Sponsor Name and Address:	Smith + Nephew, Inc. 7135 Goodlett Farms Parkway Cordova, TN 38016
Investigational Product(s)	NOVOSTITCH PRO™ Meniscal Repair System
Protocol Author(s):	Kirsten Wall, MHS, CCRP, PMP Clinical Study Manager Smith + Nephew, Inc. Darvin Griffin, PhD Global Clinical Strategy Lead Smith + Nephew, Inc. Michelle Foster, BSc Senior Biostatistician Smith + Nephew, Inc.

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 "Circumferential Compression STITCH Repairs of Complex and Horizontal Cleavage Meniscal Tears", version 2.0, dated 07/APR/2020, and agree to abide by all provisions set forth herein.
I agree to comply with the Investigator's Obligations stipulated in Section 21.5 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**	**Date Signed** (DD/MMM/YYYY)

1.2 COORDINATING INVESTIGATOR APPROVAL

I have read the attached protocol entitled “Circumferential Compression STITCH Repairs of Complex and Horizontal Cleavage Meniscal Tears”, version 2.0, dated 07/APR/2020, and agree to abide by all provisions set forth therein.

Name, Address, Professional Position	**Signature**	**Date Signed** (DD/MMM/YYYY)

1.3 SPONSOR APPROVAL

	Job title	DocuSign Stamp
Rachael Winter, Global Clinical Operations	Director of Clinical Operations	DocuSigned by: Rachael Winter Signer Name: Rachael Winter Signing Reason: I approve this document Signing Time: 07-Apr-2020 | 19:50:28 BST A32F12A80F1B4490986E80ACCB7471CB
Stephan Mangin, Global Clinical Strategy	Director of GCS Sports Medicine and ENT	DocuSigned by: Stephan Mangin Signer Name: Stephan Mangin Signing Reason: I approve this document Signing Time: 08-Apr-2020 | 21:15:33 BST 77573411150E4841B3F03589FBBD3EAD
Alan Rossington, Global Biostatistics	Director of Biostatistics	DocuSigned by: Alan Rossington Signer Name: Alan Rossington Signing Reason: I approve this document Signing Time: 09-Apr-2020 | 19:22:58 BST 556E7DBFCA8A4287A7EE3EE9B5B3ABFD
Luca Orlandini, Medical Affairs	Vice President of Global Medical Affairs	DocuSigned by: Signer Name: Luca Orlandini Signing Reason: I approve this document Signing Time: 08-Apr-2020 | 13:32:01 BST FC872951AC1C4261B85EC7A7CD09ACDC

2. SYNOPSIS

Title of Study:	Circumferential Compression STITCH Repairs of Complex and Horizontal Cleavage Meniscal Tears

Study Design:	Prospective, multi-center, non-randomized clinical trial
	• 90 subjects total at up to 8 sites
	  ○ 2 groups:
	  ▪ At least 40 subjects with horizontal cleavage meniscal tears (HCT)
	  ▪ At least 40 subjects with complex meniscal tears
	• Follow-up: 2 years

Study Type:	Observational, prospective clinical follow-up study
Study Product:	NOVOSTITCH PRO™ Meniscal Repair System (NOVOSTITCH PRO) NOVOSTITCH PRO is intended for approximation of soft tissue in meniscal repair procedures.
Study Purpose:	The purpose of this study is to collect safety and clinical outcomes data from patients who underwent meniscal repair with the NOVOSTITCH PRO Meniscal Repair System.
Primary Objective:	The primary objective of this study is to assess the clinical success rate of NOVOSTITCH PRO at 12 months, defined as rate of freedom from reoperation due to meniscal repair failure in the study knee.
Secondary Objective(s):	The secondary objectives are to: • Assess the clinical success rate of NOVOSTITCH PRO at 6 months, defined as rate of freedom from reoperation due to meniscal repair failure in the study knee;

	• Assess the clinical success rate of NOVOSTITCH PRO at 24 months, defined as rate of freedom from reoperation due to meniscal repair failure in the study knee; • Assess clinical performance of NOVOSTITCH PRO by Patient Reported Outcomes (PROs) including the Knee Injury and Osteoarthritis Outcome Score (KOOS), International Knee and Documentation Committee (IKDC) Subjective, and Lysholm; • Evaluate pre- and post-procedure magnetic resonance imaging (MRI) and radiographs, and post-procedure needle endoscopy.
Safety Objective(s):	Assess safety with reported complications, adverse events, adverse device effects, unanticipated serious adverse device effects, and device deficiencies.
Sample Size:	90 subjects With an estimated clinical success rate of 80% at 12 months for the planned study, the 95% confidence interval for clinical success was calculated between 70% and 90%. Using an 84% success rate, the minimum enrollment is N=71. With an attrition rate of 10% per year, total enrollment is set to N=90.
Number of Study Sites:	Up to 8 sites, with a minimum of 3 sites
Targeted Global Regions:	United States (US)
Inclusion Criteria:	The subject will be eligible for the study if he or she meets all of the baseline screening and arthroscopy inclusion criteria. *Subjects will be eligible for the study if they meet all of the following criteria at the Baseline Screening:*

	1. Able and willing to give informed consent by voluntarily providing written informed consent in accordance with governing Institutional Review Board; 2. 18 to 70 years of age, inclusive at the time of screening; 3. History indicative of meniscal pathology (e.g., pain, mechanical symptoms described as locking, clicking or giving way); 4. Physical exam consistent with meniscus tear (e.g., locked joint, joint line tenderness and/or pain on meniscal compression); 5. If prior ligament reconstruction, the study knee is clinically stable; 6. Meniscal repair to be performed arthroscopically; 7. Preoperative MRI evidence consistent with a horizontal cleavage or complex meniscus tear in the symptomatic compartment; 8. Willing and able to comply with all study procedures and visit requirements, including MRIs, X-rays, and Case Report Forms (CRFs) completed by the subject. *Consented subjects may be included in the study only if, upon arthroscopic inspection during the procedure, their meniscal study lesion meets all of the following criteria:* 1. Meniscal tear amenable to repair with NOVOSTITCH PRO with or without the use of adjunct devices per the exclusion criteria; 2. Tear pattern is one of the following: a. Horizontal cleavage tear (HCT), or

	b. Complex multi-planar tear (combination of at least two of the following tears: horizontal, oblique, radial, vertical).
Exclusion Criteria:	The subject will be ineligible for the study is he or she meets any of the following exclusion criteria at the baseline screening or at arthroscopy. *Subjects will be excluded from the study if they meet any of following criteria at the Baseline Screening:* 1. Arthritis in the study knee (Kellgren-Lawrence Grade 3 or higher); 2. Body Mass Index (BMI) ≥40 kg/m^2; 3. Previous surgical meniscal repair or meniscectomy of the study meniscus; 4. Unstable knee; 5. Clinically significant malalignment of the study knee, and/or requiring osteotomy, and/or correction; 6. History of constitutional/systemic inflammatory/arthritic problem or pain condition, history of knee infection, vascular condition of legs, benign neoplasms of knee, hepatitis, and/or HIV; 7. Currently on any immunosuppressive therapy; 8. Expected to undergo any other surgical treatment of either knee; 9. Previously enrolled in the study (no bilateral knee surgeries); 10. Surgical procedures other than those listed in the Indications for Use; 11. Patient conditions including insufficient quantity or quality of tissue;

	12. Insufficient blood supply or previous infections which may hinder the healing process; 13. Foreign body sensitivity. If material sensitivity is suspected, testing should be completed prior to suture implantation; 14. Conditions which may limit the patient's ability or willingness to follow postoperative care instructions; 15. Any concomitant painful or disabling disease, condition or post-procedure status of either lower extremity that would interfere with evaluation or rehabilitation of the study knee; 16. Pregnant or planning to become pregnant in the next 2 years; 17. Subject does not understand a language in which the PROs and EQ-5D-5L are available. *Subjects will be excluded from the study if their study meniscus lesion meets any of the following criteria at arthroscopy:* 1. Ramp tears; 2. Root or other tear type requiring tibial fixation; 3. Tears requiring repair of both meniscus in the study knee; 4. Intact or partially intact meniscus tear that, in the opinion of the Investigator, does not require repair; 5. Poor meniscal tissue quality such that it will not hold a suture; 6. For HCTs: a. Use of any capsular fixation device; OR b. Any portion of the meniscal tear is repaired using a device to place stitches other than NOVOSTITCH PRO, Meniscus Mender II, or

	Meniscal Stitcher, or FIRSTPASS MINI marketed by Smith + Nephew Inc.; 7. For complex tears: a. Any portion of the meniscal tear is repaired using a device to place stitches other than NOVOSTITCH PRO, Meniscus Mender II, Meniscal Stitcher, FIRSTPASS MINI, FAST-FIX 360, or ULTRA FAST-FIX marketed by Smith + Nephew Inc.; 8. Clinically significant (zone 1 and/or zone 2) tear in the contralateral compartment to the study meniscus; 9. Performance of a significant concomitant procedure (e.g. ACL reconstruction or repair, cartilage repair or restoration) intended as a therapeutic intervention on the study knee; 10. Presence of infection; 11. Articular cartilage damage in the study knee, defined as Modified Outerbridge Grade III or higher.
Study Duration:	Estimated to be 42 months (16 months for subject enrollment + 26 months for completion of follow-up)
Primary Endpoint:	Rate of reoperation due to meniscal repair failure at 12 months post-operative.
Secondary Endpoint(s):	• Rate of reoperation due to meniscal repair failure at 6 and 24 months post-operative; • MRI of structural integrity of meniscus at baseline, 12 months and 24 months; • Radiographs to evaluate tibiofemoral joint space narrowing (JSN) at baseline and 24 months;

	• Results of in-office needle endoscopy at 6 months, if available; • Patient Reported Outcomes (PRO) data will be collected on International Knee Documentation Committee (IKDC) Subjective, Knee Injury and Osteoarthritis Outcome Score (KOOS) and Lysholm score for baseline and 6, 12 and 24 month follow-up time points.
Safety Endpoint(s):	• 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 (SAE's); • Device deficiencies (DDs).
Other exploratory endpoint(s):	• Rate of reoperation at 6, 12 and 24 months by tear type (complex or HCT), demographics, procedural details (complex tear orientation, hybrid vs non-hybrid approach, types of devices used with NOVOSTITCH PRO) and rehabilitation protocol; • IKDC Subjective, KOOS and Lysholm scores at baseline, 6, 12 and 24 months by tear type, demographics, procedural details and rehabilitation protocol; • Healing status at 6, 12 and 24 months by tear type; • Quality of Life (QoL) from EQ-5D-5L at baseline, 12, and 24 months; • Patient Satisfaction at 12 and 24 months; • Device deficiencies when NOVOCUT Suture Manager is used intraoperatively;

	• Analysis of the change in meniscal signal on MRI at baseline vs at 1 and 2 years; • Analysis of the change in cartilage signal and joint space narrowing as indicators of osteoarthritis on X-rays taken at baseline vs at 2 years.

