semitendinosus hamstring tendon, which is typically 1200 N, and can be used with or without an additional tissue graft in either partial or total tissue sparing ACL reconstruction procedures (LAB 139 8.00).

The JewelACL is made from polyethylene terephthalate (polyester). The polyester has been subjected to a proprietary gas plasma process that modifies its surface properties, making it hydrophilic, without significantly altering the physical characteristics of the bulk material (LAB 139 8.00).

The polyester yarn is woven in a mock-leno pattern; an open weave structure to permit the ingrowth of tissue, which can remodel to form a 'neoligament'. It is tubular in structure to allow placing a hamstring tendon graft inside it.

The JewelACL is in the form of a tube 710 mm long with an internal diameter of 7 mm. It has a mean tensile strength of 1245 N (TR 105). When doubled, as in use, this will have a strength of up to 1977 N (TR 105).

The JewelACL is packed in a double blister in a cardboard box, supplied with an IFU and patient labels.

The device does not incorporate medicinal substances, animal/human tissues or blood products. The device is supplied sterile (by gamma irradiation; 25-50 kGy) and remains sterile unless the packaging is damaged or opened.

4.1 Intended Use

The JewelACL is intended to be used for reconstruction of the anterior cruciate ligament (ACL).

4.2 Indications

The JewelACL is indicated for all patients requiring ACL reconstruction that are not excluded by the contraindications listed below.

Contraindications

- Known hypersensitivity to implant materials. If the patient is suspected of having any foreign body sensitivity, appropriate tests should be made prior to implantation.
- Infections, or any structural or pathological condition of the bone or soft tissue that would be expected to impair healing or secure fixation.
- Patients unable or unwilling to restrict activities to prescribed levels or follow a rehabilitation programme during the healing period.
- The JewelACL may not be suitable for skeletally immature patients as it will not lengthen instep with the patients growth into adulthood, and so must not bridge, disturb, or disrupt the growth plate.
- Patients for whom it is not possible to bend the knee to at least 90º as it will not be possible to reach the correct position for drilling the bone tunnels.

4.3 Risk and Benefits of the JewelACL Device

4.3.1 JewelACL Risks

The JewelACL is a CE marked device**.** The risks of device use are low, and in line with alternative devices and techniques used in current practice. Potential device risks include:

- Infections, both deep and superficial.
- Patient body sensitivity and adverse reaction to device materials.
- Synovitis in the knee
- Laxity or reduced Range of Motion are potential adverse consequences of misplacing the ligament.
- Laxity may also result from inadequate fixation of the ligament to bone.

4.3.2 JewelACL Benefits

The JewelACL is intended to reconstruct the ACL and therefore result in:

- Significant improvement in the performance of the injured knee over that before surgery
- Rapid return to work and sport (in less than six months)
- Can be used to provide additional strength to autograft tissue

If used without any autograft:

- No pain or weakness from donor site

- Useable for revision or primary surgery where there is lack of availability of useable graft tissue.
- Quicker operation than when graft tissue is harvested.

5. BACKGROUND AND JUSTIFICATION FOR STUDY

5.1 Clinical Background

The ACL is the most commonly injured ligament in the knee (Gans et al., 2018). It serves to restrain the anterior displacement of the tibia with respect to the femur, as well as providing rotational stability to the knee and some protection from varus and valgus stress.

5.2 Introduction to ACL Treatment

There are many treatment pathways for ACL injury. The patient may have conservative treatment with rehabilitation and may fare well, even returning to sport. This is the usual approach for older patients. Young and active sports people are more likely to need surgery, which must be followed by a strict rehabilitation programme (van Melick et al (2016)). **Surgically the options are:**

- Repair in which the native tissue is sutured, but no graft is added. Examples include Internal Brace Ligament Augmentation and Dynamic Intraligamentary Stabilisation.
- Reconstruction surgery in which the ruptured ACL is replaced with a biological tendon graft fixed into bone tunnels in the femur and tibia. There are several sources of tendon graft: an autograft from the patient or an allograft from a donor. The most common autografts are the medial third of the patella tendon, a hamstring graft or a quadriceps tendon.
- Reconstruction using a synthetic ligament, such as the JewelACL or LARS ligaments, both of which are is made of polyester.

