Clinical Protocol

A Prospective, Multi-center Clinical Study to Evaluate the Safety and Performance of the FAST-FIX FLEX System for Meniscal Repairs (MR) and Meniscal Allograft Transplantations (MAT)

Sponsor Name and Address:	Smith & Nephew Inc. 1450 E. Brooks Road Memphis, TN 38116 USA
Investigational Product(s)	FAST-FIX FLEX Meniscal Repair System
Single Identification Number of Clinical Investigation	N/A
Protocol Author(s):	Lucy O'Mara, Clinical Study Manager Rupali Soeters, Clinical Strategy Lead Michelle Foster, Senior Biostatistician
Summary of Revision History	Version 2.0, 23 Nov 2021 Version 1.0, 28 Apr 2021

1 SIGNATURES

1.1 Principal Investigator Signature Page

This page will be returned to Smith & Nephew Inc. and a copy retained at the investigational site.

☒ I have read the attached protocol entitled "A Prospective, Multi-center Clinical Study to Evaluate the Safety and Performance of the FAST-FIX FLEX System for Meniscal Repairs (MR) and Meniscal Allograft Transplantations (MAT)", version 3.0, dated 05/May/2023, and agree to abide by all provisions set forth herein.

I agree to comply with the Investigator's Obligations stipulated in Section 22.8 of the protocol,

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the described clinical investigation without the prior written consent of Smith & Nephew Inc.

Name, Address, Professional Position	**Signature and Date / DocuSign Stamp**

1.2 Coordinating Investigator Approval

☒ I have read the attached protocol entitled "A Prospective, Multi-center Clinical Study to Evaluate the Safety and Performance of the FAST-FIX FLEX System for Meniscal Repairs (MR) and Meniscal Allograft Transplantations (MAT)", version 3.0, dated 05/May/2023, and agree to abide by all provisions set forth therein.

Name, Address, Professional Position	Signature and Date / DocuSign Stamp
Jorge Chahla, M.D., Ph.D. Rush University Medical Center, 1611 West Harrison Street Chicago, IL, USA Sports Medicine Division, Orthopaedic Surgery	DocuSigned by: Jorge Chahla Signer Name: Jorge Chahla Signing Reason: I approve this document Signing Time: 09-May-2023 | 16:11:35 BST 477C0B65908D4B6CA2EF20C0BA975830

1.3 Sponsor Approval

Name and Title	Signature and Date / DocuSign Stamp
Rachael Winter Senior Director, Global Clinical Operations (Head of Global Clinical Operations)	DocuSigned by: Rachael Winter Signer Name: Rachael Winter Signing Reason: I approve this document Signing Time: 16-May-2023 | 15:56:11 BST A32F12A80F1B4490986E80ACCB7471CB
Lori Fontaine VP, Global Clinical Strategy - Orthopaedics, Sports Med & ENT (Global Clinical Strategy Franchise Head or Representative)	DocuSigned by: Signer Name: Lori Fontaine Signing Reason: I approve this document Signing Time: 09-May-2023 | 14:38:49 BST 01CFB53A1ADE40E3B2C947E8353635A1
Jay Jantz Director of Global Biostatistics and Data Science (Head of Global Data Analytics)	DocuSigned by: Jay Jantz Signer Name: Jay Jantz Signing Reason: I approve this document Signing Time: 24-May-2023 | 03:59:22 BST B7D37248838E4CACAE11E7E55198A88D
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Sam Timson Senior Clinical Compliance and Training Specialist (Clinical Compliance and Training/Clinical Quality Assurance)	DocuSigned by: Sam Timson Signer Name: Sam Timson Signing Reason: I approve this document Signing Time: 09-May-2023 | 11:03:23 BST 638643A36EEA420D82707565773EC196

2 SYNOPSIS

Title of Study:	A prospective, multi-center clinical study to evaluate the safety and performance of the FAST-FIX FLEX System for Meniscal Repairs (MR) and Meniscal Allograft Transplantations (MAT).
Sponsor and Funding Source	Smith & Nephew Inc, 1450 E. Brooks Road, Memphis, Tennessee 38116, USA
Study Design:	A prospective, multi-center, clinical study, 2 study arms, 12 months follow up, with a minimum of 62 and maximum of 68 subjects (53 subjects for MR and a minimum of 9 and maximum of 15 subjects for MAT).
Study Type:	Observational, prospective clinical follow-up study.
Study Product:	The FAST-FIX FLEX Meniscal Repair System is an all-inside meniscal repair device. Each device includes two non-absorbable polymer implants, pretied with #2-0 non-absorbable suture and preloaded into a needle delivery system. The adjustable depth penetration limiter is preset to approximately 16 mm from the tip of the needle. The device can be adjusted in 4 mm increments between 12mm and 20mm. The FAST-FIX FLEX Meniscal Repair System is indicated for use in meniscal repairs and allograft transplant procedures.
Comparison Group(s)*: (*if applicable)	There is no comparison group in this study.
Study Purpose:	The purpose of this study is to collect safety and clinical outcomes data from patients who underwent meniscal repair or meniscal allograft transplantation with the next generation FAST-FIX FLEX System.

Primary Objective:	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.
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 indications as measured by Patient-Reported Outcome (PROs) Scores at baseline, 6 months and 12 months: International Knee Documentation Committee (IKDC) scores, Lysholm scores, & EuroQol 5 Dimension 5 Level (EQ-5D-5L).
Other Objective(s):	To assess safety with reported complications, adverse events, adverse device effects, unanticipated serious adverse device effects and device deficiencies.
Sample Size:	A minimum of 62 and maximum of 68 subjects will be enrolled into the study: • 53 MR subjects

- A minimum of 9 and maximum of 15 MAT subjects

The sample size for this study is precision-based and not based on statistical power considerations. Thus, no formal statistical hypothesis is formulated. The sample size for this study is determined based on the feasibility of recruitment, enrolment and follow-up considerations.

The study's primary endpoint upon which sample size is determined is meniscal repair success rate in the study device at 12 months. The publication upon which this is based, is the systematic literature review entitled: "Clinical performance of FAST-FIX family" authored by Paul Souter (2022) the repair success rate was reported 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 previous protocol version) to 90% for all-inside meniscal repair. For the full report please refer to appendix 22.10.

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 MR subjects will be enrolled.

Additionally, secondary endpoints in this study assess success rate, meniscus healing and clinical performance of PROs for meniscal allograft transplantation (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 and

	prepared 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 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).
Number of Study Sites:	Up to 5 sites
Targeted Global Regions:	United States, United Kingdom, France and Australia
Meniscal Repair Inclusion Criteria:	1. Subject provides written informed consent for study participation using an independent ethical committee (IEC) / institutional review board (IRB) approved consent form; 2. Subject is between sixteen (16) and seventy (70) years of age, inclusive at the time of screening; 3. Subject is willing and able to participate in required follow-up visits and is able to complete study activities; 4. Subject requires a meniscal repair; 5. Subject is suitable to participate in the study in the opinion of the Investigator; 6. 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.
Meniscal Repair Exclusion Criteria:	1. 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; 2. Enrolled in the treatment period of another clinical trial within thirty (30) days of operative visit, or during the study;

3. Women who are pregnant or nursing;
4. 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);
5. Subjects with a history of poor compliance with medical treatment, physical therapy (PT)/rehabilitation, or clinical study participation;
6. Patients with irreparable meniscal tears (i.e. multiple tears);
7. Subjects with full thickness cartilage defects greater than 10mm in diameter and/or serious defects;
8. Patients 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);
9. 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;
10. History of ipsilateral knee surgery, septic joint, or fracture;
11. Pathological conditions in the soft tissue that would prevent secure fixation of the device;
12. Physical conditions which would eliminate, or tend to eliminate, adequate anchor support or retard healing;
13. The presence of infection;
14. Conditions which would limit the patient's ability or willingness to restrict activities or follow directions during the healing period;
15. Malalignment: genu varus and genu valgus angles greater than 5° as evaluated by the patient's physician as per their standard of care;
16. Patients who have an Ahlback grade greater than II;

	17. Patients with a body mass index larger than 35; 18. Subjects with a medical or physical condition that, in the opinion of the Investigator, would preclude safe subject participation in the study.
Meniscal Allograft Transplantation Inclusion Criteria:	1. Subject provides written informed consent for study participation using an independent ethical committee (IEC) / institutional review board (IRB) approved consent form; 2. Subject is between sixteen (16) and seventy (70) years of age, inclusive at the time of screening; 3. Subject is willing and able to participate in required follow-up visits and is able to complete study activities; 4. Subject requires a meniscal allograft transplantation; 5. Subject is suitable to participate in the study in the opinion of the Investigator. 6. 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).
Meniscal Allograft Transplantation Exclusion Criteria:	1. 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; 2. Enrolled in the treatment period of another clinical trial within thirty (30) days of operative visit, or during the study; 3. Women who are pregnant or nursing; 4. 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);

5. Subjects with a history of poor compliance with medical treatment, physical therapy (PT)/rehabilitation, or clinical study participation;
6. Patients 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);
7. 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;
8. History of ipsilateral knee surgery, septic joint, or fracture (excluding MAT indication);
9. Pathological conditions in the soft tissue that would prevent secure fixation of the device;
10. Physical conditions which would eliminate, or tend to eliminate, adequate anchor support or retard healing;
11. The presence of infection;
12. Conditions which would limit the patient's ability or willingness to restrict activities or follow directions during the healing period;
13. Malalignment: genu varus and genu valgus angles greater than 5° as evaluated by the patient's physician as per their standard of care;
14. Patients who have an Ahlback grade greater than II;
15. Patients with a body mass index larger than 35;
16. Subjects with a medical or physical condition that, in the opinion of the Investigator, would preclude safe subject participation in the study.

Study Duration:	It is anticipated to take 39 months (21 months for subject enrolment and 14 months follow-up period).
Primary endpoint:	Rate of reoperation due to meniscal repair failure at 12 months postoperative. Failure is defined as a revision surgery at the primary site of the tear.
Secondary endpoint(s):	• 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 the allograft. • MRI to assess meniscal healing at 6 months and 12 months; • Patient-Reported Outcome (PRO) data will be collected at baseline, 6 months & 12 months: IKDC scores, Lysholm scores, & EQ-5D-5L.
Other exploratory endpoint(s):	• Analysis of reoperation rate and PROs by meniscal repair procedure (i.e., MR alone vs. MR with 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 and 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.
Safety Data	• Device-related re-intervention; • All adverse events (AEs) occurring from the time of surgery until revision or study completion; • Devices related Aes and serious adverse events (SAEs); • Device deficiencies (DDs).

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)	Unscheduled Visit
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	X
MRI assessment	X[2]				X[3]	X[3]	X
PRO: IKDC subjective	X				X	X	X
PRO: Lysholm	X				X	X	X
EQ-5D-5L CRF	X				X	X	X
Concomitant Medication/ Therapy	X	X	X	X	X	X	X
Safety Assessment (AE/SAE/ADE/DevD)		X	X	X	X	X	X
End of Study/Exit	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]

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

3 CONTENTS
3.1 Table of Contents

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3.4 List of Abbreviations/Acronyms and Definitions

Abbreviation	Definition
ACL	Anterior Cruciate Ligament
ADE	Adverse Device Effect(s)
AE	Adverse Event(s)
ALL	Anterolateral Ligament
BMI	Body Mass Index
CE	Conformité Européene
CRF	Case Report Form(s)
CV	Curriculum Vitae
DD	Device Deficiency(ies)
EQ-5D-5L	EuroQol 5 Dimension 5 Level
FAS	Full Analysis Set Population
FDA	Food and Drug Administration
FU	Follow-Up
GCP	Good Clinical Practice
HIPAA	Health Information Portability Accountability Act
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFU	Instructions for Use
IKDC	International Knee and Documentation Committee
Interventional study	A type of clinical study in which participants are assigned to groups that receive one or more intervention/treatment so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes.
IP	Investigational Product
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intention to Treat population
LCL	Lateral Collateral Ligament

MAT	Meniscal Allograft Transplantation
MCL	Medial Collateral Ligament
MedDRA	Medical Dictionary for Regulatory Activities
MR	Meniscal Repair
NA or N/A	Not Applicable
N (or n)	Total Sample Size (or subgroup sample size)
PEEK	Polyether Ether Ketone
PRO	Patient-reported Outcome
PI	Principal Investigator
PP	Per-protocol Population
S+N	Smith & Nephew Inc.
SADE	Serious Adverse Device Effect(s)
SAE	Serious Adverse Event(s)
SAF	Safety population
SAP	Statistical Analysis Plan
TGA	Therapeutic Goods Administration
USADE	Unanticipated Serious Adverse Device Effect(s)

4 INTRODUCTION

4.1 Background

Each knee has a pair of semi-lunar wedge-shaped menisci consisting of fibrocartilage, located both laterally and medially between the tibial plateaus and the femoral condyles.[1,2] Because of their location, menisci are highly susceptible to injury, the medial meniscus being two to three times more likely to be injured than the lateral meniscus.[2,3] The most common mechanism of injury is trauma during sports activity and often occurs in combination with anterior cruciate ligament (ACL) injury.[4-6] Degenerative injury is also possible and may signify the onset of osteoarthritis (OA).[7] Traumatic knee injuries more associated with radial and vertical tears, whereas degenerative tears are more associated with horizontal and complex tears.[3]

Tears along the outer edge of the meniscus (red zone) have superior healing potential as blood supply is more available in that area than in the inner two-thirds of the meniscus (red-white and white zones).[2,8] Tears can be described as horizontal, vertical, or bucket handle. Horizontal cleavage tears are primarily degenerative in nature, but can result from trauma.[9] The tear itself extends from the inner free margin of the meniscus into the intra-meniscal substance and is typically treated with partial meniscectomy.[10] These tears typically extend into the avascular zone, vascularity is poor which can affect their ability to heal, and have been historically treated with partial meniscectomy.[10]

Historically, the removal of the meniscus, known as a total meniscectomy, was the approach for managing tears of the meniscus.[11,12] However, a direct relationship between total meniscectomy and the worse clinical outcomes such as the development of early osteoarthritis, degenerative knee changes, and increased pressure loads compared to modern techniques, was observed, causing this treatment method to be largely abandoned.[11],[13-16] In a multi-center study cited by Beaufils et al.,[17], 10-year osteoarthritis rates were 31% in patients treated with meniscectomy and 11% in patients treated with a meniscal repair or non-surgical treatment. At 20 years, the rates increased to 46% and 17%, respectively.[17]

Meniscal repair attempts to suture the meniscus back together, achieve meniscal healing, and avoid the effects of meniscectomy. This technique was introduced to preserve knee function and limit the

accelerated degenerative changes associated with surgical techniques mentioned above.[18,19] The most recently developed technique is the all-inside repair technique. The all-inside technique is typically used within the meniscal body and for posterior horn tears.20 In this approach, the surgeon uses posterior accessory portals and suture hooks to shuttle sutures through meniscal tears of the posterior horn that were not easily repairable using the other approaches. This approach can reduce surgical time,[21] speed up patient recovery,11 does not require an open incision, and can prevent complications seen with external approaches.

In an attempt to optimize the healing capacity of the meniscus following meniscal repair, augmentation techniques have been developed and investigated to varying extents.[23] Advances, such as the use of biologics such as platelet-rich plasma (PRP),[24] biomaterial augmentation,[25] stem cell-based therapy,[26] and allograft transplantation.[22] Meniscal allograft transplantation (MAT) can be performed in patients who present with affected compartment-specific pain and have pain and swelling secondary to chondral overload after a subtotal meniscectomy.[22] The ideal patient age for this treatment is younger than 40 years, however no specific upper age limits have been identified.[22] Meniscal allografts are available in various forms which include, frozen, lyophilized, fresh and cryopreserved. Frozen allografts are most commonly used. Allografts need to be sized appropriately the fit the patient's anatomy.

Currently, a plethora of devices for all-inside meniscal repair is being used. One highly coveted device is the FAST-FIX 360 Meniscal Repair System (Smith & Nephew, Andover, MA, U.S.A.); this device combines the advantages of the all-inside technique with strong biomechanical properties, [12, 13] and is a modification of the previous Smith & Nephew T-FIX device. This system can be used for vertical, horizontal, or oblique meniscal tears. FAST-FIX FLEX Meniscal Repair System is S+N's next-generation meniscal repair device that will improve on the FF-360 design and will encompass: 1) reliable deployment of implants, 2) minimal disruption to the meniscus (via a smaller needle tip) and 3) more accessibility to tear locations (ability to bend the shaft to access a variety of locations, particularly the body and anterior horn). This all-inside meniscal repair device is intended to be used by healthcare professionals to repair meniscal tears and by anchoring the allograft to the capsular rim during allograft transplant procedures. The proposed study aims to evaluate the safety and

performance of arthroscopic meniscal repairs and meniscus allograft transplants using the FAST-FIX Flex System.

A summary of known and potential risks and benefits to humans of the investigational product can be found in the Instructions For Use (IFU).

4.2 Literature Summary

In the published literature, meniscal repair, allograft transplantation, and/or meniscal scaffolding using the subject devices may be concurrently performed with other procedures (such as ACL reconstruction and/or allograft transplant or meniscectomy), in combination with other techniques (such as inside-out, outside-in, meniscal root, all-inside repair), and/or using other devices (such as sutures, Endobuttons, plates or screws).

Meniscal Repair

Improvements in Lysholm scores in patients who underwent meniscal repairs using the Fast-Fix device ranged from 25-40.1 points, with a mean postop score ranging from 87.4 to 95.4, indicating good outcomes.[27-29] Improvements in IKDC Subjective scores ranged from 33 to 61.3 points, with postoperative scores ranging from 87 to 92.[26,27] Barber et al.[30] reported a 3.8 point improvement (minimal detectable change is 1) in Tegner Activity Scores, with a mean postoperative score of 7.2, and a 44.1 point improvement in Cincinnati score with a mean postoperative score of 82.8. Kamimura et al.[31] reported full recovery (per Tegner scores) in 6 cases and recovery to 1 level below preop in 6 cases, but individual specific scores were not reported.

Two studies reported pooled outcomes of the FAST-FIX or ULTRA FAST-FIX device.,[33] Improvements in Lysholm scores in patients who received the ULTRA FAST-FIX or FAST-FIX device ranged from 32.1 to 34 points, with mean postoperative scores ranging from 93.1 to 95.3 points, indicating good outcomes.[32,33] Improvements in IKDC Subjective scores ranged from 21.8 to 28.1 points, with postoperative scores ranging from 79.6 to 82.6 points, Hirtler et al.[34] reported postop objective IKDC as "normal" in 34 cases (91.9%), and "nearly normal" in 3 cases (8.1%).

Improvements in Lysholm scores in patients who received the FAST-FIX 360 device ranged from 38.4 to 44.4 points, with mean postoperative scores ranging from 87.3 to 92, indicating good outcomes.[69,91] A 35.82 point improvement in IKDC Subjective score was reported, with a mean postop score of 88.19.[35] In patients treated for Meniscal Repair with the Fast-Fix 360, the repair was clinically successful in 38 (88.3%) of the cases at final follow up.[69] Laurendon et al.[35] reported IKDC Objective scores were reported in one study as A/B (normal/nearly normal) in 85 (97.7%) patients and C/D (abnormal/severely abnormal) in 2 (2.2%) patients.

Meniscal Transplant

Two studies by Gelber et al.[36,37] reported the use of the ULTRA FAST-FIX™ device in conjunction with Orteq's ACTIFIT scaffold in 114 patients. Patient satisfaction scores and VAS scores were reported to have improved as well, but were not explicitly stated.

Improvement in Lysholm Scores ranged from 45.7 to 56.7 in patients treated with Ultra Fast-Fix for meniscal scaffolding.[36,37] Western Ontario Meniscal Evaluation Tool (WOMET) scores were reported in two studies, and improved postoperatively by 53.482 and 41.390 points.

Alentorn-Geli et al.[38] reported 2 cases (6%) where patients reported a decreased Lysholm and IKDC score after surgery and one patient had decreased Lysholm Scores. No patients reported decreased VAS scores, however, two patients had scores that remained the same. The authors' did not provide further information on why the scores decreased or did not change, still the authors reported "significant improvement" of Lysholm, subjective IKDC, and VAS post-op in the overall study cohort.

4.3 Study Purpose

The purpose of this study is to collect post-market safety and clinical outcomes data from patients who underwent meniscal repair or meniscal allograft transplantation with the next generation FAST-FIX Flex System. This is the first case-series study describing the clinical results and complications of the FAST-FIX FLEX Meniscal Repair System.

4.4 Safety Consideration

4.4.1 Intended Users

The FAST-FIX FLEX Meniscal Repair System is intended to be used by healthcare professionals in accordance with these instructions for use. The use environment is an operating room.

4.4.2 Indications

The FAST-FIX FLEX Meniscal Repair System is indicated for use in meniscal repairs, allograft transplant procedures, and anchoring the allograft to the meniscal rim during allograft transplant procedures.

4.4.3 Contraindications

The contraindications listed in the IFU include:

- Pathological conditions in the soft tissue that would prevent secure fixation of the device.
- Known hypersensitivity to the implant material. Where material sensitivity is suspected, appropriate tests should be made and sensitivity ruled out prior to implantation.

4.4.4 Potential Adverse Events

The Potential Adverse Effects listed in the IFU include:

- Mild inflammatory and foreign body reactions

<u>Warnings and Precautions stated in the IFU:</u>

- Do not use if package is damaged. Do not use if the product sterilization barrier or its packaging is compromised.
- The device is supplied sterile and is for SINGLE USE ONLY. Do not clean, resterilize, or reuse the device, as this may damage or compromise the performance resulting in product

malfunction, failure, or patient injury. Cleaning, resterilization, or reuse of the device may also expose the patient to the risk of transmitting infectious diseases.

- It is the surgeon's responsibility to be familiar with the appropriate surgical techniques prior to use of this device.
- Only bend the needle with the provided bend tool.
- Do not bend the needle along area indicated by black retaining tube. Excessive bending of the delivery needle may make it difficult or impossible to deliver the T1 and T2 implants.
- If resistance is encountered during deployment, a new delivery device may be needed.
- Do not push the deployment slider twice or the implants will deploy prematurely.
- Do not push the deployment slider until the needle is fully penetrated through the meniscus to the preset depth or T1 and T2 will deploy prematurely.
- The patient should be warned that the device does not replace normal healthy tissue, and that the implant can break or become damaged as a result of strenuous activity or trauma, and has a finite expected functional life and may need to be replaced in the future.

Bending the needle:

- Only use the bend tool provided in the carton with the needle.
- Do not bend the needle along area indicated by black retaining tube.

Deploy the first implant (T1):

- Do not push the deployment slider twice or the second implant will deploy prematurely.

Deploy the first implant (T2):

- Do not push the deployment slider until the needle is fully penetrated through the meniscus to the preset depth or T2 will deploy prematurely.

5 OBJECTIVE(S)

The primary, secondary and safety objectives of this study are listed as follows.

5.1 Primary Objective

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.

5.2 Secondary Objective(s)

The secondary objectives are to:

- 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 Patient-Reported Outcome (PROs) scores at baseline 6 months and 12 months: International Knee and Documentation Committee (IKDC) scores, Lysholm knee scores and EQ-5D-5L.

5.3 Other Objective(s)

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

5.4 Claims

The proposed Marketing Claims for this study include, but are not limited to, the following:

- Meniscal tears repaired with FAST-FIX FLEX lead to an improvement in patient symptom scores (PROs).
- The FAST-FIX FLEX Meniscal Repair System provides an increased access to tear location and increased zone of repair.

6 INVESTIGATIONAL PRODUCT(S)

The Meniscal repair device used in the investigation will be the FAST-FIX FLEX Meniscal Repair System, a suture retention device to facilitate percutaneous or endoscopic soft tissue procedures. The system is 510(k) cleared in the United States and includes two non-absorbable polymer implants, pre-tied with #2-0 non-absorbable suture and preloaded into a needle delivery system.

6.1 Identification

6.1.1 Investigational Product

The FAST-FIX FLEX Meniscal Repair System devices are intended to provide a secure repair of soft tissue tears, particularly meniscal tears, or to support meniscal allograft transplantation (Fig 1.A-B). Four device configurations having different distal needle curvature are being offered. Two are with a Bend Tool and Slotted Cannula and two configurations are packaged without a Bend Tool and Slotted Cannula.

A B

Figure 6-1-1 A-B: Images of the Fast-Fix Flex A) Curved & B) Reversed-Curved inserter, bender, cannula set.

Each device includes two non-absorbable polymer implants, pre-tied with #2-0 non-absorbable suture and preloaded into a needle delivery system. The adjustable depth penetration limiter is preset to approximately 16mm from the tip of the needle. It can be adjusted in 4mm increments between 12mm and 20mm.

The system is supplied sterile and is for SINGLE USE ONLY.

SKUs 72205324 and 72205325 contain the following:

(1) Single-use delivery needle assembly preloaded with

(2) PEEKOPTIMA™ (polyetheretherketone) implants pre-tied with #2-0 non-absorbable suture made of uncoated ultrahigh-molecular-weight polyethylene fiber braided with polypropylene monofilament fiber

(1) Single-use FAST-FIX FLEX Slotted Delivery Cannula

(1) Single-use Bend Tool

SKUs 72205676 and 72205677 contain the following:

(1) Single-use delivery needle assembly preloaded with

(2) PEEKOPTIMA™ (polyetheretherketone) implants pre-tied with #2-0 non-absorbable suture made of uncoated ultrahigh-molecular-weight polyethylene fiber braided with polypropylene monofilament fiber

SKU	Component	Description
72205324	FAST-FIX FLEX CURVED INSERTER, BENDER, CANNULA SET	Inserter: The device user interface includes a handle and deployment knob used to deploy two PEEK implants in the joint space. The handle and deployment knob are designed such that they are easy to hold/grip onto, allow for single-handed deployment, and provide tactile feedback for implant deployment. Bender: Used to adjust the curvature of the distal needle. Design is textured on either side of the bend tool to enhance grip. Cannula: Used for ease of insertion of the device into joint space.
72205325	FAST-FIX FLEX REVERSE CURVED INSERTER, BENDER, CANNULA SET	
72205676	FAST-FIX FLEX CURVED INSERTER	Inserter: The device user interface includes a handle and deployment knob used to deploy two PEEK implants in the joint space. The handle and deployment knob are designed such that they are easy to hold/grip onto, allow for single-handed deployment, and provide tactile feedback for implant deployment
72205677	FAST-FIX FLEX REVERSE CURVED INSERTER	

Refer to the Fast-Fix Flex Instructions for Use for more information.

6.1.2 Ancillary Products

Individual compatible instruments and accessories for the FAST-FIX FLEX Meniscal Repair System are sold separately and are provided sterile. Read the Instructions for Use that are enclosed with the instruments and accessories prior to use.

SKU	Component	Description
CTX-C001	NOVOCUT Suture Manager	Used to push knots in size 2-0 or 0 suture created during arthroscopic surgery, cut the resulting suture tails, and retrieve or manage suture arthroscopically.
015186	Meniscal Depth Probe	Used to measure meniscus and then set the appropriate needle exposure.
014549	45°Diamond Rasp	Used to prepare the tear prior to suturing.
014550	90° Diamond Rasp	

6.2 Product Use

Typically, total meniscal repair procedure time runs for approximately 45 minutes, during which the FAST-FIX FLEX is used in the knee for approximately 5-30 minutes. The devices are provided sterile and fully assembled to the operating room. Each device is single use only. The inserter is used to access the joint space and repair site. Once in the joint space, the inserter is used to deploy two polyether ether ketone (PEEK) implants into the soft tissue at the repair site, which will stay permanently in the patient's body. The Slotted Cannula provided with each device (currently marketed with the FF360 product line) is used for ease of insertion into the joint space. The Bend Tool provides the ability to adjust the distal needle's curvature, if desired by the surgeon for improved access in the joint space. The functionality of the FAST-FIX FLEX inserters is similar to that of the predicate FF360 product line.

Refer to the FAST-FIX FLEX IFU for detailed information on contraindications, warnings, adverse reactions and precautions.

6.3 Packaging and Labelling

Packaging and labelling will be as per commercially available product and will meet regulatory requirements.

6.3.1 Labelling of Investigational Product

The FAST-FIX FLEX Meniscal Repair System has received 510(k) clearance in the United States, CE marking in Europe, Australian Register of Therapeutic Goods (ARTG) approval in Australia and is commercially available on the market. All devices used in this study will be procured in standard commercial packaging, ordered via usual and customary Smith + Nephew procedures and managed per study site processes. The labels on FAST-FIX FLEX Meniscal Repair system contain the following information:

- Lot Number
- Catalogue Number
- Unique Device Identifier
- Package contents
- Use by Date
- Date of Manufacture
- Distributor information: Smith + Nephew, Inc.
- Manufacturer name and address
- Product name
- Customer service contact information
- Product sale restriction

6.3.2 Ancillary Products

The labels on the ancillary products contain the following information:

- Lot Number
- Catalogue Number
- Unique Device Identifier
- Package contents
- Use by Date
- Date of Manufacture
- Distributor information: Smith + Nephew, Inc.
- Manufacturer name and address
- Product name
- Product sale restriction

6.4 Product Accountability Procedures

All devices used in this study will be procured in standard commercial packaging, ordered via usual and customary Smith + Nephew procedures and managed per study site processes. Therefore, product accountability / inventory will be managed as per study site's local processes and procedures.

6.5 Surgical Technique/Medical Procedures

All study-related procedures with the FAST-FIX FLEX Meniscal Repair System must be performed according to the recommended surgical technique described in the IFU (10601463 / 10601589). In addition to the IFU, the FAST-FIX FLEX device must be the only suture retention device used in this study to perform meniscal repairs. Furthermore, a notch microfracture/venting procedure should be performed for all isolated meniscal repairs. For meniscal allograft transplantations, the variability of surgical technique is open, allowing a hybrid repair to be performed. However, the FAST-FIX FLEX device must be the only all-inside device used in this study during the meniscal allograft transplantation procedure.

Investigators participating in this study must be proficient in meniscal repairs and/or meniscal allograft transplantations. Prior to using the FAST-FIX FLEX Meniscal Repair System, medical professionals may be trained by a sales representative on the product or they will be introduced to the product at a medical education lab. In addition, a minimum of three procedures with the device under study in this protocol must be completed prior to enrolling subjects in the study.

7 SUBJECT ENROLLMENT AND WITHDRAWAL

7.1 Subject Population

A minimum 62 and maximum of 68 subjects between the ages of 16 and 70 years of age will be enrolled into the study. The subjects will be recruited from up to 5 sites in the United States, United Kingdom, France and Australia. Sites failing to enroll may be replaced.

- 53 subjects will be enrolled for meniscal repair with the use of the FAST-FIX FLEX system
- A minimum of 9 and maximum of 15 subjects will be enrolled for meniscal allograft transplantation with the use of the FAST-FIX FLEX system

For the two subgroups, the clinician has decided the subject's best treatment is a meniscal repair or meniscal allograft transplantation facilitated with the FAST-FIX FLEX system as routine medical care. This decision will be made irrespectively of study participation.

7.1.1 Vulnerable subjects

Subjects aged 16 and 17 years of age ("minors") can be enrolled in this study. The rationale for inclusion of this age group is to better align with the Investigational Product's IFU, which does not restrict use in this age group, and strengthen the evidence required for European Medical Device Regulation (EU MDR). Also, the study sites use the Investigational Product in this age group as per standard care and therefore should improve recruitment rates in this study. As this is a post-market clinical follow-up (PMCF) study, any minors who are enrolled in this study may receive the Investigational Product regardless of their participation.

