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Statistical Analysis Plan

STUDY FULL 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
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1 Table of Contents

2 Abbreviations and Definitions

ACL	Anterior Cruciate Ligament
ADE	Adverse Device Effect
AE	Adverse Event
IKDC	International Knee Documentation Committee
PROM	Patient Reported Outcome Measure
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

3 Introduction

The ACL is the most commonly injured ligament in the knee. There are many treatment pathways for ACL injury. One approach is 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 JewelACL is another method for ACL reconstruction. It is a polyester scaffold and is matched in tensile strength to the semitendinosus hamstring tendon. It can be used with or without an additional tissue graft in either partial or total tissue sparing ACL reconstruction procedures.

The multicentre study will evaluate patients who received JewelACL for their reconstruction. All patients were followed up for at least 5 years follow up post-surgery. The study will focus on the clinical outcomes of the patient group.

4 Study Objectives and Endpoints

4.1 Study Objectives

The study will assess the following research questions:

Primary objective:

- 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 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)

4.2 Endpoints

4.2.1 Primary outcome measure

The primary study endpoint is the occurrence of a re-rupture.

4.2.2 Secondary outcome measures

Secondary endpoints are as follows:

- IKDC score
- Lysholm score
- Tegner Activity score

All of the above will be analysed only for patients with 5 years minimum follow-up post-procedure.

4.2.3 Safety outcomes

Safety will be assessed by the recording of:

- Assessment of Adverse Events (AE)
- Assessment of Adverse Device Effects (ADE)

5 Study Methods

5.1 General Study Design and Plan

The study is a multicentre post-market clinical follow-up, with retrospective data collection. All patients were treated with the JewelACL for ACL between 1st October 2010 to 31st December 2014, and thus all have at least 5 years follow up post-surgery. The medical records of subjects will be evaluated, and all participants will receive a telephone call to collect patient reported outcomes.

5.2 Inclusion-Exclusion Criteria

5.2.1 Inclusion Criteria

The participants must have met ALL of the following criteria to be considered eligible for the study:

- Age >18 years
- Previously implanted with the JewelACL for ACL reconstruction (Primary JewelACL cases only, no revision cases)

5.2.2 Exclusion Criteria

Participants were not allowed to enter the study if ANY of the following applied:

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

5.3 Study Variables

5.3.1 Summary of study data and timing of measurements

The key study measurements, and the timing of these measurements are summarised in Table 1.

Table 1: Summary of study measurements

	Baseline	Procedure	Surgery to 6 months	6-24 months post	5 years post
Consent					x
Medical history	x				
Age / gender		x			
Surgical / procedure details		x			
Participation in sports	x		x	x	x
Injury mode	x				
Re-rupture			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			
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

5.3.2 Demographic and Baseline measurements

At the baseline timepoint, or time of the procedure, the following demographic and baseline characteristics of the study participants will be collected:

- Age
- Gender
- Medical History, including history of the knee(s) e.g. previous surgeries
- Participation in sports
- ACL failure injury mode
- Patient reported outcome scores

Additionally, information on the procedure will be collected:

- Hybrid (with autograft) or non-hybrid
- Fixation type (tibial and femoral)
- Other procedures during surgery (e.g. multi-ligament repair, meniscus repair)

6 Sample Size

The sample size was based on the primary outcome, occurrence of re-rupture. This was calculated to ensure an accurate estimate of this outcome. The failure rate was expected to be 10% (or less), based on data from Su et al. The sample size was calculated so that the uncertainty in the calculated value compared to the 'true' population percentage is not more than ±6%. Using a 95% level of confidence, it was calculated that 96 subjects were required for the study. In order to allow for a 20% drop-out, 120 subjects were to be recruited into the study.

7 General Considerations

7.1 Timing of Analyses

A single analysis will take place at the completion of the study, after all data is collected. No interim analyses will be performed.

7.2 Analysis Populations

The Full Analysis Population will consist of all patients recruited into the study, as long as they had a minimum of 5-years of follow-up post-procedure.

