STATISTICAL ANALYIS PLAN (SAP)

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Contents

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACL	Anterior Cruciate Ligament
ADE	Adverse Device Effect(s)
AE	Adverse Event(s)
ANOVA	Analysis of Variance
CRF	Case Report Form(s)
DevD	Device Deficiency(ies)
EQ-5D-5L	5-Level EuroQol 5D
EU MDR	European Medical Device Regulation
FAS	Full Analysis Set

Abbreviation	Definition
FU	Follow-Up
IEC	Independent Ethical Committee
IRB	Institutional Review Board
IKDC	International Knee and Documentation Committee
LCL	Lateral Collateral Ligament
MAT	Meniscal Allograft Transplantations
MCID	Minimal Clinically Important Differences
MCL	Medial Collateral Ligament
MR	Meniscal Repair
MRI	Magnetic Resonance Imaging
NA or N/A	Not Applicable
N (or n)	Total Sample Size (or subgroup sample size)
PP	Per-protocol Population
PRO	Subject Reported Outcome
R&D	Research & Development
S+N	Smith & Nephew Inc.
SADE	Serious Adverse Device Effect(s)
SAE	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SAF	Safety Analysis Set
TFL	Tables, Figures and Listing
USADE	Unanticipated Serious Adverse Device Effect(s)

2. INTRODUCTION

This study is intended to collect post-market safety and clinical outcomes data from subjects who underwent meniscal repair (MR) or meniscal allograft transplantation (MAT) with the next generation FAST-FIX FLEX System. The following Statistical Analysis Plan (SAP) details the statistical considerations, including the data analysis methods, for the Study Protocol FAST-FIX-FLEX.2020.09 version 3.0. Related documents to this SAP are the Study Protocol and Case Report Forms (CRFs).

3. STUDY DESIGN

This is a prospective, multi-center, non-randomized clinical study intended to evaluate the safety and performance of the FAST-FIX FLEX Meniscal Repair system for meniscal repairs (MR) and meniscal allograft transplantations (MAT). Up to 5 sites will participate within United States, United Kingdom, France, and Australia.

Subjects will be enrolled in one of two (2) groups based on medical indication and general practice at the site, as shown in Table 1.

Table 1. Overview of Study Groups

Group	Surgical Technique	Number of Subjects
Meniscal Repair (MR)	Smith+Nephew FAST-FIX FLEX System	53
Meniscal Allograft Transplantations (MAT)	Smith+Nephew FAST-FIX FLEX System	A minimum of 9 and a maximum of 15

3.1 Inclusion/Exclusion Criteria

3.1.1 MR Cohort

Inclusion Criteria

- Subject provides written informed consent for study participation using an independent ethical committee (IEC) / institutional review board (IRB) approved consent form.
- Subject is between sixteen (16) and seventy (70) years of age, inclusive at the time of screening.
- Subject is willing and able to participate in required follow-up visits and is able to complete study activities.

- Subject requires a meniscal repair.
- Subject is suitable to participate in the study in the opinion of the Investigator.
- Subject requires a meniscus repair concerning the red-red or red-white zones for acute or chronic 1-, 2- or 3- segment lesions, with or without associated anterior cruciate ligament (ACL) reconstruction.

Exclusion Criteria

- Contraindications (per the FAST-FIX FLEX IFU) or hypersensitivity to the use of the FAST-FIX FLEX implant material. Where material sensitivity is suspected, appropriate tests should be made and sensitivity ruled out prior to implantation.
- Enrolled in the treatment period of another clinical trial within thirty (30) days of the operative visit, or during the study.
- Women who are pregnant or nursing.
- Any subject that meets the definition of a Vulnerable Subject per ISO 14155 Section 3.55 (except for subjects aged sixteen (16) or seventeen (17) years of age with consent from their legally authorized representative).
- Subjects with a history of poor compliance with medical treatment, physical therapy (PT)/rehabilitation, or clinical study participation.
- Subjects with irreparable meniscal tears (i.e. multiple tears).
- Subjects with full thickness cartilage defects greater than 10mm in diameter and/or serious defects.
- Subjects with concomitant ligament injuries that do not require surgical repair (i.e. ACL with Grade 3 lateral collateral ligament (LCL) injury or medial collateral ligament (MCL) injury).
- Performance of a significant concomitant procedure, specifically a cartilage repair or restoration (excluding ACL reconstruction or repair, lateral extra-articular tenodesis, anterolateral ligament (ALL) reconstruction) intended as a therapeutic intervention on the study knee.
- Subjects with a history of ipsilateral knee surgery, septic joint, or fracture.
- Subjects with pathological conditions in the soft tissue that would prevent secure fixation of the device.
- Physical conditions that would eliminate, or tend to eliminate, adequate anchor support or retard healing.
- The presence of infection.
- Conditions which would limit the subject's ability or willingness to restrict activities or follow directions during the healing period.
- Malalignment: genu varus and genu valgus angles greater than 5° as evaluated by the subject's physician as per their standard of care.
- Subjects who have an Ahlback grade greater than II.

