Clinical Protocol - Device

Prospective, Multi-Center, Post-Market Clinical Follow-up Study to Evaluate Safety and Performance of the HEALICOIL° Knotless Suture Anchor in Shoulder Rotator Cuff Tendon Repair

Sponsor Name and Address:	Smith & Nephew, Inc. 150 Minuteman Road, Andover, MA 01810
Investigational Product(s)	HEALICOIL° Knotless Suture Anchor HEALICOIL Knotless PEEK Self-Tapping HEALICOIL Knotless PEEK Non-Self Tapping HEALICOIL Knotless REGENESORB° Self-Tapping HEALICOIL Knotless REGENESORB Non-Self Tapping
Single Identification Number of Clinical Investigation	Not applicable
Protocol Author(s):	Rob Bedford, Senior Clinical Study Manager Michelle Foster, Senior Biostatistician Stephan Mangin, Director, Clinical Strategy, Sports Med/ENT

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 "Prospective, Multi-Center, Post-Market Clinical Follow-up Study to Evaluate Safety and Performance of the HEALICOIL° Knotless Suture Anchor in Shoulder Rotator Cuff Tendon Repair" version 3.0, dated 25Feb2021 and agree to abide by all provisions set forth herein.

I agree to comply with the Investigator's Obligations stipulated in Section 22.5 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 and Date / DocuSign Stamp

1.2 Coordinating Investigator Approval

☐ I have read the attached protocol entitled "Prospective, Multi-Center, Post-Market Clinical Follow-up Study to Evaluate Safety and Performance of the HEALICOIL° Knotless Suture Anchor in Shoulder Rotator Cuff Tendon Repair", version 3.0, dated 25Feb2021, and agree to abide by all provisions set forth therein.

Name, Address, Professional Position	Signature and Date / DocuSign Stamp
	DocuSigned by: Dr Jonathan Bravman Signer Name: Dr Jonathan Bravman Signing Reason: I approve this document Signing Time: 22-Mar-2021 | 10:29:42 MDT EBE7DB129024445A82718F3ED0504951

1.3 Sponsor Approval

Name and Title	Signature and Date / DocuSign Stamp
Head of Global Clinical Operations Rachael Winter	DocuSigned by: Rachael Winter Signer Name: Rachael Winter Signing Reason: I approve this document Signing Time: 04-Mar-2021 | 11:45:21 GMT A32F12A80F1B4490986E80ACCB7471CB
Head of Global Clinical Strategy Stephan Mangin	DocuSigned by: Stephan Mangin Signer Name: Stephan Mangin Signing Reason: I approve this document Signing Time: 03-Mar-2021 | 19:47:47 GMT 77573411150E4841B3F03589FBBD3EAD
Head of Global Data Analytics Alan Rossington	DocuSigned by: Alan Rossington Signer Name: Alan Rossington Signing Reason: I approve this document Signing Time: 04-Mar-2021 | 12:05:14 GMT 556E7DBFCA8A4287A7EE3EE9B5B3ABFD
Medical Affairs Representative Luca Orlandini	DocuSigned by: Signer Name: Luca Orlandini Signing Reason: I approve this document Signing Time: 03-Mar-2021 | 20:59:05 GMT FC872951AC1C4261B85EC7A7CD09ACDC

2 SYNOPSIS

Title of Study:	Prospective, Multi-Center, Post-Market Clinical Follow-up Study to Evaluate Safety and Performance of the HEALICOIL° Knotless Suture Anchor in Shoulder Rotator Cuff Tendon Repair
Study Design:	Prospective, multi-center, non-randomized clinical trial • 160 subjects at up to 6 sites • 2 groups: HEALICOIL Knotless PEEK and HEALICOIL Knotless REGENESORB • Follow up: 6 and 12 months for HEALICOIL Knotless PEEK Self-Tapping, HEALICOIL Knotless PEEK Non-Self Tapping, and HEALICOIL Knotless REGENESORB Self-Tapping subgroups and 6, 12, and 24 months for HEALICOIL Knotless REGENESORB Non Self-Tapping subgroup
Study Type:	Observational, prospective, multi-center, non-randomized clinical follow-up study
Study Product:	**HEALICOIL Knotless Suture Anchor:** SKU 72205138 HEALICOIL Knotless PEEK Self-Tapping (ST) SKU 72205137 HEALICOIL Knotless PEEK Non-Self Tapping (NST) SKU 72205136 HEALICOIL Knotless REGENESORB (RG) ST SKU 72205135 HEALICOIL Knotless RG NST
Comparison Group(s)*: (*if applicable)	No comparator treatment will be used for this study
Study Purpose:	The purpose of this study is to assess safety and performance by product variant of HEALICOIL Knotless Suture Anchor.
Primary Objective:	The primary objective of this study is to assess repair failure rate defined as the need for a second repair procedure at 6 months.

Secondary Objective(s): The secondary objectives are:

- Assess post-operative repair failure rates defined as the need for a second repair procedure
- Access clinical performance with patient-reported outcomes
- To characterize tendon thickening and REGENESORB material resorption at 6 months and 24 months in the HEALICOIL Knotless REGENESORB NST subgroup
- To characterize the MRI tendon re-tear rates at 6 months and 24 months in the HEALICOIL Knotless REGENESORB NST subgroup

Sample Size: The sample size for this study is determined based on the feasibility of recruitment, enrollment and follow-up considerations. The study is therefore not powered for any statistical hypothesis testing but will be able to estimate a clinical success rate of 91% with a 95% confidence interval of 80% to 100%. Enrolling between 60 and 80 subjects per variant would provide probability greater than 90%.