Patients with missing data at a specific outcome timepoint will be excluded from this dataset only for the particular outcome for which they had missing data.

The safety population is the same as the full analysis population

7.3 Subgroups

In addition to an analysis of all patients combined, analyses for all outcomes (primary, secondary, safety) will be performed for the following subgroups:

- Patients receiving JewelACL alone
- Patients receiving JewelACL in combination with autograft

7.4 Missing Data

For the all analyses, only observed data will be analysed. Missing data will be assumed to be Missing At Random. No imputation procedures will be employed to deal with missing data.

8 Summary of Study Data

8.1 Descriptive Analysis Methods

Continuous variables will be summarised using the number of (non-missing) datapoints, mean and standard deviation if found to follow a normal distribution. Continuous variables not found to be normally distributed will be summarised by the number of datapoints, median and inter-quartile range. Categorical variables will be summarised by the frequency and percentage (based on the non-missing sample size) of values in each category.

8.2 Demographic and Baseline Variables

A summary of patient demographics and baseline measurements are outlined in Section 5.3.2. Descriptive statistics will be produced for these variables, along with baseline values of the secondary outcomes. Summaries will be produced for each site separately, and for all patients combined. The summary statistics will be produced in accordance with section 8.1.

9 Efficacy Analyses

9.1 Primary Efficacy Analysis

The primary endpoint is re-rupture, assessed as a binary outcome (yes/no). The number and percentage of patients experiencing a re-rupture at each timepoint will be reported. Additionally, a corresponding 95% confidence interval will be reported for the percentage of patients with a re-rupture.

The summary statistics for the outcome variable will be produced in accordance with Section 8.1. The primary study analysis will be performed using the Full Analysis Population (see section 7.2).

9.2 Secondary Efficacy Analyses

The secondary outcomes are PROMs, all of which are measured on a continuous scale. Summary statistics for these outcomes at 5-years will be produced in accordance with Section 8.1.

At the time of writing, it is unclear whether it will be possible to obtain data on these outcomes at baseline, or at any other point post-surgery. If any such data is obtained, outcomes at these timepoints will be summarised in an equivalent way to the 5-year values.

If data at baseline is obtained, a comparison of the scores at baseline and 5-years will be made. If the changes in outcomes between timepoints are found to follow a Normal distribution, the paired t-test will be used to compare the change in score over time. The mean change will be reported, along with a corresponding 95% confidence interval. If the changes are not found to be normally distributed, the Wilcoxon matched-pairs test will be preferred for the analysis, whilst the median change and corresponding 95% confidence interval will be reported.

10 Safety Analyses

The main safety outcome is the occurrence of adverse events and adverse device effects. The number of patients with such an adverse outcome will be reported, as will be the average number of adverse events per patient.

Additionally, a summary of all adverse outcomes will be reported descriptively as outlined in Section 8.1. The following summaries will be made:

- Description of adverse events / adverse device effects
- Related to device
- Seriousness (serious, not serious)

11 Technical Details

The data analysis will be performed using the statistical software package Stata (version 15.1). Programs recording details of all data manipulation and data analyses will be produced and kept, so that the analyses can be externally inspected and, if necessary, re-run.

12 Summary of Changes to the Analysis Plan

The changes from version 1.0 to 1.1 of the SAP were mostly cosmetic. However, additional subgroups for the primary outcome were added (separate analyses for each fixation type), as well as the addition of demographic summaries by study site.

Between versions 1.1 and 1.2, there was a removal of the plan to analyse by fixation type, as it was felt that there was insufficient variation in the fixation types used. Additionally, a justification of the figures used in the sample size has been added.

13 Reference

Su, M., et al. (2019). "Medium-Term (Least 5 Years) Comparative Outcomes in Anterior Cruciate Ligament Reconstruction Using 4SHG, Allograft, and LARS Ligament." Clin J Sport Med. 2019 March