- Subjects with a body mass index larger than 35.
- Subjects with a medical or physical condition that, in the opinion of the Investigator, would preclude safe subject participation in the study.

3.1.2 MAT Cohort

Inclusion Criteria

- Subject provides written informed consent for study participation using an independent ethical committee (IEC) / institutional review board (IRB) approved consent form.
- Subject is between sixteen (16) and seventy (70) years of age, inclusive at the time of screening.
- Subject is willing and able to participate in required follow-up visits and is able to complete study activities.
- Subject requires a meniscal allograft transplantation.
- Subject is suitable to participate in the study in the opinion of the Investigator.
- Subject requires a MAT for symptomatic meniscal insufficiency (load-related pain and swelling in the compartment post meniscectomy) for which conservative treatment has failed, with or without cartilage repair or restoration (including ACL reconstruction or repair).

Exclusion Criteria

- Contraindications (per the FAST-FIX FLEX IFU) or hypersensitivity to the use of the FAST-FIX FLEX implant material. Where material sensitivity is suspected, appropriate tests should be made and sensitivity ruled out prior to implantation.
- Enrolled in the treatment period of another clinical trial within thirty (30) days of the operative visit, or during the study.
- Women who are pregnant or nursing.
- Any subject that meets the definition of a Vulnerable Subject per ISO 14155 Section 3.55 (except for subjects aged sixteen (16) or seventeen (17) years of age with consent from their legally authorized representative).
- Subjects with a history of poor compliance with medical treatment, physical therapy (PT)/rehabilitation, or clinical study participation.
- Subjects with concomitant ligament injuries that do not require surgical repair (i.e. ACL with Grade 3 lateral collateral ligament (LCL) injury or medial collateral ligament (MCL) injury.
- Performance of a significant concomitant procedure (excluding ACL reconstruction or repair, lateral extra-articular tenodesis, anterolateral ligament (ALL) reconstruction) intended as a therapeutic intervention on the study knee.
- Subjects with a history of ipsilateral knee surgery, septic joint, or fracture (excluding MAT indication).

- Subjects with pathological conditions in the soft tissue that would prevent secure fixation of the device.
- Physical conditions that would eliminate, or tend to eliminate, adequate anchor support or retard healing.
- The presence of infection.
- Conditions which would limit the subject's ability or willingness to restrict activities or follow directions during the healing period.
- Malalignment: genu varus and genu valgus angles greater than 5° as evaluated by the subject's physician as per their standard of care.
- Subjects who have an Ahlback grade greater than II.
- Subjects with a body mass index larger than 35.
- Subjects with a medical or physical condition that, in the opinion of the Investigator, would preclude safe subject participation in the study.

3.2 Visit Schedule/Schedule of Assessments

Table 2 presents the visit schedule and schedule of assessments for subjects during this study. In total, there are 6 visits from screening through 12 months follow-up.

Table 2. STUDY SCHEDULE

Schedule of Events	Visit 1 – Screening < 8 weeks pre-op	Visit 2 – Procedure	Visit 3 - 2 weeks (± 5 days)	Visit 4 - 3 Months (+ 30 days)	Visit 5 - 6 Months (± 45 days)	Visit 6 - 12 Months (± 75 days)
Informed Consent	X					
Inclusion/Exclusion	X[1]					
Demographics/ Medical History	X					
Details of Surgery Procedure CRF		X				
Details of Pathology CRF		X				
Post-op Surgery Failure CRF			X	X	X	X
MRI assessment	X[2]				X[3]	X[3]
PRO: IKDC subjective	X				X	X
PRO: Lysholm	X				X	X
EQ-5D-5L CRF	X				X	X
Concomitant Medication/ Therapy	X	X	X	X	X	X
Safety Assessment (AE/SAE/ADE/DevD)		X	X	X	X	X
End of Study/Exit	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]

AE: Adverse Event; ADE: Adverse Device Defect; CRF: Case Report Form; DevD: Device Deficiency; EQ-5D-5L: 5-Level EuroQol 5D;IKDC: International Knee and Documentation Committee; MRI: Magnetic Resonance Imaging; PRO: Subject Reported Outcome; SAE: Serious Adverse Event.
1 Inclusion/exclusion confirmation will be performed at the time of screening and study procedure to confirm the subject meets eligibility criteria.
2 MRI to confirm eligibility criteria must be within 6 months of surgery
3 MRI 1.5 T or greater, no contrast preferred, to be reviewed by independent radiologist appointed
4 As applicable

4. STUDY OBJECTIVES

4.1 Primary Objective(s)

The primary objective of this study is:

- To assess the clinical success rate of FAST-FIX FLEX meniscal repair at 12 months. Failure of the repair is defined as revision surgery at the site of the primary tear at 12 months.