HEALICOIL Knotless PEEK patients: Minimum N=60, Maximum N=80

HEALICOIL Knotless REGENESORB patients: Minimum N=60, Maximum N=80Enrollment distribution will ensure that all variants are represented in the patient population:**HEALICOILKnotless Suture Anchor**	**Minimum**	**Maximum**
HEALICOIL Knotless PEEK Self-Tapping	30	40
HEALICOIL Knotless PEEK NST	30	40
HEALICOIL Knotless RG Self -Tapping	30	40
HEALICOIL Knotless RG NST	30	40

The statistical plan will provide a detailed approach of the statistical analysis that will be conducted on two independent subgroups: the HEALICOIL Knotless PEEK anchor group (2 variants, 60-80 patients)

	and the HEALICOIL Knotless REGENESORB anchor group (2 variants, 60-80 patients).
Number of Study Sites:	Up to 6 study sites
Targeted Global Regions:	United States / Canada (*) (*) Participation of Canada sites will be contingent on timeline for Health Canada approval
Inclusion Criteria:	Subjects will be considered qualified for enrolment if they meet the following criteria: 1. Requires reattachment of soft tissue to bone for the following shoulder indications: a. Rotator Cuff Tendon repair: i. Single or double row rotator cuff repair using HEALICOIL Knotless PEEK NST, HEALICOIL Knotless PEEK Self-Tapping, **or** HEALICOIL Knotless RG Self-Tapping; **OR** ii. Double row rotator cuff repair using HEALICOIL Knotless RG NST in lateral row (existing HEALICOIL RG device to be used in medial row of the repair); **AND/OR** b. Biceps tenodesis i. In conjunction with Rotator Cuff Tendon repair using HEALICOIL Knotless PEEK NST, HEALICOIL Knotless PEEK Self-Tapping, HEALICOIL Knotless RG NST or HEALICOIL Knotless RG Self-Tapping **OR** ii. As a stand-alone procedure for HEALICOIL Knotless PEEK NST, HEALICOIL Knotless PEEK Self-Tapping, or HEALICOIL Knotless RG Self-Tapping (not HEALICOIL Knotless RG NST

2. Has a pre-operative MRI collected within 6 months of surgery which meets one of the following criteria:
    a. MRI collected as standard-of-care has been submitted to external imaging vendor and confirmed as acceptable **OR**
    b. If standard-of-care images are unavailable or considered unacceptable by external imaging vendor, subject must undergo an additional study-specific pre-operative MRI, confirmed as acceptable by external imaging vendor **OR**
    c. MRI not required; subject not in HEALICOIL Knotless RG NST subgroup
3. Has consented to participate in the study by signing the IRB/IEC approved informed consent form.
4. Requires only one variant of the HEALICOIL Knotless Suture Anchor
5. Is ≥18 years of age at time of surgery
6. Willing and able to make all required study visits
7. Able to follow instructions (Approved translated documents supplied upon request)

Exclusion Criteria:

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

1. Known hypersensitivity to the implant material. Where material sensitivity is suspected, appropriate tests should be made and sensitivity ruled out prior to implantation.
2. Pathological conditions of bone, such as cystic changes or severe osteopenia, which would compromise secure anchor fixation.
3. Pathological conditions in the soft tissues to be attached that would impair secure fixation by suture.

	4. Comminuted bone surface, which would compromise secure anchor fixation. 5. Physical conditions which would eliminate, or tend to eliminate, adequate anchor support or retard healing. 6. The presence of infection. 7. Conditions which would limit the subject's ability or willingness to restrict activities or follow directions during the healing period. 8. Concurrent bilateral surgery. 9. Participation in the treatment period of another clinical trial within thirty (30) days of Visit 1, or during the study. 10. Women who are pregnant. 11. Prior ipsilateral surgeries performed on the joint space. 12. Subjects with a medical or physical condition that, in the opinion of the Investigator, would preclude safe subject participation in the study.
Study Duration:	Total study timeline: 36 months Enrollment period: 12 months Follow-up period: 6 and 12 months for HEALICOIL Knotless PEEK Self-Tapping, HEALICOIL Knotless PEEK NST, and HEALICOIL Knotless RG Self-Tapping subgroups and 6, 12, and 24 months for HEALICOIL Knotless RG NST subgroup
Primary endpoint:	Assess repair failure rate defined as the need for a second repair procedure at 6 months
Secondary endpoint(s):	**All endpoints to be collected and analyzed on all subjects:** • Repair failure rate at 12 months (and 24 months for the HEALICOIL Knotless RG NST subgroup). Repair failure rate is defined as the need for a second repair procedure.

	• Constant-Murley Score at 6 months and 12 months (24 months for the HEALICOIL Knotless RG NST subgroup) • American Shoulder and Elbow Surgeons (ASES) scale at 6 months and 12 months (24 months for the HEALICOIL Knotless RG NST subgroup) • ASES Visual Analog Scale (VAS) pain score at 6 months and 12 months (24 months for the HEALICOIL Knotless RG NST subgroup) • Single Assessment Numeric Evaluation (SANE) Shoulder scale at 6 months and 12 months (24 months for the HEALICOIL Knotless RG NST) • EQ-5D-3L at 6 months and 12 months (24 months for the HEALICOIL Knotless RG NST) • Only for the HEALICOIL Knotless RG NST subgroup - MRI to determine tendon thickening and anchor absorption/replacement by bone at 6 months and 24 months • Only for the HEALICOIL Knotless RG NST subgroup - MRI to determine tendon re-tear rate at 6 months and 24 months
Other exploratory endpoint(s):	Not applicable
Safety Data	• All adverse events (AEs) and complications occurring from the time of surgical implantation until study termination or study completion including intra-operative adverse events and complications • Device Deficiencies

STUDY SCHEDULE

Visit Type/name	Frequency/Time point
Pre-Operative	≤60 days of Visit 2
Operative through Discharge/Visit 2	Day 0 - Surgery
Follow-up/ Visit 3	6 months (± 30 days) post-surgery
Follow-up/Visit 4	12 months (± 30 days) post-surgery
Follow-up/Visit 5 for 30-40 HEALICOIL Knotless RG NST subjects	24 months (± 60 days) post-surgery

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3.4 List of Abbreviations and Definitions

Abbreviation	Definition
ADE	Adverse Device Effect(s)
AE	Adverse Event(s)
ASES	American Shoulder and Elbow Surgeons
BSI	British Standards Institute
CER	Clinical Evaluation Report
CMS	Constant-Murley Shoulder
CRF	Case Report Form(s)
CRO	Contract Research Organization
DD	Device Deficiency(ies)