7.2 Inclusion Criteria – Meniscal Repair ONLY

Subjects will be considered qualified for enrollment in the MR arm if they meet the following criteria:

1. Subject provides written informed consent for study participation using an independent ethical committee (IEC) / institutional review board (IRB) approved consent form.
2. Subject is between sixteen (16) and seventy (70) years of age, inclusive at the time of screening.
3. Subject is willing and able to participate in required follow-up visits and is able to complete study activities.
4. Subject requires a meniscal repair.
5. Subject is suitable to participate in the study in the opinion of the Investigator.
6. 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.

7.3 Exclusion Criteria – Meniscal Repair ONLY

Any one (1) of the following criteria will disqualify a potential subject from participation in the study:

1. 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.
2. Enrolled in the treatment period of another clinical trial within thirty (30) days of the operative visit, or during the study.
3. Women who are pregnant or nursing.

4. 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).[1]
5. Subjects with a history of poor compliance with medical treatment, physical therapy (PT)/rehabilitation, or clinical study participation.
6. Patients with irreparable meniscal tears (i.e. multiple tears).
7. Subjects with full thickness cartilage defects greater than 10mm in diameter and/or serious defects.
8. Patients 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).
9. 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.
10. Subjects with a history of ipsilateral knee surgery, septic joint, or fracture.
11. Subjects with pathological conditions in the soft tissue that would prevent secure fixation of the device.
12. Physical conditions that would eliminate, or tend to eliminate, adequate anchor support or retard healing.
13. The presence of infection.

1. ISO 14155 Section 3.55 States: Vulnerable subject – individual whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. EXAMPLE: Individuals with a lack of or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects include, for example, members of a group with a hierarchical structure such as university student's, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces and persons kept in detention.

14. Conditions which would limit the patient's ability or willingness to restrict activities or follow directions during the healing period.
15. Malalignment: genu varus and genu valgus angles greater than 5° as evaluated by the patient's physician as per their standard of care.
16. Patients who have an Ahlback grade greater than II.
17. Patients with a body mass index larger than 35.
18. Subjects with a medical or physical condition that, in the opinion of the Investigator, would preclude safe subject participation in the study.

7.4 Inclusion Criteria – Meniscal Allograft Transplantation ONLY

Subjects will be considered qualified for enrollment in the MAT arm if they meet the following criteria:

1. Subject provides written informed consent for study participation using an independent ethical committee (IEC) / institutional review board (IRB) approved consent form.
2. Subject is between sixteen (16) and seventy (70) years of age, inclusive at the time of screening.
3. Subject is willing and able to participate in required follow-up visits and is able to complete study activities.
4. Subject requires a meniscal allograft transplantation.
5. Subject is suitable to participate in the study in the opinion of the Investigator.
6. 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).

7.5 Exclusion Criteria – Meniscal Allograft Transplantation ONLY

Any one (1) of the following criteria will disqualify a potential subject from participation in the study:

1. 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.
2. Enrolled in the treatment period of another clinical trial within thirty (30) days of the operative visit, or during the study.
3. Women who are pregnant or nursing.
4. 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).[1]
5. Subjects with a history of poor compliance with medical treatment, physical therapy (PT)/rehabilitation, or clinical study participation.
6. Patients 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.
7. 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.
8. Subjects with a history of ipsilateral knee surgery, septic joint, or fracture (excluding MAT indication).
9. Subjects with pathological conditions in the soft tissue that would prevent secure fixation of the device.

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

7.6 Screening

The Investigators will continuously screen subjects during recruitment, which will continue until a minimum of 62 and maximum of 68 subjects (53 enrolled for MR and a minimum of 9 and maximum of 15 enrolled for MAT) are recruited. It remains the decision of the Sponsor to increase or decrease enrollment, as necessary.

Subjects aged 18 years and over: Once a subject has completed the informed consent procedure and signed the Informed Consent Form (ICF), the Principal Investigator (PI), or delegated study research staff, can complete the screening process to determine whether they meet all inclusion and none of the exclusion criteria.

Subjects aged 16 and 17 years: Once a subject has completed the informed consent procedure (assent), the subject's legally authorized representative (parent or legal guardian) has completed the informed consent procedure and signed the relevant ICFs, the Principal Investigator (PI), or

delegated study research staff, can complete the screening process to determine whether they meet all inclusion and none of the exclusion criteria.

Participating study sites are required to document all screened subjects considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be recorded in the subject's source documents and noted on the Screening and Enrollment Log. All screening activities that occur prior to consent shall be referred to as pre-screening.

7.7 Informed Consent

Before conducting any study procedures or examinations, the purpose and nature of the study should be explained to the subject in their native language. Subjects will have the opportunity to ask any questions.

The subject, or their legally authorized representative, will then **read**, **sign**, and **personally date** the IRB/IEC-approved informed consent document(s) (see below for difficulties with reading and writing). Additionally, the individual who obtains consent from the subject will sign and date the informed consent document. A copy of the signed informed consent document will be provided to the subject, and a copy will be placed in the subject’s medical record, with the original filed in the ISF.

If the subject is unable to read, the informed consent document and associated study information may be read aloud to the subject in the presence of an impartial witness. If possible, the subject shall sign and personally date the ICF. Where this is not possible, due to difficulties in writing, the subject shall provide verbal consent to participate in the study. The witness shall then personally sign and date the informed consent form, attesting that the information was accurately explained and that the informed consent was freely given.

In the case of vulnerable subjects (minors), the ICF must be understood and signed by the subject’s legally authorized representative (parent or legal guardian). Assent to participate in the study should be obtained for subjects 16 years of age and 17 years of age if allowed by local regulations. If the

legally authorized representative is unable to read/write, a witness signature is required as described previously.

The minor shall participate in the informed consent process in a way suitable for their age and mental maturity. Minors will receive the study information in a way adapted to their age and mental maturity from investigators or members of the investigating team who are trained or experienced in working with children. If minors express a wish or an opinion with regards to study participation this needs to be respected by the Investigator. If during the study, the minor reaches the age of 18 years (legal competence), the informed consent shall be obtained again, before the subject can continue to participate in the clinical investigation. ICFs will comply with Health Information Portability Accountability Act (HIPAA) regulations the EU Global Data Protection Regulation (GDPR), The Privacy Act 1988 in Australia and the New Zealand Privacy Act 1993 and or applicable national regulations and laws.

If new information becomes available during the course of the study that can significantly affect a subject's future health and medical care, Smith + Nephew will ensure that information shall be provided to the subject(s) affected in written form and if relevant, all affected subjects shall be asked to confirm their continuing consent in writing.

7.8 Enrollment

Subjects for whom the consent process has been completed and have been treated with the study product are considered enrolled. Any subjects who have provided consent but do not receive treatment or withdraw consent prior to surgery will be considered a screen failure.

Subjects will be assigned a Subject ID at the time of consent. Subjects requiring a bilateral meniscal repair will not be enrolled.

7.9 Lost to Follow-up

A subject will be considered lost to follow-up if he/she does not appear for the scheduled study visit for two consecutive visits and does not return for a final visit, and study personnel are unable to contact the subject.

Some actively enrolled subjects will not return for follow-up exams on time due to a variety of reasons. Study personnel must make a reasonable effort to contact the subject and document the following contact attempts before declaring a subject to be lost to follow-up (LTFU): the subject has been contacted according to the site's policies, but no fewer than two documented phone contacts and one certified letter without response. Copies of all attempts to reach the subjects by mail or email and/or the attempts to contact the subject via other means should be documented, and that documentation should be kept with the subject’s source documents.

7.10 Withdrawal

7.10.1 Withdrawal from Treatment

Subjects may be withdrawn from having the related procedures with the FAST-FIX FLEX Meniscal Repair System at a date close to surgery or during surgery for the following reasons:

- At the discretion of the Investigator due to:
  - A change in treatment is clinically warranted
  - An adverse event
  - Any other significant reason identified by the Investigator

7.10.2 Any subjects who have provided consent but do not receive treatment or withdraw consent prior to surgery will be considered a screen failure.Withdrawal from Study

The Investigator may withdraw subjects from the study for many reasons, including but not limited to the following:

- Subject noncompliance (e.g., did not follow instructions, took disallowed medications)
- Subject lost to follow-up
- If the Investigator or the Sponsor stops the study for any reason and decides to withdraw subject(s) from the study
- concurrent illness
- Adverse Events/Adverse Device Effects that affect the ability to evaluate the study product
- without bias
- Any other significant reason identified by the Investigator

If a subject receives a revision surgery of the study knee, or experiences an AE/SAE/DD, the subject shall continue to have follow-up visits in order to monitor the subject's health status until any adverse events/adverse device events are resolved, is lost to follow-up, or until 12 months post-surgery. Potential data following the revision surgery will not be included as study data but presented separately as safety data. Revision subjects will not be replaced.

For each case, the information will be obtained in the source document and the Case Report Form (CRF), detailing circumstances leading to the withdrawal.

Subjects who drop out or are withdrawn will not be re-entered into the study at a later date.

7.10.3 Subject's Withdrawal of Consent to Participate in Study

Study participation is voluntary, and subjects may withdraw at any point during the study without giving their reason for doing so. Where subjects withdraw consent, the investigator should make a

reasonable effort to ascertain the reason(s), while fully respecting the subject's privacy. The reason for withdrawal will be recorded in the CRF and source documents.

If withdrawal is after the surgical procedure, the Investigator should inform the subject of any recommended follow-up visits to monitor subject safety.

7.10.4 Use of Data Following Withdrawal

In cases where the subject withdraws consent, the data collected up to the point of withdrawal may be used, but no additional data for that subject may be collected.

8 STUDY DESIGN

8.1 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 and meniscal allograft transplantations. 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 8.1-1.

Table 8.1-1 Overview of Study Groups

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

The study is expected to be 39 months in duration, but this will depend on the enrollment rate. These include:

- 21 months for enrollment
- 14 months for follow-up
    - The final visit is 12 months post-surgery and includes a +/- 75 day window period.

The study's treatment will occur once, in the form of surgery to repair the torn portion of the meniscus or provide allograft transplantation to replace the irreparable meniscus or for patients who have had a meniscectomy.

The primary outcome measures that will be examined include whether the repair success rate at 12 months will be similar or less than historical rates (90% for all-inside meniscal repair)[39]; whether the FAST-FIX FLEX system increases access to tear location and zone of repair; whether a significant proportion of the subjects will show meniscus healing at 6 months; and whether Patient-Reported Outcomes (PROs) will be improved up to 12 months following the procedure.

Figure 8-1-1: Study Flowchart 1

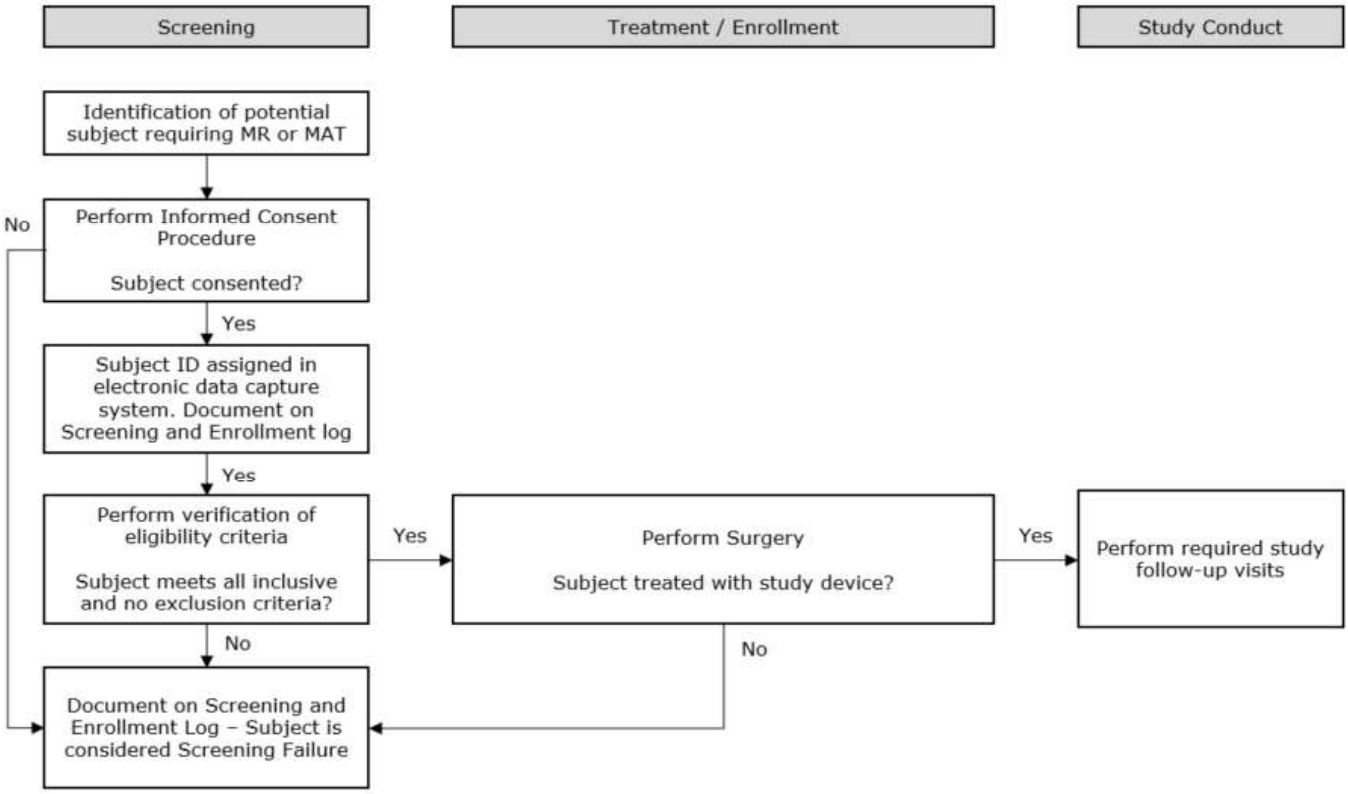


Figure 8-1-8-2: Study Stages

8.2 Allocation and Blinding

8.2.1 Treatment Allocation

This study is not randomized.

8.2.2 Blinding

This study is not blinded.

8.3 Data Management

This study utilizes a validated, 21 CFR Part 11 compliant, electronic data capture system. Access to the electronic data capture system is controlled through Smith and Nephew procedures.

A Data Management Plan (DMP) is written according to Smith and Nephew procedures containing details of the data management process. The following is a brief description of the key points detailed in this plan.

8.3.1 Data Review and Quality Assurance

Data will be transcribed from the data source to an electronic Case Report Form (eCRF). All data requested on the eCRFs are considered required. Data points not collected and/or recorded will be considered deviations unless otherwise specified.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Principal Investigator. The Principal Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. The Principal Investigator must provide

his/her electronic signature on the appropriate eCRFs to be documented in compliance with local regulations. Changes to data previously submitted to the sponsor will require a new signature by the Investigator to acknowledge/approve the changes.

Visual and computer data review will be performed in line with Smith and Nephew procedures to identify possible data discrepancies. Manual and automatic queries will be created within the electronic data capture system, and will be issued by Smith and Nephew to the site for appropriate response. Site staff are responsible for resolving all queries in the electronic data capture system.

8.3.2 Retention Period

All eCRFs will be archived once the study is completed and will be kept for a period of no less than five years after the later of the following dates: the date of which the study is terminated or completed or the date that the records are no longer required for supporting marketing applications.

8.4 Study Endpoints

8.4.1 Primary Endpoint

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.

8.4.2 Secondary Endpoints

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;
- Patient-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 patient symptoms associated with meniscal function.

8.4.3 Other Endpoints

Other study endpoints are:

- Analysis of reoperation rate and PROs by meniscal repair procedure (i.e. MR alone vs MR with 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.

8.4.4 Safety Endpoints

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).

8.5 Methods Used to Minimize Bias and Maximize Validity

8.5.1 Balanced Covariates

The inclusion/exclusion criteria will be generalizable and applicable to the widest possible subset of the population needing meniscal repair procedures. These criteria will be uniformly applied to enroll a cohort of subjects with similar symptoms and clinical requirements. This should maximise the applicability to as many subjects with similar baseline characteristics and help to bolster external validity.

8.5.2 Subject Attrition

Subject attrition due to a reduction in sample size required for precision analysis has been accounted for in the sample size calculation so that the estimate of the confidence interval (CI) to be obtained will still be valid through the most efficient use of available subjects.

8.5.3 Pre-specification of Statistical Analysis

The primary outcome measure has been pre-specified as well as the type of statistical analysis to be performed to evaluate repair failure rate to minimize reporting bias. The precision analysis planned for the study includes construction of confidence intervals for the outcome summaries and a pre-defined range in which the 95% CI for the primary outcome is expected to fall within are designed to maximize the validity of the study results.

More detailed information on analyses to be carried out will be incorporated in the Statistical Analysis Plan (SAP) so as to minimize any threats to external validity in order to yield clinically relevant estimates of effects and precision.

9 STUDY PROCEDURES

9.1 Visits and Examinations

9.1.1 Summary

For a summary of the required procedures by visit, refer to the Study Schematic Table 9.1-1: Study Procedures by Visit.

Table 9.1-1 Study Procedures by Visit

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

[1] Inclusion/exclusion confirmation will be performed at the time of screening and study procedure to confirm 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

9.1.2 Visit 1: Screening/Preoperative Visit (Baseline, <8 weeks prior to procedure)

NOTE: Any subject who signs an informed consent/assent but fails to meet the required entry criteria is considered to be a Screen Failure. For screen Failure subjects, their demographic information must be captured in the appropriate CRF with the reason for screen failure specified.

1.	Obtain written informed consent from the subject as detailed in Section 7.7 ----- **Do not proceed until consent has been obtained** -----
2.	Obtain demographic information and medical history, including information on all concomitant medications/therapies.
3.	Obtain baseline MRI and confirm eligibility.
4.	Screen the subject for protocol inclusion/exclusion criteria.
5.	Assign the subject a study number and instruct the subject on treatment procedures.
6.	Have the subject complete the IKDC Subjective Questionnaire
7.	Have the subject complete the Lysholm Questionnaire
8.	Have the subject complete the EQ-5D-5L Questionnaire
9.	Subjects will be instructed to return for the Operation Visit (Procedure) as scheduled by the site.

9.1.3 Visit 2: Operation Visit (Procedure)

1.	Query subject regarding any changes in general health and the use of concomitant medications.
2.	Commence procedure.
3.	If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12, adverse events and device deficiencies.
4.	Instruct the subject on proper postoperative care/procedures, including any contraindicated treatments/medication(s).
5.	Complete Details of Surgery Procedure CRF.
6.	Complete Details of Pathology CRF.
7.	Complete End of Study/exit information (if appropriate).
8.	Instruct the subject on follow-up procedures, including returning to the site for follow-up (FU) Visit 3 in 14 (±5) days.

9.1.4 Visit 3: Follow-up visit at 2 weeks (14 days after procedure +/- 5 days)

1. Query subject regarding any changes in general health and the use of concomitant medications.
2. If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12, adverse events and device deficiencies.
3. If any Reoperation occurred complete Post-operative Surgery Failure CRF.
4. Complete End of Study/exit information (if appropriate).
5. Instruct the subject on follow-up procedures, including returning to the site for a FU visit at 3 months.

9.1.5 Visit 4: Follow-up visit at 3 months (90 days after procedure + 30 days)

1. Query subject regarding any changes in general health and the use of concomitant medications/concomitant therapies.
2. If any adverse events, adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12, adverse events and device deficiencies.
3. If any Reoperation occurred complete Post-operative Surgery Failure CRF.
4. Complete End of Study/exit information (if appropriate).
5. Instruct the subject on follow-up procedures, including returning to the site for FU visit at 6 months.

9.1.6 Visit 5: Follow-up visit at 6 months (180 days after procedure +/- 45 days)

1. Query subject regarding any changes in general health and the use of concomitant medications/concomitant therapies.
2. If any adverse events, adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12, adverse events and device deficiencies.
3. If any Reoperation occurred complete Post-operative Surgery Failure CRF.
4. Obtain 6-month MRI.
5. Have the subject complete the IKDC Subjective Questionnaire.
6. Have the subject complete the Lysholm Questionnaire.
7. Have the subject complete the EQ-5D-5L Questionnaire.
8. Complete End of Study/exit information (if appropriate).
9. Instruct the subject on follow-up procedures, including returning to the site for FU visit at 12 months.

9.1.7 Exit Visit (Visit 6: Follow-up visit at 12 months (365 days after procedure +/- 75 days))

1.	Query subject regarding any changes in general health and the use of concomitant medications/concomitant therapies.
2.	If any adverse events, adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12, adverse events and device deficiencies.
3.	If any Reoperation occurred complete Post-operative Repair Failure CRF.
4.	Obtain a 12-month MRI.
5.	Have the subject complete the IKDC Subjective Questionnaire
6.	Have the subject complete the Lysholm Questionnaire
7.	Have the subject complete the EQ-5D-5L Questionnaire
8.	Complete Exit Visit CRF and inform the subject of End of Study.

9.1.8 Reoperations

Any reoperations will be captured in the source documents and on the Post-operative Surgery Failure CRF. Details of the reoperation will be captured, including the reason for the reoperation. At the reoperation, the use of any concomitant medications, concomitant therapies, adverse events, and device deficiencies will be collected.

9.1.9 Unscheduled Visits

All information obtained during an unscheduled visit should be recorded in the source documents and on the appropriate CRF. If any adverse events or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 - Adverse Events and Device Deficiencies. The subject should be scheduled to return for the next scheduled study visit within the acceptable time window.

9.1.10 Concomitant Medications and Therapies

Concomitant medications and concomitant therapies (e.g., physical therapy, TENS Unit, massage) are recorded at any time from enrollment into the study through the subject's last study visit.

Concomitant Medications

Excluded Concomitant Medications

Any individual who is on immunosuppressive therapy at screening is ineligible for the study. If a subject starts immunosuppressive therapy during the study, they will be withdrawn from the study. There are no other medication restrictions for this study.

Recording Concomitant Medications in CRF

All medications that the subject is on will be recorded in the CRF. The CRF Completion Guidelines will stipulate how medications should be recorded in the CRF.

Concomitant Therapies

Therapies Prohibited During the Study

No restrictions on concomitant therapies.

Recording Concomitant Therapies in the CRF

Concomitant therapies should be recorded on the designated CRF. Reference the CRF Completion Guidelines for how concomitant therapies are recorded.

9.1.11 Discontinued Subjects

Discontinued subjects are those who voluntarily discontinue participation, who are withdrawn for reasons of safety or use of prohibited concomitant medications, who are lost to follow-up, or who

have missed 2 consecutive follow-up visits, or fail to complete the procedure at baseline so are ineligible for further participation; refer to section 6.8 for further details. Where possible, a full Exit Visit should be completed for all subjects who discontinue the study early. Where consent is withdrawn, the date and any reason given for discontinuation should be captured, at a minimum (see Section 6.8.2).

Finally, if appropriate, the Investigator will also advise the subject of subsequent therapy and/or procedures necessary for their medical condition. Medical care will not be provided to the subject after the clinical investigation is completed, other than the standard care provided by the site, which is not considered a study visit(s).

9.1.12 Subject Pregnancy

Women of child-bearing potential are not excluded from the study. If a woman becomes pregnant during the study, S+N must be contacted immediately once the investigator is made aware of the pregnancy and a decision will be made regarding the continuation in the study of the pregnant woman. Pregnancy is not an adverse event; however, complications related to the pregnancy may be reportable as determined on a case-by-case basis. Pregnancy-related information will be collected until the end of the pregnancy or the end of the study.

9.2 Study Methods and Measurements

The following methods and measurements will be used for this study:

- Magnetic Resonance Imaging (MRI)
- IKDC Subjective PRO
- Lysholm PRO
- EQ-5D-5L PRO

9.2.1 Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI) is a medical imaging technique that uses magnetic field and computer-generated radio waves to create detailed images of an organ or tissue in the body.[43] For this study, MRIs will be obtained at baseline, 6 months and 1 year post-treatment to assess structural integrity and healing. Sites will make arrangements for MRIs per standard procedures and provide the images/results to the Sponsor. All MRI assessments are detailed in the Image Review Charter. MRI to confirm eligibility criteria must be within 6 months of surgery.

The specific imaging evaluation requirements will be provided in a separate document to radiologists.

9.2.2 International Knee Documentation Committee (IKDC) Subjective

The International Knee Documentation Committee (IKDC) Subjective score was developed to detect improvement or deterioration in symptoms, function, and sports activities due to knee impairment, including patients with meniscal injuries. The original IKDC form was published in 1993, and there were several revisions up to the current version published in 2001. This is a validated questionnaire if it is completed by the patient; it takes the patient about 10 minutes to complete.[43]

There are three domains: 1) symptoms, including pain, stiffness, swelling, locking/catching, and giving way (7 items), 2) sports and daily activities (10 items), and 3) current knee function and knee function prior to a knee injury (1 item, not included in the score). Responses vary for each item. The possible score ranges from 0-100, where 100 = no limitation with daily or sporting activities and the absence of symptoms. The normative data for the score are available for the general US population, stratified for age, gender, and current/prior knee problems.[43]

9.2.3 Lysholm

The Lysholm scale was first introduced into the medical community in 1982, modified in 1985, and is a validated patient or physician administered instrument to measure symptoms and function in

patients with a variety of knee injuries. This tool measures the domains of symptoms and complaints and the functioning of daily activities. The scale consists of 8 items and is scaled from 0 to 100, with a higher score indicating fewer symptoms and a higher level of functioning.[45,46]

9.2.4 EQ-5D-5L

EQ-5D-5L will be used to derive general health-related QoL scores at baseline, 6 months and 1 year. The EQ-5D-5L descriptive system comprises the following dimensions: Mobility, Self-Care, Usual Pain / Discomfort and Anxiety/ Depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The tool is widely used in cost-effectiveness analysis and is available in a variety of languages.[47]

9.3 Health Economics/Quality of Life

There are no health economics procedures in this study. EQ-5D-5L will be used to derive general health-related QoL scores at baseline, 6 months and 1 year. Please refer to section 9.2.4 for further details.

10 STATISTICAL DESIGN

A Statistical Analysis Plan (SAP) will be written and finalized prior to database lock. The following is a brief description of the analyses to be described in this plan.

10.1 General

Smith + Nephew's Global Biostatistics group or designee will conduct the statistical analysis for this study. Unless otherwise stated, all significance tests will be two-sided, performed at the 5% significance level. The resulting p-values will be quoted. Point estimates and their corresponding 95% two-sided confidence intervals will be generated where appropriate. Where data summaries are specified, categorical or 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).

10.2 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.
- 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 each of the patient populations as follows: analysis of primary and secondary reoperation rate endpoints will be performed on the SAF population; PROs will be presented separately using both the FAS and PP populations. All safety analyses will utilize the SAF population.

10.3 Baseline Data

Data to be summarized at baseline includes, but is not limited to, all collected demographic variables such as age, gender, BMI, primary diagnosis and medical history. The baseline variables will be used to describe the outcome data where necessary.

10.4 Efficacy Analysis

10.4.1 Analysis of Primary Endpoint

A binary variable will be defined for whether each patient 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, together with a percentage and 95% confidence interval for a single proportion (calculated using the Clopper-Pearson method)[40].

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.

Analysis will be carried out using the SAF population as the primary analysis population.

10.4.2 Analysis of Secondary Endpoints

The following secondary endpoints will be analysed for this study:

- 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 baseline, 6 months and 12 months will be conducted separately by an imaging vendor.
- IKDC, Lysholm and EQ-5D-5L PRO scores will be calculated and summarized for each visit appropriately for categorical or continuous variables. 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 (those which have MCID thresholds available in published literature) will be presented.

10.4.3 Analysis of Other Endpoint

The following other endpoints will be analysed for this study:

- Reoperation rate and change from baseline PROs at 6 and 12 months will be presented separately by meniscal repair procedure (i.e. MR alone vs MR with 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.

10.5 Safety Analyses

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: adverse events, serious adverse events, adverse device effects, serious adverse device effects, unanticipated adverse events, and serious unanticipated adverse events. In addition, for each adverse event, the following will be summarized: severity, the relationship to the investigational device, outcome and duration of the resolved adverse events and the duration of the adverse events at trial discontinuation.

Device deficiencies

The number of device deficiencies and the number of patients reporting a device deficiency will be summarized.

Additional summaries of safety endpoints, if applicable, will be described in the SAP.

10.6 Interim Analyses

There are no formal interim analyses planned for this study.

11 SAMPLE SIZE JUSTIFICATION

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. The publication upon which this is based, is the systematic literature review entitled: "Clinical performance of FAST-FIX family" authored by Paul Souter (2022)[39] the repair success rate was reported 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 previous protocol version) to 90% for all-inside meniscal repair. For the full report please refer to appendix 22.10.

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 meniscal allograft transplantation (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 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).

12 ADVERSE EVENTS AND DEVICE DEFICIENCIES

12.1 Definitions (ISO 14155)

The categories of adverse events are shown in table 12.1-1. The definitions for each of these categories are given in the subsequent sections.

Table 12.1-1 Categories of Adverse Event

	NOT DEVICE-RELATED	**DEVICE- OR PROCEDURE- RELATED**	
Non-Serious	**Adverse Event (AE)**	**Adverse Device Effect (ADE)**	
Serious	**Serious Adverse Event (SAE)**	**Serious Adverse Device Effect (SADE) (See 12.1.3)**	
		Anticipated	**Unanticipated**
		Anticipated Serious Adverse Device Effect (ASADE)	**Unanticipated Serious Adverse Device Effect (USADE)**

12.1.1 Adverse Event

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

Note 1: This definition includes events related to the investigational medical device or the comparator.

Note 2: This definition includes events related to the procedures involved.

Note 3: For users or other persons, this definition is restricted to events related to the use of investigational medical devices.

AE is used both to refer to AE which do not meet the definitions of Adverse Device Effects or Serious Adverse Events and as an umbrella term referring to adverse events of all classifications.

An AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease. For reporting purposes, emphasis is placed first and foremost on whether or not the event constitutes an untoward medical occurrence.

12.1.2 Adverse Device Effect

An Adverse Device Effect (ADE) is an adverse event related to the use of an investigational medical device.

Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation or operation, or any malfunction of the investigational medical device.

Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Note 3: This includes "comparator" if the comparator is a medical device.

Not Related - An AE is considered to be not related to the use of an IP or the procedure when the effect is DEFINITELY UNRELATED to have any relationship to the use of the IP or the procedure;

Related – An AE is considered to be related to the use of an IP or the procedure when there is a POSSIBLE, or DEFINITE relationship between the AE and the use of the IP or the procedure.

An ADE is further categorized depending on whether the criteria in section 12.1.3 and 12.1.4 are met.

12.1.3 Related Serious Adverse Events and Serious Adverse Device Effects

An AE or ADE is considered a **Serious** Adverse Event (SAE) or **Serious** Adverse Device Effects (SADE) if, it led to any of the following:

a) death,
b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:
    1) a life-threatening illness or injury, or
    2) a permanent impairment of a body structure or a body function including chronic diseases, or
    3) in-patient or prolonged hospitalization, or
    4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

c) foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment

Note 1: Planned hospitalization for a pre-existing condition, or a procedure required by the study protocol, without serious deterioration in health, is not considered a serious adverse event.