4.2 Secondary Objective(s)

The secondary objectives are:

- To assess the clinical success rate of FAST-FIX FLEX meniscal repair at 6 months.
- To assess the meniscal allograft transplantation success rate at 6 months & 12 months. Failure is defined as a revision of the transplantation and/or removal of the allograft.
- To evaluate the meniscus healing for both clinical indications as measured by magnetic resonance imaging (MRI) at 6 months and 12 months in comparison to pre-op.
- To assess the clinical performance for both clinical indications by Subject-Reported Outcome (PROs) scores at baseline 6 months and 12 months: International Knee and Documentation Committee (IKDC) subjective scores, Lysholm knee scores and 5-Level EuroQol 5D (EQ-5D-5L).

4.3 Other Objective(s)

The other objective is:

- To assess safety with reported complications, adverse events, adverse device effects, unanticipated serious adverse device effects and device deficiencies.

5. STUDY ENDPOINTS

5.1 Primary Endpoint(s)

The primary endpoint of this study is defined as the rate of reoperation due to meniscal repair failure at 12 months post-operative. Failure is defined as a revision at the primary site of tear.

5.2 Secondary Endpoint(s)

The secondary endpoints of this study are:

- Rate of reoperation due to meniscal repair failure at 6 months post-operative
- Rate of reoperation due to meniscal allograft transplantation failure at 6 months & 12 months post-operative. Failure is defined as a revision of the transplantation and/or removal of transplant
- MRI to assess meniscal healing for both clinical indications at 6 months and 12 months.

- Subject-Reported Outcome (PRO) data will be collected at baseline, 6 months & 12 months: International Knee Documentation Committee (IKDC) scores, Lysholm scores, & EQ-5D-5L

The secondary endpoints provide more context on whether the meniscal repair or meniscal transplantation was a success at earlier time points and whether it is durable for 12 months. MRI will allow surgeons to assess meniscal healing and help determine whether a reoperation is required or not. PROs provide meaningful quality of life measurements to assess improvement, which is ultimately the clinical goal of any successful meniscal repair. IKDC, EQ-5D-5L, and Lysholm scores are standard validated tools to measure subject symptoms associated with meniscal function.

5.3 Other Endpoint(s)

Other study endpoints are:

- Analysis of reoperation rate and PROs by meniscal repair procedure (i.e. MR alone vs MR with anterior cruciate ligament (ACL)repair), location of the repair (posterior horn, body, anterior horn) and type of tear (bucket handle, longitudinal, horizontal, radial, complex)
- Healing status at 6 months & 12 months by repair procedure, location of tear and tear type
- Surgical technique details (curvature of the distal needle: bender tool used vs bender tool not used)
- Procedural details for MR (S+N instruments used with FAST-FIX FLEX) and MAT (hybrid vs non-hybrid approach and types of devices used with FAST-FIX FLEX)
- Analysis of the change in extrusion and joint space narrowing for meniscal allograft transplantations on MRI at baseline, 6 months and 12 months
- Rate of mechanical symptoms as defined by PROs (Lysholm: section 3 & 4 and IKDC scores: question 6) and radiological evidence of repair failure at 6 months and 12 months

5.4 Safety Endpoint(s)

Safety endpoints include the collection of the following events:

- Device-related re-intervention
- All adverse events (AEs) occurring from the time of surgery until revision or study completion
- Device related AEs (ADEs) and serious adverse events (SAEs)
- Device deficiencies (DDs)

6. STATISTICAL CONSIDERATIONS

6.1 Determination of Sample Size

The sample size for this study is precision-based, and not based on statistical power considerations, thus no formal statistical hypothesis is formulated.

The primary endpoint for the study upon which sample size is determined is meniscal repair success rate in the study device at 12 months. A systemic literature review by Souter (2022)[1] reports the repair success rate to be 90% for all-inside meniscal repair. This recent systematic literature review provides sufficient evidence to increase the success rate from 85% (as defined in Study Protocol V2.0) to 90% for all-inside meniscal repair.

Assuming an overall success rate of at least 90%, 45 subjects are sufficient to obtain at least 80% probability of estimating the two-sided 95% confidence interval around the success rate to within 10%.

Assuming a 15% drop out rate at the end of the 12 months, 53 subjects will be enrolled.

Additionally, secondary endpoints in this study assess the success rate, meniscus healing and clinical performance of PROs for MAT. To have sufficient evidence to support European Medical Device Regulation (EU MDR) requirements, a minimum of 9 and maximum of 15 subjects will be recruited to provide sufficient evidence on this indication. Furthermore, internal evidence generated by the Smith+Nephew Research and Development (R&D) provides evidence that the procedural technique, device use, and resulting suture placement is identical for meniscus MR and MAT (see Study Protocol V3.0, Appendix 22.11). It will be at the discretion of the Sponsor when enrolment to the MAT indication is completed (between 9 and 15 subjects).

6.2 Randomisation

No randomization has been planned for this study as it is non-comparative.

6.3 Interim Analysis

No interim analyses are planned for this study.

7. STATISTICAL ANALYSIS

7.1 General

Smith+Nephew's Global Biostatistics group will conduct the statistical analysis for this study. Unless otherwise stated, all significance tests and hypothesis testing will be two-sided, performed at the 5% significance level. Resulting p-values will be quoted and 95% two-sided confidence intervals will be generated where appropriate. All p-values will be rounded to three decimal places, p-values less than 0.001 will be presented as '<0.001' in all tables.