FAS	Full Analysis Set Population
FDA	Food and Drug Administration
FU	Follow-Up
GCP	Good Clinical Practice
HIPAA	Health Information Portability Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFU	Instructions for Use
IP	Investigational Product
IRB	Institutional Review Board
ISF	Investigator Site File
MRI	Magnetic Resonance Imaging
NA or N/A	Not Applicable
N (or n)	Total Sample Size (or subgroup sample size)
NST	Non Self-Tapping
PI	Principal Investigator
PT	Physical Therapy
S+N	Smith + Nephew, Inc.
SADE	Serious Adverse Device Effect(s)
SAE	Serious Adverse Event(s)
SAF	Safety population
SANE	Single Assessment Numeric Evaluation
SAP	Statistical Analysis Plan
ST	Self-Tapping
TX	Treatment
USADE	Unanticipated Serious Adverse Device Effect(s)
VAS	Visual Analog Scale

4 INTRODUCTION

4.1 Background

Disease/Medical Condition State: Rotator Cuff tears

The shoulder is a ball and socket joint that is subject to repeated overhead movement common to routine and sports activities. Rotator cuff tears are injuries to the tendons involved in shoulder joint motion. The integrity of the rotator cuff repair site after surgical treatment of full-thickness rotator cuff tears has been shown to correlate with clinical improvement, particularly the return of strength. Therefore, rotator cuff tears should be fully repaired. After arthroscopic rotator cuff repair, numerous studies have reported excellent clinical outcomes. However, long-term restoration of a functional, completely healed rotator cuff may not be always attainable in primary rotator cuff repair, and retears occur frequently after arthroscopic repairs. The causes for retears vary and include poor quality of tendon tissue, pullout of suture anchor, suture breakage, and inappropriate rehabilitation. The commonly cited mechanism of failure of suture anchor-based rotator cuff repairs in most reports was failure of the repair construct, leading to repair site gapping. In an effort to improve the biomechanics of rotator cuff repair constructs, advances in repair techniques are needed to optimize the healing environment after repair to facilitate restoration of function.[2]

Current Treatment

Rotator Cuff Repair

Treatments for rotator cuff surgery can vary depending on the size of the tear, duration of symptoms, failure/duration of nonoperative treatment, nocturnal pain, history of trauma, and limitation of daily activities.[2] Patient activity level and patient expectations are important considerations when recommending treatment for rotator cuff tears.[14]

Several non-operative treatments exist and are considered effective such as physical therapy (PT), anti-inflammatory medications, and cortisone injections.[9] Non-operative treatment has shown to be effective in 75% of full-thickness atraumatic rotator cuff tears.[2] The patients who fail nonoperative treatment usually fail within the first 12 weeks of their PT program.[2] A 6-12 week structure physical therapy program should be generally prescribed prior to surgery for patients with atraumatic, symptomatic, full thickness rotator cuff tears. While conservative treatment is a good option for some patients, it is difficult to speculate which patients, or which tears will respond best to conservative treatment alone. [9]

Rotator cuff repair techniques can vary depending on the type of tear and the tendon(s) affected: supraspinatus, infraspinatus, subscapularis, and teres. Techniques used include single row or double row repair. Recent studies on structural healing after double row repair show superior biomechanical characteristics and lower rate (11%-17%) of recurrent tears.[2]

Biceps Tenodesis

Indications for tenodesis of the biceps tendon include pain associated with significant tenosynovitis, pre-rupture of the tendon, subluxation, and dislocation. This treatment typically also is implemented to address biceps "pop-eye" deformity.[2] Biceps tenodesis can be performed either in an open or arthroscopic technique. The patient should be positioned in either the lateral decubitus or beach chair position, however the beach chair position allows for easier control of the shoulder and elbow flexion and rotation during the procedure. The biceps tendon is exteriorized anteriorly, doubled on itself, and then inserted into a humeral socket, which is drilled at the top of the bicipital groove and fixed with an implant.[1] Interference screws or suture anchors can be used for the procedure. There are several techniques options, one difference is to either push or pull the biceps tendon long head into the humeral socket.

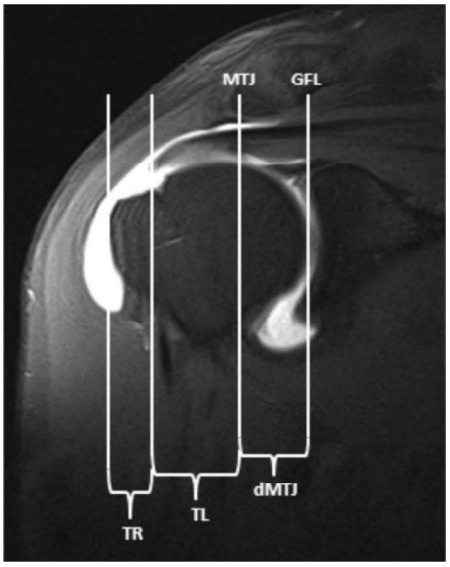
Typically, in patients treated for biceps tenodesis, full passive and active elbow flexion, extension, supination and pronation are allowed on the same day as surgery, with no immobilization. Elbow activities under stress or resistance are restricted for 6 weeks after the tenodesis procedure.[1]

4.2 Literature Summary

HEALICOIL Knotless PEEK and REGENESORB suture anchors are new products and there is no literature available for these devices. This study will provide evidence for all indications support CE marking of the project under MDR. In addition to that, this study will provide evidence related to clinical literature on Arthroscopic Rotator Cuff Repair: the general question often asked in the literature is: Is the Repair Integrity Actually Maintained?[2] Recently, arthroscopic repair has been widely accepted for treatment of rotator cuff tears, with equal or better results than those from open repair reported. With recent arthroscopic instrument development and wide surgical experience, most symptomatic tears of the rotator cuff can be managed successfully by an arthroscopic approach. However, technical advances to optimize the healing at a repaired rotator cuff insertion are needed for improving the outcome.[2] Retears may occur after arthroscopic rotator cuff repair with a retear rate as high as 94%.[6] In an effort to prevent retears, new operative techniques and new devices (such as the HEALICOIL Knotless Suture Anchor System) have evolved with time. Re-tear Type will be graded in accordance with the following definitions, adapted from Ellman et al.: Intact (No evidence of tendon tear), Low-grade Partial-Thickness Tear (covering <50% of the tendon thickness), Bursal or Articular, High-grade Partial-Thickness Tear (covering ≥50% of the tendon thickness) and finally Full-Thickness Tear (Complete tear of the tendon) with this study focusing on the last category.[4] Finally, there is some literature (albeit more limited) on

pre-operative tendon retraction and position of the Musculotendinous Junction (MTJ) of the supraspinatus tendon after initial repair: this study will contribute to the published evidence that suggests those factors impact greatly the clinical success outcome of the repair.[13]

Figure 4.2-1 T2-weighted coronal image at the midpoint (anteroposterior) of the supraspinatus fossa. dMTJ, distance from MTJ to glenoid face; GFL, glenoid face line; MTJ, musculotendinous junction; TL, tendon length; TR, tendon retraction.