12.1.4 Anticipated/Unanticipated Serious Adverse Device Effect

An Unanticipated Serious Adverse Device Effect (USADE) is a serious ADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk assessment.

Note 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment (see Section 4.4 for details).

12.1.5 Severity

The severity of every AE will be assessed by the PI or medically qualified site staff to whom the responsibility has been delegated and documented on the delegation of authority log. AE should be classified as mild, moderate, or severe, regardless of whether or not the AE is considered to be serious or non-serious. The classification should be based on the following definitions:

Mild - An event is mild if the subject is aware of, but can easily tolerate the sign or symptom;

Moderate - An event is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities;

Severe - An event is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

12.1.6 Device Deficiency

A Device Deficiency (DD) is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. DD includes malfunctions, use errors and inadequate labeling.

Note 1: DD includes malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labelling.

Note 2: This definition includes device deficiencies related to the investigational medical device or the comparator.

Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence

a) if either suitable action had not been taken,
b) if intervention had not been made, or
c) if circumstances had been less fortunate,

are considered Device Deficiencies with potential to cause SADE and shall be reported as specified in section 12.3.

12.2 AE Coding Dictionary

Coding for this study will be done per International Medical Device Regulators Forum (IMDRF) AE Terminology Annex E – Clinical signs, symptoms and conditions.

12.3 Reporting procedures

AE of any kind and DD will be recorded in the applicable CRF and source notes to include the date of occurrence, treatment and the details resolution. The Investigator will evaluate all AE for relationship to the device and procedure, seriousness, and severity (if applicable). DD will be evaluated for

potential to cause SADE. The following timescales should be followed for the AE/DD information to be submitted/entered into the CRF and reported to the Sponsor or designee (see figure 12.2-1):

- ADE and DD – without unreasonable delay
- SAE, SADE and DD with potential to cause SADE – immediately (i.e. within 24 hours of the investigator being informed about the event)
- All other events – according to usual timescales

In addition to inputting SAE and SADE information within 24 hours of being aware of the event, the investigator should email Clinical.safety@Smith-nephew.com to alert the safety representative of the events existence and to clarify details if necessary.

For ADE and DD, date of occurrence, and details of the product/procedure related to the event will be included and where applicable, pictures taken of the device. The deficient product should be retained for return to S+N unless it is contaminated. Updates to submitted information will be recorded in the CRF according to the timescales above.

All adverse events will be reviewed by a medically qualified person appointed by the Sponsor to determine which, if any, meet criteria for expedited reporting to the regulatory authorities.

The investigator will inform the regulatory agency and IRB/IEC of adverse events as per the requirements listed below: -

Unanticipated SADE's and DD's that could have led to SADE will be reported to IEC/IRB and regulatory authorities within 10 working days.

All other events will be reported on a periodic/annual basis.

Depending on the nature of the adverse event, S+N may request copies of the subject's medical records, Imaging, Operative notes, as well as results of any relevant laboratory tests performed or other documentation related to the AE. If the subject was hospitalized, a copy of the discharge summary may be requested by S+N and should be forwarded as soon as it becomes available. In

certain cases, S+N also may request a letter from the Investigator that summarizes the events related to the case. Refer to the ISF Sponsor Contact Information Sheet to report SAE, unanticipated SADE, anticipated SADE, and DD.

Figure 12.3-1: Evaluation and Reporting of AE

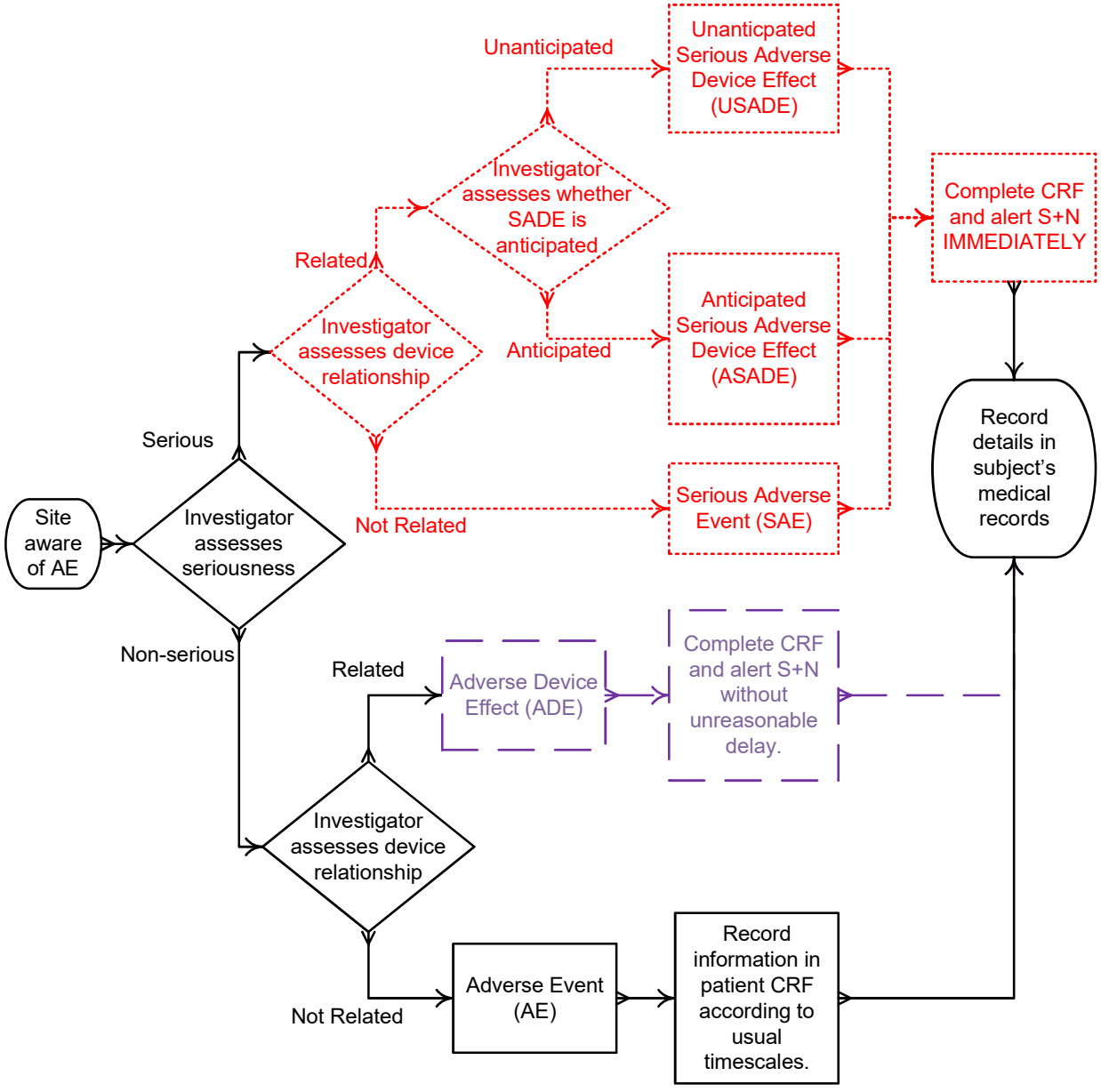
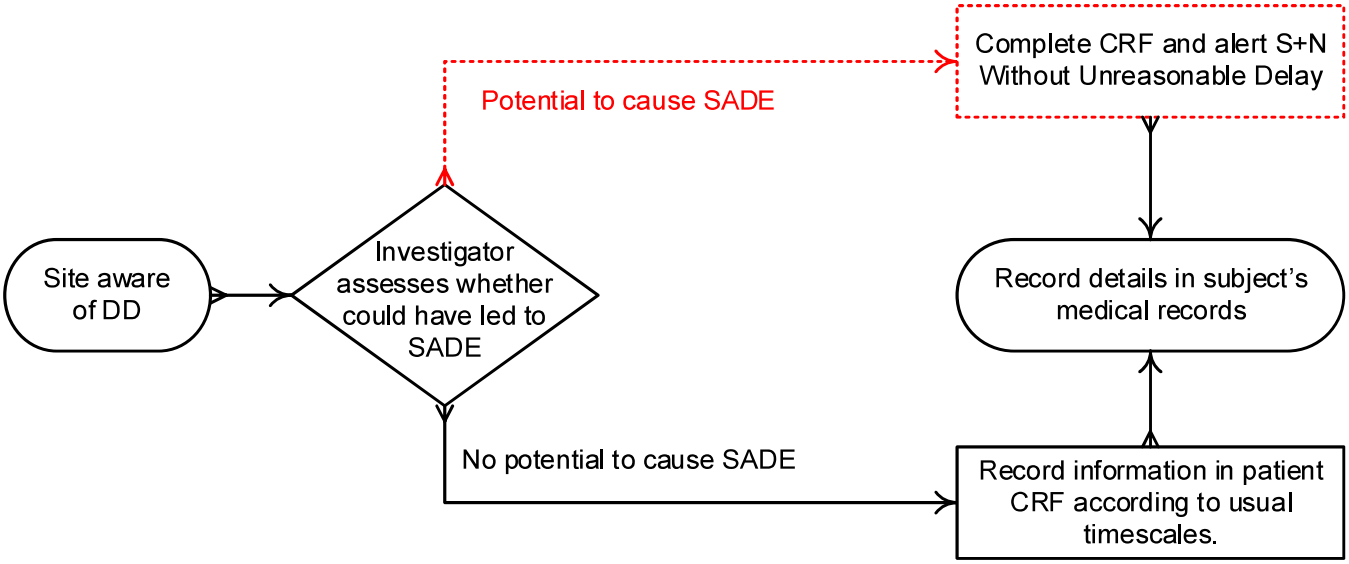


Figure 12.3-2: Evaluation and Reporting of Device Deficiencies



12.4 Unblinding of Investigational Product

Not applicable.

12.5 Follow-up of Subjects with Adverse Events

For subjects who are experiencing ongoing unresolved AE at the time of their study completion or early discontinuation from the study, it is recommended that the Investigator schedule an appropriate follow-up visit to determine the outcome of the event.

Any additional data must be documented and available to the Sponsor who will determine whether the data need to be documented in the CRF/Clinical Study Report.

12.5.1 Ongoing Adverse Events at Study Discontinuation

Adverse events which are **related** to a study procedure or S+N IP and are ongoing at the end of subject's participation: The event should be followed until it is either resolved or until the event has become chronic and is not expected to further improve based on Investigator's review of the event.

Adverse events which are **not related** to a study procedure or S+N IP and are ongoing at the end of subject's participation should be followed for 30 days after discontinuation or if the AE is resolved, whichever is sooner.

At the time of data analysis (e.g., interim or final), an evaluation of ongoing events should take place and be listed as ongoing in the safety table.

13 INVESTIGATOR OBLIGATIONS

The Principal Investigator will comply with the commitments outlined in the in the Statement of Investigator, provided by the Sponsor, and with Good Clinical Practice (GCP), and all applicable regulatory requirements as outlined in Appendix 22.8 of this protocol. Sub-Investigators, who are individual member of the investigation site team designated and supervised by the Principal Investigator at an investigation site to perform clinical investigation-related procedures or to make important clinical investigation-related and medical treatment decisions, may have responsibilities delegated to them by the Principal Investigator. However, the Principal Investigator retains overall responsibility for the clinical investigation at the site.

In addition, the PI will ensure that the Financial Disclosure Statements will be completed by the PI and the Sub-Investigator upon entry into the study and as any changes that affect their financial disclosure status occur during the course of the study and up to one year after study completion.

The Coordinating Investigator appointed by the Sponsor will assist in coordinating the work in the multicentre clinical investigation.

14 SPONSOR AND MONITOR RESPONSIBILITIES

The Sponsor will designate a monitor to conduct the appropriate site visits at the appropriate intervals. The clinical investigation will be monitored to ensure that: the rights and wellbeing of the subjects are protected; the reported data are accurate, complete, and verifiable from the source documents; and the study is conducted in compliance with the currently approved protocol and amendment(s), if applicable, with GCP regulations, and with applicable regulatory requirements.

Detailed monitoring requirements will be documented in the Clinical Monitoring Plan for this study.

14.1 Site Qualification Visit

A site qualification visit may be performed by the Sponsor prior to the execution of a clinical agreement to ensure that all Investigators have the appropriate training, staff, facilities, and resources to adequately conduct the study.

14.2 Site Initiation Visit

A site initiation visit to provide training on the specifics of the study, site obligations and expectations of study conduct will be performed by the Sponsor or qualified person designated by the Sponsor following the execution of the CTA and documented IRB/IEC approval.

14.3 Interim Monitoring Visit

Regular interim monitoring visits will be performed by the Sponsor or qualified person designated by the Sponsor.

14.4 Sponsor Audits and Regulatory Inspection

Quality Assurance auditors, whether an employee of the Sponsor or its designee, may evaluate study conduct at the study sites. These parties must have access to any and all study reports and source documentation, regardless of location and format.

14.5 Close-Out Visit

A study close-out visit will be performed by the Sponsor or designee to retrieve and account for all remaining clinical data and to resolve outstanding queries. During study close-out, the monitor will review investigator files to ensure required documents and records are on file, confirm the disposition of any other ancillary items used for the study, and review regulatory requirements regarding records retention and IRB/IEC reporting requirements. When no subjects have been included, a remote close-out visit may be conducted.

15 PROTOCOL DEVIATIONS

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. Protocol deviations reported by the Investigator or discovered during monitoring visits will be compiled in a Protocol / GCP Deviation Log (FRM-402046 Protocol/GCP Deviation Log). Significant and/or recurrent protocol/GCP deviations will be documented on a protocol deviation form (FRM-400347 Protocol/GCP Deviation) including identified root cause and, as necessary, appropriate corrective and preventive actions will be put in place and signed off by the study personnel. If it is deemed necessary full clinical Corrective and Preventive Action (CAPA) will be initiated.

It is not allowed to use waivers to allow planned deviation of the study protocol.

An investigator may be early terminated from the study upon identification of serious protocol deviations whereby there are concerns for patient safety or data quality (especially those not reported to the sponsor by the site). Early termination may also occur if there are repeated protocol deviations which have previously been addressed via corrective and preventative actions thereby suggesting an issue with site compliance.

Protocol deviations requiring reporting to the IRB/IEC should be done so in the timeframe stipulated by the IRB/IEC.

16 PROTOCOL AMENDMENTS

Amendments should be made only in necessary cases once the study has started. Protocol amendments must be approved by the protocol signatories prior to submission to the IRB/IEC. Protocol amendments need to be approved by the IRB/IEC and Regulatory Authority(ies), according to the applicable requirements prior to implementation at the site.

17 CONFIDENTIALITY OF THE STUDY

The confidentiality of this study and associated documents is governed by the terms of the Clinical Trial Agreement (CTA).

18 STATEMENTS OF COMPLIANCE

This clinical study will be performed in compliance with the ethical principles of the Declaration of Helsinki; and ISO 14155: Clinical investigation of medical devices – Good Clinical Practice.

This clinical study will not commence until the required approval/favorable opinion from the IRB/IEC or regulatory authority has been obtained. Any additional requirements imposed by the IRB/IEC or regulatory authority will be followed.

Public/Products Liability Insurance has been purchased by Smith & Nephew plc. Worldwide and incorporates coverage for personal injury in respect of clinical studies. The Sponsor agrees to operate in good faith and in accordance with ABHI (Association of British Healthcare Industries) guidelines regarding compensation for injury arising in the course of clinical studies.

The clinical study is financed by the sponsor. All financial arrangements between the sponsor and investigation sites/investigators are documented separate clinical trial agreements.

19 END OF STUDY

The end of study is defined as last subject last visit. Should circumstances arise which require the termination of the entire study prior to its planned completion (e.g., safety concerns) or circumstances arise which mean the end of the participation of an individual site (e.g., departure of Investigator, non-compliance), then this will be undertaken according to the SOPs of the Sponsor. The requirement for subject follow up in these instances will be considered as part of these processes.

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to other parties (Investigator, IRB/IEC, Sponsor and regulatory authorities). If the study is prematurely terminated or suspended, the Investigator will promptly inform the IRB/IEC and the study sites, and will provide the reason(s) for the termination or suspension. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance with study protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

The study may resume once concerns about safety, study protocol compliance, and data quality are addressed and satisfy the Sponsor and IRB/IEC.

A specific study site in this multi-center study may also warrant termination under the following conditions:

- Non-compliance to GCP or protocol
- Failure to enroll subjects
- Major protocol deviations
- Inaccurate or incomplete data
- Unsafe or unethical practices
- Safety or performance considerations
- Investigator involuntarily discontinues participation in study

20 PUBLICATION POLICY

20.1 Publication of Study Data

The study will be registered in a publicly accessible database and the results will be made available within that database. The preparation and submission for publication of manuscripts containing the study results shall be in accordance with a process determined by the Clinical Trial Agreements between the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to the Health Insurance Portability and Accountability Act of 1996.

20.2 Data Sharing

Smith+Nephew is committed to upholding the highest ethical and legal standards involved in conducting clinical trials. Smith+Nephew, therefore, supports the data sharing requirements of The International Committee of Medical Journal Editors (ICMJE) published on the 6th June 2017. In

accordance, Smith+Nephew will consider requests to share individual (de-identified) participant data that underlie the results of any interventional clinical trial, as presented from the 1st July 2018 within an ICMJE associated journal. Requests made by researchers who provide a methodologically sound proposal will be considered. Requests may include data that underlie results presented in text, tables, figures, and appendices, together with data dictionaries. Availability of these data will begin nine months and end 36 months after article publication. Data supplied may only be used by the researcher(s) named in the approved research proposal for the purposes of achieving the aims of the analyses specified therein. All proposals should be directed to datasharing.gcs@smith-nephew.com. To gain access, data requestors will need to sign a data access agreement.

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22 APPENDICES

22.1 Protocol Amendment 1

22.1.1 General Purpose

This protocol amendment has been completed to document the following changes:

1. Clarification and update to the Inclusion/Exclusion criteria for the MAT indication.
2. Removal of the date of ISO 14155 throughout the document.
3. Additional text specifying the FAST-FIX FLEX device registration approvals to fulfil the request made by the Australian Ethics Committee.

22.1.2 Rationale

Rationale 1: The majority of patients who require a meniscal allograft transplantation should have previously had a meniscectomy prior to the procedure. Therefore, minor clarifications were made to the specific MAT inclusion criteria and to number 9 of the exclusion criteria to allow prior knee surgery for the MAT indication. The changes were made before recruiting any patients for this clinical indication.

Rationale 2: Reference to date of ISO 14155 removed throughout the text to align with the latest revision of the protocol template, D.1.

Rationale 3: Additional text specifying the FAST-FIX FLEX device registration approvals was added to the product section to address the request from the Australian Ethics Committee.

22.1.3 Effect on Study Status

Not applicable; this amendment is to be in effect and implemented prior to subject enrollment to the MAT indication.

22.1.4 Details

Section	Current Text 28/Apr/2021 Version 1	Revised Text 23/Nov/2021 Version 2
Footer	TMP-CD-05-01 Clinical Protocol - Device – Revision D; SOP-CD-05 Clinical Protocol	TMP-CD-05-01 Clinical Protocol - Device – Revision D.1; SOP-CD-05 Clinical Protocol
2 Synopsis Inclusion Criteria (rationale 1)	Subject requires a MAT for symptomatic meniscal insufficiency (load-related pain and swelling in the compartment undergoing meniscectomy) for which conservative treatment has failed.	Subject requires a MAT for symptomatic meniscal insufficiency (load-related pain and swelling in the compartment post meniscectomy) for which conservative treatment has failed.
2 Synopsis Exclusion Criteria (rationale 1)	9. History of ipsilateral knee surgery, septic joint, or fracture.	9. History of ipsilateral knee surgery, septic joint, or fracture (excluding MAT indication).
Throughout the protocol (rationale 2)	• ISO/DIS 14155:2011 • 14155:2020	DIS and date removed.
6.3.1 Labelling of Investigational Product (rationale 3)	The FAST-FIX FLEX Meniscal Repair System has received 510(k) clearance in the United States.	The FAST-FIX FLEX Meniscal Repair System has received 510(k) clearance in the United States, CE marking in Europe, Australian Register of Therapeutic Goods (ARTG) approval in Australia and is commercially available on the market.
7.2 Inclusion Criteria (rationale 1)	7. Subject requires a MAT for symptomatic meniscal insufficiency (load-related pain and swelling in the compartment undergoing meniscectomy) for which conservative treatment has failed.	7. Subject requires a MAT for symptomatic meniscal insufficiency (load-related pain and swelling in the compartment post meniscectomy) for which conservative treatment has failed.
7.3 Exclusion Criteria (rationale 1)	9. Subjects with a history of ipsilateral knee surgery, septic joint, or fracture.	9. Subjects with a history of ipsilateral knee surgery, septic joint, or fracture (excluding MAT indication).

22.1.5 Approval/Notification

The changes and recruitment of subjects to the MAT indication will only be implemented following IRB/IEC approval.

22.2 Protocol Amendment 2

22.2.1 General Purpose

This protocol amendment has been completed to document the following changes:

1. Refinement of the Inclusion/Exclusion criteria for the MR and MAT indications.
2. Addition of the FAST-FIX FLEX slim packs (SKUs: 72205676 and 72205677).
3. Removed accountability procedures for the Investigational Product which was included in error.
4. Updated the 3 months follow-up visit window to 3 months +30 days rather than +/- 14 days.
5. Reduction of the MR and MAT sample size.
6. Addition of the informed consent / assent and screening process for minors
7. General correction of typographical and formatting errors, administrative changes
8. Added new sections and information required in S+N protocols
9. Remove Germany as a participating country
10. Increased study duration and enrollment timelines
11. Updated the 6 months follow-up visit window to 6 months +/- 45 days rather than +/- 30 days.
12. Updated the 12 months follow-up visit window to 12 months +/- 75 days rather than +/- 60 days.

22.2.2 Rationale

Rationale 1: Closer alignment of the Inclusion/Exclusion criteria for the MR and MAT indications with the IFU and improve generalizability. Site PIs also provided feedback and recommendations on this

refinement based on screen fail information and their patient population. The MR and MAT Inclusion/Exclusion criteria has been separated for ease of reading following site feedback.

Rationale 2: The slim packs may also be used by investigators in this study. These are a more environmentally friendly version of the FAST-FIX FLEX Meniscal Repair System.

Rationale 3: No accountability procedures are required for this post-market clinical follow-up study (as per S+N SOPs).

Rationale 4: The lifetime of the device is 12 weeks (i.e. 3 months) and therefore the 3 months follow-up visit window has been adjusted to ensure that data is captured at a minimum of 3 months. There is greater flexibility beyond 3 months (+30 days) to remove the possibility of data being captured prior to 3 months (+/- 14 days).

Rationale 5: A new systematic literature review has provided evidence that the device has a greater success rate than originally included in the protocol, therefore the sample size calculation has been adjusted for the MR indication, thus reducing the sample size. The MAT indication had no formal sample size calculation and S+N are engaging in additional retrospective clinical activities to provide evidence for the MAT indication outside of this PMCF study. S+N Research and Development have also confirmed that data collected for the MR indication can be used to support use of the device in the niche MAT indication, given that the device's success and clinical performance does not differ by indication (see Appendix 22.11). Therefore, the sample size for the MAT indication has been reduced and the study will aim to recruit a minimum of 9 and maximum of 15 MAT subjects.

Rationale 6: To provide guidance regarding the informed consent / assent and screening procedures for subjects aged 16 and 17 years of age given this addition to the Inclusion criteria, and ensure compliance with the relevant regulations.

Rationale 7: Improve readability and understanding of the protocol, remove inconsistencies and ambiguity, changes in staff, update version numbers and dates based on new document version.

Rationale 8: A new version of the S+N template protocol has been released, therefore some minor changes have been made to ensure compliance with the latest protocol template (TMP-800052, Revision 4).

Rationale 9: Germany can no longer participate due to competent authority requirements and consideration for the estimated study end date.

Rationale 10: Recruitment has been slower than anticipated, particularly due to the restricted Inclusion/Exclusion criteria. As such, an additional 12 months for study enrollment and overall duration of the study has been included.

Rationale 11 and 12: To improve follow-up visit window compliance and completion of these visits.

22.2.3 Effect on Study Status

- There is no anticipated impact on the data already collected from subjects enrolled in this study prior to this amendment, including how their data will be analyzed.
- The reconsent of enrolled subjects (who have not completed the study) will be considered and obtained where deemed appropriate, however it is not anticipated that reconsent will be required based on this amendment.
- Any previously enrolled subjects that are due to attend the 3-month, 6-month or 12-month follow-up visits will attend as per the updated visit windows, following implementation of this amendment.
- The Case Report Form (CRF) will be updated for new subjects enrolled in the study following implementation of and in accordance with this protocol amendment. For previously enrolled subjects, data collected following implementation of this protocol amendment will be

captured using the updated CRF and data already collected will remain on the superseded CRF version.

- At the time of this amendment, the approximate number of active subjects is 35, 3 subjects are withdrawn and the number of completed subjects is 5.

22.2.4 Details

Section	Current Text 23/Nov/2021 Version 2	Revised Text 05/May/2023 Version 3
Header (Rationale 7)	A Prospective, Multi-center Clinical Study to Evaluate the Safety and Performance of the FAST-FIX FLEX System for Meniscal Repairs (MR) and Meniscal Allograft Transplantations (MAT) Study Number: FAST-FIX FLEX.2020.09 Version: 1.0, 28/Apr/2021	A Prospective, Multi-center Clinical Study to Evaluate the Safety and Performance of the FAST-FIX FLEX System for Meniscal Repairs (MR) and Meniscal Allograft Transplantations (MAT) Study Number: FAST-FIX FLEX.2020.09 Version: 3.0, 05/May/2023
Footer (Rationale 7)	CONFIDENTIAL AND PROPRIETARY This document contains information that is confidential and proprietary to Smith & Nephew PLC and Smith & Nephew, Inc. and is intended for use only by Smith & Nephew and its manufacturer. It shall not be reproduced or copied in whole or in part, nor shall the contents be disclosed by any means without prior written permission from Smith & Nephew, nor shall anyone make any use of it that is contrary to the expressed or implied wishes of Smith & Nephew. TMP-CD-05-01 – Clinical Protocol-Device – Revision D; SOP-CD-05 Clinical Protocols	CONFIDENTIAL AND PROPRIETARY TMP-800052 Clinical Protocol - Device – Revision 4; PRO-201725 Clinical Protocols

Front Page (Rationale 8)	N/A	Summary of Revision History Version 2.0, 23 Nov 2021 Version 1.0, 28 Apr 2021
1.1 (Rationale 7)	2.0, dated 23/Nov/2021 Section 22.7	3.0, dated 05/May/2023 Section 22.8
1.2 (Rationale 7)	2.0, dated 23/Nov/2021 A Prospective, Multi-center Clinical Study….	3.0, dated 05/May/2023 A Prospective, Multi-center Clinical Study….
1.3 (Rationale 7)	Stephan Mangin Director of GCS Sports Medicine and ENT Head of Global Clinical Strategy Alan Rossington Senior Director, Global Data Analytics (Head of Global Data Analytics)	Lori Fontaine VP, Global Clinical Strategy - Orthopaedics, Sports Med & ENT (Global Clinical Strategy Franchise Head or Representative) Jay Jantz Senior Director, Global Data Analytics (Head of Global Data Analytics) Sam Timson Senior Clinical Compliance and Training Specialist (Clinical Compliance and Training/Clinical Quality Assurance)
2 (Rationale 8)	N/A	Sponsor and Funding Source Smith & Nephew Inc, 1450 E. Brooks Road, Memphis, Tennessee 38116, USA
2 (Rationale 5)	Sample Size: A total of 130 subjects will be enrolled into the study: • 97 MR subjects	Sample Size: A minimum of 62 and maximum of 68 subjects will be enrolled into the study: • 53 MR subjects

• 33 MAT subjects The sample size for this study is precision-based and not based on statistical power considerations. Thus, no formal statistical hypothesis is formulated. The sample size for this study is determined based on the feasibility of recruitment, enrolment and follow-up considerations. The study's primary endpoint upon which sample size is determined is meniscal repair success rate in the study device at 12 months. The publication upon which this is based, is the systematic review entitled: "Prognostic factors for all-inside meniscal repair. An 87-case series" authored by Laurendon et al. (2017) the repair success rate was reported to be 85% for all-inside meniscal repair. Assuming an overall success rate of at least 85%, 82 subjects are sufficient to obtain at least 99% probability of estimating the two-sided 95% confidence interval around the success rate to within 10%. Additionally, secondary endpoints in this study assess success rate, meniscus healing and clinical performance of PROs for meniscal allograft transplantation (MAT). To satisfy European Medical Device Regulation (EU MDR) requirements, 30 subjects will be recruited to provide sufficient evidence on this indication.	• A minimum of 9 and maximum of 15 MAT subjects The sample size for this study is precision-based and not based on statistical power considerations. Thus, no formal statistical hypothesis is formulated. The sample size for this study is determined based on the feasibility of recruitment, enrolment and follow-up considerations. The study's primary endpoint upon which sample size is determined is meniscal repair success rate in the study device at 12 months. The publication upon which this is based, is the systematic literature review entitled: "Clinical performance of FAST-FIX family" authored by Paul Souter (2022) the repair success rate was reported 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 previous protocol version) to 90% for all-inside meniscal repair. For the full report please refer to appendix 22.10. 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 MR subjects will be enrolled. Additionally, secondary endpoints in this study assess success rate, meniscus healing and clinical performance of PROs for meniscal allograft transplantation (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

	Assuming a 15% drop-out rate at the end of 12 months, 130 subjects will be enrolled in order to complete 82 evaluable subjects for MR and 30 evaluable subjects for MAT.	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 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).
2 (Rationale 9)	Number of Study Sites: Up to 6 sites	Number of Study Sites: Up to 5 sites
2 (Rationale 9)	Targeted Global Regions: United States, United Kingdom, Germany, France and Australia	Targeted Global Regions: United States, United Kingdom, France and Australia
2 (Rationale 1 and 7)	Inclusion Criteria: 1. Subject provides written informed consent for study participation using an independent ethical committee (IEC) / institutional review board (IRB) approved consent form; 2. Subject is between eighteen (18) and seventy (70) years of age, inclusive at the time of screening; 3. Subject is willing and able to participate in required follow-up visits and is able to complete study activities; 4. Subject requires a meniscal repair or meniscal allograft transplantation;	Meniscal Repair Inclusion Criteria: 1. Subject provides written informed consent for study participation using an independent ethical committee (IEC) / institutional review board (IRB) approved consent form; 2. Subject is between sixteen (16) and seventy (70) years of age, inclusive at the time of screening; 3. Subject is willing and able to participate in required follow-up visits and is able to complete study activities; 4. Subject requires a meniscal repair; 5. Subject is suitable to participate in the study in the opinion of the Investigator. 6. Subject requires a meniscus repair concerning the red-red or red-white zones for acute or chronic 1-, 2- or 3-