Where data summaries are specified, categorical and ordinal variables will be summarized with frequencies and percentages. Continuous variables will be summarized with the following summary statistics: number of observations, mean, median, standard deviation, minimum and maximum values. All analyses will be performed in SAS 9.4 (or later).

7.2 Analysis Populations

The following analysis populations will be used for this study:

- **Full Analysis Set (FAS)**, following Intention to Treat principle including all subjects who were recruited into the study and attended at least one post-surgery assessment are included in the FAS.
- **Safety Population (SAF)**, including all subjects who have received the study device.
- **Per-Protocol Population (PP)**, including all subjects in the full analysis set who have no significant protocol deviations and met the inclusion/exclusion criteria.

Statistical analysis will be performed using the subject populations shown in Table 3:

Table 3. Populations Used for Statistical Analyses

Analysis	Population(s)
Baseline (Demographics, Medical History)	FAS
Disposition	FAS
Protocol Deviations	FAS
Rate of reoperation due to meniscal repair failure at 12 months post-operative.	SAF, PP
Rate of reoperation due to meniscal repair failure at 6 months post-operative	SAF, PP

Rate of reoperation due to meniscal allograft transplantation failure at 6 months & 12 months post-operative	SAF, PP
MRI to assess meniscal healing for both clinical indications at 6 months and 12 months.	FAS
IKDC, Lysholm and EQ-5D-5L scores at baseline, 6 months, and 12 months	FAS, PP
Analysis of reoperation rate by meniscal repair procedure, location of the repair and type of tear	SAF, PP
Analysis of IKDC, Lysholm and EQ-5D-5L scores by meniscal repair procedure, location of the repair and type of tear	FAS, PP
Healing status at 6 months & 12 months by repair procedure, location of tear and tear type	FAS
Surgical technique details	FAS
Procedural details for MR	FAS
Analysis of the change in extrusion and joint space narrowing for meniscal allograft transplantations on MRI at baseline, 6 months and 12 months	FAS
Rate of mechanical symptoms	FAS
Safety Analyses	SAF
Other Data Summaries	FAS

7.2.1 Study Groups

Two study groups exist for this study:

- Meniscal Repair
- Meniscal Allograft Transplantation

Unless otherwise specified, subject tables will be presented in separate columns for the Meniscal Repair group and the Meniscal Allograft Transplantation group. A total column will also be presented, comprising all subjects from both groups.

7.3 Handling of Missing, Incomplete and Repeat Data

Missing reoperation information will result in censoring for the primary endpoint analysis. Subjects missing study start and end dates will be excluded from the primary analysis.

7.4 Derived Data

- **Baseline Definition**
  Day 0 is the day of operative with the study device. Baseline is the latest date prior to or on Day 0.

- **Visit Windows**
  Visit windows shown in Table 4 represent the minimum and maximum number of days relative to the operative date (day 0) for a visit to be considered.

Table 4. Visit Windows

		Days Relative to Operative Date (Day 0)	
Visit Number	**Visit Name**	**Lower**	**Upper**
1	Screening	-57	-1
2	Procedure	0	0
3	2 Weeks	9	19
4	3 Months	61	121
5	6 Months	137	227
6	12 Months	290	440

- **Time to Revision/Reoperation Surgery**
  Time to revision (in months) = (Revision Date – Operative Date + 1)/30.4375

- **IKDC Subjective Scores**
  When at least 16 items have been answered, the IKDC Subjective score is calculated as:

$$\left[\frac{Sum\ of\ all\ items}{Maximum\ score\ possible}\right] x100$$

  Questions, responses, and numerical values of responses for scoring are provided in Section 9.1 of the appendices. Note that question 10a (function prior to knee injury) is not included in the calculation.

- **Lysholm Knee Scores**
  When all 8 questions have been answered, the Lysholm Knee score is calculated as:

$$\left[\frac{Sum\ of\ (Limp, Using\ Cane\ or\ Crutches, Locking\ Sensation\ in\ the\ Knee, Giving\ Way\ Sensation\ from\ the\ Knee, Pain, Swelling, Climbing\ Stairs, Squatting)}{100}\right] x100$$

  Questions, responses, and numerical values of responses for scoring are provided in Section 9.2 of the appendices.

- **EQ-5D-5L Scores**
  EQ-5D-5l scores are obtained by obtaining coded values of Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression and referencing the country-specific SAS EQ-5D-5L crosswalk file to obtain an EQ index values. EQ index is set to missing if any of the 5 dimensions has a missing value.

  To note, Australia and France do not have published index values. Therefore, Australia will use the United States published crosswalk files, and France will use the published Germany crosswalk files. This is based on closeness of gross disposable household income values between countries.