Finally, there are well known factors that predispose patients to a failed rotator cuff repair: those are muscle fatty degeneration or fatty infiltration as well as muscle atrophy.[5,7,8] The overall quality of the rotator cuff repair will also rely on the well published literature on the Sugaya tendon repair classification.[12]

4.3 Study Purpose

The purpose of this post-market study is to assess safety and performance by product variant of HEALICOIL Knotless Suture Anchor.This study will be conducted to obtain the Conformité Européene (CE) Mark and will submitted to the EU for consideration.

The study has two main purposes:

- To meet EU pre-market and PMCF requirements for the HEALICOIL Knotless Suture Anchor product: the data on PEEK variants (NST and ST) will be considered PMCF data since those are already CE-marked by self-certification. The data on REGENESORB are critical to support an EU submission and are to be reviewed by the notified body BSI prior to CE marking approval.
- To support marketing claims on double row tendon repair performed with the HEALICOIL RG NST variant. Claims will be supported by collecting MRI imaging data on early tendon repair healing and anchor material resorption with new bone formation (6 months and 24 months)

4.4 Safety Consideration

The following clinical performance and benefits are anticipated with the HEALICOIL Knotless Suture Anchor:

- The HEALICOIL Knotless Suture Anchor functions to restore the rotator cuff and biceps anatomy and allow healing of the tendon back onto the tendon-bone footprint
- The HEALICOIL Knotless Suture Anchor result in improved patient reported outcomes following RC repair or biceps tenodesis procedures
- The HEALICOIL Knotless Suture Anchor (REGENESORB only) resorb over time and allow for easy revision in repeat procedures
- The open architecture of the HEALICOIL Knotless Suture Anchor results in accelerated tendon healing and thickening at 6 months post-operatively

During causality assessment activity (assessment of Unanticipated vs Anticipated), clinical judgement shall be used and relevant documents, such as the Instructions for Use (IFU) shall be consulted, as foreseeable serious adverse events and the potential risks are summarized there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

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 repair failure rate defined as the need for a second repair procedure at 6 months.

5.2 Secondary Objective(s)

The secondary objectives are to:

- Assess post-operative repair failure rates defined as the need for a second repair procedure
- Access clinical performance as assessed with patient-reported outcomes

- To characterize tendon thickening and REGENESORB material resorption at 6 months and 24 months in the HEALICOIL Knotless REGENESORB NST subgroup
- To characterize the MRI tendon re-tear rates at 6 months and 24 months in the HEALICOIL Knotless REGENESORB NST subgroup

5.3 Claims

1. Improved tendon healing with HEALICOIL REGENESORB and HEALICOIL Knotless REGENESORB

    a. Captured by looking at tendon thickness at the 6 month mark and other MRI imaging endpoints such as Sugaya repair healing classification, tendon footprint coverage and other tendon morphological features

2. Complete or near complete absorption for the REGENESORB material

    b. Captured via MRI at 6 months and 24 months as well as capturing under MRI new bone formation, bone in-growth and absence of osteolysis

6 INVESTIGATIONAL PRODUCT(S)

HEALICOIL Knotless REGENESORB Suture Anchor and HEALICOIL Knotless PEEK Suture Anchors are expressly used for reattachment of soft tissue to bone for either rotator cuff tendon repair or biceps tenodesis.

6.1 Identification

6.1.1 Investigational Product(s)

HEALICOIL Knotless PEEK Suture Anchor Non Self-Tapping and Self-Tapping

The HEALICOIL Knotless Suture Anchor consists of an anchor on an inserter fitted with a suture threader and insertion accessory instrument. The device consists of the following components: a

proximal implant composed of PEEK, a distal implant (PEEK or Titanium), and a non-absorbable internal PEEK plug.

The anchor is preloaded on a stainless steel inserter. This device is to be used with Smith & Nephew ULTRABRAID, ULTRAPE, and MINITAPE Sutures.

HEALICOIL Knotless REGENESORB Suture Anchor Non-Self-Tapping and Self-Tapping

The HEALICOIL Knotless REGENESORB Suture Anchor is a fixation device intended to provide secure reattachment of soft tissue to bone. The device consists of a knotless suture anchor assembled on to an insertion device. The device is to be used with Smith & Nephew ULTRABRAID, ULTRATAPE, and MINITAPE Sutures. This device is provided sterile, for single use only.

HEALICOIL Knotless REGENESORB is made from PLGA (poly (lacticcoglycolic acid)), ß-TCP (beta tricalcium phosphate), and calcium sulfate.

Figure 6.1.1-1: Product Description

Product Description	Proximal/ Distal	Distal Implant	Deployed Length
HEALICOIL KNOTLESS SUTURE ANCHOR, REGENESORB, 5.5mm	RG/PK	3.75mm	18.5mm
HEALICOIL KNOTLESS SUTURE ANCHOR, REGENESORB, 5.5mm, SELF TAPPING	RG/Ti	5.0mm	21.0mm
HEALICOIL KNOTLESS SUTURE ANCHOR, PK, 5.0mm	PK/PK	3.75mm	19.0mm
HEALICOIL KNOTLESS SUTURE ANCHOR, PK, 5.0mm, SELF TAPPING	PK/TI	4.5mm	22.0mm

Refer to the HEALICOIL Knotless Suture Anchor Instructions for Use for more information.

Contraindications for use include the following:

- Known hypersensitivity to the implant material. Where material sensitivity is suspected, appropriate tests should be made and sensitivity ruled out prior to implantation.
- Pathological conditions of bone, such as cystic changes or severe osteopenia, which would compromise secure anchor fixation.

Figure 6.1.1-2: Investigational Product

Refer to the HEALICOIL Knotless Suture Anchor Instructions for Use for more information.