	5. Subject is suitable to participate in the study in the opinion of the Investigator. Meniscal Repair ONLY: 1. 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. Meniscal Allograft Transplantation ONLY: 1. Subject requires a MAT for symptomatic meniscal insufficiency (load-related pain and swelling in the compartment post meniscectomy) for which conservative treatment has failed.	segment lesions, with or without associated anterior cruciate ligament (ACL) reconstruction. Meniscal Allograft Transplantation Inclusion Criteria: 1. Subject provides written informed consent for study participation using an independent ethical committee (IEC) / institutional review board (IRB) approved consent form; 2. Subject is between sixteen (16) and seventy (70) years of age, inclusive at the time of screening; 3. Subject is willing and able to participate in required follow-up visits and is able to complete study activities; 4. Subject requires a meniscal allograft transplantation; 5. Subject is suitable to participate in the study in the opinion of the Investigator. 6. 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).
2 (Rationale 1, 7 and 8)	Exclusion Criteria: 1. 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;	Meniscal Repair Exclusion Criteria: 1. 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;

	2. Participation in the treatment period of another clinical trial within thirty (30) days of operative visit, or during the study; 3. Women who are pregnant, nursing, or of child-bearing potential whoare not utilizing highly effective birth control measures; 4. Any subject that meets the definition of a Vulnerable Subject per ISO 14155 Section 3.44; 5. Subjects with a history of poor compliance with medical treatment, physical therapy (PT)/rehabilitation, or clinical study participation; 6. Patients with irreparable meniscal tears (i.e. grade 3 outerbridge osteoarthritis or greater, serious defects, multiple tears); 7. Patients with multi-ligament tears (i.e. ACL tear is not associated with lateral collateral ligament (LCL) or medial collateral ligament (MCL) tears); 8. Performance of a significant concomitant procedure, specifically a cartilage repair or restoration (excluding ACL reconstruction or repair) intended as a therapeutic intervention on the study knee; 9. History of ipsilateral knee surgery, septic joint, or fracture (excluding MAT indication); 10.Pathological conditions in the soft tissue that would prevent secure fixation of the device; 11.Physical conditions which would eliminate, or tend to eliminate, adequate anchor support or retard healing;	2. Enrolled in the treatment period of another clinical trial within thirty (30) days of operative visit, or during the study; 3. Women who are pregnant or nursing; 4. 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); 5. Subjects with a history of poor compliance with medical treatment, physical therapy (PT)/rehabilitation, or clinical study participation; 6. Patients with irreparable meniscal tears (i.e. multiple tears); 7. Subjects with full thickness cartilage defects greater than 10mm in diameter and/or serious defects; 8. Patients 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); 9. 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; 10. History of ipsilateral knee surgery, septic joint, or fracture; 11. Pathological conditions in the soft tissue that would prevent secure fixation of the device;

	12.The presence of infection; 13.Conditions which would limit the patient's ability or willingness to restrict activities or follow directions during the healing period; 14.Malalignment: genu varus and genu valgus angles greater than 5° with respect to the normal axis to indicate malalignment; 15.Patients who had an Ahlback grade greater than II; 16.Patients with a body mass index larger than 30;	12. Physical conditions which would eliminate, or tend to eliminate, adequate anchor support or retard healing; 13. The presence of infection; 14. Conditions which would limit the patient's ability or willingness to restrict activities or follow directions during the healing period; 15. Malalignment: genu varus and genu valgus angles greater than 5° as evaluated by the patient's physician as per their standard of care; 16. Patients who have an Ahlback grade greater than II; 17. Patients with a body mass index larger than 35; 18. Subjects with a medical or physical condition that, in the opinion of the Investigator, would preclude safe subject participation in the study. Meniscal Allograft Transplantation Exclusion Criteria: 1. 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; 2. Enrolled in the treatment period of another clinical trial within thirty (30) days of operative visit, or during the study; 3. Women who are pregnant or nursing; 4. 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);

	5. Subjects with a history of poor compliance with medical treatment, physical therapy (PT)/rehabilitation, or clinical study participation; 6. Patients 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); 7. 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; 8. History of ipsilateral knee surgery, septic joint, or fracture (excluding MAT indication); 9. Pathological conditions in the soft tissue that would prevent secure fixation of the device; 10. Physical conditions which would eliminate, or tend to eliminate, adequate anchor support or retard healing; 11. The presence of infection; 12. Conditions which would limit the patient's ability or willingness to restrict activities or follow directions during the healing period; 13. Malalignment: genu varus and genu valgus angles greater than 5° as evaluated by the patient's physician as per their standard of care; 14. Patients who have an Ahlback grade greater than II; 15. Patients with a body mass index larger than 35;

		16. Subjects with a medical or physical condition that, in the opinion of the Investigator, would preclude safe subject participation in the study.
2 (Rationale 10)	Study Duration: It is anticipated to take 30 months (16 months for subject enrolment and 14 months follow-up period).	Study Duration: It is anticipated to take 39 months (21 months for subject enrolment and 14 months follow-up period).
2 (Rationale 4, 11, 12)	Study Schedule: Visit 4 - 3 Months (± 14 days) Visit 5 - 6 Months (± 30 days) Visit 6 - 12 Months (± 60 days)	Study Schedule: Visit 4 - 3 Months (+ 30 days) Visit 5 - 6 Months (± 45 days) Visit 6 - 12 Months (± 75 days)
3.4 (Rationale 8)	List of Abbreviations and Definitions	List of Abbreviations/Acronyms and Definitions
3.4 (Rationale 7)	ACL Anterior Cruciate Ligament ADE Adverse Device Effect(s) AE Adverse Event(s) BMI Body Mass Index BSI British Standards Institute CE Conformité Européene CER Clinical Evaluation Report CoCr Cobalt Chrome CRF Case Report Form(s) CRO Contract Research Organization CV Curriculum Vitae	ACL Anterior Cruciate Ligament ADE Adverse Device Effect(s) AE Adverse Event(s) ALL Anterolateral Ligament BMI Body Mass Index CE Conformité Européene CRF Case Report Form(s) CV Curriculum Vitae DD Device Deficiency(ies) EQ-5D-5L EuroQol 5 Dimension 5 Level FAS Full Analysis Set Population

DD Device Deficiency(ies)
EQ-5D-5L EuroQol 5 Dimension 5 Level
FAS Full Analysis Set Population
FDA Food and Drug Administration
FU Follow-Up
GCP Good Clinical Practice
HIPAA Health Information Portability Accountability Act
IB Investigator's Brochure
ICH International Conference on Harmonisation
IEC Independent Ethics Committee
IFU Instructions for Use
IKDC International Knee and Documentation Committee
Interventional study A type of clinical study in which participants are assigned to groups that receive one or more intervention/treatment so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes.
IP Investigational Product
IRB Institutional Review Board
ISF Investigator Site File
ITT Intention to Treat population
LCL Lateral Collateral Ligament
LOCF Last Observation Carried Forward
MCL Medial Collateral Ligament
MedDRA Medical Dictionary for Regulatory Activities
MAT Meniscal Allograft Transplantation
MR Meniscal Repair

FDA Food and Drug Administration
FU Follow-Up
GCP Good Clinical Practice
HIPAA Health Information Portability Accountability Act
ICH International Conference on Harmonisation
IEC Independent Ethics Committee
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Interventional study A type of clinical study in which participants are assigned to groups that receive one or more intervention/treatment so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes.
IP Investigational Product
IRB Institutional Review Board
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ITT Intention to Treat population
LCL Lateral Collateral Ligament
MAT Meniscal Allograft Transplantation
MCL Medial Collateral Ligament
MedDRA Medical Dictionary for Regulatory Activities
MR Meniscal Repair
NA or N/A Not Applicable
N (or n) Total Sample Size (or subgroup sample size)
PEEK Polyether Ether Ketone
PRO Patient-reported Outcome
PI Principal Investigator
PP Per-protocol Population
S+N Smith & Nephew Inc.

NA or N/A Not Applicable
N (or n) Total Sample Size (or subgroup sample size)
NHS National Health Service
Non-interventional study A clinical study in which the investigational medical device of interest is used in accordance with the approved instructions for use. Assigning a subject/patient to a particular therapeutic arm is not decided in advance by a protocol but falls within current practice; use of the device is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures are used, and epidemiological methods are used to analyze the collected data.
PEEK Polyether Ether Ketone
PRO Patient-reported Outcome
PI Principal Investigator
PMA Pre-Market Authorization
PP Per-protocol Population
RCT Randomized Controlled Trial
S+N Smith & Nephew Inc.
SADE Serious Adverse Device Effect(s)
SAE Serious Adverse Event(s)
SAF Safety population
SAP Statistical Analysis Plan
TGA Therapeutic Goods Administration
TKA Total Knee Arthroplasty
TÜV Technischer Überwachungsverein/ Technical Inspection Association
Tx Treatment

SADE Serious Adverse Device Effect(s)
SAE Serious Adverse Event(s)
SAF Safety population
SAP Statistical Analysis Plan
TGA Therapeutic Goods Administration
USADE Unanticipated Serious Adverse Device Effect(s)

	USADE Unanticipated Serious Adverse Device Effect(s)	
4.1 (Rationale 8)	Each knee has a pair of semi-lunar wedge-shaped menisci consisting of fibrocartilage, located both laterally and medially between the tibial plateaus and the femoral condyles.1,2 Because of their location, menisci are highly susceptible to injury, the medial meniscus being two to three times more likely to be injured than the lateral meniscus.2,3 The most common mechanism of injury is trauma during sports activity and often occurs in combination with anterior cruciate ligament (ACL) injury.4-6 Degenerative injury is also possible and may signify the onset of osteoarthritis (OA).7 Traumatic knee injuries more associated with radial and vertical tears, whereas degenerative tears are more associated with horizontal and complex tears.3 Tears along the outer edge of the meniscus (red zone) have superior healing potential as blood supply is more available in that area than in the inner two-thirds of the meniscus (red-white and white zones).2,8 Tears can be described as horizontal, vertical, or bucket handle. Horizontal cleavage tears are primarily degenerative in nature, but can result from trauma.9 The tear itself extends from the inner free margin of the meniscus into the intra-meniscal substance and is typically treated with partial meniscectomy.10 These tears typically extend into the avascular zone, vascularity is poor which can affect their ability to	Each knee has a pair of semi-lunar wedge-shaped menisci consisting of fibrocartilage, located both laterally and medially between the tibial plateaus and the femoral condyles.1,2 Because of their location, menisci are highly susceptible to injury, the medial meniscus being two to three times more likely to be injured than the lateral meniscus.2,3 The most common mechanism of injury is trauma during sports activity and often occurs in combination with anterior cruciate ligament (ACL) injury.4-6 Degenerative injury is also possible and may signify the onset of osteoarthritis (OA).7 Traumatic knee injuries more associated with radial and vertical tears, whereas degenerative tears are more associated with horizontal and complex tears.3 Tears along the outer edge of the meniscus (red zone) have superior healing potential as blood supply is more available in that area than in the inner two-thirds of the meniscus (red-white and white zones).2,8 Tears can be described as horizontal, vertical, or bucket handle. Horizontal cleavage tears are primarily degenerative in nature, but can result from trauma.9 The tear itself extends from the inner free margin of the meniscus into the intra-meniscal substance and is typically treated with partial meniscectomy.10 These tears typically extend into the avascular zone, vascularity is poor which can affect their ability to heal, and have been historically treated with partial meniscectomy.10

heal, and have been historically treated with partial meniscectomy.10

Historically, the removal of the meniscus, known as a total meniscectomy, was the approach for managing tears of the meniscus.11,12 However, a direct relationship between total meniscectomy and the worse clinical outcomes such as the development of early osteoarthritis, degenerative knee changes, and increased pressure loads compared to modern techniques, was observed, causing this treatment method to be largely abandoned.11,13-16 In a multi-center study cited by Beaufils et al.,17, 10-year osteoarthritis rates were 31% in patients treated with meniscectomy and 11% in patients treated with a meniscal repair or non-surgical treatment. At 20 years, the rates increased to 46% and 17%, respectively.17

Meniscal repair attempts to suture the meniscus back together, achieve meniscal healing, and avoid the effects of meniscectomy. This technique was introduced to preserve knee function and limit the accelerated degenerative changes associated with surgical techniques mentioned above.18,19 The most recently developed technique is the all-inside repair technique. The all-inside technique is typically used within the meniscal body and for posterior horn tears.20 In this approach, the surgeon uses posterior accessory portals and suture hooks to shuttle sutures through meniscal tears of the posterior horn that were not easily repairable using the other approaches. This

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approach can reduce surgical time,21 speed up patient recovery,11 does not require an open incision, and can prevent complications seen with external approaches.11, 22

In an attempt to optimize the healing capacity of the meniscus following meniscal repair, augmentation techniques have been developed and investigated to varying extents.23 Advances, such as the use of biologics such as platelet-rich plasma (PRP),24 biomaterial augmentation,25 stem cell-based therapy,26 and allograft transplantation.22 Meniscal allograft transplantation (MAT) can be performed in patients who present with affected compartment-specific pain and have pain and swelling secondary to chondral overload after a subtotal meniscectomy.22 The ideal patient age for this treatment is younger than 40 years, however no specific upper age limits have been identified.22 Meniscal allografts are available in various forms which include, frozen, lyophilized, fresh and cryopreserved. Frozen allografts are most commonly used. Allografts need to be sized appropriately the fit the patient's anatomy.

Currently, a plethora of devices for all-inside meniscal repair is being used. One highly coveted device is the FAST-FIX 360 Meniscal Repair System (Smith & Nephew, Andover, MA, U.S.A.); this device combines the advantages of the all-inside technique with strong biomechanical properties, 12, 13 and is a modification of the previous Smith & Nephew T-FIX device. This

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Currently, a plethora of devices for all-inside meniscal repair is being used. One highly coveted device is the FAST-FIX 360 Meniscal Repair System (Smith & Nephew, Andover, MA, U.S.A.); this device combines the advantages of the all-inside technique with strong biomechanical properties, 12, 13 and is a modification of the previous Smith & Nephew T-FIX device. This system can be used for vertical, horizontal, or oblique meniscal tears. FAST-FIX FLEX Meniscal Repair System is S+N's next-generation meniscal repair device that will improve on the FF-360 design and will encompass: 1) reliable deployment of implants, 2) minimal disruption to the

	system can be used for vertical, horizontal, or oblique meniscal tears. FAST-FIX FLEX Meniscal Repair System is S+N's next-generation meniscal repair device that will improve on the FF-360 design and will encompass: 1) reliable deployment of implants, 2) minimal disruption to the meniscus (via a smaller needle tip) and 3) more accessibility to tear locations (ability to bend the shaft to access a variety of locations, particularly the body and anterior horn). This all-inside meniscal repair device is intended to be used by healthcare professionals to repair meniscal tears and by anchoring the allograft to the capsular rim during allograft transplant procedures. The proposed study aims to evaluate the safety and performance of arthroscopic meniscal repairs and meniscus allograft transplants using the FAST-FIX Flex System.	meniscus (via a smaller needle tip) and 3) more accessibility to tear locations (ability to bend the shaft to access a variety of locations, particularly the body and anterior horn). This all-inside meniscal repair device is intended to be used by healthcare professionals to repair meniscal tears and by anchoring the allograft to the capsular rim during allograft transplant procedures. The proposed study aims to evaluate the safety and performance of arthroscopic meniscal repairs and meniscus allograft transplants using the FAST-FIX Flex System. A summary of known and potential risks and benefits to humans of the investigational product can be found in the Instructions For Use (IFU).
4.2 (Rationale 7)	Improvements in IKDC Subjective scores ranged from 21.8 to 28.1 points, with postoperative scores ranging from 79.6 to 82.6 points.84 Hirtler et al.[34]	Improvements in IKDC Subjective scores ranged from 21.8 to 28.1 points, with postoperative scores ranging from 79.6 to 82.6 points, Hirtler et al.[34]
5.4 (Rationale 7)	Claims The proposed Marketing Claims for this study include, but are not limited to, the following: • Meniscal tears repaired with FAST-FIX FLEX have a clinical success rate of 85% or higher (low re-op rate); • Meniscal tears repaired with FAST-FIX FLEX lead to a significant improvement in patient	Claims • Meniscal tears repaired with FAST-FIX FLEX lead to an improvement in patient symptom scores (PROs). • The FAST-FIX FLEX Meniscal Repair System provides an increased access to tear location and increased zone of repair.

	symptom scores (PROs). • The FAST-FIX FLEX Meniscal Repair System provides an increased access to tear location and increased zone of repair.	
6.1.1 (Rationale 2)	Two device configurations having different distal needle curvature are being offered and are each packaged with a Bend Tool and Slotted Cannula.	Four device configurations having different distal needle curvature are being offered. Two are with a Bend Tool and Slotted Cannula and two configurations are packaged without a Bend Tool and Slotted Cannula.
6.1.1 (Rationale 2)	The package contains the following: (1) Single-use delivery needle assembly preloaded with (2) PEEKOPTIMA™ (polyetheretherketone) implants pre-tied with #2-0 non-absorbable suture made of uncoated ultrahigh-molecular-weight polyethylene fiber braided with polypropylene monofilament fiber (1) Single-use FAST-FIX FLEX Slotted Delivery Cannula (1) Single-use Bend Tool	SKUs 72205324 and 72205325 contain the following: (1) Single-use delivery needle assembly preloaded with (2) PEEKOPTIMA™ (polyetheretherketone) implants pre-tied with #2-0 non-absorbable suture made of uncoated ultrahigh-molecular-weight polyethylene fiber braided with polypropylene monofilament fiber (1) Single-use FAST-FIX FLEX Slotted Delivery Cannula (1) Single-use Bend Tool SKUs 72205676 and 72205677 contain the following: (1) Single-use delivery needle assembly preloaded with (2) PEEKOPTIMA™ (polyetheretherketone) implants pre-tied with #2-0 non-absorbable suture made of uncoated ultrahigh-molecular-weight polyethylene fiber braided with polypropylene monofilament fiber 72205676 FAST-FIX FLEX CURVED INSERTER 72205677 FAST-FIX FLEX REVERSE CURVED INSERTER Inserter: The device user interface includes a handle and deployment knob used to deploy two PEEK implants in the joint space. The handle and deployment knob are

		designed such that they are easy to hold/grip onto, allow for single-handed deployment, and provide tactile feedback for implant deployment
6.2 (Rationale 7)	The devices are provided sterile and fully assembled to the OR.	The devices are provided sterile and fully assembled to the operating room.
6.3.1 (Rationale 7 and 8)	6.3.1 Labelling of Investigational Product The FAST-FIX FLEX Meniscal Repair System has received 510(k) clearance in the United States, CE marking in Europe, Australian Register of Therapeutic Goods (ARTG) approval in Australia and is commercially available on the market. All devices used in this study will be procured in standard commercial packaging, ordered via usual and customary Smith + Nephew procedures and managed per study site processes. •Lot Number •Catalogue Number •Unique Device Identifier •Package contents •Use by Date •Date of Manufacture •Distributor information: Smith + Nephew, Inc. •Manufacturer name and address •Product name and cartridge size •Customer service contact information •Product sale restriction	6.3.1 Labelling of Investigational Product The FAST-FIX FLEX Meniscal Repair System has received 510(k) clearance in the United States, CE marking in Europe, Australian Register of Therapeutic Goods (ARTG) approval in Australia and is commercially available on the market. All devices used in this study will be procured in standard commercial packaging, ordered via usual and customary Smith + Nephew procedures and managed per study site processes. The labels on FAST-FIX FLEX Meniscal Repair system contain the following information: •Lot Number •Catalogue Number •Unique Device Identifier •Package contents •Use by Date •Date of Manufacture •Distributor information: Smith + Nephew, Inc. •Manufacturer name and address •Product name •Customer service contact information •Product sale restriction

6.3.2 (Rationale 8)	N/A	6.3.2 Ancillary Products The labels on the ancillary products contain the following information: •Lot Number •Catalogue Number •Unique Device Identifier •Package contents •Use by Date •Date of Manufacture •Distributor information: Smith + Nephew, Inc. •Manufacturer name and address •Product name •Product sale restriction
6.4 (Rationale 3)	The investigational site will maintain an inventory of the Investigational Device. The Sponsor or its designee will provide a log(s) to facilitate Investigational Device inventory control. The log will contain details of receipt, use, returns etc. of Investigational Devices. All Investigational Device accountability logs must be retained in the Investigator Site File (ISF). These records must be available for inspection by the Sponsor, its designees, or by regulatory agencies at any time. The Sponsor will provide Investigational Device Management Instructions to the site detailing all additional forms that might need completion (e.g., confirmation of receipt) for Investigational Device control.	All devices used in this study will be procured in standard commercial packaging, ordered via usual and customary Smith + Nephew procedures and managed per study site processes. Therefore, product accountability / inventory will be managed as per study site's local processes and procedures.

	The study monitor will ensure that the procedures and records are in place for the appropriate reconciliation of all Investigational Devices. As part of monitoring, the study monitor will check that site personnel are following the proper procedures for accountability and completing all necessary documentation.	
6.5 (Rationale 8)	Surgical Technique	Surgical Technique/Medical Procedures
6.5 (Rationale 2)	All study-related procedures with the FAST-FIX FLEX Meniscal Repair System must be performed according to the recommended surgical technique described in the IFU (10601463).	All study-related procedures with the FAST-FIX FLEX Meniscal Repair System must be performed according to the recommended surgical technique described in the IFU (10601463 / 10601589).
7.1 (Rationale 1, 5 and 9)	A total of 130 subjects between the ages of 18 and 70 years of age will be enrolled into the study. The subjects will be recruited from up to 6 sites in the United States, United Kingdom, Germany, France and Australia. Sites failing to enroll may be replaced. • 97 subjects will be enrolled for meniscal repair with the use of the FAST-FIX FLEX system • 30 subjects will be enrolled for meniscal allograft transplantation with the use of the FAST-FIX FLEX system For the two subgroups, the clinician has decided the subject's best treatment is a meniscal repair or	A minimum of 62 and maximum of 68 subjects between the ages of 16 and 70 years of age will be enrolled into the study. The subjects will be recruited from up to 5 sites in the United States, United Kingdom, France and Australia. Sites failing to enroll may be replaced. • 53 subjects will be enrolled for meniscal repair with the use of the FAST-FIX FLEX system • A minimum of 9 and maximum of 15 subjects will be enrolled for meniscal allograft transplantation with the use of the FAST-FIX FLEX system For the two subgroups, the clinician has decided the subject's best treatment is a meniscal repair or meniscal allograft transplantation facilitated with the FAST-FIX

	meniscal allograft transplantation facilitated with the FAST-FIX FLEX system as routine medical care. This decision will be made irrespectively of study participation.	FLEX system as routine medical care. This decision will be made irrespectively of study participation.
7.1.1 (Rationale 1 and 7)	N/A	Subjects aged 16 and 17 years of age ("minors") can be enrolled in this study. The rationale for inclusion of this age group is to better align with the Investigational Product's IFU, which does not restrict use in this age group, and strengthen the evidence required for European Medical Device Regulation (EU MDR). Also, the study sites use the Investigational Product in this age group as per standard care and therefore should improve recruitment rates in this study. As this is a post-market clinical follow-up (PMCF) study, any minors who are enrolled in this study may receive the Investigational Product regardless of their participation.
7.2 (Rationale 1 and 7)	Inclusion Criteria Subjects will be considered qualified for enrollment if they meet the following criteria: 1. Subject provides written informed consent for study participation using an independent ethical committee (IEC) / institutional review board (IRB) approved consent form. Subject is between eighteen (18) and seventy (70) years of age, inclusive at the time of screening. 3. Subject is willing and able to participate in required follow-up visits and is able to complete	Inclusion Criteria – Meniscal Repair ONLY Subjects will be considered qualified for enrollment in the MR arm if they meet the following criteria: 1. Subject provides written informed consent for study participation using an independent ethical committee (IEC) / institutional review board (IRB) approved consent form. 2. Subject is between sixteen (16) and seventy (70) years of age, inclusive at the time of screening. 3. Subject is willing and able to participate in required follow-up visits and is able to complete study activities. 4. Subject requires a meniscal repair.

	study activities. 4. Subject requires a meniscal repair or meniscal allograft transplantation. 5. Subject is suitable to participate in the study in the opinion of the Investigator. 6. Meniscal Repair ONLY: 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. 7. Meniscal Allograft Transplantation ONLY: Subject requires a MAT for symptomatic meniscal insufficiency (load-related pain and swelling in the compartment post meniscectomy) for which conservative treatment has failed.	5. Subject is suitable to participate in the study in the opinion of the Investigator. 6. 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.
7.3 (Rationale 1, 7 and 8)	Exclusion Criteria Any one (1) of the following criteria will disqualify a potential subject from participation in the study: 1. 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. 2. Participation in the treatment period of another clinical trial within thirty (30) days of the operative visit, or during the study.	Exclusion Criteria – Meniscal Repair ONLY Any one (1) of the following criteria will disqualify a potential subject from participation in the study: 1. 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. 2. Enrolled in the treatment period of another clinical trial within thirty (30) days of the operative visit, or during the study. 3. Women who are pregnant or nursing.

	3. Women who are pregnant, nursing, or of child-bearing potential who are not utilizing highly effective birth control measures. 4. Any subject that meets the definition of a Vulnerable Subject per ISO 14155 Section 3.44.1 5. Subjects with a history of poor compliance with medical treatment, physical therapy (PT)/rehabilitation, or clinical study participation. 6. Patients with irreparable meniscal tears (i.e. grade 3 outerbridge osteoarthritis or greater, serious defects, multiple tears). 7. Patients with multi-ligament tears (i.e. ACL tear is not associated with lateral collateral ligament (LCL) or medial collateral ligament (MCL) tears). 8. Performance of a significant concomitant procedure, specifically a cartilage repair or restoration (excluding ACL reconstruction or repair) intended as a therapeutic intervention on the study knee. 9. Subjects with a history of ipsilateral knee surgery, septic joint, or fracture (excluding MAT indication). 10. Subjects with pathological conditions in the soft tissue that would prevent secure fixation of the device. 11. Physical conditions that would eliminate, or tend to eliminate, adequate anchor support or retard healing. 12. The presence of infection.	4. 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). 5. Subjects with a history of poor compliance with medical treatment, physical therapy (PT)/rehabilitation, or clinical study participation. 6. Patients with irreparable meniscal tears (i.e. multiple tears). 7. Subjects with full thickness cartilage defects greater than 10mm in diameter and/or serious defects; 8. Patients 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). 9. 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. 10. Subjects with a history of ipsilateral knee surgery, septic joint, or fracture. 11. Subjects with pathological conditions in the soft tissue that would prevent secure fixation of the device. 12. Physical conditions that would eliminate, or tend to eliminate, adequate anchor support or retard healing. 13. The presence of infection.

	13. Conditions which would limit the patient's ability or willingness to restrict activities or follow directions during the healing period. 14. Malalignment: genu varus and genu valgus angles greater than 5° with respect to the normal axis to indicate malalignment. 15. Patients who had an Ahlback grade greater than II 16. Patients with a body mass index larger than 30 17. Subjects with a medical or physical condition that, in the opinion of the Investigator, would preclude safe subject participation in the study. 1. ISO 14155 Section 3.44 States: Vulnerable subject – individual whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. EXAMPLE: Individuals with a lack of or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects include, for example, members of a group with a hierarchical structure such as university student's, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces and persons kept in detention.	14. Conditions which would limit the patient's ability or willingness to restrict activities or follow directions during the healing period. 15. Malalignment: genu varus and genu valgus angles greater than 5° as evaluated by the patient's physician as per their standard of care. 16. Patients who have an Ahlback grade greater than II. 17. Patients with a body mass index larger than 35. 18. Subjects with a medical or physical condition that, in the opinion of the Investigator, would preclude safe subject participation in the study. 1. ISO 14155 Section 3.55 States: Vulnerable subject – individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response
7.4 (Rationale 1 and 7)	N/A – section was screening and is covered below.	Inclusion Criteria – Meniscal Allograft Transplantation ONLY Subjects will be considered qualified for enrollment in the MAT arm if they meet the following criteria:

		1. Subject provides written informed consent for study participation using an independent ethical committee (IEC) / institutional review board (IRB) approved consent form. 2. Subject is between sixteen (16) and seventy (70) years of age, inclusive at the time of screening. 3. Subject is willing and able to participate in required follow-up visits and is able to complete study activities. 4. Subject requires a meniscal allograft transplantation. 5. Subject is suitable to participate in the study in the opinion of the Investigator. 6. 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).
7.5 (Rationale 1 and 7)	N/A – section was informed and is covered below.	Exclusion Criteria – Meniscal Allograft Transplantation ONLY Any one (1) of the following criteria will disqualify a potential subject from participation in the study: 1. 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. 2. Enrolled in the treatment period of another clinical trial within thirty (30) days of the operative visit, or during the study.

	3. Women who are pregnant or nursing. 4. 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). 5. Subjects with a history of poor compliance with medical treatment, physical therapy (PT)/rehabilitation, or clinical study participation. 6. Patients 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. 7. 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. 8. Subjects with a history of ipsilateral knee surgery, septic joint, or fracture (excluding MAT indication). 9. Subjects with pathological conditions in the soft tissue that would prevent secure fixation of the device. 10. Physical conditions that would eliminate, or tend to eliminate, adequate anchor support or retard healing. 11. The presence of infection. 12. Conditions which would limit the patient's ability or willingness to restrict activities or follow directions during the healing period.