5.3 Knee Outcome scoring methods

There are several methods of assessing the outcomes of knee surgery, of which three of the most used are briefly described below:

IKDC (International Knee Documentation Committee) – a score based on a questionnaire with three components: symptoms, sports activity and knee function. The score may range between 0 (very poor outcome) and 100 (very good outcome).

Lysholm – a scoring system especially for ACL surgery consisting of eight items which are summed to give a total: pain (25 points), instability (25 points), locking (15 points), swelling (10 points), limp (5 points), stair climbing (10 points), squatting (5 points) and need for support (5 points). The best outcome would be 100 points.

Tegner – a scale to identify the graded level of activity of a patient, usually used in conjunction with the Lysholm scale. The scale ranges from 0, very low level of activity, to 10 extremely active, such as an international elite sportsman or woman. A score of greater than 6 is only achievable with participation in sport.

5.4 Justification of study

The clinical evaluation for the JewelACL (CER 007 v2) identified that there was a lack of long term follow up data for the device, with most studies reporting on two years outcomes. Therefore, this study aims to assess the long-term performance of the JewelACL when used for ACL reconstruction (in total and partial tissue sparing procedures), by means of clinical outcomes. It will also review the adverse events observed in patients implanted with the JewelACL, and whether fixation type or use with an autograft affects the outcomes. This study will be collating data from sites which have previously used the JewelACL and have patients with at least 5 years follow up data. Data will be collected on patients who have been implanted with the JewelACL to reconstruct the ACL between 01 October 2010 to 31 December 2014

6. DEVICES USED IN THE STUDY

6.1 Name of Device

JewelACL

6.2 Manufacturer Name

Neoligaments™ A division of Xiros™

Springfield House,

White House Lane,

Leeds LS19 7UE

UK

6.3 Principles of Operation of the device

The reconstruction of a ruptured ACL can be performed by passing a replacement ligament graft/scaffold such as the JewelACL, along the same path as the native ligament between the femur and the tibia. The JewelACL is attached to the bones by passing it through bone tunnels in the distal femur and proximal tibia and securing it to the bone cortices. Placement of the tunnels is critical and should observe isometry of the implant, which means retaining its length during flexion and extension, as the device is stiff and permits only small extensions. The JewelACL is held in the femoral tunnel by doubling it over a suspension device. Both ends of the device are secured at the tibia with a soft thread interference screw in the bone tunnel or a staple in the bone cortex.

The JewelACL is designed as a scaffold for tissue ingrowth, a process which may be assisted by the incorporation of a tendon graft into the tubular structure of the device.

6.4 Intended Users

The JewelACL is for use by orthopaedic surgeons who are thoroughly familiar with the recommended surgical procedure.

7. OBJECTIVES

7.1 Primary Objective

The primary objective of the study is to assess at least 5-year re-rupture rate from subjects who were implanted with the JewelACL device for ACL reconstruction.

7.2 Secondary Objectives

Secondary objectives of the study are:

- to report on all recorded adverse events;
- to assess whether fixation type and autograft use have an effect on failure rates;
- To assess patient reported outcomes at 5 years minimum (PROMS: IKDC; Lysholm; Tegner)
- To assess changes in patient reported outcome scores from baseline, if available (PROMS: IKDC; Lysholm; Tegner).

7.3 Endpoints

Primary

- Reconstruction failure at final follow-up

Secondary

Clinical

- Assessment of adverse events

Patient Outcomes

- IKDC Subjective Knee Evaluation
- Lysholm knee scoring scale
- Tegner Activity

8. STUDY DESIGN

This is multicentre clinical study, collating real-world clinical outcomes for the JewelACL device used to reconstruct the ACL. Medical records of subjects who were treated using the JewelACL device for ACL reconstruction, between 01 October 2010 to 31st December 2014 will be reviewed against the inclusion and exclusion criteria. Subjects that meet all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study. Data will be collected as per the endpoints and entered in the Electronic Case Report Form used for this study.