Contraindications for use include the following:

- Known hypersensitivity to the implant material. Where material sensitivity is suspected, appropriate tests should be made and sensitivity ruled out prior to implantation.

- Pathological conditions of bone, such as cystic changes or severe osteopenia, which would compromise secure anchor fixation.
- Pathological conditions in the soft tissues to be attached that would impair secure fixation by suture.
- Comminuted bone surface, which would compromise secure anchor fixation.
- Physical conditions which would eliminate, or tend to eliminate, adequate anchor support or retard healing.
- The presence of infection.
- Conditions which would limit the patient's ability or willingness to restrict activities or follow direction during the healing period.
- Contraindications may be relative or absolute and must be carefully weighed against the patient's entire evaluation.

The legal manufacturer for the HEALICOIL Knotless 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

There are two ancillary products provided for the conduct of this study. All sites will be provided with at least one Manual Muscle Tester (MMT), often referred to as a dynamometer, packaged in a Pelican type storage case. MMTs are ergonomic devices used to objectively quantify muscle strength. Additionally, all sites will be provided with at least one long-arm isometric goniometer which is used to measure joint range of motion. Both devices are required to complete the Constant-Murley score at the pre-op and follow-up visits.

6.2 Product Use

Refer to the HEALICOIL Knotless Suture Anchor Instructions for Use (IFU) for detailed information on contraindications, warnings, adverse reactions and precautions.

Sites that are familiar with the use of the study device will be selected or will receive training prior to enrolling any subjects per standard Smith + Nephew procedures if not familiar; no additional training is required.

6.3 Packaging and Labelling

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

6.3.1 Labelling of Investigational Product

The HEALICOIL Knotless Suture Anchors have received 510k 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 HEALICOIL Knotless Suture Anchors 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

As this is a post-market study, the sites will be responsible for obtaining and maintaining an inventory of HEALICOIL Knotless Suture Anchors. Sites will document the device that was used in a subject on a Case Report Form (CRF) that will include batch, lot, and UDI numbers. 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 HEALICOIL Knotless Suture Anchor must be performed according to the recommended surgical technique described in the IFU.

Surgeons selected to participate in this study will be familiar with implanting HEALICOIL Knotless Suture Anchors and have written evidence of training and expertise in the study procedure. Sites not familiar with this product will receive and show evidence of training prior to activation per S+N procedures.

7 SUBJECT ENROLLMENT AND WITHDRAWAL

7.1 Subject Population

This study will enroll a minimum of 30 and a maximum of 40 subjects for each variant of the HEALICOIL Knotless Suture Anchor treated for either rotator cuff repair and/or biceps tenodesis.

Ethnic minorities are classed as vulnerable subjects according to 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:

1. Requires reattachment of soft tissue to bone for the following shoulder indications:
    a. Rotator Cuff Tendon repair:
        i. Single or double row rotator cuff repair using HEALICOIL Knotless PEEK NST, HEALICOIL Knotless PEEK Self-Tapping, **or** HEALICOIL Knotless RG Self-Tapping; **OR**
        ii. Double row rotator cuff repair using HEALICOIL Knotless RG NST in lateral row (existing HEALICOIL RG device to be used in medial row of the repair); **AND/OR**
    b. Biceps tenodesis
        i. In conjunction with Rotator Cuff Tendon repair using HEALICOIL Knotless PEEK NST, HEALICOIL Knotless PEEK Self-Tapping, HEALICOIL Knotless RG NST or HEALICOIL Knotless RG Self-Tapping **OR**
        ii. As a stand-alone procedure for HEALICOIL Knotless PEEK NST, HEALICOIL Knotless PEEK Self-Tapping, or HEALICOIL Knotless RG Self-Tapping (not HEALICOIL Knotless RG NST

2. Has a pre-operative MRI collected within 6 months of surgery which meets one of the following criteria:
    a. MRI collected as standard-of-care has been submitted to external imaging vendor and confirmed as acceptable **OR**
    b. If standard-of-care images are unavailable or considered unacceptable by external imaging vendor, subject must undergo an additional study-specific pre-operative MRI, confirmed as acceptable by external imaging vendor **OR**
    c. MRI not required; subject not in HEALICOIL Knotless RG NST subgroup

3. Has consented to participate in the study by signing the IRB/IEC approved informed consent form.

4. Requires only one variant of the HEALICOIL Knotless Suture Anchor

5.	Is ≥18 years of age at time of surgery
6.	Willing and able to make all required study visits
7.	Able to follow instructions (Approved translated documents supplied upon request)

7.3 Exclusion Criteria

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

1.	Known hypersensitivity to the implant material. Where material sensitivity is suspected, appropriate tests should be made and sensitivity ruled out prior to implantation.
2.	Pathological conditions of bone, such as cystic changes or severe osteopenia, which would compromise secure anchor fixation.
3.	Pathological conditions in the soft tissues to be attached that would impair secure fixation by suture.
4.	Comminuted bone surface, which would compromise secure anchor fixation.
5.	Physical conditions which would eliminate, or tend to eliminate, adequate anchor support or retard healing
6.	The presence of infection.
7.	Conditions which would limit the subject's ability or willingness to restrict activities or follow directions during the healing period.
8.	Concurrent bilateral surgery.
9.	Participation in the treatment period of another clinical trial within thirty (30) days of Visit 1, or during the study.
10.	Women who are pregnant.
11.	Prior ipsilateral surgeries performed on the joint space.

12. Subjects with a medical or physical condition that, in the opinion of the Investigator, would preclude safe subject participation in the study.

7.4 Screening

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

Of the total 120-160 subjects, a minimum of 60 subjects and a maximum of 80 subjects will be in the HEALICOIL Knotless PEEK Suture Anchor group (to include 30-40 of the Self-Tapping and 30-40 of the NST variants) and a minimum of 60 subjects and a maximum of 80 subjects will be in HEALICOIL Knotless REGENESORB group (to include 30-40 of the Self-Tapping and 30-40 of the NST variants). Subjects will be enrolled as they meet eligibility, consent to the study, and are treated with the study product. Therefore, once a variant has met the 30-40 subjects, screening will stop within that group, and screening and enrollment will continue only in the other variants until all 120-160 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 should be explained to the subject in their native language. The subject, or their legally authorized representative, will then read, sign, and personally date the IRB/IEC-approved informed consent document(s) (see below for difficulties with reading and writing). Additionally, the individual who obtains consent from the subject will sign and date the informed consent document. A copy of the signed informed consent document will be provided to the subject, a copy 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.