STUDY SCHEDULE

Visit Type/name	Frequency / Time point
Visit 1: Screening/Consent/ Initial Assessment	Day 0
Visit 2: Procedure	Within 8 weeks from screening
Visit 3: 7-15 Days	7-15 days after procedure
Visit 4: 90 Days	90 days +/- 14 days after procedure
Visit 5: 185 Days	185 days +/- 30 days after procedure
Visit 6: 365 Days	365 days +/- 60 days after procedure
Visit 7: 730 Days	730 days +/- 60 days after procedure

3. CONTENTS

3.1 TABLE OF CONTENTS

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3.3 LIST OF FIGURES

3.4 LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ACL	Anterior Crucial Ligament
ADE	Adverse Device Effect(s)
AE	Adverse Event(s)
ASADE	Anticipated Severe Device Effect(s)
BMI	Body Mass Index
CAR	Clinical Activity Report
CI	Confidence Interval
CRF	Case Report Form(s)
CV	Curriculum Vitae
DD	Device Deficiency(ies)
FAS	Full Analysis Set Population
FU	Follow-Up
GCP	Good Clinical Practice
HIPAA	Health Information Portability Accountability Act
HCT	Horizontal Cleavage Tear
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IFU	Instructions for Use
IKDC	International Knee Documentation Committee
IMDRF	International Medical Device Regulators Forum
IP	Investigational Product
IRB	Institutional Review Board

Abbreviation	Definition
ISF	Investigator Site File
ISO	International Organization for Standardization
JSN	Joint Space Narrowing
KOOS	Knee Injury and Osteoarthritis Outcome Score
LAR	Legally Authorized Individual
MCID	Minimal Clinically Important Difference
MRI	Magnetic Resonance Imaging
NA or N/A	Not Applicable
N (or n)	Total Sample Size (or subgroup sample size)
OA	Osteoarthritis
PI	Principal Investigator
PP	Per-protocol Population
PRO	Patient Reported Outcomes
QoL	Quality of Life
S+N	Smith + Nephew, Inc.
SADE	Serious Adverse Device Effect(s)
SAE	Serious Adverse Event(s)
SAF	Safety population
SAP	Statistical Analysis Plan
TKA	Total Knee Arthroplasty
USADE	Unanticipated Serious Adverse Device Effect(s)

4. INTRODUCTION

4.1 BACKGROUND

The meniscus is an important component of the knee that is involved in stability and shock absorption as well as lubrication and distributing nutrients to the articular cartilage.[1-4] Because of their location, menisci are highly susceptible to injury.[1] The most common mechanism of injury is trauma during sports activity and often occurs in combination with anterior cruciate ligament (ACL) injury.[5,6] Degenerative injury is also possible and may signify the onset of osteoarthritis (OA).[7]

Meniscal tear pattern and location have a direct effect on healing potential; tear patterns include radial, longitudinal, horizontal, and complex lesions. The central third of the meniscus, known as the white zone, has less healing potential than the middle third, known as the red-white zone, and the peripheral third, known as the red zone.[8,9] Tears along the outer edge of the meniscus have superior healing potential as blood supply is more available in that area than in the inner two-thirds of the meniscus.[1] Horizontal cleavage tears are meniscal tears that extend from the inner free margin of the meniscus into the intra-meniscal substance. These tears typically extended into the avascular zone, which can affect their ability to heal, and have been historically treated with partial meniscectomy.[10] Tears that occur over a long period of time are considered degenerative and are typically complex tears.[11] Complex tears are where two or more tear patterns exist; they are more common in the elderly and have associated osteoarthritic changes in the knee.[11] There are several options when treating meniscal tears, including non-operative treatment (physical therapy), partial meniscectomy, and meniscal repair.

Non-operative treatment including physical therapy can be successful in treating some meniscal tears. In a systematic review conducted by Monk et al.[3], the outcomes of meniscal resection (debridement) versus physical therapy was analyzed. It was determined that there was a difference between the two groups in the short term, but both groups still met the minimally important difference. The long term differences were not statistically significant between the two

groups. For patients who do not respond to physical therapy, surgical treatment is recommended.[3]

Partial meniscectomy with single leaflet resection has been recommended to relieve symptoms, preserve meniscal tissue, and create a stable construct.[12] Evidence has shown minimal biomechanical benefit for single leaflet resection because the total contact area decreases by 82% and the peak contact pressure is similar to that of dual leaflet resection.[13,14]

In the US, of the estimated 850,000 cases per year, 10% to 20% of orthopedic surgeries involve surgical repair of the meniscus.[15] A recently developed meniscal technique is the all-inside repair technique.[9] 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[8], doesn't require an open incision, and can prevent complications seen with the external approaches.[16] Disadvantages of the external approach can include neurovascular injury[16], cysts, device migration or device breakage.[17]

NOVOSTITCH PRO, a meniscus suture-passing device, enables placement of a circumferential compression stitch by use of a low-profile curved upper jaw, as well as a protractible retractable lower jaw, to allow reversible encasement of the meniscus without injury to surrounding structures. Circumferential stitching for meniscus repair has been shown in the laboratory to impact root repair strength by 38-70% stronger[18], normalize horizontal cleavage tear contact pressures[19] and be stronger than inside-out for radial repairs[20]. Recent technique studies have highlighted methods of using NOVOSTITCH PRO to deliver circumferential compression stitch repairs in an all-inside manner[21,22]. However, to date there is very limited data that documents the clinical success of horizontal cleavage and complex repairs with NOVOSTITCH PRO. A summary of known and potential risks and benefits to humans can be found in the NOVOSTITCH PRO Instructions for Use (IFU).

4.2 LITERATURE SUMMARY

A systematic review of the literature of isolated meniscal repair was performed by O'Donnell et al.[23] Success rates ranged from 62%-100%, with one study reporting a 25% success rate. In comparing the tear types, a systematic review performed by Kurzweil et al.[10] reported success rates of horizontal repairs was 76%, bucket handle tears was 84% and vertical tears was 68%. Rubman et al.[24] published their series of 198 complex repairs that extended into the avascular zone, and 80% were clinical successful with 20% requiring reoperation.

Smith and Dougherty presented an unpublished manuscript of a retrospective case series of 19 patients who underwent an all-inside meniscal repair using the NOVOSTITCH PRO device and reported IKDC outcome scores.[25] The NOVOSTITCH PRO device was used to deliver 2-0 non-absorbable ultra high molecular weight polyethylene suture. The mean number of stitches delivered was 3.3, ranging from 1-7. Mean postoperative IKDC subjective score was 83 (range 52-100) at an average of 18 months postop (range 14-24 months). Two of these patients returned for a reoperation of the meniscus due to (1) re-injury during sporting event and (1) stitch failure. Apart from the reoperation due to stitch failure, there were no other device specific complications reported. Additional records of 36 patients who were treated with the NOVOSTITCH PRO device during the same timeframe, but did not report IKDC results were reviewed, and one reoperation was reported due to non-compliance with the rehab protocol.

Kurzweil et al. presented an abstract on a non-randomized multicenter study of 30 patients treated with the NOVOSTITCH PRO (referred to as STITCH 1.0 study).[26] Six patients were lost to follow-up and 24 patients were included in the one year follow-up. Two patients required reoperation, reason for revision was not discussed. Significant improvement in KOOS, Tegner, IKDC and Lysholm scores were reported. 16/24 (66.7%) and 15/24 (62.5%) of patients met the minimal clinically important difference (MCID) for improvement in IKDC and Lysholm scores, respectively. These subjects are to be followed for 2 years.

4.3 STUDY PURPOSE

The purpose of this post-market study is to collect safety and clinical outcomes data from patients with horizontal cleavage tear (HCT) and complex tears who underwent meniscal repair with the NOVOSTITCH PRO Meniscal Repair System. Increasing evidence suggest that a broader set of meniscal tears, such as vertical, longitudinal, radial, complex, HCT, may be more repairable than previously thought.[10,27,28] The feasibility of repairing HCT and complex tears is still unclear; these tears have been thought to have minimal healing capacity with current available surgical techniques as they are often located within the avascular zone. As such, this study will begin that process by examining and documenting the ability to successfully repair horizontal cleavage and complex meniscus tears using all-suture based techniques.

4.4 SAFETY CONSIDERATIONS

Potential Adverse Effects listed in the IFU include:

- Wound dehiscence, calculi formation in urinary and biliary tracts when prolonged contact with salt solutions such as urine and bile occur, infected wounds, minimal acute inflammatory reaction and transitory local irritation;
- As with any foreign body, prolonged contact with this suture with salt solutions, such as those found in urinary or biliary tracts, may result in calculus formation;
- Allergies and other reactions to device materials.

Potential Device Deficiencies for the product include, but are not limited to, the following:

- Suture deployed prematurely;
- Handle does not fully retract;
- Lower jaw does not retract;
- Distal or central miss in which the suture does not go through the meniscus;
- Suture cartridge not loaded properly / suture cartridge not in track;
- Suture drop from the upper jaw where the suture pulls out of the meniscus.

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 clinical success rate of NOVOSTITCH PRO at 12 months, defined as rate of freedom from reoperation due to meniscal repair failure in the study knee.