A telephone follow-up will be conducted for each subject enrolled into the study; this follow up call will collect the following:

- Reconstruction Failure (any ACL failure and if so, what, when and how?)
- Details of any complications or revision of the reconstruction (including date of procedure,
- IKDC Subjective Evaluation, Lysholm knee scoring scale and Tegner Activity

8.1 Study Population

Consecutive patients who have had the JewelACL device used to reconstruct the ACL, between the period of 01 October 2010 to 31 December 2014.

8.1.1 Inclusion Criteria

Eligible patients who meet all of the following:

1. Age >18 years
2. Patients previously implanted with the JewelACL for ACL reconstruction (Primary JewelACL cases only, no revision cases)

8.1.2 Exclusion Criteria

Patients will be excluded if they meet any of the following

1. Age <18 years
2. Any implantations for non-indicated conditions, as stated in the IFU
3. Revision cases

9. STUDY PROCEDURES

Approval from the Sponsor and Ethics Committee must be received prior to initiating study procedures.

The following sections provide a detailed description of procedures required by this CIP.

9.1 Patient Recruitment

Only patients treated with the JewelACL for ACL reconstruction between 01 October 2010 to 31 December 2014 will be reviewed for the purpose of this study. Data will only be collected from the medical records of patients who meet all of the inclusion criteria and none of the exclusion criteria.

9.2 Informed Consent Process

The study design is retrospective data collection with a telephone call follow up at 5 years post-surgery. Verbal consent will be required for all eligible patients who agree to consent to the telephone follow-up, and this process is required to be recorded within the medical notes. The Principal Investigator or his/her authorised designee will conduct the verbal informed consent. This process will include a verbal discussion of all aspects of the study that are relevant to the subject's decision to participate, such as the purpose of the study and anticipated benefits. During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the subject and will respect the subject's legal rights. If the subject agrees to give their verbal consent, then the Principal Investigator or his/her authorised designee must document this process in the medical or research notes and the process will be recorded within the Electronic Case Report Form.

Failure to obtain verbal informed consent from a subject to participate in the telephone follow up will mean that the follow up telephone call must not take place. Retrospective data will still be collected as no patient identifying data will be recorded.

The justification for verbal consent within this study is that it prevents the subject having to return to the site to sign an informed consent form in person. This would put additional burden on the patient, when the only data collected during the telephone follow up will be the collection of patient outcomes using questionnaires e.g. IKDC Subjective Knee Evaluation, Lysholm knee scoring scale and Tegner Activity and asking about any complications experienced, all of which can be conducted over the phone.

9.3 Point of Enrolment

All subjects who meet all inclusion criteria and do not meet any of the exclusion criteria will be considered enrolled into the study.

The Principal Investigator or delegated study personnel will record enrolment information in the medical records and complete and submit all applicable CRFs in a timely manner.

9.4 Scheduled Procedures

The Principal Investigator is responsible for ensuring all clinical data is collected as required per CIP scheduled procedures. The data collection elements required for each study visit are summarised in Table 1.

TABLE 1: Summary of study procedures

Study activities (Data Collection)	Baseline	Procedure	Surgery to 6 months (if available)	6 months to 24 months (if available)	Telephone call follow up (at least 5 years post-surgery)
Verbal Consent					X
Medical History	X				
Age and gender at time of JewelACL implantation		X			
Participation in sports	X*		X*	X*	X
Date of surgery/follow-up		X	X	X	X
ACL failure injury mode	X				
Reconstruction Failure			X	X	X
Hybrid (with autograft) or non-hybrid (JewelACL only)		X			
Fixation type (tibial and femoral)		X			
Any other procedures recorded during ACL procedure		X			

Study activities (Data Collection)	Baseline	Procedure	Surgery to 6 months (if available)	6 months to 24 months (if available)	Telephone call follow up (at least 5 years post-surgery)
Details of any complications or revision of the reconstruction		X	X	X	X
IKDC Subjective Knee Evaluation	*X		*X	*X	X
Lysholm and Tegner	*X		*X	*X	X

* If available in medical records

9.4.1 Baseline Visit (Data collection from medical notes)

For patients treated with the JewelACL device to reconstruct the ACL, during the period from the 01 October 2010 to 31st December 2014, a baseline data collection visit will occur retrospectively. Data available in the patient's medical records will be used to fulfil baseline requirements.