For sites in the United States, 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.

Subjects will be assigned a Subject ID at the time of consent. Subjects with bilateral rotator cuff tear repairs and/or bicep tenodesis 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. 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 contacts and one certified letter without response. Copies of all attempts to reach the subjects by mail or email and/or the attempts to contact the subject via other means should be documented, and that documentation should be kept with the subject's source documents.

7.8 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)
- Subject lost to follow-up
- If the Investigator or the Sponsor stops the study for any reason and decides to withdraw subject(s) from the study
- Concurrent illness
- Adverse Events/Adverse Device Effects
- Any other significant reason identified by the Investigator

If a subject receives a revision surgery of the study shoulder, or experiences an AE/SAE/DD, the subject shall continue to have follow-up visits in order to monitor the subject's health status until any adverse events/adverse device events are resolved, is lost to follow-up, or until 12 months post-surgery for subjects enrolled in the HEALICOIL Knotless PEEK ST and NST and HEALICOIL Knotless REGENESORB Self- tapping subgroups and 24 months for the subjects enrolled in the HEALICOIL Knotless REGENESORB NST subgroup. 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 CRF detailing circumstances leading to the withdrawal.

Subjects who drop out or are withdrawn following enrollment (i.e., treatment with study device) 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 shoulder 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 after consent, but prior to enrollment will be replaced. Subjects who are withdrawn following enrollment 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.

If a subject withdrawals following enrollment (i.e., treatment with study device), he/she will not be replaced.

7.8.3 Use of Data Following Withdrawal

In cases where the subject withdraws consent, the data collected up to the point of withdrawal may be used, but no additional data for that subject may be collected 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 shoulder as detailed in section 7.8.1 above (until the end of the study).In cases where the subject withdraws consent, the data collected up to the point of withdrawal may be used, but no additional data for that subject may be collected.

8 STUDY DESIGN

8.1 Study Design

This is a prospective, multi-center, non-randomized clinical trial. The study is divided in to 2 groups: HEALICOIL Knotless PEEK and HEALICOIL Knotless REGENESORB.

Follow up: 6 and 12 months for HEALICOIL PEEK Self-Tapping, HEALICOIL PEEK Non-Self Tapping, and HEALICOIL REGENESORB Self-Tapping subgroups and 6, 12, and 24 months for HEALCOIL REGENESORB Non Self-Tapping subgroup.

The study will enroll at up to 6 clinical sites in the United States/ Canada (*) Participation of Canada sites will be contingent on timeline for Health Canada approval

The study is expected to be 36 months in duration, but will depend on enrollment rate. This includes:

- 12 months enrollment
- 12 months follow up (HEALICOIL Knotless PEEK ST and NST and REGENESORB ST sub-groups)
- 24 months follow up (HEALICOIL Knotless REGENESORB NST sub-group)

This study was designed as a prospective, multi-center, non-randomized study of rotator cuff repairs and biceps tenodesis. No formal hypotheses testing will be done.

8.2 Allocation and Blinding

8.2.1 Treatment Allocation

This study is not randomized. Selection of the surgical approach (repair using HEALICOIL Knotless PEEK NST, HEALICOIL Knotless PEEK Self-Tapping, HEALICOIL Knotless RG NST, or HEALICOIL Knotless RG Self-Tapping) will be at the discretion of the Investigator, in consultation with the subject, as appropriate. Treatment allocation must follow requirements of inclusion criteria 1 and 4.

To ensure an equal number of subjects are enrolled into each treatment sub-group, the Sponsor will continuously monitor enrollment and will close enrollment into the faster enrolling sub-group once the targeted enrollment has been reached. Enrollment into the slower enrolling sub-group will continue until the study is fully enrolled.

8.2.2 Blinding

This study is not blinded.

8.3 Data Management

The study uses an electronic data capture system. Data will be transcribed from the data source to an electronic Case Report Form (eCRF).

8.4 Study Endpoints

8.4.1 Primary Endpoint

The primary endpoint of this study is to assess repair failure rate defined as the need for a second repair procedure at 6 months.

8.4.2 Secondary Endpoints

Following are the secondary endpoints for this study:

All endpoints to be collected and analyzed on all subjects:

- Repair failure rate at 12 months (and 24 months for the HEALICOIL Knotless RG NST subgroup). Repair failure rate is defined as the need for a second repair procedure.
- Constant-Murley Shoulder scale at 6 months and 12 months (24 months for the HEALICOIL Knotless RG NST subgroup)
- ASES scale at 6 months and 12 months (24 months for the HEALICOIL REGENESORB NST subgroup)
- ASES Visual Analog Scale (VAS) pain score at 6 months and 12 months (24 months for the HEALICOIL Knotless RG NST subgroup)
- SANE Shoulder scale at 6 months and 12 months (24 months for the HEALICOIL Knotless RG NST subgroup)
- EQ-5D-3L at 6 months and 12 months (24 months for the HEALICOIL Knotless RG NST)
- Only for the HEALICOIL Knotless RG NST subgroup - MRI to determine tendon thickening and anchor absorption/replacement by bone at 6 months and 24 months.
- Only for the HEALICOIL Knotless RG NST subgroup - MRI to determine tendon re-tear rate at 6 months and 24 months

8.4.3 Safety Endpoints

Following are the safety endpoints for this study:

- All adverse events (AEs) and complications occurring from the time of surgical implantation until study termination or study completion including intra-operative adverse events and complications.
- Device Deficiencies

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 14155:2020.