5.2 SECONDARY OBJECTIVE(S)

The secondary objectives are to:

- Assess the clinical success rate of NOVOSTITCH PRO at 6 months, defined as rate of freedom from reoperation due to meniscal repair failure in the study knee;
- Assess the clinical success rate of NOVOSTITCH PRO at 24 months, defined as rate of freedom from reoperation due to meniscal repair failure in the study knee;
- Assess clinical performance of NOVOSTITCH PRO by Patient Reporting Outcomes (PROs) including the Knee Injury and Osteoarthritis Outcome Score (KOOS), International Knee and Documentation Committee (IKDC) Subjective, and Lysholm;
- Evaluate pre- and post-procedure magnetic resonance imaging (MRI) and radiographs, and post-procedure needle endoscopy.

5.3 SAFETY OBJECTIVE(S)

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:

- HCT and Complex meniscal tears repaired with NOVOSTITCH PRO have a clinical success rate of 80% or higher;
- HCT and Complex meniscal tears repaired with NOVOSTITCH PRO have reoperation rates similar to other commonly repaired tear types (<20%);
- HCT meniscal tears repaired with NOVOSTITCH PRO lead to a significant improvement in patient symptom scores; and
- Complex meniscal tears repaired with NOVOSTITCH PRO lead to a significant improvement in patient symptom scores.

6. INVESTIGATIONAL PRODUCT(S)

The Meniscal repair device used in the investigation will be the NOVOSTITCH PRO Meniscal Repair System, expressly intended for approximation of soft tissue in meniscal repair procedures. The system is 510(k) cleared in the United States and available for use with size 2-0 or 0 ultra-high-molecular-weight polyethylene suture cartridges.

6.1 IDENTIFICATION

6.1.1 Investigational Product

The NOVOSTITCH PRO Meniscal Repair System is a system with a pre-loaded implant designed for all-suture, all-inside meniscal repair procedures. The device is 510(k) cleared in the United States with an indication of “NOVOSTITCH PRO is intended for approximation of soft tissue in meniscal repair procedures.” The use of the NOVOSTITCH PRO device in this post-market study is consistent with this cleared indication for use and not investigational. The study is designed to further demonstrate repair success in a subset of meniscal repairs for potential comparison to other known treatment methods in order for surgeons to determine the best potential treatments for those patients. The devices being used in this study are:

- NOVOSTITCH PRO Meniscal Repair System, size 2-0 (product number: CTX-A003)
- NOVOSTITCH PRO Meniscal Repair System, size 0 (product number: CTX-A004)
- NOVOSTITCH Meniscal Repair Cartridge, size 2-0 (product number: CTX-R001)

- NOVOSTITCH Meniscal Repair Cartridge, size 0 (product number: CTX-R002)

Figure 6.1-1: Image of the NOVOSTITCH PRO Device

The NOVOSTITCH PRO non-absorbable surgical suture is supplied sterile in 80 cm lengths preloaded in the device.

- The size 2-0 suture is composed of undyed (white) ultra-high-molecular-weight polyethylene braided with one or two strands of blue polypropylene to add color.
- The size 0 suture is composed of undyed (white) ultra-high-molecular-weight polyethylene braided with two strands of green polyethylene terephthalate to add color.

Refer to the NOVOSTITCH PRO Instructions for Use for more information.

Contraindications for use include the following:

- The device is not to be used on bone or other hard tissue.
- Surgical procedures other than those listed in the INDICATION FOR USE section.
- Presence of infection.

- Patient conditions including insufficient quantity or quality of tissue.
- Insufficient blood supply or previous infections which may hinder the healing process.
- Foreign body sensitivity. If material sensitivity is suspected, testing should be completed prior to suture implantation.
- Conditions which may limit the patient's ability or willingness to follow postoperative care instructions.

The NOVOSTITCH PRO and its cartridges are covered by numerous method and device patents issued in the US which indicate that the device is designed for use in meniscal repair procedures. The intellectual property does not cover any investigational materials or biologics relevant to this study.

Each surgery in the study typically requires:

- 1 NOVOSTITCH PRO Meniscal Repair System, which consists of a handle and one pre-loaded replacement cartridge filled with either 2-0 or 0 suture (CTX-A003 or CTX-A004, respectively);
- Between 0-6 additional NOVOSTITCH Cartridges filled with either 2-0 or 0 suture (CTX-R001 or CTX-R002, respectively). The average procedure uses 2 replacement cartridges.

The legal manufacturer for the NOVOSTITCH PRO device is:

Smith + Nephew, Inc.
150 Minuteman Rd.
Andover, MA 01810

6.1.2 Comparator Treatment

No comparator treatment will be used for this study.

6.1.3 Ancillary Product

No ancillary products will be used related to the direct repair of investigated meniscus.

6.2 PRODUCT USE

Typically, total meniscal repair procedure time runs for approximately 45 minutes, during which the NOVOSTITCH PRO is used in the knee for approximately 5-30 minutes.

Potential adverse reactions related to treatment and or exposure to associated treatment materials include:

- Adverse effects associated with the use of the device, including wound dehiscence, calculi formation in urinary and biliary tracts with prolonged contact with salt solutions such as urine and bile occur, infected wounds, minimal acute inflammatory tissue reaction and transitory local irritation.
- As with any foreign body, prolonged contact of the suture with salt solutions, such as those found in urinary or biliary tracts, may result in calculus formation.

Refer to the NOVOSTITCH PRO IFU for detailed information on contraindications, warnings, adverse reactions and precautions.

6.3 PACKAGING AND LABELING

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

6.3.1 Labeling of Investigational Product

The NOVOSTITCH PRO Meniscal Repair System, has received 510(k) clearance in the United States. All devices used in this study will be procured in standard commercial packaging, ordered via normal and customary Smith + Nephew procedures and managed per study site processes.

The NOVOSTITCH PRO Meniscal Repair System and Suture Cartridges contain the following information:

- Lot Number
- Catalog 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

6.4 PRODUCT ACCOUNTABILITY PROCEDURES

Sites will be responsible for obtaining and maintaining an inventory of NOVOSTITCH PRO. Sites will document the device that was used in a subject on a CRF that will include unique identifiers. The CRFs will also document any device deficiencies, including if any products were wasted or returned to the Sponsor. All records must be available for inspection by the Sponsor, its designees, or by regulatory agencies at any time. As part of monitoring, the Study Monitor will check that site personnel are following the proper procedures for completing all necessary documentation.

6.5 SURGICAL TECHNIQUE

All study related procedures with the NOVOSTITCH PRO Meniscal Repair System must be performed according to the recommended surgical technique described in the IFU. Surgeons selected to participate in this study will be familiar with the NOVOSTITCH PRO product, or will receive training prior to enrolling any subjects per standard SN procedures if not familiar.

7. SUBJECT ENROLLMENT AND WITHDRAWAL

7.1 SUBJECT POPULATION

This study will enroll 90 subjects between the ages of 18 and 70 years of age. Although horizontal cleavage and complex meniscal tears can occur in any age group, enrolling subjects 18-70 years of age allows inclusion of knees with less likelihood of growth changes or significant arthritic changes which may mask measurement of knee pain and function improvements following the treatment procedure. Subjects will be enrolled at a minimum of 3 sites, and a maximum of 8 sites, across the United States.

Ethnic minorities are classed as vulnerable subjects according to International Organization for Standardization (ISO) 14155:2011 however they will be included providing they meet other inclusion criteria and there are informed consent documents and personnel to lead the consent process in a language that is fully understood by the potential subject.

7.2 INCLUSION CRITERIA

Subjects will be considered qualified for enrollment if they meet the following criteria at screening:

1. Able and willing to give informed consent by voluntarily providing written informed consent in accordance with governing Institutional Review Board;
2. 18 to 70 years of age, inclusive at the time of screening;
3. History indicative of meniscal pathology (e.g., pain, mechanical symptoms described as locking, clicking or giving way);
4. Physical exam consistent with meniscus tear (e.g., locked joint, joint line tenderness and/or pain on meniscal compression);
5. If prior ligament reconstruction, the study knee is clinically stable;
6. Meniscal repair to be performed arthroscopically;

7. Preoperative MRI evidence consistent with a horizontal cleavage or complex meniscus tear in the symptomatic compartment;
8. Willing and able to comply with all study procedures and visit requirements, including MRIs, X-rays, and Case Report Forms (CRFs) completed by the subject.

Consented subjects may be included in the study only if, upon arthroscopic inspection, their meniscal study lesion meets all of the following criteria:

1. Meniscal tear amenable to repair with NOVOSTITCH PRO with or without the use of adjunct devices per the exclusion criteria;
2. Tear pattern is one of the following:
    a. Horizontal cleavage tear (HCT),
    b. Complex multi-planar tear (combination of at least two of the following tears: horizontal, oblique, radial, vertical).

7.3 EXCLUSION CRITERIA

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

1. Arthritis in the study knee (Kellgren-Lawrence Grade 3 or higher);
2. Body Mass Index (BMI) ≥40 kg/m^2;
3. Previous surgical meniscal repair or meniscectomy of the study meniscus;
4. Unstable knee;
5. Clinically significant malalignment of the study knee, and/or requiring osteotomy, and/or correction;

6. History of constitutional/systemic inflammatory/arthritic problem or pain condition, history of knee infection, vascular condition of legs, benign neoplasms of knee, hepatitis, and/or HIV;
7. Currently on any immunosuppressive therapy;
8. Expected to undergo any other surgical treatment of either knee;
9. Previously enrolled in the study (no bilateral knee surgeries);
10. Surgical procedures other than those listed in the Indications for Use;
11. Patient conditions including insufficient quantity or quality of tissue;
12. Insufficient blood supply or previous infections which may hinder the healing process;
13. Foreign body sensitivity. If material sensitivity is suspected, testing should be completed prior to suture implantation;
14. Conditions which may limit the patient's ability or willingness to follow postoperative care instructions;
15. Any concomitant painful or disabling disease, condition or post-procedure status of either lower extremity that would interfere with evaluation or rehabilitation of the study knee;
16. Pregnant or planning to become pregnant in the next 2 years;
17. Subject does not understand a language in which the PROs and EQ-5D-5L are available.