		13. Malalignment: genu varus and genu valgus angles greater than 5° as evaluated by the patient's physician as per their standard of care. 14. Patients who have an Ahlback grade greater than II. 15. Patients with a body mass index larger than 35. 16. Subjects with a medical or physical condition that, in the opinion of the Investigator, would preclude safe subject participation in the study.
7.6 (Rationale 1, 5, 6 and 7)	Section 7.4 Screening The Investigators will continuously screen subjects during recruitment, which will continue until a total of 130 subjects (97 enrolled for MR and 33 enrolled for MAT) are recruited. It remains the decision of the Sponsor to increase or decrease enrollment, as necessary. Once a subject has completed the informed consent procedure and signed the Informed Consent Form (IFU), the Principal Investigator (PI), or delegated study research staff, can complete the screening process to determine whether they meet all inclusion and none of the exclusion criteria. Participating study sites are required to document all screened subjects considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be recorded in the subject's source documents and noted on the Screening and Enrollment Log. All screening activities that occur prior to consent shall be referred to as pre-screening.	Section 7.6 Screening The Investigators will continuously screen subjects during recruitment, which will continue until a minimum of 62 and maximum of 68 subjects (53 enrolled for MR and a minimum of 9 and maximum of 15 enrolled for MAT) are recruited. It remains the decision of the Sponsor to increase or decrease enrollment, as necessary. Subjects aged 18 years and over: Once a subject has completed the informed consent procedure and signed the Informed Consent Form (ICF), the Principal Investigator (PI), or delegated study research staff, can complete the screening process to determine whether they meet all inclusion and none of the exclusion criteria. Subjects aged 16 and 17 years: Once a subject has completed the informed consent procedure (assent), the subject's legally authorized representative (parent or legal guardian) has completed the informed consent procedure and signed the relevant ICFs, the Principal Investigator (PI), or delegated study research staff, can

	Part of the screening process will include documentation of women's childbearing potential. If the woman is not of childbearing potential this should be documented in the medical history (e.g., surgically postmenopausal, postmenopausal [i.e., at least one year without menses]). For women of childbearing potential, their method of birth control should be documented in the source. Acceptable birth control methods include abstinence, condoms, birth control pills, IUDs, and other hormonal or physical methods.	complete the screening process to determine whether they meet all inclusion and none of the exclusion criteria. Participating study sites are required to document all screened subjects considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be recorded in the subject's source documents and noted on the Screening and Enrollment Log. All screening activities that occur prior to consent shall be referred to as pre-screening.
7.7 (Rationale 6, 7 and 8)	7.5 Informed Consent Before conducting any study procedures or examinations, the purpose and nature of the study should be explained to the subject in their native language. The subject, or their legally authorized representative, will then read, sign, and personally date the IRB/IEC-approved informed consent document(s) (see below for difficulties with reading and writing). Additionally, the individual who obtains consent from the subject will sign and date the informed consent document. A copy of the signed informed consent document will be provided to the subject, and a copy will be placed in the subject's medical record, with the original filed in the ISF.	7.7 Informed Consent Before conducting any study procedures or examinations, the purpose and nature of the study should be explained to the subject in their native language. Subjects will have the opportunity to ask any questions. The subject, or their legally authorized representative, will then read, sign, and personally date the IRB/IEC-approved informed consent document(s) (see below for difficulties with reading and writing). Additionally, the individual who obtains consent from the subject will sign and date the informed consent document. A copy of the signed informed consent document will be provided to the subject, and a copy will be placed in the subject's medical record, with the original filed in the ISF. If the subject is unable to read, the informed consent document and associated study information may be read

	If the subject is unable to read, the informed consent document and associated study information may be read aloud to the subject in the presence of an impartial witness. If possible, the subject shall sign and personally date the Informed Consent Form (ICF). Where this is not possible, due to difficulties in writing, the subject shall provide verbal consent to participate in the study. The witness shall then personally sign and date the informed consent form, attesting that the information was accurately explained and that the informed consent was freely given. ICFs will comply with Health Information Portability Accountability Act (HIPAA) regulations the EU Global Data Protection Regulation (GDPR), The Privacy Act 1988 in Australia and the New Zealand Privacy Act 1993 and or applicable national regulations and laws.	aloud to the subject in the presence of an impartial witness. If possible, the subject shall sign and personally date the ICF. Where this is not possible, due to difficulties in writing, the subject shall provide verbal consent to participate in the study. The witness shall then personally sign and date the informed consent form, attesting that the information was accurately explained and that the informed consent was freely given. In the case of vulnerable subjects (minors), the ICF must be understood and signed by the subject's legally authorized representative (parent or legal guardian). Assent to participate in the study should be obtained for subjects 16 years of age and 17 years of age if allowed by local regulations. If the legally authorized representative is unable to read/write, a witness signature is required as described previously. The minor shall participate in the informed consent process in a way suitable for their age and mental maturity. Minors will receive the study information in a way adapted to their age and mental maturity from investigators or members of the investigating team who are trained or experienced in working with children. If minors express a wish or an opinion with regards to study participation this needs to be respected by the Investigator. If during the study, the minor reaches the age of 18 years (legal competence), the informed consent shall be obtained again, before the subject can continue to participate in the clinical investigation. ICFs will comply with Health Information Portability Accountability Act

		(HIPAA) regulations the EU Global Data Protection Regulation (GDPR), The Privacy Act 1988 in Australia and the New Zealand Privacy Act 1993 and or applicable national regulations and laws. If new information becomes available during the course of the study that can significantly affect a subject's future health and medical care, Smith + Nephew will ensure that information shall be provided to the subject(s) affected in written form and if relevant, all affected subjects shall be asked to confirm their continuing consent in writing.
7.8 (Rationale 7)	7.6 Enrollment	7.8 Enrollment
7.9 (Rationale 7)	7.7 Lost to Follow-up	7.9 Lost to Follow-up
7.10 (Rationale 7)	7.8 Withdrawal	7.10 Withdrawal
7.10.1 (Rationale 7 and 8)	7.8.1 Withdrawal from Treatment Subjects may be withdrawn from having the related procedures with the FAST-FIX FLEX Meniscal Repair System at a date close to surgery or during surgery for the following reasons: •At the discretion of the Investigator due to: oA change in treatment is clinically warranted oAn adverse event oAny other significant reason identified by the Investigator	7.10.1 Withdrawal from Treatment Subjects may be withdrawn from having the related procedures with the FAST-FIX FLEX Meniscal Repair System at a date close to surgery or during surgery for the following reasons: •At the discretion of the Investigator due to: oA change in treatment is clinically warranted oAn adverse event oAny other significant reason identified by the Investigator

		Any subjects who have provided consent but do not receive treatment or withdraw consent prior to surgery will be considered a screen failure.
7.10.2 (Rationale 7)	7.8.2 Withdrawal from Study	7.10.2 Withdrawal from Study
7.10.3 (Rationale 7)	7.8.3 Subject's Withdrawal of Consent to Participate in Study	7.10.3 Subject's Withdrawal of Consent to Participate in Study
7.10.4 (Rationale 7)	7.8.4 Use of Data Following Withdrawal	7.10.4 Use of Data Following Withdrawal
8.1 (Rationale 8)	N/A	Figure 8-1 8 2: Study Stages
8.1 (Rationale 5, 7, 10, 11 and 12)	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 and meniscal allograft transplantations. Up to 5 sites will participate within United States, United Kingdom, Germany, Spain, 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 8.1-1. Table 8.1 1 Overview of Study Groups Group Surgical Technique Number of Subjects	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 and meniscal allograft transplantations. 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 8.1-1. Table 8.1 1 Overview of Study Groups Group Surgical Technique Number of Subjects Meniscal Repair Smith+Nephew FAST-FIX FLEX System 53

Meniscal Repair Smith+Nephew FAST-FIX FLEX System 97 Meniscal Allograft Transplantations Smith+Nephew FAST-FIX FLEX System 33 The study is expected to be 30 months in duration, but this will depend on the enrollment rate. These include: 16 months for enrollment 14 months for follow-up o The final visit is 12 months post-surgery and includes a +/-2-month window period. The study's treatment will occur once, in the form of surgery to repair the torn portion of the meniscus or provide allograft transplantation to replace the irreparable meniscus or for patients who have had a meniscectomy. The primary outcome measures that will be examined include whether the repair success rate at 12 months will be similar or less than historical rates (85% for all-inside meniscal repair).35; whether the FAST-FIX FLEX system increases access to tear location and zone of repair; whether a significant proportion of the subjects will show meniscus healing at 6 months; and whether Patient-Reported Outcomes (PROs) will be improved up to 12 months following the procedure.	Meniscal Allograft Transplantations Smith+Nephew FAST-FIX FLEX System A minimum of 9 and maximum of 15 The study is expected to be 39 months in duration, but this will depend on the enrollment rate. These include: • 21 months for enrollment • 14 months for follow-up O The final visit is 12 months post-surgery and includes a +/- 75 day window period. The study's treatment will occur once, in the form of surgery to repair the torn portion of the meniscus or provide allograft transplantation to replace the irreparable meniscus or for patients who have had a meniscectomy. The primary outcome measures that will be examined include whether the repair success rate at 12 months will be similar or less than historical rates (90% for all-inside meniscal repair)39; whether the FAST-FIX FLEX system increases access to tear location and zone of repair; whether a significant proportion of the subjects will show meniscus healing at 6 months; and whether Patient-Reported Outcomes (PROs) will be improved up to 12 months following the procedure.

8.3.2 (Rationale 7)	All eCRFs will be archived once the study is completed and will be kept for a period of no less than five years after the later of the following dates: the date of which the study is terminated or completed or; the date that the records are no longer required supporting marketing applications.	All eCRFs will be archived once the study is completed and will be kept for a period of no less than five years after the later of the following dates: the date of which the study is terminated or completed or the date that the records are no longer required for supporting marketing applications.
8.4.4 (Rationale 7)	• Device related AEs (ADEs) and serious adverse events (SAE's);	• Device related AEs (ADEs) and serious adverse events (SAEs);
9.1.1 (Rationale 4, 11 and 12)	Table 9.1 1 Study Procedures by Visit Visit 4 - 3 Months (± 14days) Visit 5 – 6 months (± 30 days) Visit 6 – 12 months (± 60 days)	Table 9.1 1 Study Procedures by Visit Visit 4 - 3 Months (+ 30 days) Visit 5 – 6 months (± 45 days) Visit 6 – 12 months (± 75 days)
9.1.2 (Rationale 7)	Screen Failure subjects should not be assigned randomization numbers, but their demographic information must be captured in the appropriate CRF with the reason for screen failure specified. 1. Obtain written informed consent from the subject as detailed in Section 7.5 ----- Do not proceed until consent has been obtained ----- 2. Obtain demographic information and medical history, including information on all concomitant	For screen Failure subjects, their demographic information must be captured in the appropriate CRF with the reason for screen failure specified. 1. Obtain written informed consent from the subject as detailed in Section 7.7 ----- Do not proceed until consent has been obtained ----- 2. Obtain demographic information and medical history, including information on all concomitant medications/therapies. 3Obtain baseline MRI and confirm eligibility.

	medications/therapies. 3 Obtain baseline MRI and confirm eligibility. 4. Screen the subject for protocol inclusion/exclusion criteria. 5. Assign the subject a study number and instruct the subject on treatment procedures. 6. Have the subject complete the IKDC Questionnaire 7 Have the subject complete the Lysholm Questionnaire 8 Have the subject complete the EQ-5D-5L Questionnaire 9. Subjects will be instructed to return for the Operation Visit (Procedure) as scheduled by the site.	4. Screen the subject for protocol inclusion/exclusion criteria. 5. Assign the subject a study number and instruct the subject on treatment procedures. 6. Have the subject complete the IKDC Subjective Questionnaire 7. Have the subject complete the Lysholm Questionnaire 8. Have the subject complete the EQ-5D-5L Questionnaire 9. Subjects will be instructed to return for the Operation Visit (Procedure) as scheduled by the site.
9.1.5 (Rationale 4)	Visit 4: Follow-up visit at 3 months (90 days after procedure +/- 14 days)	Visit 4: Follow-up visit at 3 months (90 days after procedure + 30 days)
9.1.6 (Rationale 7 and 11)	9.1.6 Visit 5: Follow-up visit at 6 months (180 days after procedure +/- 30 days) Have the subject complete the IKDC Questionnaire.	9.1.6 Visit 5: Follow-up visit at 6 months (180 days after procedure +/- 45 days) Have the subject complete the IKDC Subjective Questionnaire.
9.1.7 (Rationale 8 and 12)	9.1.7 Visit 6: Follow-up visit at 12 months (365 days after procedure +/- 60 days)	9.1.7 Exit Visit (Visit 6: Follow-up visit at 12 months (365 days after procedure +/- 75 days))
9.1.7 (Rationale 7)	Have the subject complete the IKDC Questionnaire.	Have the subject complete the IKDC Subjective Questionnaire.

9.1.12 (Rationale 1)	Women of child-bearing potential are not excluded from the study as long as adequate birth control methods are being used by the subject as outlined in the protocol's exclusion criteria. However, if a woman becomes pregnant during the study, S+N must be contacted immediately once the investigator is made aware of the pregnancy and a decision will be made regarding the continuation in the study of the pregnant woman.	Women of child-bearing potential are not excluded from the study. If a woman becomes pregnant during the study, S+N must be contacted immediately once the investigator is made aware of the pregnancy and a decision will be made regarding the continuation in the study of the pregnant woman.
9.2 (Rationale 7)	The following methods and measurements will be used for this study: • Magnetic Resonance Imaging (MRI) • IKDC Subjective PRO • Lysholm PRO • EQ-5D-5L	The following methods and measurements will be used for this study: • Magnetic Resonance Imaging (MRI) • IKDC Subjective PRO • Lysholm PRO • EQ-5D-5L PRO
9.2.1 (Rationale 7)	Magnetic Resonance Imaging (MRI) is a medical imaging technique that uses magnetic field and computer-generated radio waves to create detailed images of an organ or tissue in the body.[42] For this study, MRIs will be obtained at baseline, 6 months and 1 years post-treatment to assess structural integrity and healing. Sites will make arrangements for MRIs per standard procedures and provide the images/results to the Sponsor. All MRI assessments are detailed in the Image Review Charter.	Magnetic Resonance Imaging (MRI) is a medical imaging technique that uses magnetic field and computer-generated radio waves to create detailed images of an organ or tissue in the body.[43] For this study, MRIs will be obtained at baseline, 6 months and 1 year post-treatment to assess structural integrity and healing. Sites will make arrangements for MRIs per standard procedures and provide the images/results to the Sponsor. All MRI assessments are detailed in the Image Review Charter. MRI to confirm eligibility criteria must be within 6 months of surgery.

9.2.3 (Rationale 7)	The Lysholm scale was first introduced into the medical community in 1982, modified in 1985, and is a validated patient or physician administered instrument to measure symptoms and function in patients in patients with a variety of knee injuries. This tool measures the domains of symptoms and complaints and the functioning of daily activities. The scale consists of 8 items and is scaled from 0 to 100, with a higher score indicating fewer symptoms and a higher level of functioning.[44,45]	The Lysholm scale was first introduced into the medical community in 1982, modified in 1985, and is a validated patient or physician administered instrument to measure symptoms and function in patients with a variety of knee injuries. This tool measures the domains of symptoms and complaints and the functioning of daily activities. The scale consists of 8 items and is scaled from 0 to 100, with a higher score indicating fewer symptoms and a higher level of functioning.[45,46]
9.2.4 (Rationale 7)	The tool is widely used in cost-effectivess analysis and is available in a variety of languages.[46]	The tool is widely used in cost-effectiveness analysis and is available in a variety of languages.[47]
10.2 (Rationale 7)	Statistical analysis will be performed using each of the patient populations as follows: analysis of primary and secondary endpoints will be performed separately using both the FAS and PP populations.	Statistical analysis will be performed using each of the patient populations as follows: analysis of primary and secondary reoperation rate endpoints will be performed on the SAF population; PROs will be presented separately using both the FAS and PP populations.
10.4.1 (Rationale 5 and 7)	A binary variable will be defined for whether each patient 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, together with a percentage and 95% confidence interval for a single proportion (calculated using the Clopper-Pearson method)[39]. The following hypotheses will be tested to establish that the rate of reoperations of the Fast-Fix Flex is	A binary variable will be defined for whether each patient 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, together with a percentage and 95% confidence interval for a single proportion (calculated using the Clopper-Pearson method)[40]. As a further analysis of the primary endpoint, if the data allows, the time taken for reoperation to occur will be

	strictly no worse (lower) than the literature derived value: H0 - 0 < 0 Ha - 0 0 In the stated hypthothesis, μ represents the rate of reoperations for the Fast-Fix Flex and μ0 represents the literature derived value (85%)35. A t-test with alpha = 0.05 will be used to evaluate the hypothesis and the corresponding 95% CIs will also be presented. As a further analysis of the primary endpoint, 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. Analysis will be carried out using the FAS population as the primary analysis population with the PP population used for sensitivity analysis.	assessed as a survival endpoint for both indications in order to assess the trend of incidence of reoperation over time. Analysis will be carried out using the SAF population as the primary analysis population.
10.4.2 (Rationale 5 and 7)	For Lysholm and IKDC, the numbers and proportions of subjects, together with a 95% confidence interval (calculated using the Clopper-Pearson Exact method), meeting the minimal clinically important differences (MCID) from baseline to appropriate post-operative visit (those which have MCID thresholds available in published literature) 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 (those which have MCID thresholds available in published literature) will be presented.
10.4.3 (Rationale 7)	The following other endpoints will be analysed for this study.	The following other endpoints will be analysed for this study:

11 (Rationale 5 and 7)	The sample size for this study is precision-based, and not based on statistical power considerations, thus no formal statistical hypothesis is formulated. The sample size for this study is determined based on the feasibility of recruitment, enrolment and follow-up considerations. The primary endpoint for the study upon which sample size is determined is meniscal repair success rate in the study device at 12 months. This is based on the systematic review entitled:"Prognostic factors for all-inside meniscal repair. An 87-case series" authored by Laurendon et al.35 (2017) where the repair success rate was reported to be 85% for all-inside meniscal repair. Assuming an overall success rate of at least 85%, 82 subjects are sufficient to obtain at least 99% probability of estimating the two-sided 95% confidence interval around the success rate to within 10%. Additionally, secondary endpoints in this study assess the success rate, meniscus healing and clinical performance of PROs for meniscal allograft transplantation (MAT). To satisfy European Medical Device Regulation (EU MDR) requirements, 30 subjects will be recruited to provide sufficient evidence on this indication. Assuming a 15% drop-out rate at the end of 12 months, 130 subjects (97 MR and 33 MAT) will	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. The publication upon which this is based, is the systematic literature review entitled: "Clinical performance of FAST-FIX family" authored by Paul Souter (2022)39 the repair success rate was reported 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 previous protocol version) to 90% for all-inside meniscal repair. For the full report please refer to appendix 22.10. 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 meniscal allograft transplantation (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 by the Smith+Nephew

	be enrolled in order to complete 82 evaluable subjects for MR and 30 evaluable subjects for MAT.	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 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).
13 (Rationale 7 and 8)	The Principal Investigator will comply with the commitments outlined in the in the Statement of Investigator, provided by the Sponsor, and with Good Clinical Practice (GCP), and all applicable regulatory requirements as outlined in Appendix 23.7 of this protocol. In addition, the PI will ensure that the Financial Disclosure Statements will be completed by the PI and the Sub-Investigator upon entry into the study and as any changes that affect their financial disclosure status occur during the course of the study and up to one year after study completion.	The Principal Investigator will comply with the commitments outlined in the in the Statement of Investigator, provided by the Sponsor, and with Good Clinical Practice (GCP), and all applicable regulatory requirements as outlined in Appendix 22.8 of this protocol. Sub-Investigators, who are individual member of the investigation site team designated and supervised by the Principal Investigator at an investigation site to perform clinical investigation-related procedures or to make important clinical investigation-related and medical treatment decisions, may have responsibilities delegated to them by the Principal Investigator. However, the Principal Investigator retains overall responsibility for the clinical investigation at the site. In addition, the PI will ensure that the Financial Disclosure Statements will be completed by the PI and the Sub-Investigator upon entry into the study and as any changes that affect their financial disclosure status occur during the course of the study and up to one year after study completion.

		The Coordinating Investigator appointed by the Sponsor will assist in coordinating the work in the multicentre clinical investigation.
15 (Rationale 7 and 8)	An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. Protocol deviations reported by the Investigator or discovered during monitoring visits will be compiled in a Protocol / GCP Deviation Log (TMP-CD-31-02 Protocol/GCP Deviation Log). Significant and/or recurrent protocol/GCP deviations will be documented on a protocol deviation form (TMP-CD-31-01 Protocol/GCP Deviation) including identified root cause and, as necessary, appropriate corrective and preventive actions will be put in place and signed off by the study personnel. If it is deemed necessary full clinical CAPA will be initiated. It is not allowed to use waivers to allow planned deviation of the study protocol. An investigator may be early terminated from the study upon identification of serious protocol deviations whereby there are concerns for patient safety or data quality (especially those not reported to the sponsor by the site). Early termination may also occur if there are repeated protocol deviations which have previously been addressed via corrective and preventative actions thereby suggesting an issue with site compliance.	An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. Protocol deviations reported by the Investigator or discovered during monitoring visits will be compiled in a Protocol / GCP Deviation Log (FRM-402046 Protocol/GCP Deviation Log). Significant and/or recurrent protocol/GCP deviations will be documented on a protocol deviation form (FRM-400347 Protocol/GCP Deviation) including identified root cause and, as necessary, appropriate corrective and preventive actions will be put in place and signed off by the study personnel. If it is deemed necessary full clinical Corrective and Preventive Action (CAPA) will be initiated. It is not allowed to use waivers to allow planned deviation of the study protocol. An investigator may be early terminated from the study upon identification of serious protocol deviations whereby there are concerns for patient safety or data quality (especially those not reported to the sponsor by the site). Early termination may also occur if there are repeated protocol deviations which have previously been addressed via corrective and preventative actions thereby suggesting an issue with site compliance.

	Give notification requirements and timeframes here for site staff and monitor to report to S+N and PI to report to IRB/IEC (which may be conducted by CSM).	Protocol deviations requiring reporting to the IRB/IEC should be done so in the timeframe stipulated by the IRB/IEC.
18 (Rationale 7 and 8)	This clinical study will be performed in compliance with the ethical principles of the Declaration of Helsinki; and ISO 14155: Clinical investigation of medical devices – Good Clinical Practice. This clinical study will not commence until the required approval/favorable opinion from the IRB/IEC or regulatory authority has been obtained. Any additional requirements imposed by the IRB/IEC or regulatory authority will be followed. Public/Products Liability Insurance has been purchased by Smith & Nephew plc. Worldwide and incorporates coverage for personal injury in respect of clinical studies. The Sponsor agrees to operate in good faith and in accordance with ABHI (Association of British Healthcare Industries) guidelines regarding compensation for injury arising in the course of clinical studies.	This clinical study will be performed in compliance with the ethical principles of the Declaration of Helsinki; and ISO 14155: Clinical investigation of medical devices – Good Clinical Practice. This clinical study will not commence until the required approval/favorable opinion from the IRB/IEC or regulatory authority has been obtained. Any additional requirements imposed by the IRB/IEC or regulatory authority will be followed. Public/Products Liability Insurance has been purchased by Smith & Nephew plc. Worldwide and incorporates coverage for personal injury in respect of clinical studies. The Sponsor agrees to operate in good faith and in accordance with ABHI (Association of British Healthcare Industries) guidelines regarding compensation for injury arising in the course of clinical studies. The clinical study is financed by the sponsor. All financial arrangements between the sponsor and investigation sites/investigators are documented separate clinical trial agreements.
19 (Rationale 7 and 8)	Should circumstances arise which require the termination of the entire study prior to its planned completion (e.g., safety concerns) or circumstances arise which mean the end of the participation of an individual site (e.g., departure of Investigator, non-	The end of study is defined as last subject last visit. Should circumstances arise which require the termination of the entire study prior to its planned completion (e.g., safety concerns) or circumstances arise which mean the end of the participation of an individual site (e.g.,

	compliance), then this will be undertaken according to the SOPs of the Sponsor.	departure of Investigator, non-compliance), then this will be undertaken according to the SOPs of the Sponsor.
20.1 (Rationale 8)	The preparation and submission for publication of manuscripts containing the study results shall be in accordance with a process determined by the Clinical Trial Agreements between the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to the Health Insurance Portability and Accountability Act of 1996.	The study will be registered in a publicly accessible database and the results will be made available within that database. The preparation and submission for publication of manuscripts containing the study results shall be in accordance with a process determined by the Clinical Trial Agreements between the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to the Health Insurance Portability and Accountability Act of 1996.
21 (Rationale 5 and 7)	39.Clopper, CJ, Pearson ES. In: Biometrika. The use of confidence or fiducial limits illustrated in the case of the binomial. 1934, 26 p. 404–413. 40.McCormick F, Harris JD, Abrams GD, Hussey KE, Wilson H, Frank R, Gupta AK, Bach BR Jr, Cole BJ. Survival and reoperation rates after meniscal allograft transplantation: analysis of failures for 172 consecutive transplants at a minimum 2-year follow-up. Am J Sports Med. 2014 Apr;42(4):892-7. doi: 10.1177/0363546513520115. Epub 2014 Feb 14. PMID: 24532597. 41.Taichman, DB, et al. Data Sharing Statements for Clinical Trials: A Requirement of the	39. Souter, P. Clinical performance of FAST-FIX family. 2022 p. 1-24. 40. Clopper, CJ, Pearson ES. In: Biometrika. The use of confidence or fiducial limits illustrated in the case of the binomial. 1934, 26 p. 404–413. 41. McCormick F, Harris JD, Abrams GD, Hussey KE, Wilson H, Frank R, Gupta AK, Bach BR Jr, Cole BJ. Survival and reoperation rates after meniscal allograft transplantation: analysis of failures for 172 consecutive transplants at a minimum 2-year follow-up. Am J Sports Med. 2014 Apr;42(4):892-7. doi: 10.1177/0363546513520115. Epub 2014 Feb 14. PMID: 24532597. 42. Taichman, DB, et al. Data Sharing Statements for Clinical Trials: A Requirement of the International

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Committee of Medical Journal Editors. Ann Intern Med. 2017. 6th June. doi:10.7326/M17-1028
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44. Collins NJ, Misra D, Felson DT, Crossley KM, Roos EW. "Measures of Knee Function," [Internet]. Arthritis Care Res; 2011 Nov [cited 2020 Feb 6] Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4336550/
45. Van Meer BL, Reijman M, et al. [Internet]. In: The Anterior Cruciate Ligament (Second Edition). A Comparison of the Standardized Rating Forms for Evaluation of Anterior Cruciate Ligament Injured or Reconstructed Patients. 2018. [updated 2020, cited 2020 Feb 6]. Available from: https://www.sciencedirect.com/book/9780323389624/the-anterior-cruciate-ligament
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22.1 (Rationale 7)	Protocol Amendment	Protocol Amendment 1
22.4 (Rationale 2)	22.3 Instructions for Use • Smith+Nephew. FAST-FIX FLEX Meniscal Repair System IFU (Document ID: 10601463)	22.4 Instructions for Use • Smith+Nephew. FAST-FIX FLEX Meniscal Repair System IFU (Document ID: 10601463) • Smith+Nephew. FAST-FIX FLEX Meniscal Repair System IFU slim pack (Document ID: 10601589)
22.8 (Rationale 7 and 8)	22.7 Principal Investigator Obligations (ISO 14155) 1. General: a. The role of the PI 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.	22.8 Principal Investigator Obligations (ISO 14155) 1. General: a. The role of the PI 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. b. The PI is responsible for ensuring adequate training and qualification of the investigation site team and for maintaining oversight of their activities. The principal investigator may delegate tasks to qualified members of the investigation site team but retains responsibility for the clinical investigation (see also 7.6). This also applies when activities are outsourced to an external organization by the principal investigator in which case he/she shall implement procedures to ensure the integrity of all tasks

		performed and any data generated by this external organization.
22.8 (Rationale 7 and 8)	22.7 Principal Investigator Obligations (ISO 14155) 3. Qualification of investigation site. The PI shall be able to demonstrate that the proposed investigation site: a. has the required number of eligible subjects needed within the agreed recruitment period, and; b. has one or more qualified investigators, a qualified investigation site team and adequate facilities for the foreseen duration of the clinical investigation.	22.8 Principal Investigator Obligations (ISO 14155) 3. Qualification of investigation site. The PI shall be able to demonstrate that the proposed investigation site: a. has the required number of eligible subjects needed within the agreed recruitment period, and; b. has an investigation site team that is: qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation in accordance with this document; evidence of such qualifications for members of the investigation site team shall be documented through up-to-date CVs or other relevant documentation; c. has adequate facilities.
22.8 (Rationale 7 and 8)	22.7 Principal Investigator Obligations (ISO 14155) 6. Compliance with the protocol. The Principal Investigator shall: a. indicate his/her acceptance of the protocol in writing, b. conduct the clinical investigation in compliance with the protocol, c. create and maintain source documents throughout the clinical investigation and make them available as requested during monitoring visits or audits, d. ensure that the investigational device is used solely by authorized users as specified in 6.2, and in accordance with the protocol and instructions for use,	22.8 Principal Investigator Obligations (ISO 14155) 6. Compliance with the protocol. The Principal Investigator shall: a. indicate his/her acceptance of the protocol in writing, b. conduct the clinical investigation in compliance with the protocol, c. create and maintain source documents throughout the clinical investigation and make them available as requested during monitoring visits or audits, d. ensure that the investigational device is used solely by authorized users as specified in 6.2, and in accordance with the protocol and instructions for use,

	e. propose to the Sponsor any appropriate modification(s) of the protocol or investigational device or of the use of the investigational device, f. refrain from implementing any modifications to the protocol without agreement from the Sponsor, IEC and regulatory authorities, if required, g. document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation, h. ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation, i. ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable, j. ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRF and in all required reports, k. maintain the device accountability records, l. allow and support the Sponsor to perform monitoring and auditing activities, m. be accessible to the monitor and respond to questions during monitoring visits, n. allow and support regulatory authorities and the IEC when performing auditing activities, o. ensure that all clinical-investigation-related records are retained as required taking measures to prevent accidental or premature destruction, and	e. propose to the Sponsor any appropriate modification(s) of the protocol or investigational device or of the use of the investigational device, f. refrain from implementing any modifications to the protocol without agreement from the Sponsor, IEC and regulatory authorities, if required, g. document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation, h. ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation, i. ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable, j. ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRF and in all required reports, k. maintain the device accountability records, l. Comply with the procedure for the safe return of investigational devices including potentially hazardous devices and, in the case of reported device deficiencies, collaborate with the sponsor to provide the necessary information allowing an accurate analysis where appropriate. requirements and provide any information need to analyze device deficiencies, if applicable. m. allow and support the Sponsor to perform monitoring and auditing activities,

	p. review and sign the clinical investigation report, as applicable.	n. be accessible to the monitor and respond to questions during monitoring visits, o. determine the cause and implement appropriate corrective and preventative actions to address significant noncompliance p. allow and support regulatory authorities and the IEC when performing auditing activities, q.ensure that all clinical-investigation-related records are retained as required taking measures to prevent accidental or premature destruction, and r. review and sign the clinical investigation report, as applicable.
22.8 (Rationale 7 and 8)	8. Safety reporting. The Principal Investigator shall: a. record every adverse event and observed device deficiency, together with an assessment, b. report to the Sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports, as specified in the protocol, c. report to the IEC serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the national regulations or protocol or by the IEC, d. report to regulatory authorities, serious adverse events and device deficiencies that could have led to a	8. Safety reporting. The Principal Investigator shall: a. record every adverse event and observed device deficiency, together with an assessment, b. report to the Sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports, as specified in the protocol, c. report to the IEC serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the national regulations or protocol or by the IEC, d. report to regulatory authorities, serious adverse events and device deficiencies that could have led to a serious adverse device effect, as required by the national regulations, and

serious adverse device effect, as required by the national regulations, and
e. supply the Sponsor, upon Sponsor's request, with any additional information related to the safety reporting of a particular event.
Note, for studies conducted under 21 CFR Part 812 Investigational Device Exemption Regulations, an investigator shall prepare and submit the following complete, accurate, and timely reports:
(1)Unanticipated Adverse Device Effects An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
(2)Withdrawal of IRB approval. An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
(3)Progress. An investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.
(4)Deviations from the investigational plan. An investigator shall notify the sponsor and the

e. supply the Sponsor, upon Sponsor's request, with any additional information related to the safety reporting of a particular event.
Note, for studies conducted under 21 CFR Part 812 Investigational Device Exemption Regulations, an investigator shall prepare and submit the following complete, accurate, and timely reports:
(1) Unanticipated Adverse Device Effects An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
(2) Withdrawal of IRB approval. An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
(3) Progress. An investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.
(4) Deviations from the investigational plan. An investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or

	reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB also is required. (5)Informed consent. If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.	deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB also is required. (5) Informed consent. If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs. (6) Final report. An investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB. (7) Other. An investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.
22.9 (Rationale 8)	N/A – new section	22.9 Clinical Study Sites Smith + Nephew will maintain a list of the name and address of involved sites in the Trial Master File. This list is available upon request.
22.10 (Rationale 8)	N/A – new section	22.10 Evidence Analysis Report The full Evidence Analysis Report, authored by Paul Souter on 29th November 2022 and titled "Clinical performance of FAST-FIX family"[39] is appended below.
22.11 (Rationale 5)	N/A – new section	22.11 R&D internal evidence generated for MAT Indication

The full R&D internal evidence, dated 03/Apr/2023, for the MAT indication is appended below.