- **Conversions**
  - Inches (in) to centimeters (cm):

    1 in = 2.54 cm

  - Pounds (lb) to kilograms (kg):

    1 lb = 0.4536 kg

- **Adverse Events**
  Investigator events do not receive a classification and so S+N classify events as follows:
  - An event will be classified as an ADE if the relationship to the study device and/or the relationship to the study procedure is possibly/definitely
  - An event will be classified as an SAE if the event is serious
  - An event will be classified as an SADE if it is an ADE which is also serious

- An event will be classified as a USADE if it is an SADE which is also unanticipated
- Otherwise, the event will be a non-device, non-procedure related, non-serious AE

For adverse events that have been resolved, duration of adverse event is calculated as end date minus start date

Due to system updates, checks need to be performed to ensure the most stringent classification is being reported. When comparing Investigator assessments (classifications as above) with adverse event monitoring board classifications, the most stringent classification should be reported according to Table 5, as follows:

Table 5. Most Stringent Classifications

Investigator assessment	Sponsor classification	Most stringent
AE	SAE	SAE
SAE	AE	SAE
AE	ADE	ADE
ADE	AE	ADE
ADE	SADE	SADE
SADE	ADE	SADE
SAE	SADE	SADE
SADE	SAE	SADE
SADE	USADE	USADE

7.5 Baseline Data

The following data will be descriptively summarized:

- Demographic
  - Age (years)
  - Sex

  - Ethnicity
  - Race
  - Height (cm)
  - Weight (kg)
  - BMI (kg/m^2)
  - Tobacco Use Status (former, current, never)

- Medical History
  - No formal table will be presented. A listing will be presented instead.

7.6 Disposition Data

The following information will be summarized:

- The number and percentage of subjects that entered the study and attended each of the follow up visits
- The number and percentage of subjects that:
  - Completed the study
  - Withdrew from the study prior to completion, including reasons for withdrawal
- The study duration of all subjects will be summarised using descriptive statistics for continuous variables.

7.7 Protocol Deviations

The frequency of protocol deviations will be summarized along with the number of subjects experiencing each.

A listing will be provided for all protocol deviations.

7.8 Multiplicity

No adjustments for multiplicity are planned for this study.

7.9 Analysis of Primary Endpoint(s)

A binary variable will be defined for whether each subject had reoperation due to meniscal repair failure for all treatment visits. This variable will be used to present the proportion of reoperations

due to meniscal repair failure at 12 months post-operative, together with a percentage and 95% confidence interval for a single proportion (calculated using the Clopper-Pearson method)[2].

As a further analysis of the primary endpoint, if the data allows, the time taken for reoperation to occur will be assessed as a survival endpoint for both indications in order to assess the trend of incidence of reoperation over time.

The Kaplan-Meier product limit survival estimates would be used to estimate MR/MAT survivorship, S(t) where S(t) is the proportion of subjects at time t, without reoperation. Time to reoperation would be the endpoint of interest in the determination of MR/MAT survivorship. The Cumulative proportion of subjects with implant survivorship at 6 months and 12 months would be calculated and displayed accordingly. Subjects who are still on-study without a revision by the data snapshot/extraction date would be censored on that date. A subject who prematurely discontinues from study as a result of death or for any other reason would be censored on the discontinuation date. A subject lost to follow-up prior to the database extraction date would be censored at the last known contact date. Kaplan-Meier estimates for implant survivorship would be presented with the corresponding two-sided 95% Confidence Intervals (CIs). Kaplan-Meier survival graphs would also be displayed.

A listing of subjects with reoperations will be provided and includes data from the Device Deficiency form.

7.10 Analysis of Secondary Endpoint(s)

The following secondary endpoints will be analysed:

- Rate of reoperations due to meniscal repair failure at 6 months post-operative will be summarized using frequency and percentage. A 95% exact confidence interval for the percentage will also be presented using the Clopper-Pearson method.
- Rate of reoperations due to meniscal allograft transplantation failure at 6 months & 12 months post-operative will be summarized using frequency and percentage. A 95% exact confidence interval for the percentage will also be presented using the Clopper-Pearson method.
- Analysis of meniscal healing as assessed by MRI at 6 months and 12 months will be conducted separately by an imaging vendor. Meniscal healing, as indicated by the Meniscal Repair Status variable in MRI data will be summarized descriptively 6 and 12 months. Values of "NR" are considered missing.

- IKDC, Lysholm and EQ-5D-5L PRO scores will be calculated and summarized for each visit appropriately for categorical or continuous variables. Mean change from baseline score to each post-operative visit (6 and 12 months) score will be presented.
- For Lysholm and IKDC, the numbers and proportions of subjects, together with a 95% confidence interval, meeting the minimal clinically important differences (MCID) from baseline to appropriate post-operative visit. MCIDs for this SAP have been obtained for the MR and MAT groups from Migliorini et. al (2023) and Liu et. al (2019), respectively and for Lysholm and IKDC outcome measures. These MCIDs are shown below in Table 6.

Table 6. MCIDs for Lysholm and IKDC Outcome Measures

	Lysholm MCID[3]	Subjective IKDC MCID[4]
MR and MAT	$\geq$ 8.9	$\geq$ 11.5

- Listings will be separately provided for IKDC, Lysholm and EQ-5D-5L PROs.