8.5 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 Rotator Cuff Tendon repair and/or Bicep tenodesis 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 9.1.1-1: Study Procedures by Visit

Table 9.1.1-1: Study Procedures by Visit

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Unscheduled visit
Schedule of events	**Pre-Operative (≤ 60 Days of Visit 2**	**Operative through Discharge Day 0**	**Follow Up 6 Months (± 30 days)**	**Follow Up 12Months (± 30 days)**	**Follow Up (RG NST ONLY) 24 Months (± 60 days)**	**Unscheduled Visit**
Informed Consent	✓					
Inclusion/Exclusion	✓					
Demographics/ Medical History	✓					
Surgical Summary		✓				
Post-op Repair Failure			✓	✓	✓	✓
ASES	✓		✓	✓	✓	✓
Constant-Murley	✓		✓	✓	✓	✓
SANE Score	✓		✓	✓	✓	✓
EQ-5D-3L	✓		✓	✓	✓	✓
MRI	✓***		✓***		✓***	
Adverse Event Assessment		✓	✓	✓	✓	✓
Concomitant medications/therapies		✓	✓	✓	✓	✓
End of Study/Exit	✓**	✓**	✓**	✓**	✓**	✓**

** If necessary
***Required only for 30-40 HEALICOIL Knotless REGENESORB NST subjects. Pre-operative MRI must meet criteria per inclusion criterion #2.
(+/- tolerances are relative to surgery date)

9.1.2 Screening/Preoperative Visit (≤ 60 days)

NOTE: All subjects who sign an informed consent form must be assigned a study number and have demographic information recorded. Consented subjects who fail to meet all inclusion and exclusion criteria will be considered a screen fail and an End of Study CRF must be completed. The inclusion/exclusion CRF must also be updated to indicate which criterion has not been met. Subjects who are consented but have not received one of the study devices are not considered enrolled.

1.	Obtain written informed consent from the subject as detailed in Section 7.5 ----- **Do not proceed until consent has been obtained** -----
2.	Add new subject into EDC to assign an ID
3.	Screen the subject for protocol inclusion/exclusion criteria
4.	Obtain demographic information and medical history. Record height, weight, smoking status and history of diabetes.
5.	Compete the Screening and Enrollment Log
6.	Obtain baseline Patient Reported Outcomes (PROs): ASES, Constant-Murley, SANE, EQ-5D-3L
7.	Collect pre-operative standard of care MRI and submit to imaging vendor for qualification. If images are not available or submitted images are unacceptable perform an additional study specific pre-operative MRI; see Image Acquisition Protocol for sequences to be used (For HEALICOIL Knotless REGENESORB NST subjects ONLY).
8.	Complete Pre-Operative Visit CRFs
9.	Subjects will be instructed to return to the treatment facility for the Treatment/Operation Visit 2 in ≤ 60 days.
10.	Complete End of Study form, if applicable

9.1.3 Operative Visit (Day 0)

1.	Query subject regarding any changes in general health and the use of concomitant medications.
2.	Commence treatment/operation

3.	Update information in the Screening and Enrollment Log
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. Also record concomitant medications/therapies used to treat AEs.
5.	Record device identification information for the anchors (e.g., Unique Device Identifier, Lot Number, Serial Number, Catalogue Number), suture type used with HEALICOIL Knotless PEEK and HEALICOIL Knotless REGENESORB anchors, and position of anchors.
6.	Instruct the subject on proper postoperative care/procedures
7.	Instruct the subject on follow-up procedures, including returning to the treatment facility in 6 months (± 30 days) for follow-up visit
8.	Complete Operation and Discharge Visit CRFs.
9.	Complete End of Study form, if applicable

9.1.4 Follow-up 6months (+/- 30 days)

1.	Query subject regarding any changes in general health and the use of concomitant medications.
2.	Record post-op repair failure, if any. (Post-op failure are AEs that need to be recorded on the AE CRFs.)
3.	Obtain subject PROs: ASES, Constant-Murley, SANE, EQ-5D-3L
4.	Perform MRI according to Imaging Protocol. (For HEALICOIL Knotless REGENESORB NST subjects).
5.	If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12, Adverse Events and Device Deficiencies. Also record concomitant medications/therapies used to treat AEs
6.	Instruct the subject on follow-up procedures, including returning to the treatment facility at 12 months post-operative (± 30 days) for follow-up visit.
7.	Complete 6-Month Follow-up Visit (Visit 3) and/or End of Study CRFs, if applicable.

9.1.5 Follow-up 12months (+/-30 days)

1.	Query subject regarding any changes in general health and the use of concomitant medications.
2.	Record post-op repair failure, if any. (Post-op failure are AEs that need to be recorded on the AE CRFs.)
3.	Obtain subject PROs: ASES, Constant-Murley, SANE, EQ-5D-3L
4.	If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12, Adverse Events and Device Deficiencies. Also record concomitant medications/therapies used to treat AEs
5.	Complete End of Study Visit (Visit 4) CRFs for HEALICOIL Knotless REGENESORB Self-Tapping and HEALICOIL Knotless PEEK Self-Tapping and Non Self-Tapping subjects
6.	Instruct HEALICOIL Knotless REGENESORB NST subjects on follow-up procedures, including returning the treatment facility at 24 months post-operative (± 60 days) for follow-up visit.

9.1.6 Follow-up 24 months HEALICOIL Knotless REGENESORB NST (+/-60 days)

1.	Query subject regarding any changes in general health and the use of concomitant medications.
2.	Record post-op repair failure, if any. (Post-op failure are AEs that need to be recorded on the AE CRFs.)
3.	Obtain subject PROs: ASES, Constant-Murley, SANE, EQ-5D-3L
4.	Perform MRI according to Imaging Protocol.

5.	If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12, Adverse Events and Device Deficiencies. Also record concomitant medications/therapies used to treat AEs
6.	Complete End of Study (Visit 5) CRF's

9.1.7 Unscheduled Visit

An unscheduled visit is an in-office visit that occurs between the scheduled study visits and is conducted to assess subjects who are deemed to be symptomatic or require evaluation for AEs or DDs. Unscheduled examinations may be conducted at the discretion of the Investigator. All information obtained during an unscheduled visit should be recorded in the source documents and on the appropriate CRF

1.	Query subject regarding any changes in general health and the use of concomitant medications.
2.	Record post-op repair failure, if any. (Post-op failure are AEs that need to be recorded on the AE CRFs.)
3.	Obtain subject PROs: ASES, Constant-Murley, SANE, EQ-5D-3L
4.	If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 Adverse Events and Device Deficiencies. Also record concomitant medications/therapies used to treat AEs
5.	Complete End of Study (Visit 5) CRFs, if applicable

9.1.8 Concomitant Medications and Therapies

Concomitant medications and concomitant therapies are recorded at any time from enrollment into the study through the subject's last study visit.