The Baseline visit consists of the following activities:

- Medical History including history of the knee(s) e.g. previous surgeries.
- Participation in sports (if available).
- Patient reported outcome score e.g. IKDC Subjective Knee Evaluation, Lysholm knee scoring scale, Tegner Activity (if available).

9.4.2 Procedure Visit (Data collection from medical notes)

Procedure data will be collected retrospectively if available in the patient's medical records, to be used to fulfil the procedure requirements.

The Procedure visit consists of the following activities:

- Date of surgery.

- Age and gender at time of JewelACL implantation.
- ACL failure injury mode (whether failure occurred in a sport's accident, or any other documented accident)/date.
- Information on the procedure:
  - Hybrid (with autograft) or non-hybrid (JewelACL only).
  - Fixation type (tibial and femoral).
- Any other procedures during surgery (e.g. multi-ligament repair, meniscus repair).

9.4.3 Medical record follow up, from surgery to 6 months (Data collection from medical notes, if available)

Follow up data from surgery to 6 months will be collected retrospectively to be used to fulfil the follow up requirements:

- Date of follow up.
- Reconstruction Failure (any graft failure and if so, what, when and how?).
- Details of any complications or revision of the reconstruction (including date, and cause of failure if known).
- Patient reported outcome score e.g. IKDC Subjective Knee Evaluation, Lysholm knee scoring scale, Tegner Activity.

9.4.4 Medical record follow up, 6 months to 24 months (Data collection only, if available)

Follow up data from 6 months to 24 months will be collected retrospectively to be used to fulfil the follow up requirements:

- Date of follow up.
- Reconstruction Failure (any graft failure and if so, what, when and how?).

- Details of any complications or revision of the reconstruction (including date, indication and cause of failure if known).
- Patient reported outcome score e.g. IKDC Subjective Knee Evaluation, Lysholm knee scoring scale, Tegner Activity.

9.4.5 Telephone call follow up (at least 5 years post-surgery)

A patient telephone follow-up will be conducted only on subjects who have given verbal informed consent. Please refer to Informed Consent procedure Section 9.2

The following will be collected during the telephone follow up

- Verbal consent (ensure this process is documented).
- Date of Follow Up.
- Participation in sports.
- Reconstruction Failure (any graft failure and if so, what, when and how?).
- Details of any complications or revision of the reconstruction.
- Completion of IKDC Subjective Knee Evaluation.
- Completion of Lysholm and Tegner scores.

The IKDC, Lysholm and Tegner scoring at final follow up, must be completed by hand and filed within the site file. Paper copies will be provided to each site participating in the study. Lysholm and Tegner final follow up scores will be entered directly into the Electronic Case Report Form. IKDC at final follow up will be collected and calculated by the sponsor and scores will be included in the final clinical report.

9.6 Electronic Case Report Form

All retrospective data will be entered directly from the subject's medical notes into the Electronic Case Report Form. Final telephone follow up data, Lysholm and Tegner scores

will be entered directly into the Electronic Data Capture System. IKDC scores will be calculated by the sponsor, therefore entry of the score will not be required at final follow up

9.7 Subject Study Completion

Subject participation in the clinical investigation will conclude upon completion of the data collection point from 6 months to 24 months post-surgery for ACL reconstruction using the JewelACL device.

For patients who give verbal informed consent to take part in the telephone follow up, the clinical investigation will conclude upon completion of the follow up phone call.

10. INVESTIGATOR RESPONSIBILITIES

The role of the Investigator at each site is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation. They are required to adhere to this CIP.

The Principal Investigator shall be qualified by education, training and experience to assume responsibility for the proper conduct of the clinical investigation. Evidence of this will be provided to the sponsor through up-to-date CVs.

Principal Investigators must be experienced and have implanted the JewelACL device for ACL reconstruction. They must disclose any potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results, and be knowledgeable with the method of obtaining informed consent.

11. SAFETY REPORTING

Definitions

Device deficiency:

Any alleged inadequacy related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution.