22.2.5 Approval/Notification

The changes outlined for this amendment will only be implemented following IRB/IEC approval.

22.3 Sponsor Details

Smith & Nephew Inc.
1450 E. Brooks Road
Memphis, TN 38116
USA

22.4 Instructions for Use

- Smith+Nephew. FAST-FIX FLEX Meniscal Repair System IFU (Document ID: 10601463)
- Smith+Nephew. FAST-FIX FLEX Meniscal Repair System IFU slim pack (Document ID: 10601589)

22.5 Equipment and Special Instructions

Not applicable.

22.6 Health Economic Outcome Measures/Quality of Life measures

Not applicable.

22.7 Additional Information

Not applicable.

22.8 Principal Investigator Obligations (ISO 14155)

1. General:
    a. The role of the PI 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.
    b. The PI is responsible for ensuring adequate training and qualification of the investigation site team and for maintaining oversight of their activities. The principal investigator may delegate tasks to qualified members of the investigation site team but retains responsibility for the clinical investigation (see also 7.6). This also applies when activities are outsourced to an external organization by the principal investigator in which case he/she shall implement procedures to ensure the integrity of all tasks performed and any data generated by this external organization.
2. Qualification of the PI. The PI shall:
    a. be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation in accordance with this International Standard; evidence of such qualifications of the PI and key members of the investigation site team shall be provided to the Sponsor through up-to-date Curriculum Vitae (CV) or other relevant documentation,
    b. be experienced in the field of application and trained in the use of the investigational device under consideration,
    c. disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results, and
    d. be knowledgeable with the method of obtaining informed consent.
3. Qualification of investigation site. The PI shall be able to demonstrate that the proposed investigation site:
    a. has the required number of eligible subjects needed within the agreed recruitment period, and;

b. has an investigation site team that is: qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation in accordance with this document; evidence of such qualifications for members of the investigation site team shall be documented through up-to-date CVs or other relevant documentation;
c. has adequate facilities.

4. Communication with the IEC. The PI shall:
   a. provide the Sponsor with copies of any clinical-investigation-related communications between the PI and the IEC,
   b. comply with the requirements described in 4.5 of ISO 14155.
      i. Submit to the IEC the following information, any amendments and any additional documentation required by the IEC: The Protocol; IB or equivalent; informed consent form and any other written information provided to subjects; procedures for recruiting subjects and advertising materials, if any; a copy of the CV of the PI(s) for with the IEC has oversight.
      ii. Provide documentation of the IECs approval/favorable opinion, identifying the documents and amendments on which the opinion was based, to the Sponsor, prior to commencing the clinical investigation.
      iii. Submit the following to the IEC if required by national regulations, the protocol or IEC, whichever is more stringent:

         1. SAEs
         2. Requests for deviations, and reports of deviations, if the deviation affects subject's rights, safety, and well-being, or the scientific integrity of the clinical investigation. Document and report to the Sponsor and IEC a report of deviations made to protect the rights, safety, and well-being of human subjects under emergency circumstances.
         3. Progress reports, including safety summary and deviations
         4. Amendments to any documents already approved by the IEC.

5. If applicable, notifications of suspension or premature termination
6. If applicable, justification and request for resuming the clinical investigation after suspension.
7. Clinical investigation report or summary.

iv. As a minimum, during the clinical investigation, the following information shall be obtained in writing from the IEC prior to implementation:

1. Approval/favorable opinion of amendments
2. Approval of the request for deviations that can affect the subject's rights, safety, and well-being or scientific integrity of the clinical investigation
3. Approval for resumption of a suspended clinical investigation if applicable.

c. obtain the written and dated approval/favorable opinion of the IEC for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required,

d. promptly report any deviations from the protocol that affect the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances, if required by the IEC, protocol or national regulations. In particular circumstances, the communication with the IEC can be performed by the Sponsor, partly or in full, in which case the Sponsor shall keep the Principal Investigator informed.

5. Informed consent process. The PI shall:

a. General:

i. Informed consent shall be obtained in writing from the subject and the process shall be documented before any procedure specific to the clinical investigation is applied to the subject; except when special circumstances for emergency treatments apply (see below)

b. Process of obtaining informed consent. The general process for obtaining informed consent shall be documented in the protocol and shall comply with the following. These requirements

also apply with respect to informed consent obtained from a subject's legally authorized representative:

i. Ensure that the PI or his/her authorized designee conducts the informed consent process
ii. Include all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation
iii. Avoid any coercion or undue improper influence on, or inducement of, the subject to participate
iv. Not waive or appear to waive the subject's legal rights
v. Use native non-technical language that is understandable to the subject
vi. Provide ample time for the subject to read and understand the informed consent form and to consider participation in the clinical investigation
vii. Include personally dated signatures and the PI or an authorized designee responsible for conducting the informed consent process
viii. Show how informed consent will be obtained in special circumstances (see below) where the subject is unable to provide him or herself, and
ix. Ensure important new information is provided to new and existing subjects throughout the clinical investigation.

c. Special circumstances for informed consent (the following provisions are subject to national regulations):
   i. Subject needing legally authorized representatives: informed consent may be given by the legally authorized representative only if a subject is unable to make the decision to participate in a clinical investigation (e.g., infant, child, or juvenile, seriously ill or unconscious subject, mentally ill person, mentally handicapped person). In such cases, the subject shall also be informed about the clinical investigation within his/her ability to understand.
   ii. Subject unable to read or write: informed consent shall be obtained through a supervised oral process if a subject or legally authorized representative is unable to read or write. An independent witness shall be present throughout the process. The written

informed consent form and any other information shall be read aloud and explained to the prospective subject or his/her legally authorized representative and, whenever possible, either shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent for attesting that the information was accurately explained and that the informed consent was freely given.

iii. Emergency treatments:

1. For clinical investigations involving emergency treatments, when prior informed consent of the subject is not possible because of the subject's medical condition, the informed consent of the subject's legally authorized representative, if present, shall be requested.
2. When it is not possible to obtain prior informed consent from the subject, and the subject's legally authorized representative, is not available, the subject may still be enrolled if a specific process has been described in the protocol.
3. Arrangements shall be made to inform the subject or legally authorized representative, as soon as possible, about the subject's inclusion in the clinical investigation and about all aspects of the clinical investigation.
4. The subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows.

d. The Principal Investigator may not enroll a subject without obtaining informed consent of the subject or his/her legally authorized representative only when the following conditions are fulfilled: the prospective subject fulfils the emergency conditions and is obviously in a life-threatening situation; no sufficient clinical benefits are anticipated from the currently available treatment; there is a fair possibility that the life-threatening risk to the prospective subject can be avoided if the investigational device is used; anticipated risks are outweighed by the potential benefits of applying the investigational device ; the legally authorized representative cannot be promptly reached and informed.

e. Information provided to the subject. All information pertinent to the clinical investigation, including at least the following, shall be provided in writing and in native, non-technical language that is understandable to the subject (or the subject's legally authorized representative):
   i. Description and purpose
   ii. Potential benefits
   iii. Risks and inconveniences or the subject and, when applicable, for any embryo, fetus or nursing infant
   iv. Alternative procedures
   v. Confidentiality
   vi. Compensation
   vii. Anticipated expenses, if any, to be borne by the subject for participating in the clinical investigation
   viii. Information on the role of Sponsor's representative in the clinical investigation
   ix. Contact persons
   x. Statement declaring that new findings or the reasons for any amendment to the protocol that affect the subject's continued participation shall be made available to the subject.
   xi. Statement indicating that, upon the subject's approval, the subject's personal physician will be informed of the subject's participation in the clinical investigation
   xii. Termination procedures

f. Informed consent signature shall contain the following:
   i. The voluntary agreement to participate in the clinical investigation and follow the investigator's instructions
   ii. A statement declaring that refusal of participation incurs no penalty for the subject
   iii. A statement declaring that discontinuation at any time incurs no penalty for the subject
   iv. A statement with regard to the possible consequences of withdrawal
   v. An acknowledgment of the information provided and confirmation that all the subject's questions were answered

vi. A statement confirming that the subject or his/her legally authorized representative agrees to the use of the subject's relevant personal data for the purpose of the clinical investigation

vii. A statement confirming that the subject or his/her legally authorized representative agrees that Sponsor's representatives, regulatory authorities and IEC representatives will be granted direct access to the subject's medical records.

g. New information: if new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the subject(s) affected in written form. If relevant, all affected subjects shall be asked to confirm their continuing consent in writing.

h. ensure compliance with the applicable regulatory requirements and ethical principles for the process of obtaining informed consent, and

i. ensure and document appropriate training if an authorized designee is appointed to conduct the informed consent process.

6. Compliance with the protocol. The Principal Investigator shall:

a. indicate his/her acceptance of the protocol in writing,

b. conduct the clinical investigation in compliance with the protocol,

c. create and maintain source documents throughout the clinical investigation and make them available as requested during monitoring visits or audits,

d. ensure that the investigational device is used solely by authorized users as specified in 6.2, and in accordance with the protocol and instructions for use,

e. propose to the Sponsor any appropriate modification(s) of the protocol or investigational device or of the use of the investigational device,

f. refrain from implementing any modifications to the protocol without agreement from the Sponsor, IEC and regulatory authorities, if required,

g. document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation,

h. ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation,
i. ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable,
j. ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRF and in all required reports,
k. maintain the device accountability records,
l. Comply with the procedure for the safe return of investigational devices including potentially hazardous devices and, in the case of reported device deficiencies, collaborate with the sponsor to provide the necessary information allowing an accurate analysis where appropriate. requirements and provide any information need to analyze device deficiencies, if applicable.
m. allow and support the Sponsor to perform monitoring and auditing activities,
n. be accessible to the monitor and respond to questions during monitoring visits,
o. determine the cause and implement appropriate corrective and preventative actions to address significant noncompliance
p. allow and support regulatory authorities and the IEC when performing auditing activities,
q. ensure that all clinical-investigation-related records are retained as required taking measures to prevent accidental or premature destruction, and
r. review and sign the clinical investigation report, as applicable.

7. Medical care of subjects. The Principal Investigator shall
   a. provide adequate medical care to a subject during and after a subject's participation in a clinical investigation in the case of adverse events,
   b. inform the subject of the nature and possible cause of any adverse events experienced,
   c. provide the subject with the necessary instructions on proper use, handling, storage, and return of the investigational device, when it is used or operated by the subject,
   d. inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required,

e. provide the subject with well-defined procedures for possible emergency situations related to the clinical investigation, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed,
f. ensure that clinical records are clearly marked to indicate that the subject is enrolled in a particular clinical investigation,
g. if appropriate, subjects enrolled in the clinical investigation shall be provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided),
h. inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation, and
i. make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from the clinical investigation while fully respecting the subject's rights.

8. Safety reporting. The Principal Investigator shall:
   a. record every adverse event and observed device deficiency, together with an assessment,
   b. report to the Sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports, as specified in the protocol,
   c. report to the IEC serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the national regulations or protocol or by the IEC,
   d. report to regulatory authorities, serious adverse events and device deficiencies that could have led to a serious adverse device effect, as required by the national regulations, and
   e. supply the Sponsor, upon Sponsor's request, with any additional information related to the safety reporting of a particular event.

Note, for studies conducted under 21 CFR Part 812 Investigational Device Exemption Regulations, an investigator shall prepare and submit the following complete, accurate, and timely reports:

(1) Unanticipated Adverse Device Effects An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

(2) Withdrawal of IRB approval. An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.

(3) Progress. An investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.

(4) Deviations from the investigational plan. An investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB also is required.

(5) Informed consent. If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.

(6) Final report. An investigator shall, within 3 months after termination or completion of the investigation or the investigator's part of the investigation, submit a final report to the sponsor and the reviewing IRB.

(7) Other. An investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

22.9 Clinical Study Sites

Smith + Nephew will maintain a list of the name and address of involved sites in the Trial Master File. This list is available upon request.

22.10 Evidence Analysis Report

The full Evidence Analysis Report, authored by Paul Souter on 29th November 2022 and titled "Clinical performance of FAST-FIX family"[39] is appended below.

Smith+Nephew

Smith+Nephew

Global Clinical and Medical Affairs

Evidence Analysis Report

Title	Clinical performance of FAST-FIX family
Author	Paul Souter (Clinical Evidence Specialist)
Requestor	Hadi El Heneidi (Director, Global Marketing)
Franchise	SPM
Reviewer	Matthew Sedgwick (Senior Clinical Evidence Specialist)
Issue date	29th Nov 2022
Report Reference	EA/SPM/FASTFIX/007/v3

For further explanation about the use of this report or its findings, please contact the author or a member of Evidence Analysis.

Contents

Abbreviations

ACLR	Anterior cruciate ligament reconstruction
IKDC	International Knee Documentation Committee
MRI	Magnetic Resonance Imaging
PROMs	Patient-reported outcome measures
sd	Standard deviation

1. Executive Summary

1.1. Purpose

To establish the success rate and patient reported outcomes (PROMs) following the repair of meniscal body tears using a device from the FAST-FIX family.

This is an update to the previously completed systematic literature review and meta-analyses performed in 2019 to determine the success rates (EO/SPM/FASTFIX/002/v2) and patient reported outcomes (PROMs) (EO/SPM/FASTFIX/003/v2) when FAST-FIX was utilised for meniscus repair.

1.2. Key Findings

The systematic literature review identified 38 studies reporting on the success rate of FAST-FIX devices in meniscal repair. Of these publications, 27 also reported patient-reported outcome measures (PROMs).

- ***Meniscal repair success/failure:*** Meta-analysis revealed successful meniscal repair, as defined by individual studies, in 88% (95% CI: 86-90) of cases at a mean follow-up of 34.4 months. Of those patients undergoing surgery for isolated meniscal repair or with concomitant anterior cruciate ligament reconstruction (ACLR), success was reported in 92% (95% CI: 89-94) and 89% (95% CI: 87-91), respectively.

- ***Re-operation:*** Meta-analysis revealed a success rate of 90% (95% CI: 86-93) success with 10% (95% CI: 7-14) requiring re-operation at a weighted mean follow-up of 39.7 months. Of those patients undergoing surgery for

isolated meniscal repair or with concomitant (ACLR), re-operation was reported in 6% (95% CI: 4-9) and 11% (95% CI: 9-14), respectively.

- ***PROM:*** Meta-analysis revealed a mean International Knee Documentation Committee (IKDC), Lysholm and Tegner activity scores of 86.34 (95% CI: 83.89-88.79; weighted mean follow-up, 37.4 months), 89.43 (95% CI: 86.77-92.09; weighted mean follow-up, 28.3 months) and 6.22 (95% CI: 5.81-6.62; weighted mean follow-up, 54.5 months), respectively. Post-operative scores were similar when only considering isolated meniscal repair and meniscal repair with concomitant ACLR.

2. Search Methodology

A systematic literature review was performed using Embase and PubMed to identify clinical studies that detailed the use of a FAST-FIX family device. The search terms utilised were:

Embase: fastfix OR 'fast fix'

PubMed: fast-fix or "fast fix" or "fastfix"

These searches were initially performed on 5th April 2019 (Embase) and 8th April 2019 (PubMed) as detailed in EO/SPM/FASTFIX/002/v2 and EO/SPM/FASTFIX/003/v2. These searches were then updated on 26th (PubMed) and 27th (Embase) June 2022 with limits placed on publication date to only capture publications following the initial searches.

Additional relevant publications were identified from reference lists.

The following inclusion/exclusion criteria were applied to the resulting publications.

Inclusion criteria:

- Patients of any age undergoing meniscal body repair
- Sole use of FAST-FIX devices (any variant) for meniscal repair
- ≥10 patients
- Meniscal repair as either an isolated procedure or in conjunction with anterior cruciate ligament reconstruction (ACLR)
- Reporting an outcome of interest: Success rate (as defined by individual study), re-operation rate or PROMs (Lysholm, Tegner, International Knee Documentation Committee (IKDC))
- Primary empirical clinical study
- Full-text publication or conference abstract
- English language

Exclusion criteria:

- Meniscal root tear repair
- Meniscal ramp lesion repair
- Use of meniscal allograft
- Hybrid repairs (e.g. concurrent use of FASTFIX and inside-out repair techniques)
- Outcome data not specific to the FAST-FIX only (i.e. pooled with other procedures or devices)

- Studies not in English
- <10 patients
- Studies performed on animals
- Cadaveric studies
- Laboratory-based studies
- Surgical technique description without clinical data
- Reviews, systematic literature reviews, editorials and meta-analyses

Data extraction

Data were extracted from included studies by one reviewer using a predefined data extraction form. Extracted data included procedure (meniscus repair or meniscus repair with ACLR), tear type, mean follow-up, definition of successful repair, sample sizes, number of successful meniscal repairs, number of re-operations, IKDC (mean, standard deviation), Lysholm score (mean, standard deviation) and Tegner activity score (mean, standard deviation).

Statistical analyses:

Meta-analyses were performed using R statistical programming software (version 4.0.2). Proportional meta-analysis was utilised for dichotomous outcome data and continuous meta-analysis was utilised for continuous outcome data to provide a mean score representative of included studies. All procedures were initially analysed and partitioned by surgical procedure (meniscal repair or meniscal repair with concomitant ACLR). Heterogeneity of included studies was assessed using the I^2 statistic. When I^2 was less than 50% (indicating no substantial heterogeneity), a fixed-effect/common effect model was used; when I^2 was over 50%, a random-effects model was used. Weighted mean of follow-up (months) were calculated from those for which they were provided and was based on patient number.

When a median was provided along with a range or interquartile range the mean and standard deviation was determined using the estimates presented by Wan *et al*[1]. Where no variation data were provided, the sd was calculated as the mean of those for which the sd was stated in the publication[2].

3. Results

Thirty-eight relevant studies[3-40] were identified to meet the inclusion/exclusion criteria of this review (Figure 1). These publications totaled 2007 patients, detailing the outcomes across vertical, longitudinal, horizontal, bucket-handle, radial and complex tears, and across both the medial and lateral menisci.

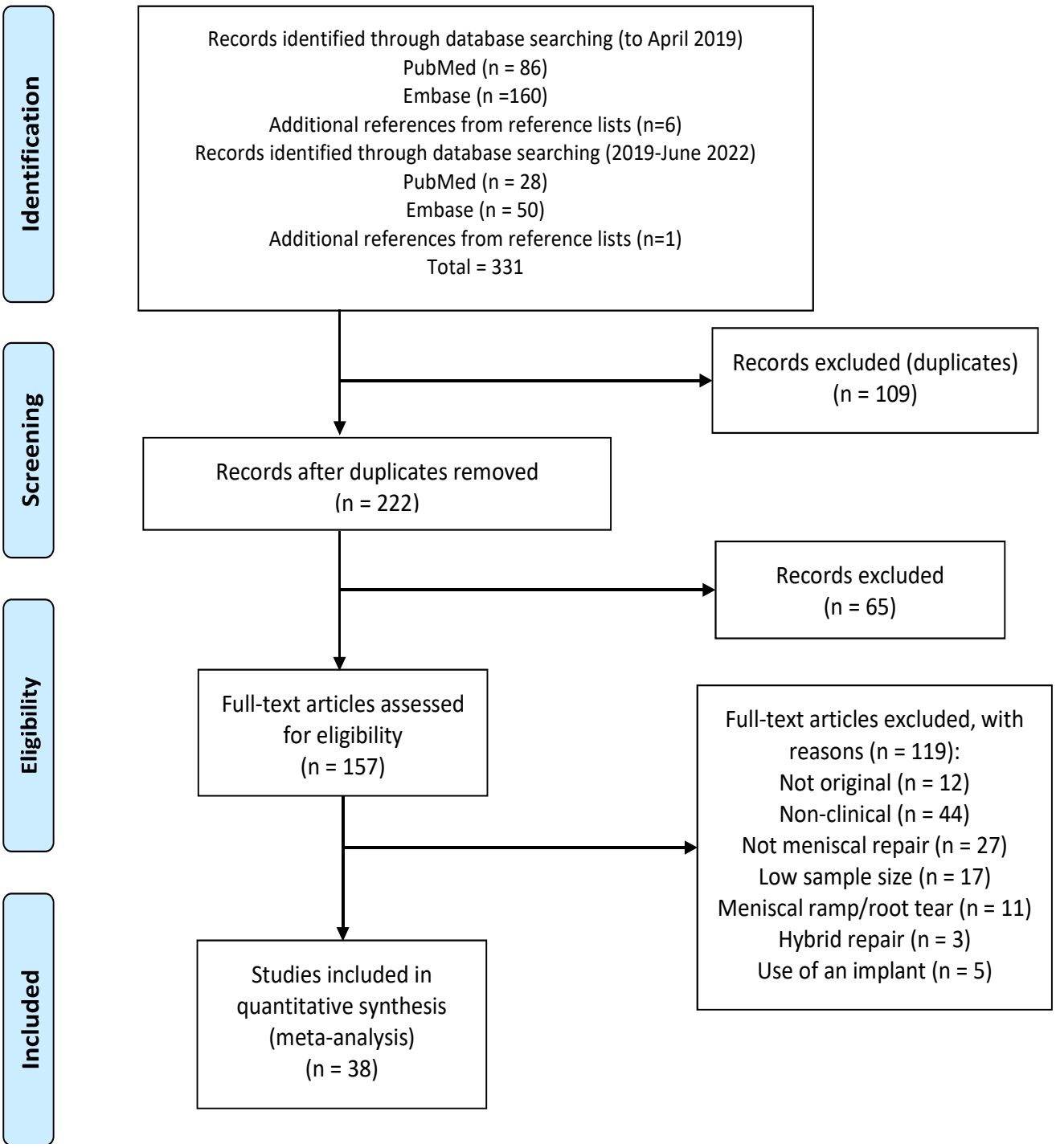

Figure 1 Study selection flow chart.

3.1 Meniscal repair success/failure

Thirty-eight studies reported on meniscal repair success following meniscal repair with FAST-FIX[3-40]. Meniscal repair success/failure was determined through several methods including: second look arthroscopy[6,12,23,27,29,35], re-operation[5,10,13,15,18,21,26,28,30,33,34,37-40], magnetic resonance imaging (MRI)[9,16], clinical assessment (i.e. absence of effusion or pain on palpation at the height of the intra-articular space and negative tests for meniscal injury)[3,7,8,11,17,20,22,24,25,31,36], threshold score from PROMs[14,32], or multiple factors (re-operation, clinical assessment, MRI, PROM)[4,19].

Across 2114 tears, meniscal repair with FAST-FIX was determined to be successful in 88% (95% CI: 86-90) of cases (**Figure 2**) at a weighted mean follow-up of 34.4 months. Choi *et al*[9] and Song *et al*[29] reported on the degree of healing (complete, partial, failed), success was considered as complete or partial healing and failure as failed healing.

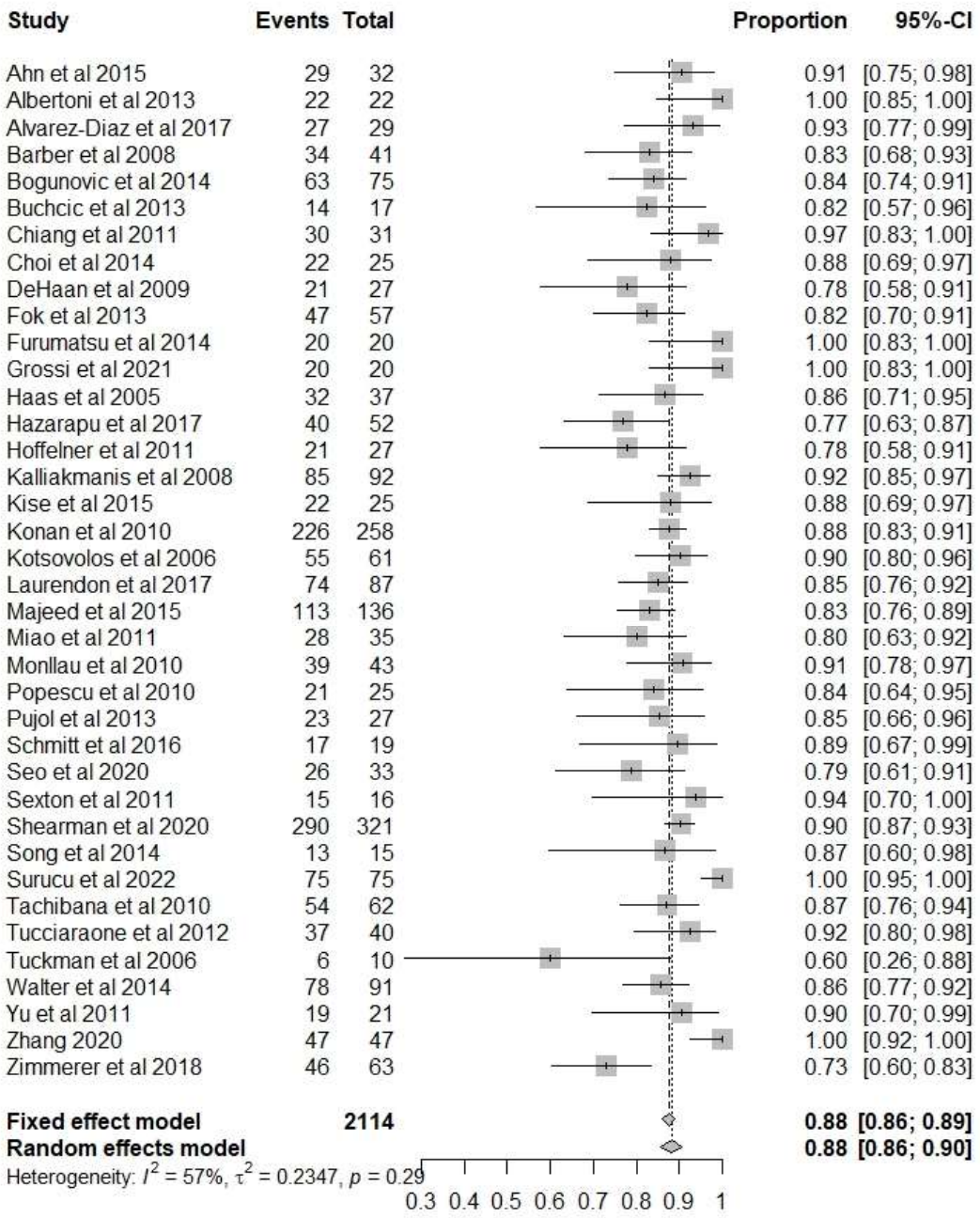

Figure 2: Success of meniscal repairs using FAST-FIX.

Seventeen publications reported success rates for isolated meniscal repair [3-8,13,14,18,20,24,25,28,30,32,38,39] and 23 publications for meniscal repair with concomitant ACLR[4-6,8-10,12-14,17,20,23-25,27,29,31,32,35,36,38-40]. Meta-analysis of the 365 isolated meniscal repairs reported a success rate of 92% (95% CI: 89-94) (**Figure 3**) at a weighted mean follow-up of 32.2 months. Meta-analysis of the 941 tears repaired alongside

ACLR reported a success rate of 89% (95% CI: 87-91) (**Figure 4**) at a weighted mean follow-up of 37.2 months. Ahn *et al* performed their isolated repairs with a 'marrow-stimulating' technique via reaming of the intercondylar notch[3]. While this technique has potential similarities to ACLR+, this was also assigned to the isolated tear analysis since ligament function had not been compromised.

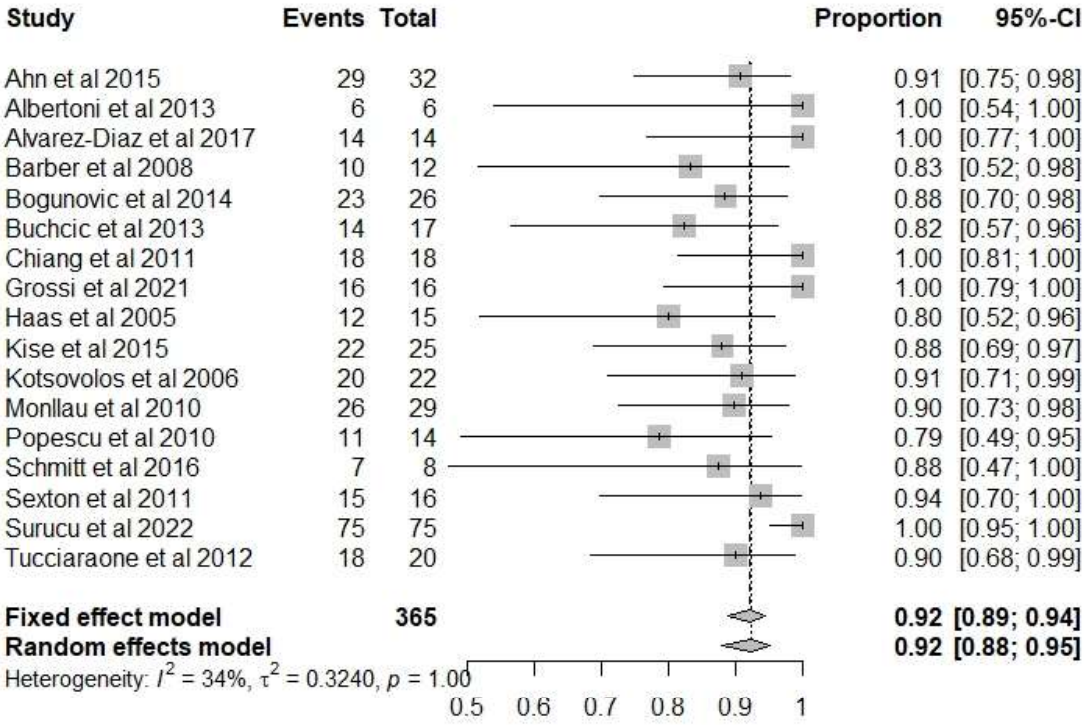

Figure 3: Success rate of isolated meniscal repairs using FAST-FIX.