Subjects will be excluded from the study if their study meniscus lesion meets any of the following criteria at arthroscopy:

1. Ramp tears;
2. Root or other tear type requiring tibial fixation;
3. Tears requiring repair of both meniscus in the study knee;

4. Intact or partially intact meniscus tear that, in the opinion of the Investigator, does not require repair;
5. Poor meniscal tissue quality such that it will not hold a suture;
6. For HCTs:
    a. Use of any capsular fixation device; OR
    b. Any portion of the meniscal tear is repaired using a device to place stitches other than NOVOSTITCH PRO, Meniscus Mender II, or Meniscal Stitcher, FIRSTPASS MINI marketed by Smith + Nephew, Inc.;
7. For complex tears:
    a. Any portion of the meniscal tear is repaired using a device to place stitches other than NOVOSTITCH PRO, Meniscus Mender II, Meniscal Stitcher, FIRSTPASS MINI, FAST-FIX 360, or ULTRA FAST-FIX marketed by Smith + Nephew Inc.;
8. Clinically significant (zone 1 and/or zone 2) tear in the contralateral compartment to the study meniscus;
9. Performance of a significant concomitant procedure (e.g. ACL reconstruction or repair, cartilage repair or restoration) intended as a therapeutic intervention on the study knee;
10. Presence of infection;
11. Articular cartilage damage in the study knee, defined as Modified Outerbridge Grade III or higher.

7.4 SCREENING

Subjects will be recruited for the study through the clinical practices of the Investigators.

Of the 90 subjects, at least 40 subjects will have horizontal cleavage meniscal tears and at least 40 will have complex meniscal tears. Subjects will be enrolled as they meet eligibility and

consent to the study. Therefore, if a group enrolls 50 subjects, screening will stop within that group, and screening and enrollment will continue only in the other group until all 90 subjects are enrolled.

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 documented 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.

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.

7.5 INFORMED CONSENT

Before conducting any study procedures or examinations, the purpose and nature of the study must be explained to the subject in their native language. The subject will be allowed to ask any questions and consider whether he or she would like to participate in the study. He/she may consent to the study when it is introduced, or may wish to take time to review the study, including, but not limited to, speaking to friends and family about participation in the study. Consent cannot be coerced and must be completed at any time prior to the first study activity.

If the subject consents to the study, or their legally authorized representative (LAR) agrees to the study, the subject or LAR will then **read**, **sign**, and **personally date** the Institutional Review Board (IRB)-approved informed consent document(s) (see below non-English speakers and for difficulties with reading and writing). Signature may be handwritten or electronic if a secure and compliant e-consent process is used. Additionally, the individual who obtains consent from the subject will sign and date the informed consent document.

If the subject does not speak English, the individual will be given a consent form in their native language, or a bilingual study member or an in-person or telephone interpreter will be used and the entire consent form will be translated for the subject. The subject will be able to ask any questions that will be answered by study personnel, and as required through the use of the interpreter. If an interpreter is used, the subject will sign a short consent form, along with a witness, and documentation of the translator will be included on the form. A copy of the signed consent form, or short informed consent document and a copy of the English consent form as applicable, will be provided to the subject, and copies will be placed in the subject's record or chart as required by the site, with the original filed in the Investigator Site File (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 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.

In the case of vulnerable subjects, the ICF must be understood and signed by the subject's legally authorized representative (parent or legal guardian). If the legally authorized representative is unable to read/write, a witness signature is required as described previously.

As required by the IRB and the site, all Health Information Portability Accountability Act (HIPAA) regulations and documentation will be followed.

7.6 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 fail.

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

7.7 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 2 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; any visits not completed on-time will be considered protocol deviations. 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: the subject has been contacted according to the site's policies, but no fewer than two documented phone or text contacts and one certified letter without response. Subjects may also be contacted by email. Copies of all attempts to reach the subjects by phone, 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.

7.8 WITHDRAWAL

Subjects may be withdrawn from the study per the reasons listed below.

7.8.1 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) or misses 2 consecutive study visits;
- 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 debilitating 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 24 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, information will be obtained in the source document and entered on the End of Study Case Report Form (CRF) detailing circumstances leading to the withdrawal.

Subjects who drop out or are withdrawn will be re-entered into the study at a later date if he or she returns to the site for a subsequent follow-up visit, has not received a revision surgery of the study knee, or was withdrawn for a medical reason that is resolved, and the Principal Investigator (PI) agrees to re-entry in the study. Subjects who are withdrawn from the study will not be replaced.

7.8.2 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. No further study activities will occur once a subject withdraws consent.

If a subject withdraws, he/she will not be replaced.

7.8.3 Use of Data Following Withdrawal

In cases where the subject withdraws consent, or the subject is withdrawn from the study by the PI, data collected up to the point of withdrawal may be used, but no additional data for that subject may be collected except for subjects who have consented and have an adverse event that is being followed to resolution or receive a revision surgery of the study knee as detailed in section 7.8.1 above.

8. STUDY DESIGN

8.1 STUDY DESIGN

This is a prospective, multi-center, non-randomized clinical trial. The study is divided into 2 groups that are allocated by tear type at surgery:

- Horizontal cleavage meniscal tear,
- Complex meniscal tear.

This study will enroll at up to 8 clinical sites in the United States, with a minimum of 3 sites.

The study is expected to be 42 months in duration, but will depend on enrollment rate. This includes:

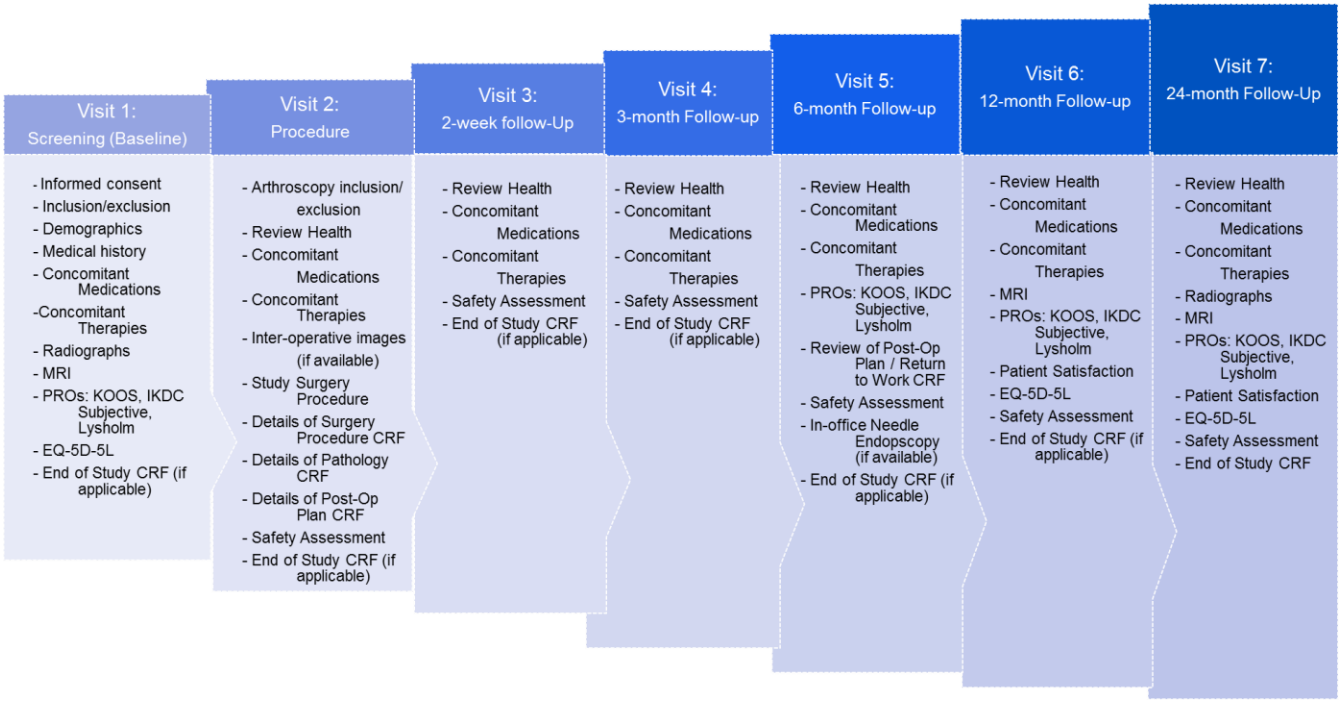
- 16 months for enrollment
- 26 months for follow-up
    - The final visit is 24 months post-surgery and includes a +/-2-month window period.

Treatment of the study meniscus will occur once, in the form of a surgery to repair the torn portion of the meniscus.

This study was designed as a prospective, multi-center, non-randomized study of repairs of horizontal cleavage and complex tears of the meniscus using commercially available products.

No formal hypotheses testing will be done. However, primary outcome measures that will be examined include whether the reoperation survival rate at 12 months will be similar or less than historical rates (78-91%)[10,27]; 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 2 years following the procedure.

Figure 8.1-1: Study Flowchart



8.2 ALLOCATION AND BLINDING

8.2.1 Treatment Allocation

This study is not randomized. Subjects will be enrolled in the horizontal cleavage tear or complex tear group pending the type of meniscal tear at surgery.

8.2.2 Blinding

This study is not blinded.

8.3 STUDY ENDPOINTS

8.3.1 Primary Endpoint

The primary endpoint of this study is rate of reoperation due to meniscal repair failure at 12 months post-operative.

This endpoint is a clinically relevant measure of repair success that surgeons use, and the percentage of reoperations for a given tear type in the literature impacts how surgeons choose to treat that tear type.

8.3.2 Secondary Endpoints

Following are the secondary endpoints for this study:

- Rate of reoperation due to meniscal repair failure at 6 and 24 months post-operative;
- MRI of structural integrity of meniscus at baseline, 12 months and 24 months;
- Radiographs to evaluate tibiofemoral joint space narrowing (JSN) at baseline and 24 months;
- Results of in-office needle endoscopy at 6 months, if available;
- Patient Reported Outcomes (PRO) data will be collected on IKDC, KOOS & Lysholm score for baseline and 6, 12 and 24 month follow-up time points.