7.11 Analysis of Other Endpoint(s)

The following other endpoints will be analysed for this study:

- Reoperation rate, stratified by:
  - MR alone vs MR with ACL repair
  - Location of the repair (posterior horn, body, anterior horn)
  - Type of tear (bucket handle, longitudinal, horizontal, radial, complex, ramp lesion)

- Change from baseline PROs at 6 and 12 months, stratified by:
  - MR alone vs MR with ACL repair
  - Location of the repair (posterior horn, body, anterior horn)
  - Type of tear (bucket handle, longitudinal, horizontal, radial, complex, ramp lesion)

- Healing status at 6 months & 12 months, stratified by:
  - Surgery technique (inside-out, outside in, all inside, other)
  - Location of repair (posterior horn, body, anterior horn)
  - Tear type (bucket handle, longitudinal, horizontal, radial, complex, ramp lesion)

- Procedural and Surgical details for MR and MAT:
  - Curvature of the distal needle (bender tool used, bender tool not used)
  - S+N instruments used with FAST-FIX FLEX (FAST-FIX FLEX CURVED INSERTER BENDER CANNULA SET, FAST-FIX FLEX REVERSE CURVED INSERTER BENDER

CANNULA SET, NOVOCUT Suture Manager, Meniscal Depth Probe, 45=Diamond Rasp, 90o=Diamond Rasp, FAST-FIX FLEX CURVED INSERTER, FAST-FIX FLEX REVERSE CURVED INSERTER)
  - Fixation method for MAT (bone tunnels, dovetail)

- Analysis of the change in extrusion and joint space narrowing for meniscal allograft transplantations on MRI at baseline, 6 months and 12 months. The following variables will be used summarized at each timepoint, and change from baseline will be summarized at 6 months and 12 months:
  - **Extrusion**
    - Extruded Meniscal Width (Radial) (mm)
    - Extruded Meniscal Width (Anterior) (mm)
    - Extruded Meniscal Width (Posterior) (mm)
  - **Joint Space Narrowing**
    - Meniscal Width (Radial) (mm)
    - Meniscal Width (Anterior) (mm)
    - Meniscal Width (Posterior) (mm)

- Rate of mechanical symptoms as defined by PROs (Lysholm: section 3 & 4 and IKDC scores: question 6) and radiological evidence of repair failure at 6 months and 12 months

  A mechanical symptom is indicated if a subject experiences all of the following on the same visit:
  - Lysholm Score
    - Section 3: Locking sensation in the knee < 15
    - Section 4: Giving way sensation from the knee < 25
  - IKDC Score
    - During the past 4 weeks, or since your injury, did your knee lock or catch is "Yes"
  - Radiological evidence of repair failure

7.12 Analysis of Safety Endpoint(s)

All safety endpoints will be summarized using the safety population.

- **Adverse Events**

  The number of events and the number of subjects reporting events will be summarized by the following:

- All adverse events
- Serious adverse events
- Adverse device effects
- Serious adverse device effects
- Unanticipated adverse events
- Serious unanticipated adverse events.

In addition, for each adverse event, the following will be summarized:

- Severity
- Relationship to the investigational device
- Relationship to study procedure
- Action(s) taken
- Outcome
- Duration of the resolved adverse events
- Duration of the adverse events at trial discontinuation.

- **Device Deficiencies**
  - The number of device deficiencies and the number of subjects reporting a device deficiency will be summarized.

Listings will be presented separately for adverse events and device deficiencies.

7.13 Other Data Summaries

Other data summaries to be presented include:

- **Concomitant Medications**
  - No formal table will be presented.
  - A listing of concomitant medications will be presented to include medication/therapy name, start date, stop date, indication, dose (unit), frequency, route, and whether or not it was used to treat an adverse event

- **MRI** (at screening, 6 months, 12 months, and unscheduled)

- A listing of MRI data will be presented to include Meniscal Morphology,Meniscal Morphology <Abnormal>, Meniscal Signal (Entire Mensiscus), Meniscal Tear Type, Meniscal Tear Type <Present>, Meniscal Tear Location, Meniscal Tear Location <Present>, Meniscal Repair Status, Meniscal Root Repair Status, Displaced Meniscal Fragment, Displaced Meniscal Fragment <Present>, Extruded Meniscal Width (Radial) (mm), Meniscal Width (Radial) (mm), RPE (Radial) (Derived) (%), Extruded Meniscal Width (Anterior) (mm), Meniscal Width (Anterior) (mm), RPE (Anterior) (Derived) (%), Extruded Meniscal Width (Posterior) (mm), Meniscal Width (Posterior) (mm), RPE (Posterior) (Derived) (%), Meniscal Transplant Status (Derived), Meniscal Allograft Shrinkage, Bone Marrow Lesion - Med Femur, Bone Marrow Lesion - Med Tibia, Bone Marrow Lesion - Lat Femur, Bone Marrow Lesion - Lat Tibia, Additional Observations