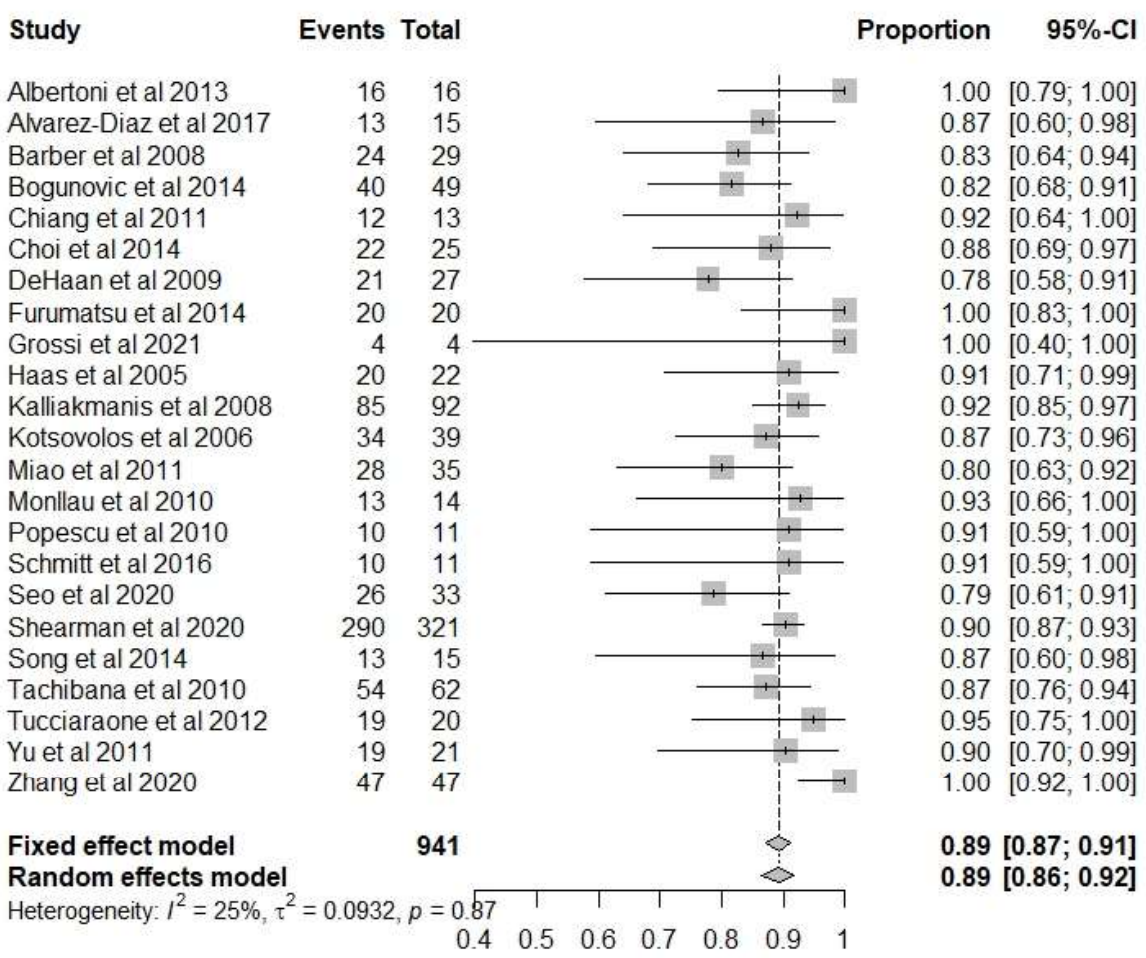

Figure 4: Success rate of meniscal repair using FAST-FIX with concomitant ACLR.

3.2 Re-operation

Twenty-six publications reported on the requirement for re-operation [3-5,8,10,11,13-15,17,18,20-23,25,26,28,30,32-34,37-40]. Meta-analysis of the 1484 tears reported 90% (95% CI: 86-93) success with 10% (95% CI: 7-14) requiring re-operation (**Figure 5**) at a weighted mean follow-up of 39.7 months.

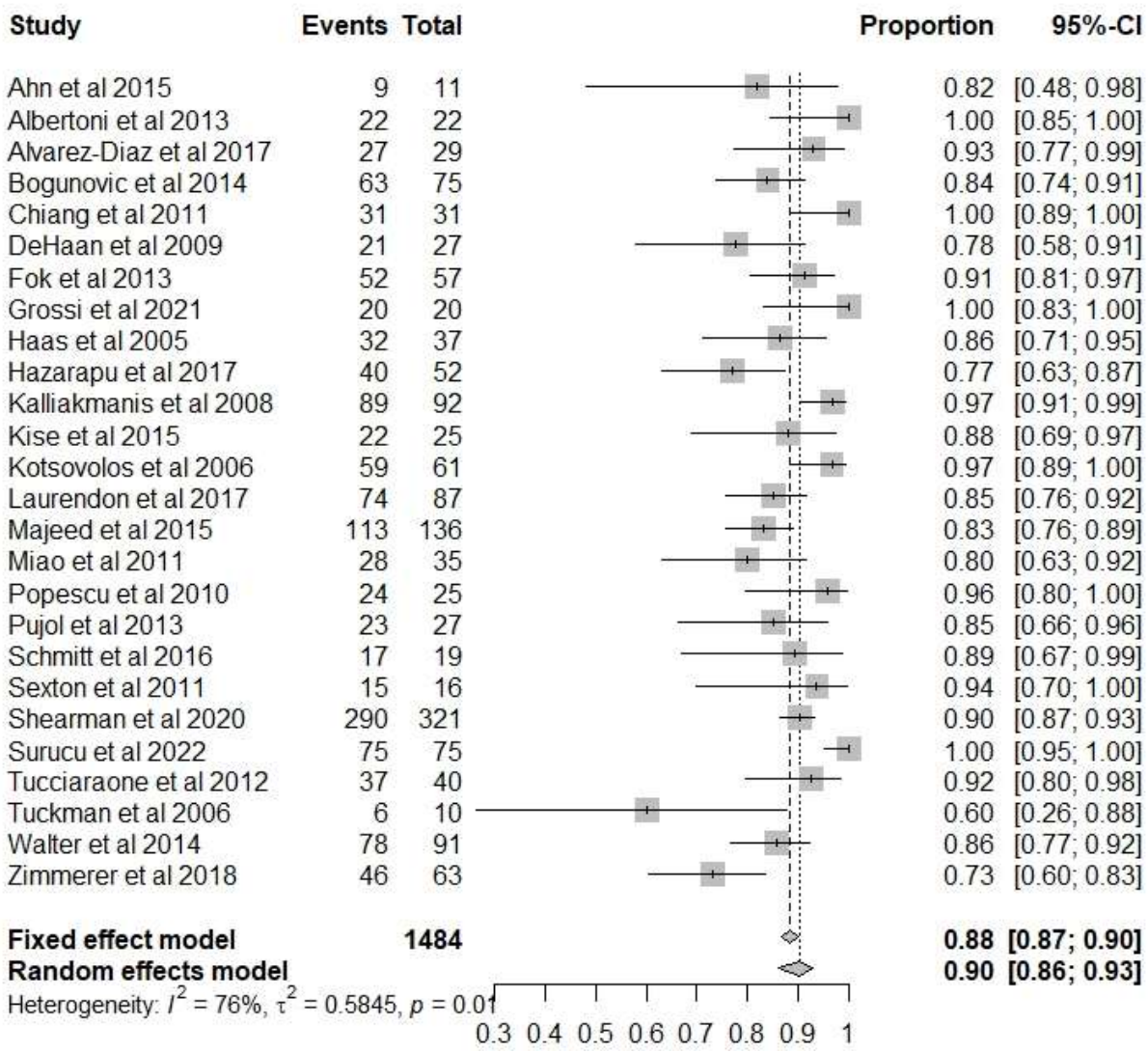

Figure 5: Rate of meniscal repair success (defined as not requiring meniscal re-operation) using FAST-FIX.

Fourteen studies reported reoperation rates for patients who underwent isolated meniscal repair[3-5,8,13,14,18,25,26,30,32,38,39,41]. Meta-analysis of 273 tears revealed 94% (95% CI: 91-96) success, with 6% (95% CI: 4-9) requiring re-operation (**Figure 6**) at a mean weighted follow-up of 36.5 months. Meta-analysis of 562 tears from 13 studies reporting on re-operation rate following repair of meniscal tear with concomitant ACLR found 89% (95% CI: 86-91) success with 11% (95% CI: 9-14) requiring re-operation (**Figure 7**) at a mean weighted follow-up of 42.9 months[4,5,8,10,13,14,23,25,26,32,38-40].

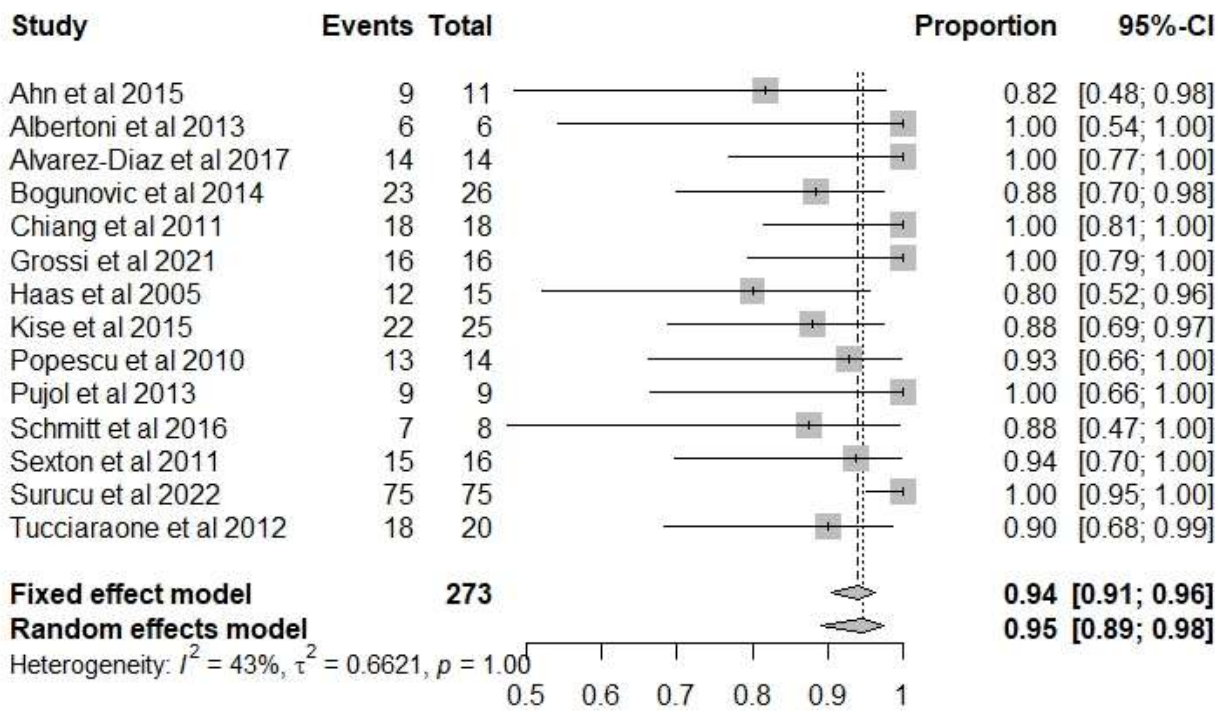

Figure 6: Rate of isolated meniscal repair success (defined as not requiring meniscus re-operation) using FAST-FIX.

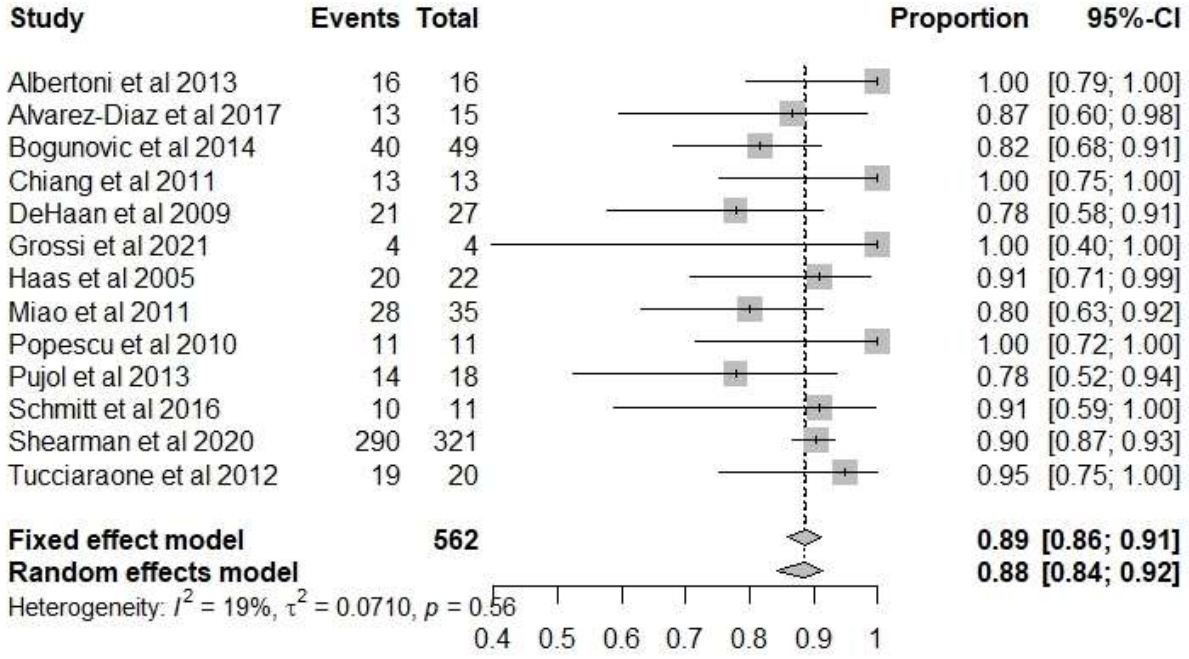

Figure 7: Rate of meniscal repair using FAST-FIX with concomitant ACLR success (defined as not requiring meniscus re-operation).

4.4 Patient reported outcome measures

The systematic literature review identified 27 publications reporting one or more of PROMs of interest: IKDC (nine studies)[4,11,14,21,24,27,32,36,38], Lysholm (18 studies)[3,4,6-10,12,14,16,17,20,24,25,27,29,30,36] and Tegner activity scores (11 studies)[3,5,6,8,9,18,20,25,28,29,37].

IKDC is an assessment tool that measures seven items related to patient symptoms, two related to function and two to sport activities. Scoring ranges from '0' (lowest function, highest symptom), to 100 (highest function, lowest symptom)[42]. Analysis of IKDC was performed from 9 studies, with data from Bogunovic *et al*[38] and Tucciaraone *et al*[32] provided as separate isolated tear and ACLR+ series. Two publications within the systematic literature review contained IKDC scores, however had excluded those patients with failed healing[26,39]. Due to the bias this may have on outcomes, these two studies were excluded from analysis. All other data were provided as a complete study population. Following meniscal repair, weighted mean IKDC was calculated as 86.34 (95% CI: 83.89-88.79) across 439 patients (**Figure 8**) at a weighted mean follow-up of 37.4 months.

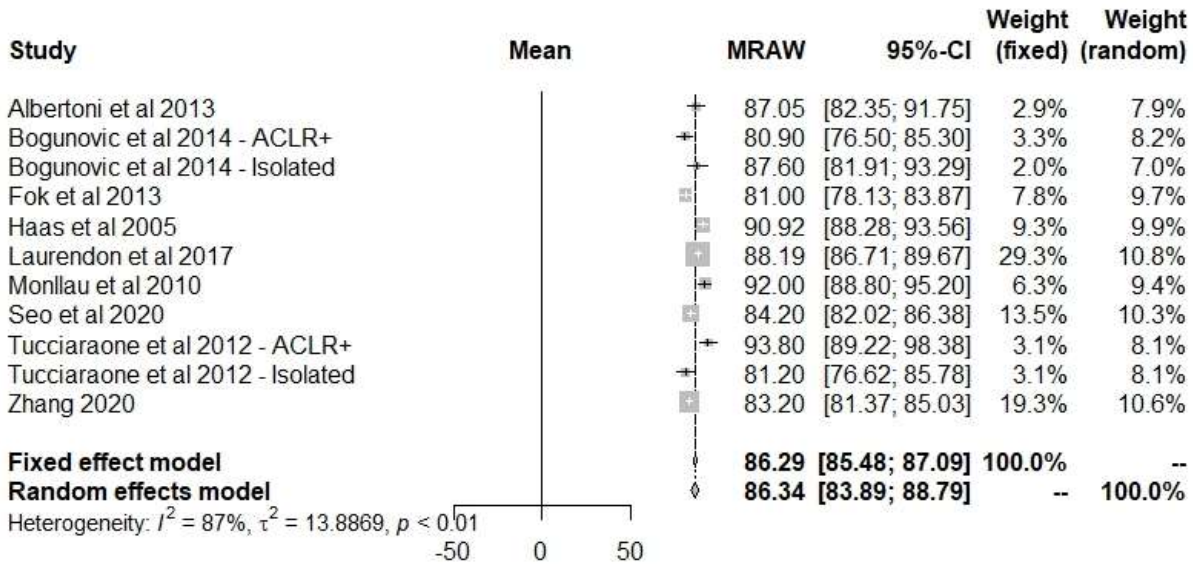

Figure 8: IKDC scores following meniscal repair using FAST-FIX.

Meta-analysis of 46 patients receiving repair of isolated meniscal repair reported a weighted mean IKDC of 84.60 (95% CI: 78.34-90.86) (**Figure 9**) at a weighted mean follow-up of 58.6 months[32,38]. Following meniscal repair with concomitant ACLR,

weighted mean IKDC was calculated as 84.84 (95% CI: 81.70-87.98) across 186 patients (**Figure 10**) at a weighted mean follow-up of 41.1 months[11,27,32,36,38].

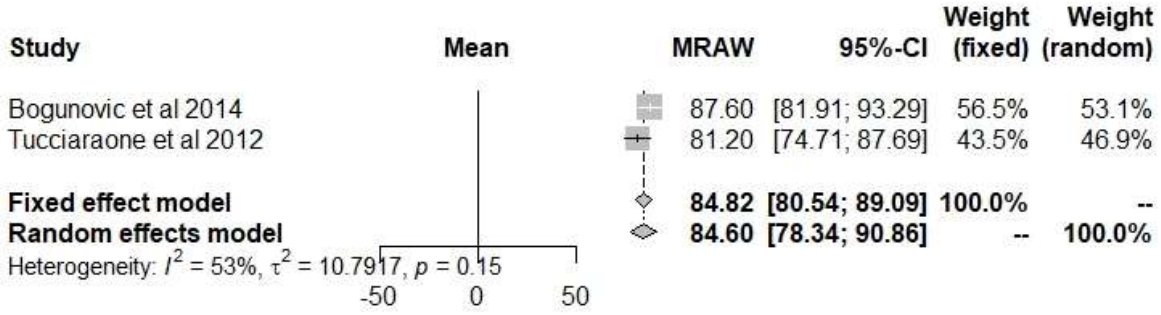

Figure 9: IKDC scores of isolated meniscal repair using FAST-FIX.

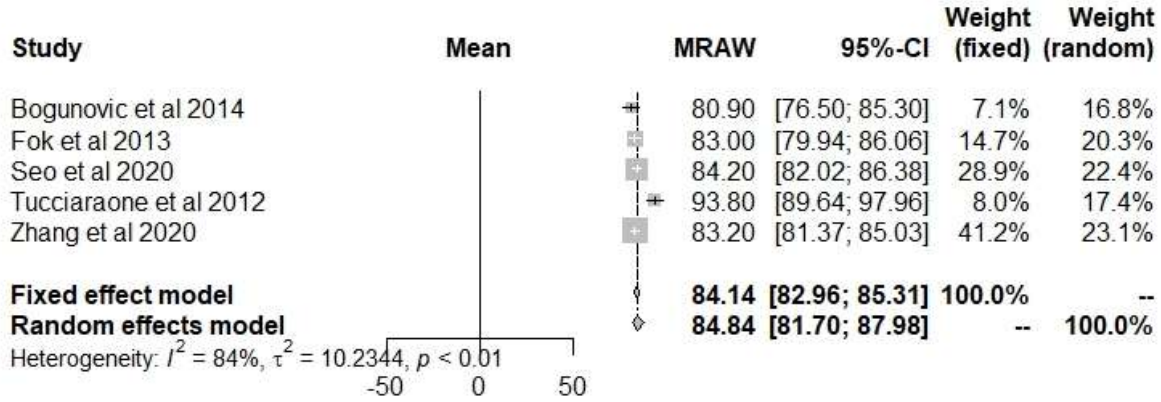

Figure 10: IKDC scores of meniscal repair using FAST-FIX with concomitant ACLR.

Lysholm score consists of eight items (pain, instability, locking, swelling, limp, stair climbing, squatting, support), with a range of 0-100 (greater score indicating better function with few symptoms). An overall score of 95-100 is considered excellent, with 84-94, good; 65-83, fair; and <65, poor[42]. As with IKDC, Lysholm score was reported as isolated and concomitant ACLR series from Hoffelner *et al*[16], with the other 17 publications providing full study cohort data. One publication within the systematic literature review contained mean Lysholm scores, however had separated the scores depending on success/failed healing[40]. Due to this split, these data were excluded from the analysis. Weighted mean Lysholm score was calculated as 89.43 (95% CI: 86.77-92.09) for 665 patients (**Figure 11**) at a weighted mean follow-up of 28.3 months. From this analysis, Surucu *et al*[30] reported a Lysholm score considerably

lower (69.63 sd 8.49; 75 patients) than that of the remaining 17 publications (all >81.0). While all patients within this study were >40 years of age and received isolated repair, the authors did not discuss any defining factor could be attributed to this lower score and believed the outcome to be successful.

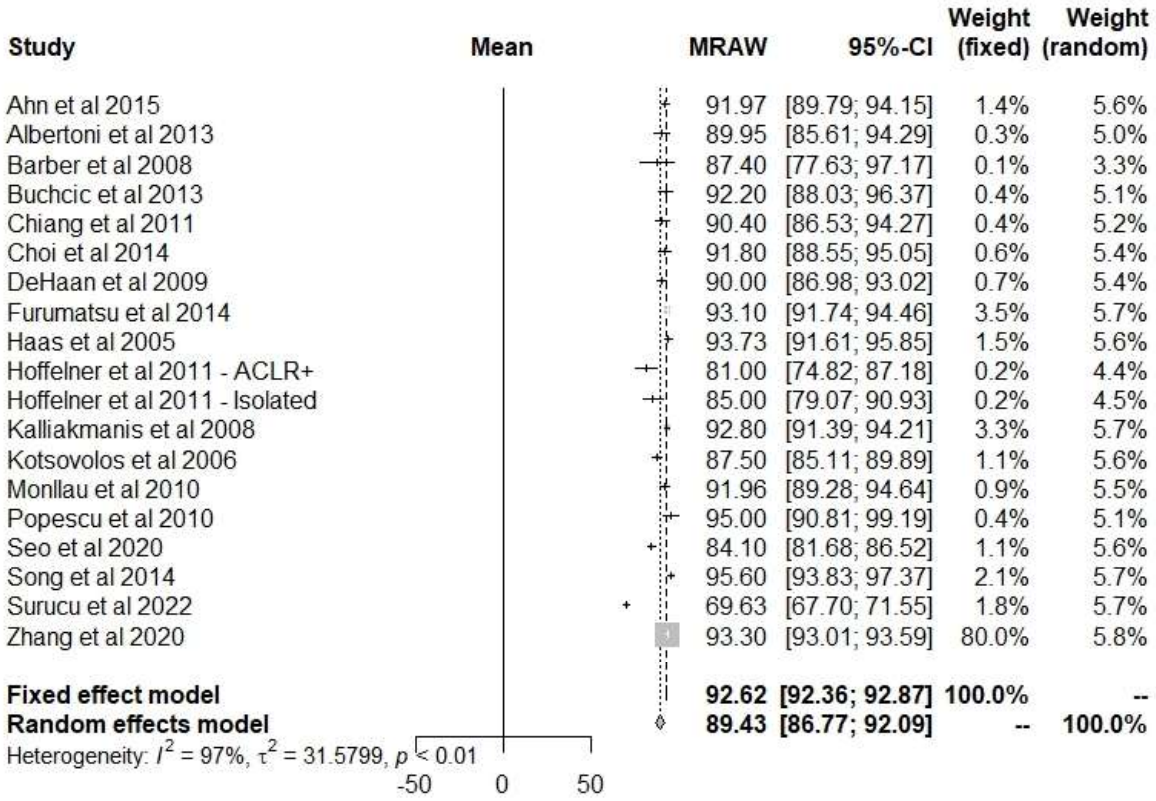

Figure 11: Lysholm scores following meniscal repair using FAST-FIX.

Meta-analysis of 151 patients receiving repair of isolated meniscal repair reported a weighted mean Lysholm of 85.64 (95% CI: 73.85-97.43) (**Figure 12**) at a weighted mean follow-up of 29.6 months[3,8,16,20,30]. Following meniscal repair with concomitant ACLR, weighted mean Lysholm was calculated as 90.78 (95% CI: 89.07-92.50) across 345 patients (**Figure 13**) at a weighted mean follow-up of 26.7 months[7-10,12,16,17,20,27,29,36].

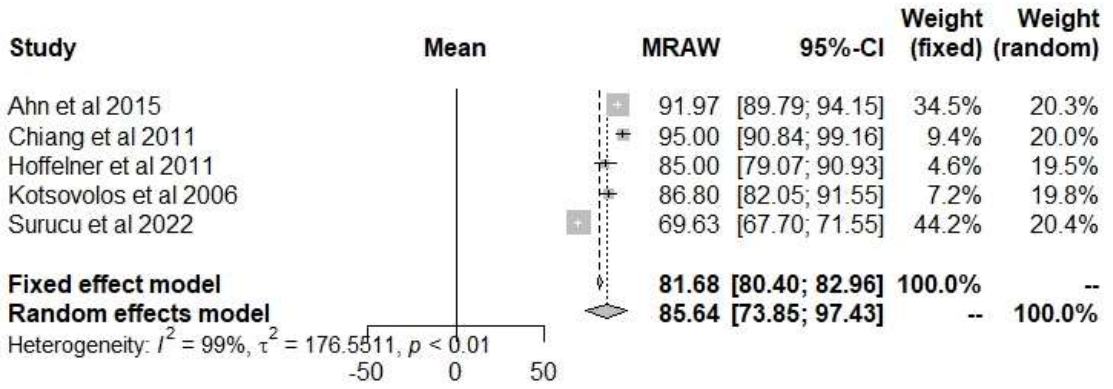

Figure 12: Lysholm scores following isolated meniscal repair using FAST-FIX.

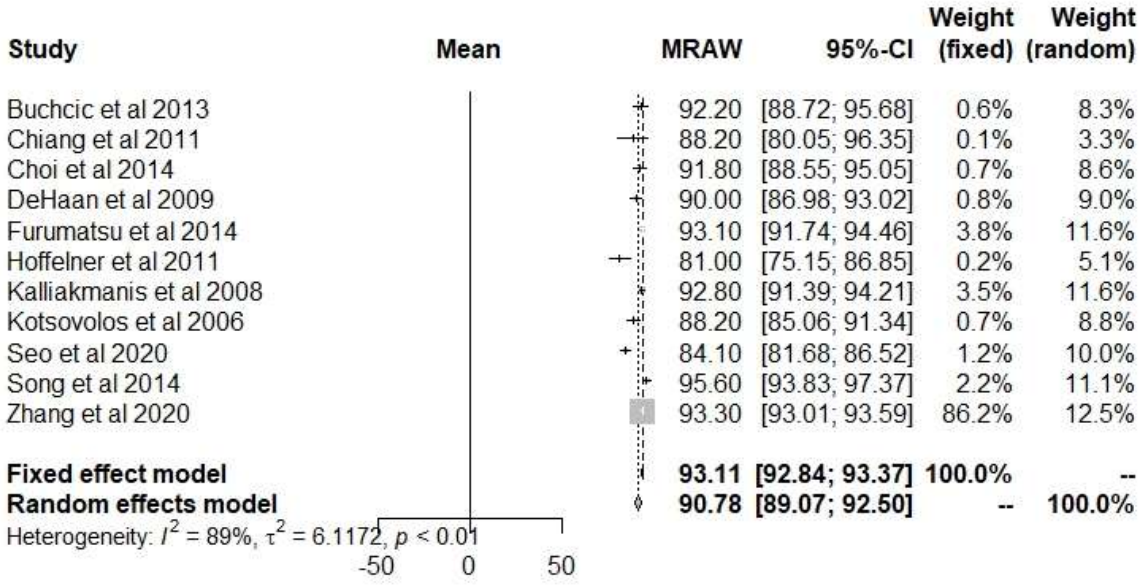

Figure 13: Lysholm scores following meniscal repair using FAST-FIX with concomitant ACLR.

Tegner activity scale is a single-item list of activities (rated 0-10) from which a patient selects their activity level (0-sick leave, 10-competitive sports (national elite)). Its purpose is to provide a method of grading work and sporting activity that may not be assessed using Lysholm. Of the 11 publications reporting Tegner scores, two only reported details for their isolated and ACLR+ cohorts (Alvarez-Diaz *et al*[5] and Chiang *et al*[8]) and have therefore been included as separate items. One publication within the systematic literature review contained mean Lysholm scores, however had separated the scores depending on success/failed healing[40]. Due to this split, these data were excluded from the analysis. Weighted mean Tegner score was calculated

as 6.22 (95% CI: 5.81-6.62, **Figure 14**) across 355 patients at a weighted mean follow-up of 54.5 months, equating to 'Recreational sports - tennis and badminton, handball, racquetball, down-hill skiing, jogging at least 5 times per week' on the Tegner activity scale[43].

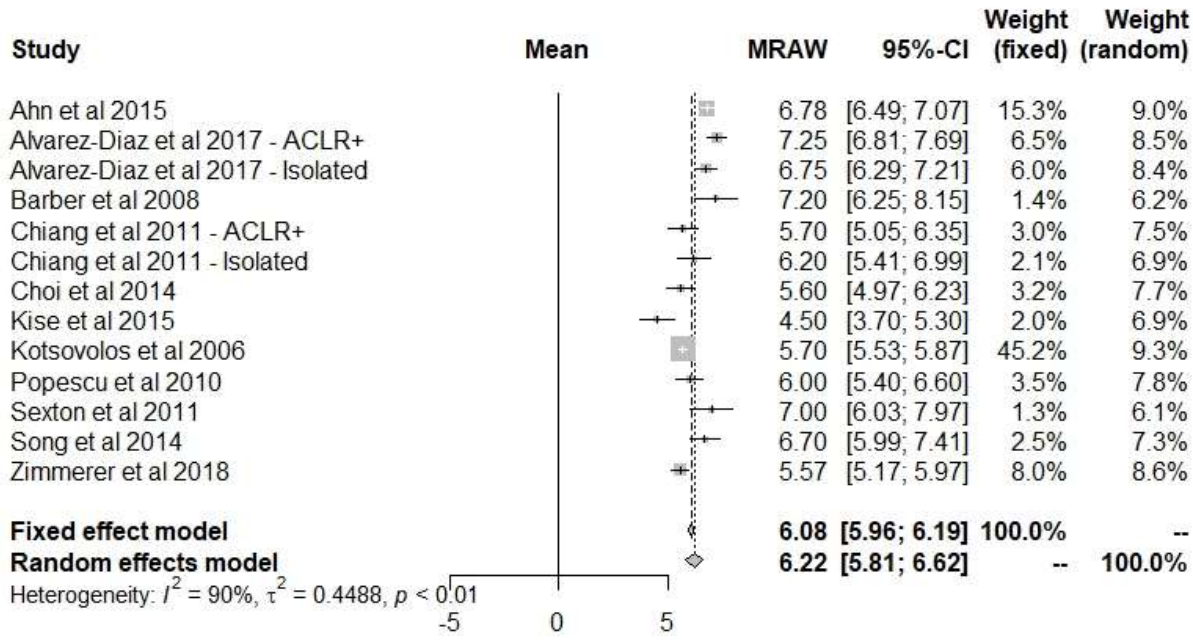

Figure 14: Tegner activity score following meniscal repair using FAST-FIX.

Meta-analysis of 136 patients receiving repair of isolated meniscal repair reported a weighted mean Tegner activity score of 6.15 (95% CI: 5.63-6.67) (**Figure 15**) at a weighted mean follow-up of 46.5 months[3,5,8,18,20,28,37]. Following meniscal repair with concomitant ACLR, weighted mean Tegner activity score was calculated as 6.07 (95% CI: 5.50-6.64) across 158 patients (**Figure 16**) at a weighted mean follow-up of 72.2 months[5,8,9,20,29,37].