The secondary endpoints provide more context on whether the meniscal repair was a success at earlier time points and whether it is durable for two years. MRI and endoscopy measurements allow surgeons to assess meniscal healing, whether a reoperation is performed or not. Radiographs of joint space narrowing (JSN) will indicate whether patients have progressively worse osteoarthritis which is an indicator for future risk of needing a Total Knee Arthroplasty (TKA). PROs provide meaningful quality of life measurements to assess improvement, which is

ultimately the clinical goal of any successful meniscal repair. IKDC Subjective, KOOS, and Lysholm scores are common validated tools to measure patient symptoms associated with meniscal function.

8.3.3 Safety Endpoints

Following are the safety endpoints for this study:

- 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 (SAE's);
- Device deficiencies (DDs).

All safety events will be documented on the appropriate CRF and followed either until resolution or marked as unresolved at the end of study. All AEs will be categorized in terms of seriousness and relatedness to the study device or to the surgical procedure. All Serious Adverse Device Effects will be further categorized as Anticipated or Unanticipated. The definitions for each of these categories are based on ISO 14155:2011.

8.3.4 Exploratory Endpoints

Exploratory endpoints proposed, but not limited to, the following:

- Rate of reoperation at 6, 12 and 24 months by tear type (complex or HCT), demographics, procedural details (complex tear orientation, hybrid vs non-hybrid approach, types of devices used with NOVOSTITCH PRO) and rehabilitation protocol;
- IKDC Subjective, KOOS and Lysholm scores at baseline, 6, 12 and 24 months by tear type, demographics, procedural details and rehabilitation protocol;
- Healing status at 6, 12 and 24 months by tear type;
- Quality of Life (QoL) from EQ-5D-5L at baseline, 12, and 24 months;
- Patient Satisfaction at 12 and 24 months;

- Device deficiencies when NOVOCUT Suture Manager is used intraoperatively;
- Analysis of the change in meniscal signal on MRI at baseline vs at 1 and 2 years;
- Analysis of the change in cartilage signal and joint space narrowing as indicators of osteoarthritis on X-rays taken at baseline vs at 2 years.

8.4 METHODS USED TO MINIMIZE BIAS AND MAXIMIZE VALIDITY

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 so as 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.

Subject Attrition

Subject attrition due to 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.

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 so as 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 are 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. Not included directly in the table are unscheduled visits and reoperations, which will be completed as required for the study.

Table 9.1.1-1: Study Procedures by Visit

Activity	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Screen < 8 weeks pre-op	Procedure	7-15 Days post-op	90 Day ±14 days post-op	185 Day ±30 days post-op	365 Day ±60 days post-op	730 Day ±60 days post-op
Informed Consent	X						
Screening Inclusion/ Exclusion	X						
Demographics/Medical History/Concomitant Medications/ Concomitant Therapies	X						
Radiographs	X[1,2]						X[1]
MRI	X[2]					X[3]	X[3]
PRO: KOOS[4]	X				X	X	X
PRO: IKDC Subjective[4]	X				X	X	X
PRO: Lysholm[4]	X				X	X	X
EQ-5D-5L CRF[4]	X					X	X
End of Study Form	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]
Review General Health/ Concomitant Medications/ Concomitant Therapies		X	X	X	X	X	X
Arthroscopy Inclusion/ Exclusion		X					

Inter-operative Images/Videos		X[6]					
Study Surgery Procedure		X					
Details of Surgery Procedure CRF		X					
Details of Pathology CRF		X					
Details of Post-Operative Plan CRF		X					
Safety Assessment (AE/SAE/ADE/DD)[7]		X	X	X	X	X	X
Review Post-Operative Plan/Return to Work CRF[4]					X		
In-office Needle Endoscopy					X[8]		
Patient Satisfaction CRF[4]						X	X

[1]Standing AP X-ray; Radiographic CRF completed by reader post-visit
[2]Within 6 months prior to procedure; MRI CRF completed by reader post-visit
[3]MRI 1.5 T or greater, no contrast, to be reviewed by independent radiologist appointed by sponsor
[4]CRF completed by subject
[5]As applicable
[6]If available, still photographs and diagrams of procedure; Image CRF completed post-visit
[7]If the AE/SAE/ADE/DD includes an unscheduled visit or reoperation, the Unscheduled Visit or Reoperation CRFs will be completed as applicable
[8]If available; Endoscopy CRF completed post-visit

Subjects may complete the patient CRFs (PROs (KOOS, IKDC Subjective, and Lysholm), Post-Operative Plan/Return to Work, Patient Satisfaction, and EQ-5D-5L) either on paper, or on a secure electronic device such as a computer, mobile phone, or tablet.

Subjects who are unable to return to the site for follow-up visits may complete the PROs (KOOS, IKDC Subjective, and Lysholm), Post-Operative Plan/Return to Work**,** Patient Satisfaction, and EQ-5D-5L CRFs on paper and return by mail, electronically by email, or online through a secure link provided by the site. The follow-up general health/concomitant medications and concomitant therapies CRF and safety assessment may be conducted over the telephone with study staff. As required, documents will be translated into the appropriate language for the individual, and an interpreter will be used over the telephone.

Subjects may be provided participant stipends as agreed upon by Sponsor and the site, and as allowed by the site's standard operating procedures/regulations and the IRB. Stipends amounts may cover costs associated with the study participant to complete follow-up visits, but cannot be coercive.

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

Below are the procedures that will be done at the Screening/Preoperative visit.

NOTE: Any subject who signs an informed consent/assent but fails to meet the required entry criteria is considered to be a Screen Failure. Screen Failure subjects who are consented but do not complete the baseline screening will be assigned a Subject ID number, and their demographic information captured in the appropriate CRF and/or log 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 medications/concomitant therapies.
3. Screen the subject for protocol inclusion/exclusion criteria.
4. Assign the subject a study ID number and instruct the subject on treatment procedures.
5. Obtain baseline radiographs.
6. Obtain baseline MRI.
7. Obtain baseline PROs: KOOS, IKDC Subjective, and Lysholm.
8. Obtain baseline EQ-5D-5L CRF.
9. Subjects will be instructed to return for the Operation Visit (Procedure) as scheduled by the site.
10. If applicable, complete an End of Study CRF.

9.1.3 Visit 2: Operation Visit (Procedure)

1. Query subject regarding any changes in general health and the use of concomitant medications/concomitant therapies.
2. Commence procedure.
3. Complete arthroscopy inclusion/exclusion; if subject is excluded, no further information is obtained and the subject is considered a Screen Fail.
4. Obtain inter-operative images/videos, if available.
5. 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.
6. Instruct the subject on proper postoperative care/procedures, including any contraindicated treatments/medication(s).

7.	Instruct the subject on follow-up procedures, including returning the site for follow-up (FU) Visit 1 in 7-15 days.
8.	Complete Details of Surgery Procedure CRF.
9.	Complete Details of Pathology CRF.
10.	Complete Details of Post-Operative Plan CRF.
11.	If applicable, complete an End of Study CRF.

9.1.4 Visit 3: Safety Follow-Up (7-15 days after procedure)

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.	Instruct the subject on follow-up procedures, including returning the site for a FU visit at 3 months.
4.	If applicable, complete an End of Study CRF.

9.1.5 Visit 4: 3-Month Follow-Up (90 days after procedure +/- 14 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.	Instruct the subject on follow-up procedures, including returning the site for FU visit at 6 months.
4.	If applicable, complete an End of Study CRF.

9.1.6 Visit 5: 6-Month Follow-Up (185 days after procedure +/-30 days)

1.	Query subject regarding any changes in general health and the use of concomitant medications/concomitant therapies.
2.	Complete Review Post-Operative Plan/Return to Work CRF.
3.	Obtain 6-month PROs: KOOS, IKDC Subjective, and Lysholm.
4.	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.
5.	Obtain in-office needle endoscopy, if available.
6.	Instruct the subject on follow-up procedures, including returning the site FU visit at 12 months.
7.	If applicable, complete an End of Study CRF.

9.1.7 Visit 6: 12-Month Follow-Up (365 days after procedure +/-60 days)

1.	Query subject regarding any changes in general health and the use of concomitant medications/concomitant therapies.
2.	Obtain 12-month PROs: KOOS, IKDC Subjective, and Lysholm.
3.	Obtain 12-month EQ-5D-5L CRF.
4.	Obtain 12-month Patient Satisfaction CRF.
5.	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.
6.	Obtain 12-month MRI.
7.	Instruct the subject on follow-up procedures, including returning the site for FU visit at 24 months.
8.	If applicable, complete an End of Study CRF.

9.1.8 Visit 7: Exit Visit / 24-Month Follow-Up (730 days after procedure +/-60 days)

1.	Query subject regarding any changes in general health and the use of concomitant medications/concomitant therapies.
2.	Obtain 24-month PROs: KOOS, IKDC Subjective, and Lysholm.
3.	Obtain 24-month EQ-5D-5L CRF.
4.	Obtain 24-month Patient Satisfaction CRF.
5.	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.
6.	Obtain 24-month radiographs.
7.	Obtain 24-month MRI.
8.	Complete an End of Study CRF.

9.1.9 Reoperations

Any reoperations of the study knee will be captured in the source documents and on the Reoperation CRF. Details of the reoperation will be captured, including the reason for the reoperation. At the reoperation, use of any concomitant medications, concomitant therapies, adverse events, and device deficiencies will be collected. As applicable, the study implant disposition will be obtained.

9.1.10 Unscheduled Visits

Any unscheduled visits of the study knee will be captured in the source documents and on the Unscheduled Visit CRF. At the visit, general health, use of any concomitant medications, adverse events, and device deficiencies will be collected.

9.1.11 Concomitant Medications and Concomitant 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.

9.1.11.1 Concomitant Medications

9.1.11.1.1 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.

9.1.11.1.2 Recording Concomitant Medications in the 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.

9.1.11.2 Concomitant Therapies

9.1.11.2.1 Therapies Prohibited During the Study

For this study there are no restrictions on concomitant therapies.

9.1.11.2.2 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.

9.1.12 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 7.8 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 7.8.2).

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).