- **Discharge Information**

  - Frequency and percentage of the following variables:
    - Antibiotics prescribed during subject's hospital stay
    - Medications for deep vein thrombosis prescribed
    - Pain relief medications prescribed during subject's hospital stay
    - Any other changes/updates to existing concomitant medication
    - Blood transfused during surgery or prior to discharge
      - If yes, provide packed red blood cell units
    - Primary ambulatory support on discharge (none, cane/quad cane, cane walker, 1 crutch, 2 crutches, wheelchair, stretcher, other)
    - Post-operative physical therapy prescribed
    - Convalescent rehabilitation at the hospital
    - Outpatient physical therapy
    - Therapist-led home exercise program
    - Self-guided home exercise program
    - Discharge location (home, chronic care facility/nursing home, rehabilitation/skilled nursing facility)

7.14 Changes in Analysis Methods Specified in the Protocol

Not applicable

8. REFERENCES

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3. Briggs KK, Lysholm J, Tegner Y, Rodkey WG, Kocher MS, Steadman JR. The reliability, validity, and responsiveness of the Lysholm score and Tegner activity scale for anterior cruciate ligament injuries of the knee: 25 years later. Am J Sports Med. 2009;37(5):890-897.

4. Smith MV, Klein SE, Clohisy JC, Baca GR, Brophy RH, Wright RW. Lower extremity-specific measures of disability and outcomes in orthopaedic surgery. Journal of Bone and Joint Surgery - Series A. 2012;94(5):468-477.

9. APPENDIX

9.1 IKDC Scoring

United States Version

Question	Response	Numeric Value
What is the highest level of activity that you can perform without significant knee pain?	Very strenuous activities like jumping or pivoting as in basketball or soccer	4
	Strenuous activities like heavy physical work, skiing or tennis	3
	Moderate activities like moderate physical work, running or jogging	2
	Light activities like walking, housework or yard work	1
	Unable to perform any of the above activities due to knee pain	0
During the past 4 weeks, or since your injury, how often have you had pain?	Never (10) to Constant (0)	0 to 10
If you have pain, how severe is it?	Worst Pain Imaginable (0) to No pain (10)	0 to 10
During the past 4 weeks, or since your injury, how stiff or swollen was your knee?	Not at all	4
	Mildly	3
	Moderately	2

	Very	1
	Extremely	0
What is the highest level of activity you can perform without significant swelling in your knee?	Very strenuous activities like jumping or pivoting as in basketball or soccer	4
	Strenuous activities like heavy physical work, skiing or tennis	3
	Moderate activities like moderate physical work, running or jogging	2
	Light activities like walking, housework, or yard work	1
	Unable to perform any of the above activities due to knee swelling	0
During the past 4 weeks, or since your injury, did your knee lock or catch?	Yes	0
	No	1
What is the highest level of activity you can perform without significant giving way in your knee?	Very strenuous activities like jumping or pivoting as in basketball or soccer	4
	Strenuous activities like heavy physical work, skiing or tennis	3
	Moderate activities like moderate physical work, running or jogging	2
	Light activities like walking, housework, or yard work	1
	Unable to perform any of the above activities due to knee giving way	0

What is the highest level of activity you can perform on a regular basis?	Very strenuous activities like jumping or pivoting as in basketball or soccer	4
	Strenuous activities like heavy physical work, skiing or tennis	3
	Moderate activities like moderate physical work, running or jogging	2
	Light activities like walking, housework, or yard work	1
	Unable to perform any of the above activities	0
How does your knee affect your ability to:		
Go up stairs	Not difficult at all	4
	Minimally difficult	3
	Moderately difficult	2
	Extremely difficult	1
	Unable to do	0
Go down stairs	Not difficult at all	4
	Minimally difficult	3
	Moderately difficult	2
	Extremely difficult	1
	Unable to do	0
Kneel on the front of knee	Not difficult at all	4

	Minimally difficult	3
	Moderately difficult	2
	Extremely difficult	1
	Unable to do	0
Squat	Not difficult at all	4
	Minimally difficult	3
	Moderately difficult	2
	Extremely difficult	1
	Unable to do	0
Sit with knee bent	Not difficult at all	4
	Minimally difficult	3
	Moderately difficult	2
	Extremely difficult	1
	Unable to do	0
Rise from a chair	Not difficult at all	4
	Minimally difficult	3
	Moderately difficult	2
	Extremely difficult	1
	Unable to do	0
Run straight ahead	Not difficult at all	4

	Minimally difficult	3
	Moderately difficult	2
	Extremely difficult	1
	Unable to do	0
Jump and land on involved leg	Not difficult at all	4
	Minimally difficult	3
	Moderately difficult	2
	Extremely difficult	1
	Unable to do	0
Stop and start quickly	Not difficult at all	4
	Minimally difficult	3
	Moderately difficult	2
	Extremely difficult	1
	Unable to do	0
Current function of knee	Couldn't perform daily activities (0) to No limitation in daily activities (10)	0 to 10