Note: This definition includes malfunctions, use errors, and inadequate labelling.

Malfunction:

A malfunction is a failure of the device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labelling for the device. A malfunction should be considered reportable if a serious adverse event has occurred or could occur as a result of a recurrence of the malfunction.

Adverse Event (AE):

An AE or adverse event is:

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.

Adverse Device Effect (ADE):

All untoward and unintended responses to the medical device.

The phrase "responses to a medical device" means that a causal relationship between the device under investigation and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the device qualifies as a device effect.

This also includes any event resulting from insufficiencies or inadequacies in the instruction for use or deployment of the device and includes any event that is a result of a user error.

Serious Adverse Event (SAE):

'Serious adverse event' means any adverse event that led to any of the following:

- death,
- serious deterioration in the health of the subject, that resulted in any of the following:
    - life-threatening illness or injury,
    - permanent impairment of a body structure or a body function,
    - hospitalisation or prolongation of patient hospitalisation,
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
    - chronic disease,
- foetal distress, foetal death or a congenital physical or mental impairment or birth defect

Serious Adverse Device Effects (SADE):

A serious adverse device effect (SADE) is any untoward medical occurrence seen in a patient that can be attributed wholly or partly to the device which resulted in any of the characteristics or led to a characteristics of a Serious adverse event.

SADE is also any event that may have led to these consequences if suitable action had not been taken or intervention had not been made or if circumstances has been less opportune.

All cases judged by either the reporting medically qualified professional or the sponsor.

Unanticipated Adverse Device Effect (UADE):

Any serious adverse device effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in

nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that related to the rights, safety or welfare of the subject.

Reporting of AE

All AE's occurring during the study observed by the investigator or reported by the participant, whether or not attributed to the device under investigation will be recorded on the CRF as specified in the protocol. All ADE's will be recorded in the CRF.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to device, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The relationship of AEs to the device will be assessed by a medically qualified investigator or the sponsor/manufacturer and will be followed up until resolution or the event is considered stable.

All ADE that result in a participant's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.

Where relevant, any pregnancy occurring during the clinical study and the outcome of the pregnancy, should be recorded and followed up for congenital abnormality or birth defect.

Reporting Procedures for All SAEs/ SADEs/ UADEs

Considering the data collected in this study is on a CE marked product being used within its intended use, and the retrospective nature of the study, all SAE/SADE/UADEs reported as part of the study will be managed in accordance with Xiros Standard Procedure for Product Events Reports and Vigilance.

12. STATISTICS

Description of Statistical Methods

The primary analysis will summarise the re-rupture rate of patients. The number and percentage of patients who have experienced a re-rupture will be reported. Additionally, a corresponding confidence interval will be reported for the percentage of patients with a re-rupture. The analysis will be performed for all patients combined, and also separately for the subgroups of patients receiving JewelACL alone, and those receiving JewelACL in combination with autograft.

A single analysis will be performed at the end of the study, no interim analyses will be performed.

The Number of Participants

The sample size was calculated to ensure an accurate estimate of the re-rupture rate in patients receiving JewelACL. Based on previous data and clinical experience, the re-rupture rate is expected to be 10% (or less). The sample size was calculated so that the uncertainty in the calculated compared to the 'true' population percentage is not more than ±6%. Using a 95% level of confidence, it is calculated that 96 subjects are required for the study. In order to allow for a 20% drop-out, 120 subjects will be recruited into the study.

The Level of Statistical Significance

As there are no planned hypothesis tests, the level of significance is not relevant to this study. All confidence intervals will be calculated using a 95% confidence level.

Criteria for the Termination of the Study

Not Applicable. The study will not be terminated based on any data collected.

Procedure for Accounting for Missing, Unused, and Spurious Data

The primary analysis will be performed on the collected data. No data imputations will take place, with patients with missing data excluded from the analysis. Any spurious data values will be checked against source material to verify the validity.

Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviations from the original analysis plan will be documented and justified in the final analysis report.

Inclusion in Analysis

All patients who meet the entry criteria will be included in the study.