9.1.13 Subject Pregnancy

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. 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:

- Radiographs
- Magnetic Resonance Imaging (MRI)
- Inter-operative images/videos
- KOOS

- IKDC Subjective
- Lysholm
- In-office needle endoscopy
- Health Economics/Quality of Life

9.2.1 Radiographs

Radiography is an imaging technique using X-rays, gamma rays, or similar ionizing radiation and non-ionizing radiation to view the internal form of an object.[29] For this study, radiographs will include x-ray images of the treatment knee. Radiographs will be obtained at baseline and 2 years post-treatment to assess cartilage signal and joint space narrowing (JSN). Sites will make arrangements for radiographs per standard procedures and provide the images/results to the Sponsor.

9.2.2 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.[30] For this study, MRIs will be obtained at baseline, and 1 and 2 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.

9.2.3 Inter-operative Images/Video

Inter-operative images are pictures and videos that are taken during a procedure using a small camera inserted into the body during treatment. In this study, inter-operative images and videos will be taken if available during the meniscal repair to obtain information regarding surgical technique and can be used, if necessary, to assess the cause of any adverse events. Sites will use their own equipment to take inter-operative images/videos and provide to Sponsor.

9.2.4 Knee Injury and Osteoarthritis Outcome Score (KOOS)

The Knee Injury and Osteoarthritis Outcome Score (KOOS) is a validated Patient Reported Outcome measurement tool. The KOOS was developed in the 1990s as an instrument to assess the patient's opinion about their knee and associated problems. Since it was first published in 1998, the psychometric properties of the KOOS have been assessment in more than twenty individual studies from all over the world, as well as being compared to other instruments in multiple reviews. The instrument has been validated for consequences in different populations with varying diseases and durations and at varying ages and activity levels.[31,32,33]

There are five patient-relevant subscales of the KOOS, and each are scored separately:

- Pain (9 items)
- Symptoms (7 items)
- ADL function (17 items)
- Sport and Recreation Function (5 items)
- Quality of Life (4 items)

A Likert scale is used and all items have five possible answer options scored from 0 (no problems) to 4 (extreme problems). Each of the 5 scores is calculated as the sum of the items included and then each score is transformed to a 0-100 scale, with 0 representing extreme knee problems and 100 representing no knee problems as common in orthopedic assessment scales and generic measures. An aggregate score is not calculated so that each of the 5 dimensions can be assess separately.[31,32]

9.2.5 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.[32]

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 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.[32]

9.2.6 Lysholm

The Lysholm scale was first introduced into the medical community in 1982, and 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 functioning of daily activities. The scale consists of 8 item and is scaled from 0 to 100, with a higher score indicating fewer symptoms and higher level of functioning.[33,34]

9.2.7 In-Office Needle Endoscopy

In-office needle endoscopy is a minimally invasive procedure in which a needle-sized camera is inserted into tissue for observation and/or biopsy purposes. For this study, a needle-sized endoscopy will be inserted to record video and images of the meniscal repair site and visually assess healing. This will be performed on up to 30 subjects (up to 15 HCT and up to 15 complex meniscal tears) at sites that are able to conduct this type of imaging using existing equipment.

9.3 HEALTH ECONOMICS/QUALITY OF LIFE

Following secondary outcomes will be collected:

1. Employment status pre-surgery: Currently working/employed category) and job type.

2. Nature of work: Laborer/Sedentary work (Sedentary deined as “involves occasional lifting of no more than ten pounds and sitting with occasional walking and standing”).

3. Return to work after surgery (Days) and type of work.

4. Patient Satisfaction at 1 year and 2 years.

5. EQ-5D-5L will be used to derive general health-related QoL scores at baseline, 1 year, and 2 years. 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-effectivess analysis and is available in a variety of languages.[35]

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. 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 endpoints will be performed 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 reoperation 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).[36]

The following hypotheses will be tested to establish that the rate of reoperation of the NOVOSTITCH PRO is strictly no worse (lower) than the literature derived value:

$$H_0: \mu - \mu_0 \leq 0$$

$$H_a: \mu - \mu_0 > 0$$

In the stated hypthothesis, μ represents the rate of reoperation for the NOVOSTITCH PRO and μ_0 represents the literature derived value (80%).[24] A one sided t-test with alpha = 0.025 will be used to evaluate the hypothesis and the corresponding 95% CIs will also be presented.

Analysis will be carried out using the FAS population as the primary analysis population with the PP population used for sensitivity analysis.

10.4.2 Analysis of Secondary Endpoint(s)

The following secondary endpoints will be analyzed for this study.

- Rate of reoperation due to meniscal repair failure at 6 and 24 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.[36]
- Analysis of MRI of structural integrity of meniscus at baseline, 12 months and 24 months will be conducted separately by an imaging vendor. The change in meniscal signal between baseline and 1 and 2 years will be summarized.
- Analysis of radiographs to evaluate tibiofemoral joint space narrowing (JSN) at baseline and 24 months will be conducted separately by an imaging vendor. The change in cartilage signal and joint space narrowing as indicators of osteoarthritis on X-rays taken baseline vs at 2 years will be summarized.
- Results of in-office needle endoscopy of healing at the repair site at 6 months will be presented by frequency and percentage.

- IKDC Subjective, KOOS & Lysholm 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, 12 and 24 months) score will be presented. For Lysholm and IKDC Subjective, the numbers and proportions of subjects, together with a 95% confidence interval (calculated using the Clopper-Pearson Exact method)[36], 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(s)

- Patient Satisfaction and EQ-5D-5L results will be summarized for each visit appropriately for categorical or continuous variables. Any open-ended questions will be presented as a listing.
- Multivariate analysis of demographic and procedural predictors on rate of reoperation, improvement in PROs or attaining MCID thresholds will be presented. Variables of interest are; age, complex tear orientation, hybrid vs non-hybrid approach, types of devices used with NOVOSTITCH PRO and other patient demographics.
- Rate of reoperation, PRO scores and healing status will be presented by tear type (complex and HCTs).
- The number and proportion of subjects experiencing device deficiencies where NOVOCUT Suture Manager has been used alongside the NOVOSTITCH PRO with a 95% confidence interval (calculated using the Clopper-Pearson Exact method)[36].

10.5 SAFETY ANALYSES

All safety endpoints will be summarized using the safety population.

<u>Adverse Events</u>

The number of subjects reporting: adverse events, serious adverse events, severe adverse events, device-related adverse events, serious device-related adverse events, unanticipated adverse events, and serious unanticipated adverse events will be summarized. 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, however Clinical Activity Reports (CAR) may be produced to faciliate the publication of the results (in part of in whole) for scientific conferences and publications. Additional adhoc analyses may occur as needed (e.g. for abstracts or publications).

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 sample size for this study is determined based on the feasibility of recruitment, enrollment and follow-up considerations.

With an estimated clinical success rate of 80% at 12 months for the planned study, the 95% confidence interval for clinical success was calculated between 70% and 90%. Using an 84% success rate, the minimum enrollment is N=71. With an attrition rate of 10% per year, total

enrollment is set to N=90; a minimum of N=40 horizontal cleavage tears and N=40 complex tears.

12. ADVERSE EVENTS AND DEVICE DEFICIENCIES

12.1 DEFINITIONS

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

<table>
<tr><th></th><th>NOT DEVICE-RELATED</th><th colspan="2">DEVICE- OR PROCEDURE-RELATED</th></tr>
<tr><td>NON-SERIOUS</td><td>ADVERSE EVENT
(AE)</td><td colspan="2">ADVERSE DEVICE EFFECT
(ADE)</td></tr>
<tr><td rowspan="3">SERIOUS</td><td rowspan="3">SERIOUS ADVERSE EVENT
(SAE)</td><td colspan="2">SERIOUS ADVERSE DEVICE EFFECT
(SADE) (SEE 12.1.3)</td></tr>
<tr><td>ANTICIPATED</td><td>UNANTICIPATED</td></tr>
<tr><td>ANTICIPATED SERIOUS ADVERSE DEVICE EFFECT
(ASADE)</td><td>UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT
(USADE)</td></tr>
</table>

12.1.1 Adverse Event

An Adverse Event (AE) is any untoward medical occurrence, unintended disease of untoward clinical sign (including abnormal laboratory findings) in subjects, users or other persons, whether or not causally related to the IP.

Note 1: This definition includes events related to the IP.

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 IP.

An 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 that, in the opinion of the investigator, is related to the use of the IP.

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.

Not Related - An AE is considered to be not related to the use of an Investigational Product (IP) or the procedure when the effect is DEFINITELY UNRELATED or UNLIKELY 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, PROBABLE, 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 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, in the view of either the Investigator or the Sponsor, it:

- a) led to death,
- b) led to serious deterioration in the health of the subject, that either resulted in
  - 1) a life-threatening illness or injury, or
  - 2) a permanent impairment of a body structure or a body function, 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) led to fetal distress, fetal death or a congenital abnormality or birth defect

Note: 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 analysis report.

Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

Anticipated device effects include the following:

- Suture deployed prematurely;
- Handle does not fully retract;

- Lower jaw does not retract;
- Distal or central miss in which the suture does not go through the meniscus;
- Suture cartridge not loaded properly / suture cartridge not in track;
- Suture drop from the upper jaw where the suture pulls out of the meniscus.

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. An 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. A DD includes malfunctions, use errors and inadequate labeling.

12.2 AE CODING DICTIONARY

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

12.3 REPORTING PROCEDURES

AEs of any kind and DDs will be recorded in the applicable CRF and source notes. The Investigator will evaluate all AEs for relationship to the device and procedure, if applicable, seriousness, and severity. The following timescales should be followed for the AE/DD information to be 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)

For ADEs and DDs, 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 (e.g., used dressings must not be retained). Updates to submitted information will be recorded in the CRF according to the timescales above.