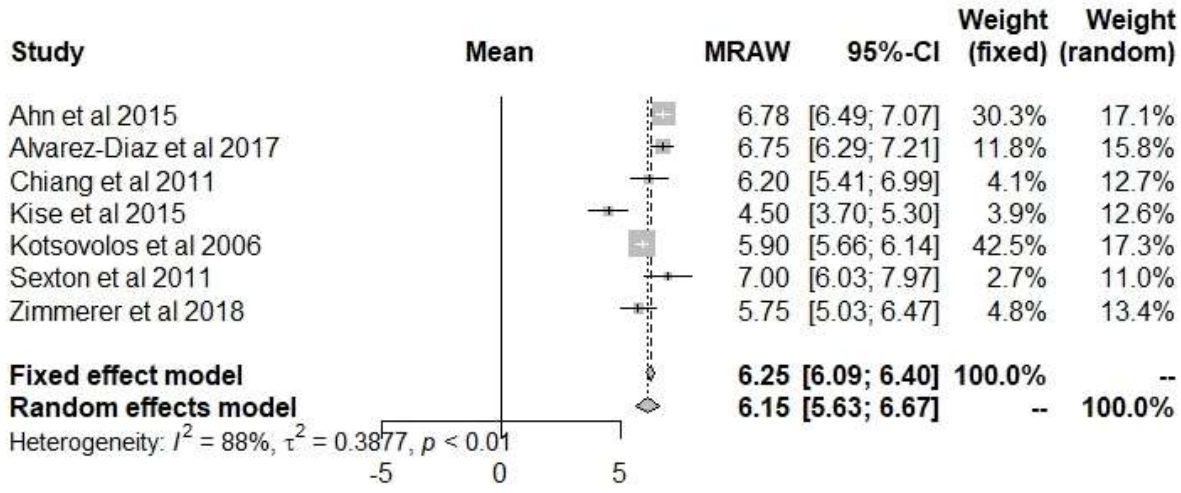

Figure 15: Tegner activity score following isolated meniscal repair using FAST-FIX.

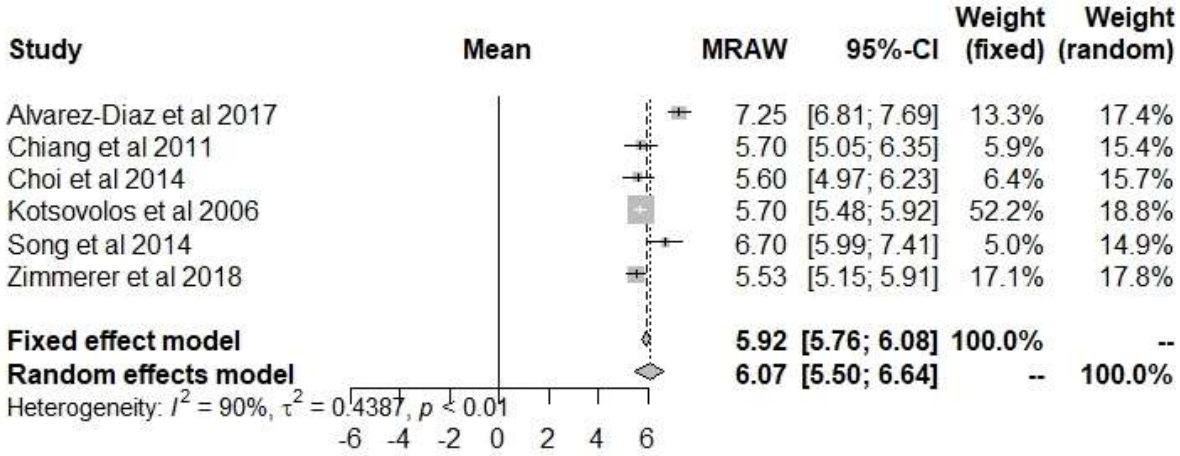

Figure 16: Tegner activity score following meniscal repair using FAST-FIX with concomitant ACLR.

4. Discussion

A volunteer cohort (n=488, 244 male, 244, female; >18 years, range: 18-85) who considered themselves to have normal knee function, without previous injury reported a mean Lysholm score of 94 and Tegner score of 5.7[44]. Categorising the Lysholm results according to the previously mentioned criteria, 66% were 'excellent', 25% 'good', 9% 'fair' and <1 % 'poor'. These normative scores are similar to the post-operative study cohort Lysholm and Tegner scores reported in this meta-

analysis (89.43 (95% CI: 86.77-92.09) and 6.22 (95% CI: 5.81-6.62); respectively). In the present study the mean Lysholm score would be considered a good score. It should be noted that Tegner scores are likely to have a ceiling effect for each patient determined by their sporting involvement and level prior to injury.

A similar healthy volunteer study of 2670 individuals was conducted to assess IKDC scores across eight age/gender categories[45]. The report identified a negative correlation between score and age, and a higher score for men (mean range: 95.5 (18-24 years old), 88.4 (51-65 years old)) than women (mean range: 93.4 (18-24 years old), 84.7 (51-65 years old). The mean IKDC for the population of patients reported in this systematic literature review (86.34; 95% CI: 83.89-88.79) is on average 4 points lower than the overall population normative data (91.67; 95% CI: 89.65-93.68).

5. References

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Reviewer (Title)	Signature	Date
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Version	Date issued	Reason for re-issue
V1	9th August 2022	Initial release
V2	7th October 2022	Update to include additional analyses of PROM and minor correction of numerical errors
V3	29th Nov 2022	Correction to IKDC ACLR+ Zhang score

22.11 R&D Internal Evidence for MAT Indication

The full R&D internal evidence, dated 03/Apr/2023, for the MAT indication is appended below.

FAST-FIX™ FLEX Memo

FAST-FIX™ FLEX

Memo

Product	FAST-FIX FLEX
Risk Management File Number	RM-M-16500559

Smith+Nephew

FAST-FIX™ FLEX Memo

1. FAST-FIX FLEX KNEE INDICATIONS RATIONALE

The FAST-FIX™ family of All-Inside Meniscal Repair devices have been designed to meet all clinical needs when utilized to repair or reconstruct multiple types of tissue tears. This memo will describe the biomechanical requirements of the knee indications listed below and demonstrate the clinical value of the FAST-FIX FLEX family of devices.

Catalog #	Name
72205324	FAST-FIX™ FLEX CURVED INSERTER, BENDER, CANNULA SET
72205325	FAST-FIX™ FLEX REVERSE CURVED INSERTER, BENDER, CANNULA SET
72205676	FAST-FIX™ FLEX CURVED INSERTER
72205677	FAST-FIX™ FLEX REVERSE CURVED INSERTER

INDICATIONS per IFU 10601463 & 10601589

> **The FAST-FIX FLEX Meniscal Repair System is indicated for use in meniscal repairs, allograft transplant procedures, and anchoring the allograft to the meniscal rim during allograft transplant procedures.**

BACKGROUND

FAST-FIX™ represents a family of meniscal repair devices that are designed to provide reliable tissue fixation in Meniscus Repair (MR). The devices are also used for Meniscal Allograft Transplantation (MAT), which is a surgical option to treat patients with symptomatic compartmental overload after total or subtotal meniscectomies. In clinical practice, meniscal allograft transplantation (MAT) is a well-established surgical procedure that has demonstrated satisfactory results in terms of survival, clinical outcomes, return to sport, and efficacy in preventing or delaying osteoarthritic changes. Satisfactory clinical results for pain reduction and improved knee function have been demonstrated in more than 55 studies and 1500 patients.[1]

The purpose of this memo is to provide a rationale for pooling a singular patient population for both Meniscal Repair (MR) and Meniscal Allograft Transplantation (MAT) reconstruction procedures using the FAST-FIX family of Meniscal Devices. Multiple tear types are repaired using the All-Inside technique by using a combination of longitudinal and horizontal stitch patterns. The rationale explained in this Memo will consider (A) Similarities in tear configurations between longitudinal vertical tears and MAT approximation to the native tissue, (B) restoration of native Biomechanical kinematics post-MAT, and (C) clinical uses of all-inside meniscus fixation devices for MAT reconstruction. The common surgical technique used for both repair and the graft attachment method utilized across all indications will be highlighted.

FAST-FIX™ FLEX Memo

(A) LONGITUDINAL VERTICAL MENISCUS TEAR PRESENTATION VS MAT

The meniscus is an important structure in load distribution, shock absorption, joint lubrication, stability, and proprioception. The dramatic consequences of total meniscectomy, together with advances in surgical techniques, has resulted in a significant increase in meniscus preservation/repair procedures. Meniscal tissue is relatively avascular. The peripheral third of the meniscus, referred to as the red-red zone, is vascularized, supplied by the medial and lateral genicular arteries. The central transition zone, called the red-white zone, also has some nutrition from blood, while the remaining inner third of the meniscus, referred to as the white-white zone, must receive its nutrition through synovial fluid diffusion. Due to the avascular nature of the tissue, meniscectomy of the inner third is presently the standard of care.

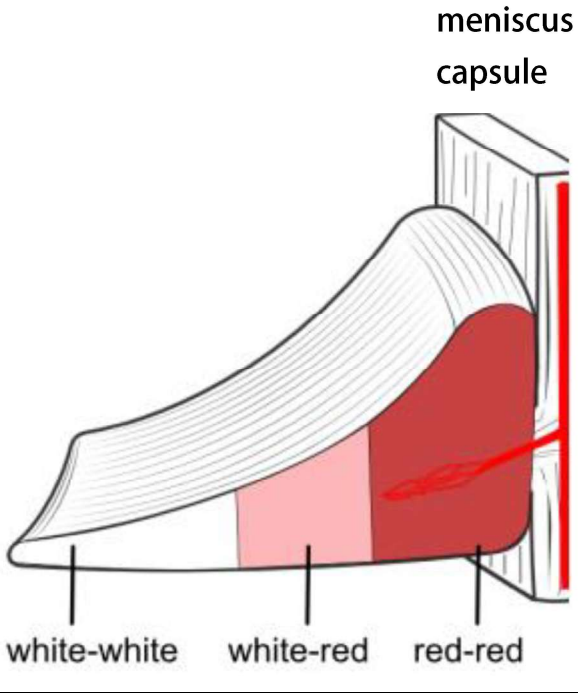

Figure 1: Meniscus Zones

As shown above, the outer vascular meniscal tissue is tightly integrated with the surrounding capsule. Research has shown that the meniscus capsule, which circumferentially covers the meniscus, sustains the hoop stress in part by showing about 4.2% to 30.0% circumferential tensile modulus of the corresponding adjacent meniscus. Also, the meniscus capsule is thick and circumferentially oriented, showing morphological similarity with the meniscus itself that is presumed to effectively sustain the hoop stress. [2]

Longitudinal vertical tears present as a tear running parallel to the outer perimeter of the meniscus and extending vertically, either completely or partially, through the meniscus. Vertical tears are one of the

most common tear types, and, if left untreated, can progress into large bucket-handle tears. Repair is important to preserve ~~the~~ meniscus integrity and function.

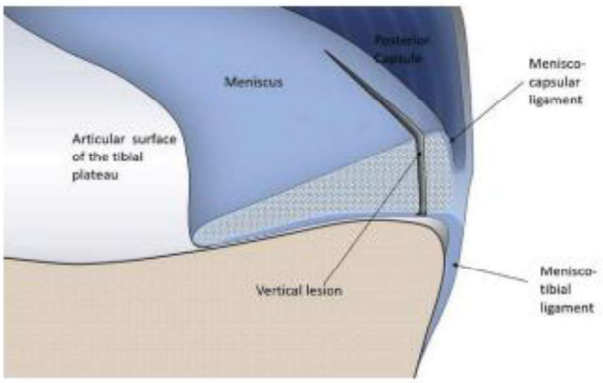

Figure 2: Longitudinal vertical meniscus tear. [3]

The all-inside repair technique is often used to repair longitudinal vertical tears. This technique takes advantage of the load-sharing capabilities of the thick meniscus capsule to anchor the two PEEK implants. As shown below, both the curved and reverse curved FAST-FIX devices provide access necessary to place repair stitches in a vertical fashion on the superior (curved device) and inferior (reverse-curved device) surfaces. Small, partial thickness tears can be repaired using a single device, as shown in Figure 3A. For larger tears or tears extending completely through the meniscus, several stitches are used to complete the repair, as shown in Figure 3B. The repair suture pattern used is referred to as a vertical mattress suture.

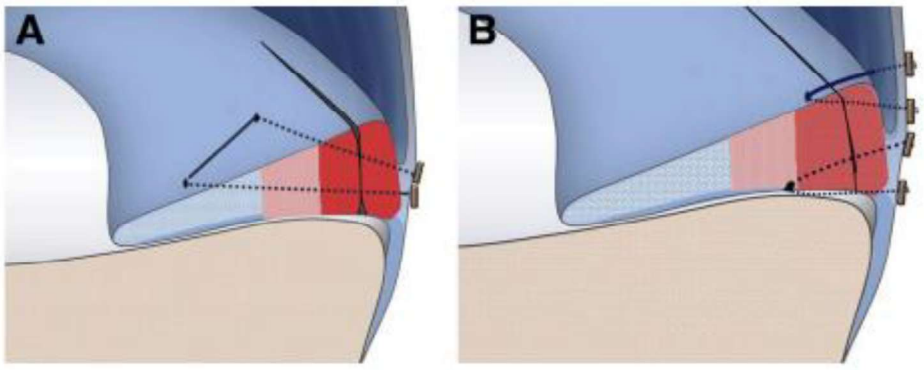

Figure 3: All-Inside Repair techniques for longitudinal vertical tears. (A) represents a single curved device used to position two PEEK anchors along the outer capsule, and (b) demonstrates a curved device used to place the upper suture combined with a reverse curve device used to place the lower suture. [3]

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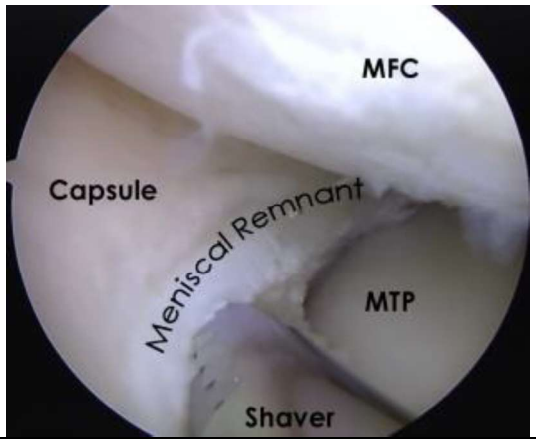
The MAT surgical technique includes a step to prepare the native meniscus to receive the allograft. The preparation step removes the avascular portion of the native meniscus, while preserving a portion of the vascular circular rim adjacent to the capsule, as shown in Figure 4. Comparing the longitudinal vertical tear above to the MAT tissue remnant, one can see the same vertical gap presentation as the longitudinal vertical tear. As such, the same all-inside repair techniques used for longitudinal vertical tears is also employed to re-approximate the allograft to the preserved native vascular tissue. All-inside devices have historically been used to attach the posterior region of the allograft. The added bend capabilities of the FAST-FIX FLEX device has extended All-Inside usage to the mid and anterior thirds of the meniscus as well.



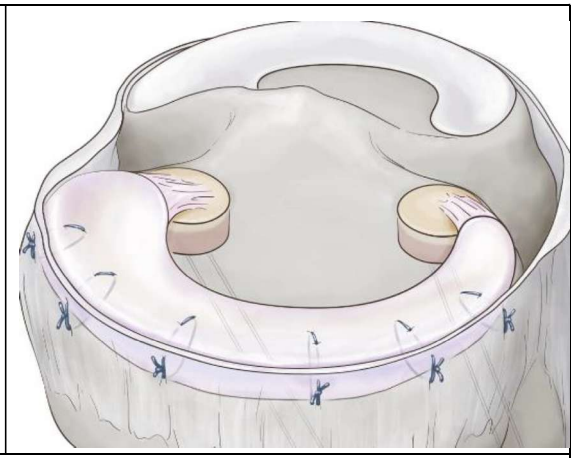


Figure 4: MAT native remnant preserved for attachment of allograft.

The most significant advantages of the All-Inside meniscal repair technique include ease of use, reduced surgical times, and reduced risk to the neurovascular structures. Many tear types can be repaired using the FAST-FIX FLEX device, including longitudinal vertical, horizontal, radial, oblique, and complex tears.

(B) BIOMECHANICAL FORCES POST-MAT PROCEDURE

Real in-vivo compartment loads experienced by menisci have been studied using experimental cadaveric data under limited simulated loading conditions or numerical simulations data to give us rough estimation of forces experienced under dynamic loading conditions. These simulation data are highly dependent on types and accuracy of assumptions, simulation model, boundary conditions, etc. However, the similarities in the results from these studies combined with the clinical evidence of success provide valuable insight into the benefits of MAT.

McDermott completed human cadaveric biomechanics study that simulated four different contact pressure testing conditions for each knee: 1. Intact 2. Meniscectomy 3. Graft with bone block plus sutures 4. Graft with sutures only. A significant difference was not found between the peak contact pressure after the reconstructions and that of the intact knee when loaded in axial compression up to 700 N. [4] Brial conducted a similar joint contact mechanics study that assessed the contact area, peak contact stress, and

the distribution of stress across the tibial plateau at 14% and 45% of the gait cycle, at which axial forces are at their highest. Translation of the weighted center of contact stress throughout simulated gait was computed. The native intact meniscus and several MAT transplantation fixation techniques keyhole technique was not significantly different from the intact condition. [5]

Macchiarola demonstrated strong improvement in several key biomechanical metrics using an in-vivo surgical navigation system on 10 consecutive patients undergoing lateral MAT. The biomechanical effect of MAT restored knee functionality to clinically acceptable values. MAT improved knee kinematics of the ACL-intact knee. Several key metrics were significantly improved postoperatively. This is the first study to analyze the in vivo kinematics of MAT.[6]

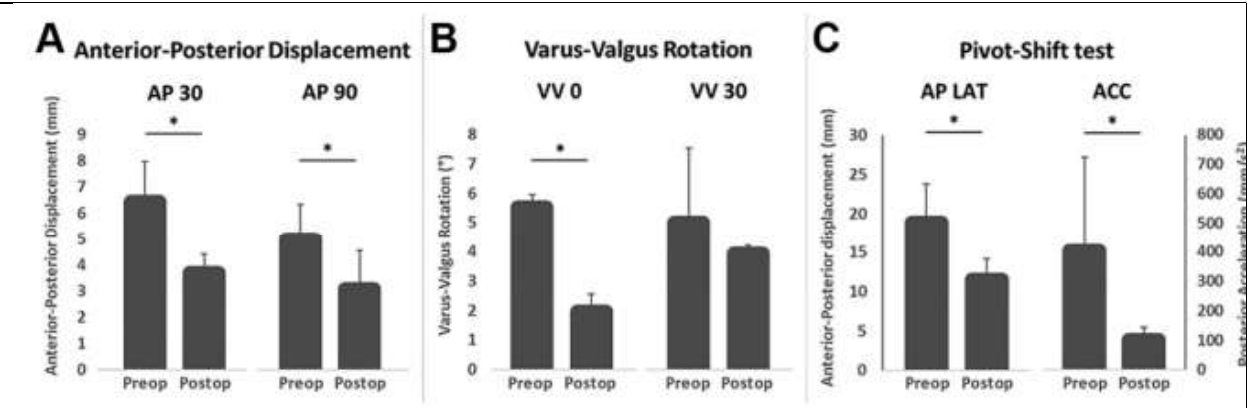


Figure 5: Pre- and postoperative in-vivo improvement in AP Displacement, Varus-Valgus Rotation, and dynamic laxity during Pivot Shift testing.

It is important to note that during healing period, generally the graft does not reach the level of its normal physiological loadings. In rehabilitation period, only controlled exercises are recommended to patients and the intensity of loadings are increases gradually over a period of months to reach normal loadbearing scenarios.

Additional studies corroborate the conclusions expressed above, including Spang [7] and Novaretti [8]. These biomechanical studies conclude that MAT procedures can restore intra-articular knee kinematics, resulting in a similar biomechanical environment to the native intact meniscus.

(C) CLINICAL APPLICATION OF ALL-INSIDE DEVICES FOR MAT

All-Inside Meniscal Repair devices, such as the Smith+Nephew FAST-FIX products, are commonly being used for MAT procedures. These fixation devices approximate the meniscal allograft to the preserved outer rim of the native meniscus. This interface presents as a vertical surface between the allograft and vascular tissue of the native meniscus. The FAST-FIX device utilizes a high strength non-absorbable suture and allows the repair to be performed with a vertical mattress suture. A literature search was completed to provide representative examples of the common surgical technique and graft fixation method used to complete MAT procedures using All-Inside Meniscal Repair devices.

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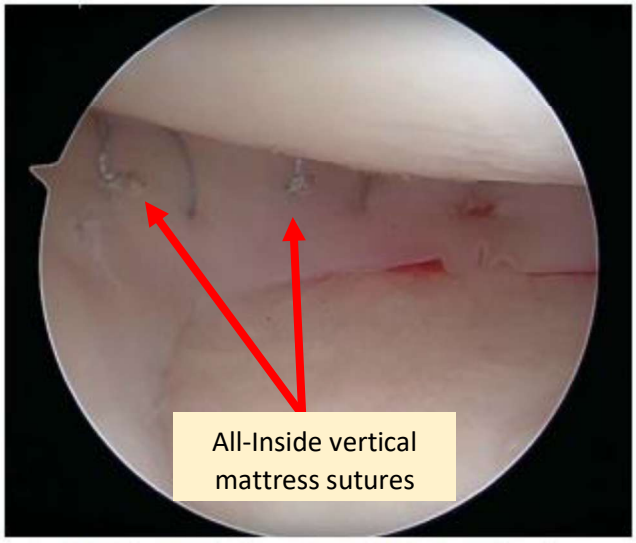
1. Meniscal Allograft Transplantation surgical technique is described by Cole [9]. An All-Inside fixation technique is described to secure the posterior portion of the allograft to the preserved native meniscal remnant using vertical mattress sutures. Comparing to Figure 3, the same vertical mattress suture pattern is used for this MAT procedure.



Arthroscopic image of a knee shows the meniscal allograft secured posteriorly via an all-inside technique. The peripheral aspects of the graft are secured with the use of 8 to 10 vertical mattress sutures via an inside-out technique.

Figure 6: Example of All-Inside vertical mattress sutures used in a MAT procedure.

2. Cugat also demonstrate a surgical technique using FAST-FIX devices to attach the posterior horn of the allograft to the vertical native meniscal rim preserved to provide vascular attachment. [10] Again, comparing to Figure 3, the same vertical mattress suture pattern is used for this MAT procedure to couple the posterior portion of the allograft.

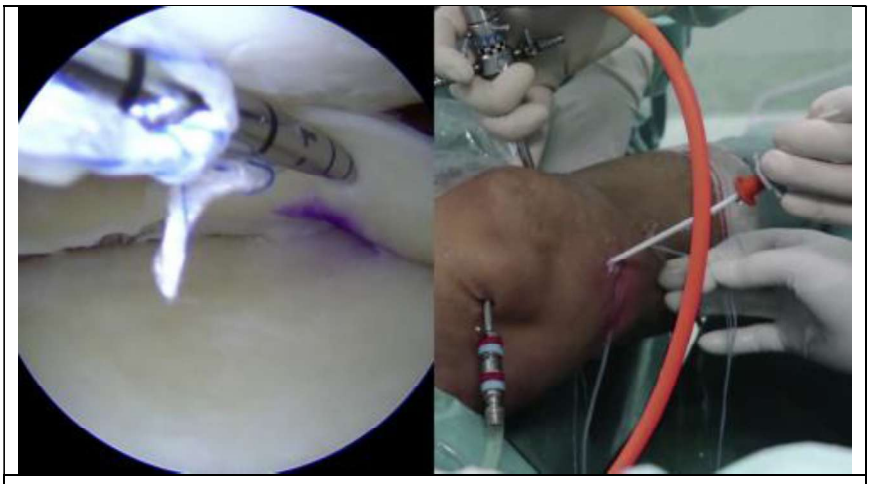


Figure 7: All-Inside reinforcement of the attachment of the posterior horn of the meniscal allograft to the posterior meniscal rim using a FAST-FIX 360 device.[10]

In each of the MAT procedure scenarios listed above, the device is used to reapproximate two opposing vertical surfaces in a common manner using a vertical mattress stitch. The PEEK implants are placed along the outer surface of the capsule adjacent to the meniscus. Suture reduction follows to bring the tissue together with the desired tension.

Post-operative protocols are similar to MR. At 4-6 weeks, patients are allowed full weightbearing and unrestricted ROM. Stationary biking with low resistance and straight leg swimming are also started at that time. Progressive, low-impact strengthening is implemented when the gait pattern has returned to normal.

Several important similarities have been highlighted in this memo. Firstly, All-Inside meniscus repair of longitudinal vertical tears using vertical mattress sutures is representative of the tissue re-approximation method used in MAT procedures. Secondly, numerous studies have concluded that MAT procedures can restore intra-articular contact pressures and knee kinematics, resulting in a similar biomechanical environment to the native intact meniscus. Therefore, based on the anticipated clinical loading for the stated knee indications, the All-Inside implant performance requirements are the same for both MR and MAT environments. In general, the mechanical fixation demand is the highest during the healing period and does reduce by biological incorporation of the tissue. Thirdly, the same use steps and sequence are utilized to complete the repair/reconstruction. The procedural technique, device use, and resulting suture placement is identical for meniscus MR and MAT.

Based on the above-mentioned factors, the benefit from efficacy pooling with the larger sample size provides increased coverage, despite the added heterogeneity, given the common method of assessing effectiveness, surgical technique, surgical instrumentation, and identical surgeon populations.

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3. Author Signature

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Matthew.Cunningham@smith-nephew.com
IP Address: 216.222.208.4

Record Tracking

Status: Original
03-Apr-2023 | 17:22

Holder: Matthew Cunningham
Matthew.Cunningham@smith-nephew.com

Location: DocuSign

Signer Events	Signature	Timestamp
Martin Ma martin.ma@smith-nephew.com Clinical Director Smith & Nephew Security Level: Email, Account Authentication (Required)	Martin Ma Signature Adoption: Pre-selected Style Signature ID: 01600B76-EFFA-4F53-899A-9447514407BF Using IP Address: 216.222.208.4 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 03-Apr-2023 | 17:26 Viewed: 03-Apr-2023 | 20:03 Signed: 03-Apr-2023 | 20:04
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Matthew Cunningham matthew.cunningham@smith-nephew.com Principal Development Engineer Smith & Nephew Security Level: Email, Account Authentication (Required)	Matthew Cunningham Signature Adoption: Pre-selected Style Signature ID: A1C7C571-95EE-4394-BE1F-C307A0DCDDF1 Using IP Address: 216.222.208.4 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 03-Apr-2023 | 17:26 Viewed: 03-Apr-2023 | 17:26 Signed: 03-Apr-2023 | 17:27
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	03-Apr-2023 | 17:26
Certified Delivered	Security Checked	03-Apr-2023 | 17:26
Signing Complete	Security Checked	03-Apr-2023 | 17:27
Completed	Security Checked	03-Apr-2023 | 20:04

Payment Events	Status	Timestamps

DocuSign

Certificate Of Completion

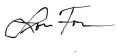
Envelope Id: 624B2A8301204E9E911A5804BEE3A20C
Status: Completed
Subject: Complete with DocuSign: FAST-FIX_FLEX.2020.09_Protocol_V3.0 dated_05May2023 clean FINAL.pdf
Source Envelope:
Document Pages: 187
Signatures: 6
Certificate Pages: 6
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC) Dublin, Edinburgh, Lisbon, London

Envelope Originator:
Lucy O'Mara
TJ Smith & Nephew Limited
101 Hessle Road
Hull, Hull HU3 2BN
Lucy.O'Mara@smith-nephew.com
IP Address: 216.222.214.6

Record Tracking

Status: Original
09-May-2023 | 10:52
Holder: Lucy O'Mara
Lucy.O'Mara@smith-nephew.com
Location: DocuSign

Signer Events	Signature	Timestamp
Jay Jantz Jay.Jantz@smith-nephew.com Security Level: Email, Account Authentication (Required), Login with SSO	 Signature Adoption: Pre-selected Style Signature ID: B7D37248-838E-4CAC-AE11-E7E55198A88D Using IP Address: 216.222.219.1 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 09-May-2023 | 10:55 Resent: 16-May-2023 | 13:38 Resent: 16-May-2023 | 15:57 Viewed: 24-May-2023 | 03:58 Signed: 24-May-2023 | 03:59
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Jorge Chahla jorge.chahla@rushortho.com MOR Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 477C0B65-908D-4B6C-A2EF-20C0BA975830 Using IP Address: 50.202.185.10 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 09-May-2023 | 10:55 Viewed: 09-May-2023 | 16:11 Signed: 09-May-2023 | 16:16
Electronic Record and Signature Disclosure: Accepted: 30-Apr-2021 | 23:32 ID: dd14962a-83ee-4dd9-8fa4-e08242acdc2d		

Signer Events	Signature	Timestamp
Lori Fontaine Lori.Fontaine@smith-nephew.com Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 01CFB53A-1ADE-40E3-B2C9-47E8353635A1 Using IP Address: 216.222.208.4 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 09-May-2023 | 10:55 Viewed: 09-May-2023 | 14:37 Signed: 09-May-2023 | 14:38
Electronic Record and Signature Disclosure: Accepted: 17-Sep-2021 | 13:04 ID: 4dde530c-4aa7-43e7-8d25-4a80b3ea0c2c		
Martin Ma martin.ma@smith-nephew.com Clinical Director Smith & Nephew Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 01600B76-EFFA-4F53-899A-9447514407BF Using IP Address: 204.9.32.4 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 09-May-2023 | 10:55 Viewed: 10-May-2023 | 02:09 Signed: 10-May-2023 | 02:10
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Rachael Winter rachael.winter@smith-nephew.com Clinical Sr. Director Smith & Nephew Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: A32F12A8-0F1B-4490-986E-80ACCB7471CB Using IP Address: 194.207.232.40 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 09-May-2023 | 10:55 Resent: 16-May-2023 | 13:38 Viewed: 16-May-2023 | 15:55 Signed: 16-May-2023 | 15:56
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Sam Timson sam.timson@smith-nephew.com Clinical Research Analyst 3 Smith & Nephew Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: 638643A3-6EEA-420D-8270-7565773EC196 Using IP Address: 208.127.123.112 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 09-May-2023 | 10:55 Viewed: 09-May-2023 | 10:56 Signed: 09-May-2023 | 11:03
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp
Rupali Soeters Rupali.Soeters@smith-nephew.com clinical strategy lead Security Level: Email, Account Authentication (Required) **Electronic Record and Signature Disclosure:** Accepted: 13-Jul-2021 | 16:29 ID: 43167dde-f2a2-4118-97f9-c646f0466a18	COPIED	Sent: 09-May-2023 | 10:55

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	09-May-2023 | 10:55
Certified Delivered	Security Checked	09-May-2023 | 10:56
Signing Complete	Security Checked	09-May-2023 | 11:03
Completed	Security Checked	24-May-2023 | 03:59

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

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