13. RISK AND BENEFITS

13.1 Benefits

The information collected in this clinical investigation will be added to the current knowledge and understanding of treatment options for patients requiring ACL reconstruction. It is expected that recipient patients of the JewelACL device will have the same benefits as patients implanted with autografts and other commercially available ACL devices used for ACL reconstruction. It will also provide long term outcome data to reassure surgeons of the device's performance.

A minimum of 5 year follow up data on the JewelACL device will be beneficial to surgeons as it will provide assurance of the device's safety and performance over the long term.

13.2 Risks

With the review of medical records, the primary risk is that of breach of confidentiality of data. All source data is to be held within the reporting hospital site and no identifiable details are to be included in any data reports.

13.3 Anticipated Adverse Device Effects

Adverse events potentially associated with the use of the JewelACL device and potential complications are documented in the Instructions for Use. Instructions for Use are available upon request.

13.4 Risk Control Measures

Actions to control or mitigate risks at the clinical investigation centre will include the selection of qualified and experienced investigators. No patient identifying data will be collected for the study.

13.5 Risk to Benefit

The risks associated with the use of the JewelACL device are anticipated to be comparable to those associated with the use of other commercially available devices used for ACL reconstruction. Given that the study is retrospective in nature and does not introduce any new clinical risks to the patient, the benefit of this study outweighs any risks to the patient.

14. CLINICAL DATA HANDLING

The Sponsor will be responsible for the handling of study data. All study data will be entered on the Electronic Case Report Form.

14.1 Direct Access to Source Data/Documents

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring audits and inspections.

14.2 Protection of Personally Identifiable Information

The participants enrolled into this study will only be identified by a study specific participants number and/or code in any database. The name or any other identifying details of the participant will NOT be included in any study data electronic file. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data. Confidentiality of data will be observed by all parties involved at all times throughout the clinical study. All data will be secured against unauthorized access. The study will comply with the General Data Protection Regulations.

14.3 Document and Data Control

14.3.1 Traceability of Documents and Data

The Investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the Sponsor on the CRFs and in all required reports.

14.3.2 Recording Data

The CRF will be reviewed by the authorised site personnel. The data reported on the CRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing or added as comments via the CRF. Any change or correction to data reported on a CRF shall be dated, initialed and explained if necessary, and shall not obscure the original entry (i.e. an

audit trail shall be maintained); this applies to both written and electronic changes or corrections.

15. MONITORING

It is the responsibility of the Sponsor to ensure the clinical investigation is conducted, recorded and reported according to the approved CIP, subsequent amendment(s), applicable regulations and guidance documents.

The Sponsor will arrange for a monitoring visit once the first ten subjects have been enrolled. A subsequent visit will be scheduled, where ten subjects will be randomly selected and then monitored.

The Principal Investigator or institution will provide direct access to source data during and after the clinical study for monitoring, audits, EC review and regulatory authority inspections, as required. The Principal Investigator or institution will obtain permission for direct access to source documents from the hospital administration and national regulatory authorities before starting the clinical study.

16. ETHICS

16.1 Declaration of Helsinki

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

16.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice and in accordance with ISO14155.

16.3 Approvals

The protocol 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.

17. COMPLIANCE

17.1 Clinical Trial Agreement

The Investigator will sign a Clinical Trial Agreement and agrees to be compliant with the agreement. The Investigator will not start enrolling patients or requesting verbal consent from any subject prior to obtaining EC approval and relevant regulatory approval, if applicable, and authorisation from the Sponsor in writing before the clinical investigation. If additional requirements are imposed by the EC or relevant regulatory authority, those requirements will be followed. If any action is taken by an EC or a relevant regulatory authority with respect to the clinical study, that information will be forwarded to the Sponsor.

17.2 Insurance

As the Sponsor, Xiros has taken up general liability insurance in accordance with the requirements of the applicable local laws. Insurance certificates/documentation will be provided to the Investigator upon request.

18. SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

The Sponsor reserves the right to terminate the clinical study at any stage, with appropriate written notice to the Investigators, ECs and relevant authorities, if required.

A Principal Investigator, EC or regulatory authority may suspend or prematurely terminate participation in a clinical study at the study centres for which they are responsible. The Investigators will follow requirements specified in the Clinical Trial Agreement.