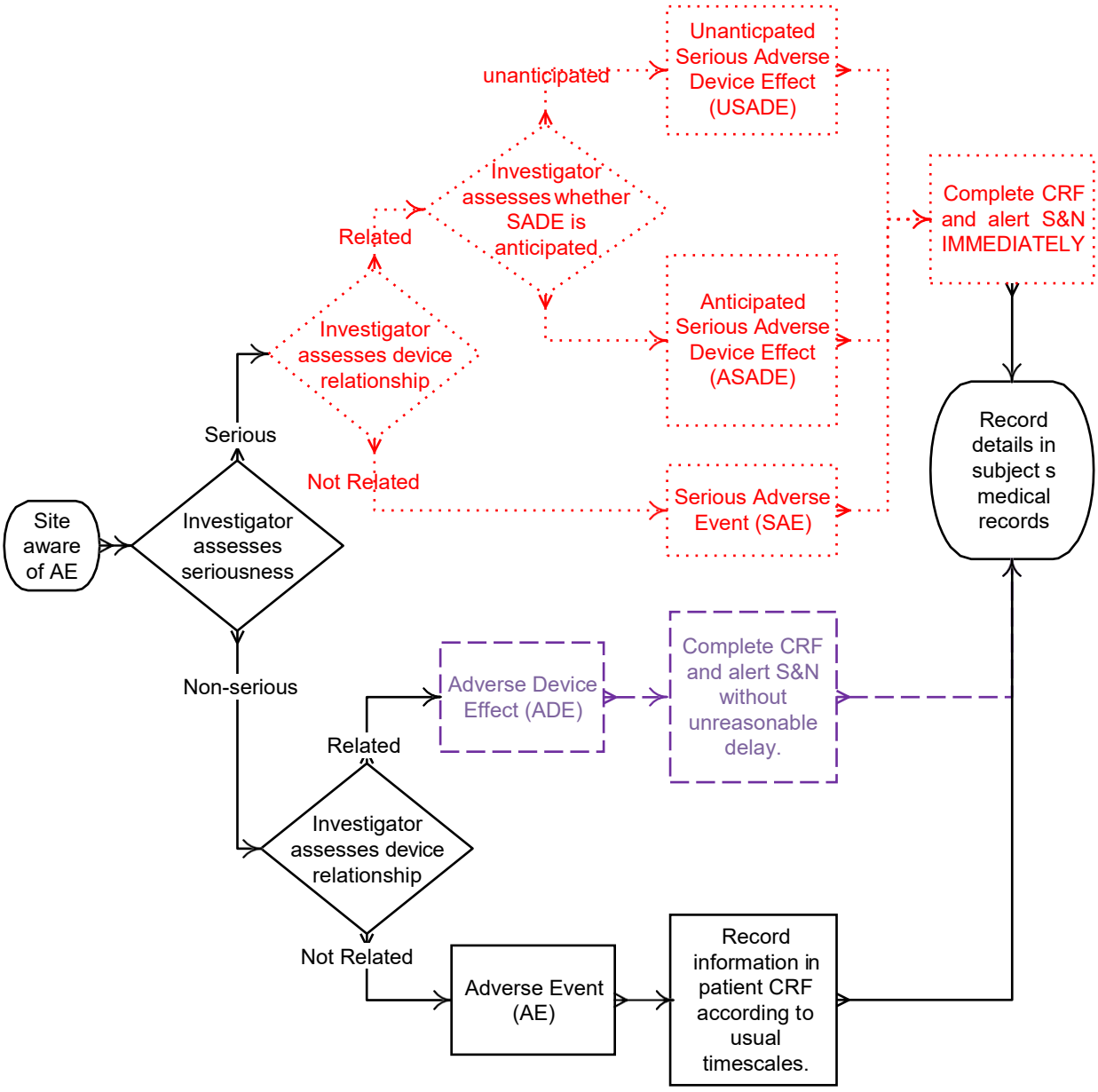
All adverse events will be reviewed by a medically qualified person appointed by the Sponsor to determine which, if any, meet criteria for expedited reporting to the regulatory authorities.

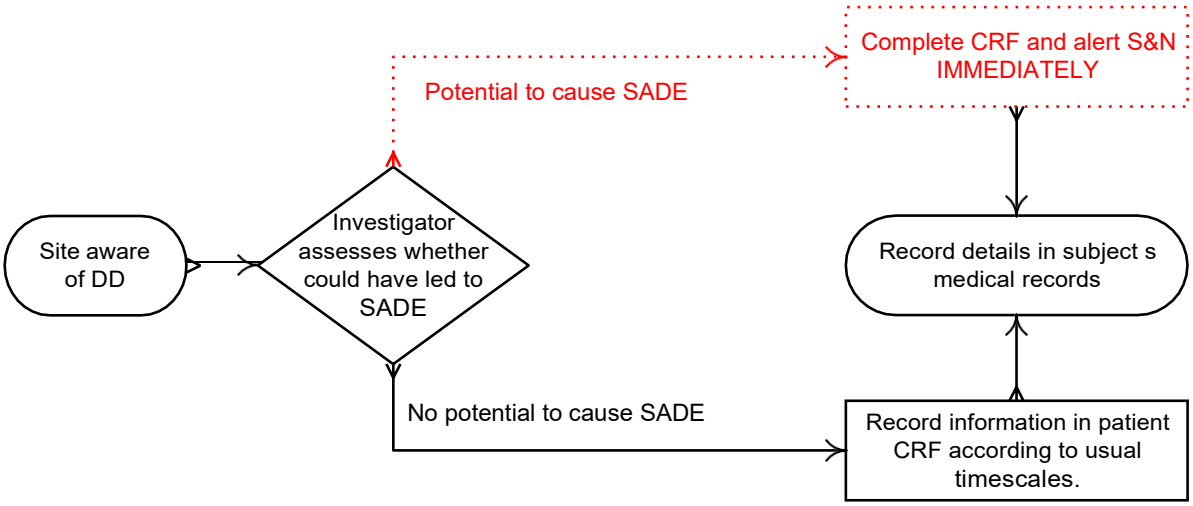
The investigator will inform the IRB of adverse events according to the IRB requirements.

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 Investigator Site File (ISF) Sponsor Contact Information Sheet to report SAE, unanticipated ADE and SADE, anticipated SADE, and DD.

Figure 12.3-1: Evaluation and Reporting of AE





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, and as required, the 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 21.7 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.

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 will 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 approval.

14.3 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.

14.4 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 reporting requirements. When no subjects have been included, a remote close-out visit may be conducted.

15. 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. Protocol amendments need to be approved by the IRB according to the applicable requirements prior to implementation at the site.

16. CONFIDENTIALITY OF THE STUDY

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

17. STATEMENTS OF COMPLIANCE

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

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

18. END OF STUDY

The end of study is considered the last visit of the last subject undergoing treatment in the study. It is expected that this study will last 42 months total.

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.

An End of Study CRF needs to be completed for any subject that does not complete the study, to document the reason for termination.

The entire study may be terminated if deemed necessary by the Sponsor (e.g. the product is determined to not be safe). Sites may be terminated for reasons that include, but are not limited to non-compliance to the protocol, ethical violations, or inability to recruit subjects.

19. PUBLICATION POLICY

19.1 PUBLICATION OF STUDY DATA

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.

19.2 DATA SHARING

Smith + Nephew, Inc. (S+N) is committed to upholding the highest ethical and legal standards involved in conducting clinical trials. S+N, therefore, supports the data sharing requirements of The International Committee of Medical Journal Editors (ICMJE) published on the 6th June 2017. In accordance, S+N 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 the Sponsor. To gain access, data requestors will need to sign a data access agreement.

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21. APPENDICES

21.1 PROTOCOL AMENDMENT 2.0

21.1.1 General Purpose

The following amendments were made to correct and clarify the protocol. These updates were made prior to any IRB submission. This study will start subject enrollment with Protocol Version 2.0.

21.1.2 Rationale

The rational for the changes are as follows:

Rationale 1: Correction of errors, changes for consistency in the protocol, and minor clarifications. Note that some changes are not listed in the table below (e.g. spelling errors).

Rationale 2: Clarification of the eligibility criteria, both inclusion and exclusion at screening and arthroscopy. The changes were made after receiving feedback on the protocol at Site Qualification Visits with PIs, Sub-Investigators, and Study Coordinators.

Rationale 3: Removed the PROs (KOOS, IKDC Subjective, and Lysholm) from the 3 month visit throughout the protocol as these questionnaires are not included in any of the planned analysis, and subjects are still recovering from surgery at 3 months.

Rationale 4: Clarified that the enrollment will be a minimum of 40 subjects per tear type rather than 45 of each type as it is not necessary to have exactly 45 of each tear type to meet the objectives of the study.

Rationale 5: Clarified the exploratory endpoint for NOVOCUT to only be assessed during the procedure rather than at follow-up as the device is only used during the procedure.

Rationale 6: Clarified claims and removed claims that are not expected to reach statistical significance.

Rationale 7: Separated the Patient Satisfaction score from the EQ-5D-5L as during development of the Case Report Forms, they became independent (the EQ-5D-5L is a standard questionnaire and the Patient Satisfaction is only required after the surgery at 1 and 2 years).

Rationale 8: Moved and clarified the information regarding how the CRFs are to be completed from under Visit 7 to the general section 9.1.1 Summary as this information applies to more than just Visit 7.