United Kingdom Version

Question	Response	Numeric Value
What is the highest level of activity that you can perform without significant knee pain?	Very strenuous activities like jumping or pivoting as in gymnastics or football	4
	Strenuous activities like heavy physical work, skiing or tennis	3
	Moderate activities like moderate physical work, running or jogging	2
	Light activities like walking, housework or gardening	1
	Unable to perform any of the above activities due to knee pain	0
During the past 4 weeks, or since your injury, how often have you had pain?	Never (10) to Constant (0)	0 to 10
If you have pain, how severe is it?	Worst Pain Imaginable (0) to No pain (10)	0 to 10
During the past 4 weeks, or since your injury, how stiff or swollen was your knee?	Not at all	4
	Mildly	3
	Moderately	2
	Very	1
	Extremely	0

What is the highest level of activity you can perform without significant swelling in your knee?	Very strenuous activities like jumping or pivoting as in gymnastics or football	4
	Strenuous activities like heavy physical work, skiing or tennis	3
	Moderate activities like moderate physical work, running or jogging	2
	Light activities like walking, housework, or gardening	1
	Unable to perform any of the above activities due to knee swelling	0
During the past 4 weeks, or since your injury, has your knee locked or caught?	Yes	0
	No	1
What is the highest level of activity you can perform without significant giving way in your knee?	Very strenuous activities like jumping or pivoting as in gymnastics or football	4
	Strenuous activities like heavy physical work, skiing or tennis	3
	Moderate activities like moderate physical work, running or jogging	2
	Light activities like walking, housework, or gardening	1
	Unable to perform any of the above activities due to knee	0
	Very strenuous activities like jumping or pivoting as in gymnastics or football	4

What is the highest level of activity you can participate in on a regular basis?	Strenuous activities like heavy physical work, skiing or tennis	3
	Moderate activities like moderate physical work, running or jogging	2
	Light activities like walking, housework, or gardening	1
	Unable to perform any of the above activities due to knee	0
How does your knee affect your ability to:		
Go up stairs	Not difficult at all	4
	Minimally difficult	3
	Moderately difficult	2
	Extremely difficult	1
	Unable to do	0
Go down stairs	Not difficult at all	4
	Minimally difficult	3
	Moderately difficult	2
	Extremely difficult	1
	Unable to do	0
Kneel on the front of knee	Not difficult at all	4
	Minimally difficult	3

	Moderately difficult	2
	Extremely difficult	1
	Unable to do	0
Squat	Not difficult at all	4
	Minimally difficult	3
	Moderately difficult	2
	Extremely difficult	1
	Unable to do	0
Sit with knee bent	Not difficult at all	4
	Minimally difficult	3
	Moderately difficult	2
	Extremely difficult	1
	Unable to do	0
Rise from a chair	Not difficult at all	4
	Minimally difficult	3
	Moderately difficult	2
	Extremely difficult	1
	Unable to do	0
Run straight ahead	Not difficult at all	4
	Minimally difficult	3

	Moderately difficult	2
	Extremely difficult	1
	Unable to do	0
Jump and land on involved leg	Not difficult at all	4
	Minimally difficult	3
	Moderately difficult	2
	Extremely difficult	1
	Unable to do	0
Stop and start quickly	Not difficult at all	4
	Minimally difficult	3
	Moderately difficult	2
	Extremely difficult	1
	Unable to do	0
Current function of knee	Couldn't perform daily activities (0) to No limitation in daily activities (10)	0 to 10

9.2 Lysholm Knee Scoring

Question	Response	Numeric Value
Limp	I have no limp when I walk	5
	I have a slight or periodical limp when I walk	3
	I have a severe and constant limp when I walk	0
Using a cane or crutches	I do not use a cane or crutches	5
	I use a cane or crutches with some weight-bearing	2
	Putting weight on my hurt leg is impossible	0
Locking sensation in the knee	I have no locking and no catching sensations in my knee	15
	I have catching sensation but no locking sensation in my knee	10
	My knee locks occasionally	6
	My knee locks frequently	2
	My knee feels locked at this moment	0
Giving way sensation from the knee	My knee never gives way	25
	My knee rarely gives way, only during athletics or other vigorous activities	20

	My knee frequently gives way during athletics or other vigorous activities, in turn I am unable to participate in these activities	15
	My knee occasionally gives way during daily activities	10
	My knee often gives way during daily activities	5
	My knee gives way every step I take	0
Pain	I have no pain in my knee	25
	I have intermittent or slight pain in my knee during vigorous activities	20
	I have marked pain in my knee during vigorous activities	15
	I have marked pain in my knee during or after walking more than 1 mile	10
	I have marked pain in my knee during or after walking less than 1 mile	5
	I have constant pain in my knee	0
Swelling	I have no swelling in my knee	10
	I have swelling in my knee only after vigorous activities	6
	I have swelling in my knee after ordinary activities	2
	I have swelling constantly in my knee	0

Climbing stairs	I have no problems climbing stairs	10
	I have slight problems climbing stairs	6
	I can climb stairs only one at a time	2
	Climbing stairs is impossible for me	0
Squatting	I have no problems squatting	5
	I have slight problems squatting	4
	I cannot squat beyond a 90 degree bend in my knee	2
	Squatting is impossible because of my knee	0

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