The clinical investigation will be concluded when:

- All centres are closed AND
- The final report has been provided to Investigators or the Sponsor has provided formal documentation of clinical study closure.

19. PUBLICATION

Publications or presentations of clinical study results may be published in an appropriate journal.

20. REPORTING RESULTS ON CLINICALTRIALS.GOV

This clinical investigation will be registered on ClinicalTrials.gov. A full report of the pre-specified outcomes, regardless of the results, will be made public through ClinicalTrials.gov website no later than 12 months after the clinical investigation completion. If this clinical investigation is terminated early, the Sponsor will make every effort to hasten the release of the pre-specified outcomes through the ClinicalTrials website.

21. REFERENCES

Gans I, et al . Orthop J Sports Med. 2018;6(6):2325967118777823

LAB 139 8.00 JewelACL Instructions for Use

JewelACL Clinical Evaluation Report CER 007 revision 02, August 2019

van Melick N, van Cingel REH, Brooijmans F, et al. Br J Sports Med 2016;50:1506–1515.

APPENDIX 1

PATIENT REPORTED OUTCOMES

IKDC Subjective Knee Evaluation

SYMPTOMS*:

*Grade symptoms at the highest activity level at which you think you could function without significant symptoms, even if you are not actually performing activities at this level.

1. What is the highest level of activity that you can perform without significant knee pain?
   - 4❑ Very strenuous activities like jumping or pivoting as in gymnastics or football
   - 3❑ Strenuous activities like heavy physical work, skiing or tennis
   - 2❑ Moderate activities like moderate physical work, running or jogging
   - 1❑ Light activities like walking, housework or gardening
   - 0❑ Unable to perform any of the above activities due to knee pain

2. During the past 4 weeks, or since your injury, how often have you had pain?

	0	1	2	3	4	5	6	7	8	9	10	
Never	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	Constant

3. If you have pain, how severe is it?

	0	1	2	3	4	5	6	7	8	9	10	
No pain	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	Worst pain imaginable

4. During the past 4 weeks, or since your injury, how stiff or swollen has your knee been?
   - 4❑ Not at all
   - 3❑ Mildly
   - 2❑ Moderately
   - 1❑ Very
   - 0❑ Extremely

5. What is the highest level of activity you can perform without significant swelling in your knee?
   - 4❑ Very strenuous activities like jumping or pivoting as in gymnastics or football
   - 3❑ Strenuous activities like heavy physical work, skiing or tennis
   - 2❑ Moderate activities like moderate physical work, running or jogging
   - 1❑ Light activities like walking, housework or gardening
   - 0❑ Unable to perform any of the above activities due to knee swelling

6. During the past 4 weeks, or since your injury, has your knee locked or caught?

   0❑Yes 1❑No

7. What is the highest level of activity you can perform without significant giving way in your knee?
   - 4❑ Very strenuous activities like jumping or pivoting as in gymnastics or football
   - 3❑ Strenuous activities like heavy physical work, skiing or tennis
   - 2❑ Moderate activities like moderate physical work, running or jogging
   - 1❑ Light activities like walking, housework or gardening
   - 0❑ Unable to perform any of the above activities due to giving way of the knee

SPORT ACTIVITIES:

8. What is the highest level of activity you can participate in on a regular basis?

- 4❑ Very strenuous activities like jumping or pivoting as in gymnastics or football
- 3❑ Strenuous activities like heavy physical work, skiing or tennis
- 2❑ Moderate activities like moderate physical work, running or jogging
- 1❑ Light activities like walking, housework or gardening
- 0❑ Unable to perform any of the above activities due to knee

9. How does your knee affect your ability to:

		Not difficult at all	Minimally difficult	Moderately Difficult	Extremely difficult	Unable to do
a.	Go up stairs	4❑	3❑	2❑	1❑	0❑
b.	Go down stairs	4❑	3❑	2❑	1❑	0❑
c.	Kneel on the front of your knee	4❑	3❑	2❑	1❑	0❑
d.	Squat	4❑	3❑	2❑	1❑	0❑
e.	Sit with your knee bent	4❑	3❑	2❑	1❑	0❑
f.	Rise from a chair	4❑	3❑	2❑	1❑	0❑
g.	Run straight ahead	4❑	3❑	2❑	1❑	0❑
h.	Jump and land on your involved leg	4❑	3❑	2❑	1❑	0❑
i.	Stop and start quickly	4❑	3❑	2❑	1❑	0❑

FUNCTION:

10. How would you rate the function of your knee on a scale of 0 to 10 with 10 being normal, excellent function and 0 being the inability to perform any of your usual daily activities which may include sport?