21.1.3 Effect on Study Status

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

21.1.4 Details

Section	Current Text 27/FEB2020 Version #1.0	Revised Text 07/APR/2020 Version #2.0
Throughout protocol (rationale 1)	1.0 dated 27/FEB/2020	2.0 dated 07/APR/2020
Table of Contents (rationale 1)	Various	Updated to reflect the current sections and page numbers
Throughout protocol (rationale 1)	EQ-5Q-5L	EQ-5D-5L
Throughout protocol inclusion criteria (rationale 2)	1. Meniscus to meniscus repair in circumferential (zone 1, 2, or 3) and/or radial locations (posterior or mid-body)	Text removed

Throughout protocol inclusion criteria (rationale 2)	3. Tear amenable to repair with NOVOSTITCH PRO with or without the use of adjunct devices per the exclusion criteria.	1. Meniscal tear amenable to repair with NOVOSTITCH PRO with or without the use of adjunct devices per the exclusion criteria.
Throughout protocol exclusion criteria (rationale 2)	Malalignment of the study knee >5 degrees and/or requiring osteotomy and/or correction;	Clinically significant malalignment of the study knee, and/or requiring osteotomy, and/or correction
Throughout protocol exclusion criteria (rationale 2)	Tears that impinge at meniscocapsular junction (ramp tears);	Ramp tears
Throughout protocol exclusion (rationale 2)	Physician discretion per the Instructions for Use (IFU);	Text removed
Throughout protocol exclusion (rationale 2)	Arthritis in the study knee Modified Outerbridge Grade III or higher	Articular cartilage damage in the study knee as, defined as by Modified Outerbridge Grade III or higher
Throughout protocol PROs (rationale 3)	Removal of PROs at 3-month visits	Text removed
Throughout protocol (rationale 1)	Meniscus Stitcher	Meniscal Stitcher
Throughout protocol (rationale 1)	re-operation	reoperation

2.0 Protocol synopsis Exclusion (rationale 1)	13. If material is suspected, testing should be completed prior to suture implantation; 14. Conditions which may limited the patient's ability or willingness to follow postoperative care instructions;	13. If material sensitivity is suspected, testing should be completed prior to suture implantation; 14. Conditions which may limit the patient's ability or willingness to follow postoperative care instructions;
3.4 List of Abbreviations (rationale 1)	None	MCID Minimal Clinically Important Difference
4.2 Literature summary (rationale 1)	Approximately 30% of all meniscal repair failures occur after 2 years.[16]	None
5.4 Claims (rationale 6)	• HCT and Complex repairs with NOVOSTITCH PRO have a clinical success rate of 80% or higher; • HCT and Complex tears repaired with NOVOSTITCH PRO have reoperation rates similar to other commonly repaired tear types (<20%); • HCT and Complex tears repaired with NOVOSTITCH PRO can heal at clinically	• HCT and Complex meniscal tears repaired with NOVOSTITCH PRO have a clinical success rate of 80% or higher; • HCT and Complex meniscal tears repaired with NOVOSTITCH PRO have reoperation rates similar to other commonly repaired tear types (<20%); • HCT meniscal tears repaired with NOVOSTITCH PRO lead

	acceptable rates as seen on MRI; • HCT and Complex tears repaired with NOVOSTITCH PRO can heal at clinically acceptable rates as seen on 2nd look needle endoscopy; • HCT and Complex tear repaired with NOVOSTITCH PRO lead to a significant improvement in patient symptom scores; • HCT and Complex tears repaired with NOVOSTITCH PRO may protect the knees against joint space narrowing (JSN) associated with osteoarthritis; • Patients with HCT and Complex tears repaired with NOVOSTITCH PRO are able to return to work within 6 months; and	to a significant improvement in patient symptom scores; and • Complex meniscal tears repaired with NOVOSTITCH PRO lead to a significant improvement in patient symptom scores;

	• Patients with HCT and Complex tears repaired with NOVOSTITCH PRO have significant improvements in Quality of Life (EQ-5Q-5L) at 1 year.	
6.5 Surgical Technique (rationale 1)	Surgeons selected to participate in this study will be familiar with the NOVOSTITCH PRO product, or will receive training per standard SN procedures if not familiar.	Surgeons selected to participate in this study will be familiar with the NOVOSTITCH PRO product, or will receive training prior to enrolling any subjects per standard SN procedures if not familiar.
7.3 Exclusion Criteria (rationale 1)	Previously enrolled in the study (no bilateral subjects);	Previously enrolled in the study (no bilateral knee surgeries);
7.4 Screening (rationale 1)	Of these 90 subjects, 45 subjects will have horizontal cleavage meniscal tears and 45 will have complex meniscal tears. Subjects will be enrolled as they meet eligibility and consent to the study. Therefore, once a group has met the 45 subjects, screening will stop within that group, and screening and enrollment will continue only in the other group until all 90 subjects are enrolled.	Of the 90 subjects, at least 40 subjects will have horizontal cleavage meniscal tears and at least 40 will have complex meniscal tears. Subjects will be enrolled as they meet eligibility and consent to the study. Therefore, if a group enrolls 50 subjects, screening will stop within that group, and screening and enrollment will continue only in the other group until all 90 subjects are enrolled.

7.5 Informed Consent (rationale 1)	Consent cannot be coerced and can be completed at any time prior to the meniscus surgery. If the subject does not speak English, an in-person or telephone interpreter will be used and the entire consent form will be translated for the subject. The subject will be able to ask any questions that will be answered by study personnel through the use of an interpreter. If an interpreter is used, the subject will sign a short consent form, along with a witness, and documentation of the translator will be included on the form. A copy of the signed short informed consent document and a copy of the English consent form will be provided to the subject, and copies will be placed in the subject's record or chart as required by the site, with the original filed in the Investigator Site File (ISF).	Consent cannot be coerced and must be completed at any time prior to the first study activity. If the subject does not speak English, the individual will be given a consent form in their native language, or a bilingual study member or an in-person or telephone interpreter will be used and the entire consent form will be translated for the subject. The subject will be able to ask any questions that will be answered by study personnel, and as required through the use of the interpreter. If an interpreter is used, the subject will sign a short consent form, along with a witness, and documentation of the translator will be included on the form. A copy of the signed consent form, or short informed consent document and a copy of the English consent form as applicable, will be provided to the subject, and copies will be placed in the subject's record or chart as required by the site, with the original filed in the Investigator Site File (ISF).

7.8.1 Withdrawal from Study (rational 1)	Concurrent illness	Concurrent debilitating illness
7.8.3 Use of Data Following Withdrawal (rationale 1)	In cases where the subject withdraws consent, or the subject is withdrawn from the study by the PI, data collected up to the point of withdrawal may be used, but no additional data for that subject may be collected except for subjects who have consented and have an adverse event that is being followed to resolution or receive a revision surgery of the study knee as detailed in section 7.8.1 above (until the end of the study).	In cases where the subject withdraws consent, or the subject is withdrawn from the study by the PI, data collected up to the point of withdrawal may be used, but no additional data for that subject may be collected except for subjects who have consented and have an adverse event that is being followed to resolution or receive a revision surgery of the study knee as detailed in section 7.8.1 above.
8.1 Study Design (rationale 1)	However, primary outcome measures that will be examined include whether the re-operation survival rate will be similar or less than historical rates (78-91%)[10,27]	However, primary outcome measures that will be examined include whether the reoperation survival rate at 12 months will be similar or less than historical rates (78-91%)[10,27]
Figure 8.1-1 Study Flowchart (rationales 3 and 7)	Original image	Updated image removing the PROs from the 3-month visit, separating the EQ-5D-5L from the Patient Satisfaction CRF, and removing the Patient Satisfaction CRF at baseline

Table 9.1-1 Study Procedures by Visit (rationales 3 and 7)	Original table	Updated table by correcting the typographical error in which the explanation was written as 5 instead of 4, removing the PROs from the 3-month visit, separating the EQ-5D-5L from the Patient Satisfaction CRF, and removing of the Patient Satisfaction CRF at baseline
9.1.2 Visit 1 (rationale 1)	Screen Failure subjects should not be assigned a Subject ID number, but their demographic information must be captured in the appropriate CRF and/or log with the reason for screen failure specified.	Screen Failure subjects who are consented but do not complete the baseline screening will be assigned a Subject ID number, and their demographic information captured in the appropriate CRF and/or log with the reason for screen failure specified.
9.1.1 Summary (rationale 8)	Previously in Section 9.1.8	Subjects may complete the patient CRFs (PROs (KOOS, IKDC Subjective, and Lysholm), Post-Operative Plan/Return to Work, Patient Satisfaction, and EQ-5D-5L) either on paper, or on a secure electronic device such as a computer, mobile phone, or tablet. Subjects who are unable to return to the site for follow-up visits may

		complete the PROs (KOOS, IKDC Subjective, and Lysholm), Post-Operative Plan/Return to Work**,** Patient Satisfaction, and EQ-5D-5L CRFs on paper and return by mail, electronically by email, or online through a secure link provided by the site. The follow-up general health/concomitant medications and concomitant therapies CRF and safety assessment may be conducted over the telephone with study staff. As required, documents will be translated into the appropriate language for the individual, and an interpreter will be used over the telephone. Subjects may be provided participant stipends as agreed upon by Sponsor and the site, and as allowed by the site's standard operating procedures/regulations and the IRB. Stipends amounts may cover costs associated with the study participant to complete follow-up visits, but cannot be coercive.

9.3 Health Economics (rationales 1 and 7)	1. Employment status pre-surgery: Currently working/employed (Yes/No). 2. Nature of work: Laborer/Sedentary work (Sedentary deined as “involves occasional lifting of no more than ten pounds and sitting with occasional walking and standing”). 3. Return to work after surgery (Days). 4. Patient Satisfaction at baseline, 1 year, and 2 years.	1. Employment status pre-surgery: Currently working/employed category) and job type. 2. Nature of work: Laborer/Sedentary work (Sedentary deined as “involves occasional lifting of no more than ten pounds and sitting with occasional walking and standing”). 3. Return to work after surgery (Days) and type of work. 4. Patient Satisfaction at 1 year and 2 years.
10.4.3 Analysis of Other Endpoint(s) (rationale 1)	The number and proportion of subjects experiencing freedom from re-operation where NOVOCUT Suture Manager has been used alongside the NOVOSTITCH PRO will be presented at 6 months, 1 year and 2 years together with a 95% confidence interval (calculated using the Clopper-Pearson Exact method)[36].	The number and proportion of subjects experiencing device deficiencies where NOVOCUT Suture Manager has been used alongside the NOVOSTITCH PRO with a 95% confidence interval (calculated using the Clopper-Pearson Exact method)[36].

21.2 INSTRUCTIONS FOR USE

Refer to the Instruction for Use supplied with this protocol.

21.3 EQUIPMENT AND SPECIAL INSTRUCTIONS

Not applicable.

21.4 ADDITIONAL INFORMATION

Not applicable.

21.5 PRINCIPAL INVESTIGATOR OBLIGATIONS (ISO14155:2011)

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.
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 one or more qualified investigators, a qualified investigation site team and adequate facilities for the foreseen duration of the clinical investigation.

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 14155:2011:
      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. 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

p. 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.