FUNCTION PRIOR TO YOUR KNEE INJURY:

Couldn't perform daily activities	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑	6 ❑	7 ❑	8 ❑	9 ❑	10 ❑	No limitation in daily activities

CURRENT FUNCTION OF YOUR KNEE:

Cannot perform daily activities	0 ❑	1 ❑	2 ❑	3 ❑	4 ❑	5 ❑	6 ❑	7 ❑	8 ❑	9 ❑	10 ❑	No limitation in daily activities

Lysholm Knee Questionnaire / Tegner Activity Scale

Name: First Last **Date:**

Physician:

1. Limp:

- ◯ a) None
- ◯ b) Slight or periodical
- ◯ c) Severe and constant

2. Support:

- ◯ a) None
- ◯ b) Stick or crutch
- ◯ c) Weight-bearing impossible

3. Locking:

- ◯ a) No locking and no catching sensations
- ◯ b) Catching sensation but no locking
- ◯ c) Locking occasionally
- ◯ d) Locking frequently
- ◯ e) Locked joint on examination

4. Instability:

- ◯ a) Never giving way
- ◯ b) Rarely during athletics or other severe exertion
- ◯ c) Frequently during athletics or other severe exertion (or incapable of participation)
- ◯ d) Occasionally in daily activities
- ◯ e) Often in daily activities
- ◯ f) Every step

5. Pain:

- ◯ a) None
- ◯ b) Inconstant and slight during severe exertion
- ◯ c) Marked during severe exertion
- ◯ d) Marked on or after walking more than 2 km
- ◯ e) Marked on or after walking less than 2 km
- ◯ f) Constant

6. Swelling:

- ◯ a) None
- ◯ b) On severe exertion
- ◯ c) On ordinary exertion
- ◯ d) Constant

7. Stair-climbing:

- ◯ a) No problems
- ◯ b) Slightly impaired
- ◯ c) One step at a time
- ◯ d) Impossible

8. Squatting:

- ◯ a) No problems
- ◯ b) Slightly impaired
- ◯ c) Not beyond 90°
- ◯ d) Impossible

Activity Level Before Injury	Current Activity Level	Activity Level Following Surgery if applicable	
○	○	○	Competitive sports Soccer - national and international elite
○	○	○	Competitive sports Soccer, lower divisions Ice hockey Wrestling Gymnastics
○	○	○	Competitive sports Bandy Squash or badminton Athletics (jumping, etc.) Downhill skiing
○	○	○	Competitive sports Tennis Athletics (running) Motorcross, speedway Handball Basketball Recreational sports Soccer Bandy and ice hockey Squash Athletics (jumping) Cross-country track findings both recreational and competitive
○	○	○	Recreational sports Tennis and badminton Handball Basketball Downhill skiing Jogging, at least five times per week
○	○	○	Work Heavy labor (*e.g.*, building, forestry) Competitive sports Cycling Cross-country skiing Recreational sports Jogging on uneven ground at least twice weekly
○	○	○	Work Moderately heavy labor (*e.g.*, truck driving, heavy domestic work) Recreational sports Cycling Cross-country skiing Jogging on even ground at least twice weekly
○	○	○	Work Light labor (*e.g.*, nursing) Competitive and recreational sports Swimming Walking in forest possible
○	○	○	Work Light labor Walking on uneven ground possible but impossible to walk in forest
○	○	○	Work Sedentary work Walking on even ground possible
○	○	○	Sick leave or disability pension because of knee problems

Tegner: ☐ ☐ ☐ Lysholm Score: ☐ Print Form Submit