Concomitant Medication

Excluded Concomitant Medications

For this study there are no restrictions on concomitant medications. Concomitant medications used to treat AEs should be recorded on the designated CRF.

Recording Concomitant Medications in CRF

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

Concomitant Therapies

Therapies Prohibited During the Study

For this study there are no restrictions on concomitant therapies. Concomitant therapies used to treat AEs should be recorded on the designated CRF.

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.

9.1.9 Discontinued Subjects

Discontinued subjects are those who: voluntarily discontinue participation; are withdrawn for reasons of safety; are lost to follow-up; have missed 2 study visits; undergo a surgical procedure not listed in the protocol; or receive non-study devices or study devices in an incompatible combination as listed in the inclusion criteria. . 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).

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).

9.1.10 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.

9.2 Study Methods and Measurements

The investigational device failure will be assessed by the surgeon during surgery, at 6 months post-operative and at 12 months post-operative visits (and 24 months for the HEALICOIL Knotless REGENESORB NST subgroup). Criteria used for assessment of device failure and/or re-intervention will be provided by the surgeon on the designated case report form (CRF).

All subjects:

American Shoulder and Elbow Surgeons (ASES): The ASES instrument is composed of 2 sections containing participant self-reported and clinician assessments. The ASES score is a 0 to 100-point rating based solely on participant responses and is a combination of the participant's shoulder pain rating (VAS Pain) and self-reported ability to perform 10 different activities of daily living (ADLs).[10] ASES scores will be recorded pre-operatively, at 6 and 12 months for HEALICOIL Knotless PEEK ST and NST and REGENESORB ST subgroups and at 6, 12 and 24 months for the HEALICOIL Knotless REGENESORB NST subgroup.

Constant-Murley Shoulder (CMS) scale assesses four aspects related to shoulder pathology; two subjective: pain and activities of daily living (ADL) and two objective: range of motion (ROM) and strength. The subjective components can receive up to 35 points and the objective 65, resulting in a possible maximum total score of 100 points (best function). Pain and ADL are answered by the subject; ROM and strength require a physical evaluation and are answered by the orthopaedic surgeon or the physiotherapist.[11]

CMS scores will be recorded pre-operatively, at 6 and 12 months for HEALICOIL Knotless PEEK ST and NST and REGENESORB ST subgroups and at 6, 12 and 24 months for the HEALICOIL Knotless REGENESORB NST subgroup.
Single Assessment Numeric Evaluation (SANE): The SANE is a simple, single-question, patient-based shoulder function assessment tool: "How would you rate your shoulder today as a percentage of normal (0% to 100% scale with 100% being normal)?" It is popular because of its simplicity and ability to be applied to a wide variety of clinical situations. It has not been validated and no minimal clinically important difference has been reported.[15] SANE scores will be recorded pre-operatively, at 6 and 12 months for HEALICOIL PEEK ST and NST AND REGENESORB ST subgroups and at 6, 12 and 24 months for the HEALICOIL REGENESORB NST subgroup.

Magnetic Resonance Imaging (MRI) will be used to determine tendon thickening and anchor absorption/replacement by bone at 6 and 24 months in the RG NST variant only. MRI will be used to determine tendon re-tear rate at 6 months and 24 months. Refer to Imaging Protocol for assessment details.
The subject's standard of care pre-operative MRI will be collected to determine their baseline. If a pre-operative standard-of-care MRI is available it must be submitted to the study imaging vendor for qualification. The vendor will provide a response to sites within 3 business days confirming if the images are: acceptable, suboptimal or unacceptable. If MRI is unavailable or considered unacceptable an additional study-specific MRI must be performed. Only subjects with an acceptable pre-operative MRI will be able to proceed with surgery and receive a Healicoil Knotless Regensorb NST device. 6 month and 24 month MRI images must be obtained using the post-operative sequences listed in the Image Acquisition Protocol.

9.3 Health Economics/Quality of Life

Using the EQ-5D-3L questionnaire the following secondary outcomes will be collected:

- Mobility
- Self-care
- Activities
- Pain/discomfort
- Anxiety/depression

EQ-5D-3L scores will be recorded pre-operatively, at 6 and 12 months for HEALICOIL Knotless PEEK ST and NST and REGENESORB ST subgroups and at 6, 12 and 24 months for the HEALICOIL Knotless REGENESORB NST subgroup.

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.

10.3 Baseline Data

Data to be summarized at baseline includes, but is not limited to, all collected demographic variables such as age, gender, race, ethnicity, 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

Repair failure rate will be summarized by the number and percentage of patients that have had a second repair procedure by their 6 month visit. A 95% exact confidence interval for the proportion will be presented using the Clopper-Pearson method.[3]

Repair failure rate will be presented by group (PEEK or REGENESORB) and by primary diagnosis (rotator cuff repair or biceps tenodesis). Analysis of Secondary Endpoint(s)

All summaries will be provided overall by group (PEEK or REGENESORB), and will be further broken down for each sub-group (PEEK ST, PEEK NST, REGENESORB ST, REGENESORB NST) as appropriate (all 24 month summaries will only be for the REGENESORB NST sub-group specifically). Tables will be split by primary diagnosis (rotator cuff repair or biceps tenodesis) where necessary.

Repair failure rate at 12 and 24 months will be summarized cumulatively by the number and proportion of patients that have had a second repair procedure up to that respective time point. Percentages will be based on the number of available patients at each time point (e.g. excluding any lost-to-follow-up patients as we will not know their outcome). A 95% exact confidence interval for the proportion will be presented using the Clopper-Pearson method.[3]

The Constant-Murley Shoulder score, ASES Shoulder score, SANE and EQ-5D-3L will be derived for each patient at each visit and summary statistics will be presented. Change from baseline score to each post-operative visit (6, 12 and 24 months) will also be presented. The number and proportion of subjects, together with a 95% confidence interval, meeting the Minimal Clinically Important Differences (MCID) from baseline to each post-operative visit will be presented.

Separate summary statistics will be provided for the ASES VAS pain score for each visit, and for the change from baseline to each post-operative visit.

Endpoints determined by MRI include tendon thickening, anchor absorption/replacement by bone and tendon re-tear rates at 6 months and 24 months. These will be summarized appropriately for categorical or continuous variables.

10.5 Safety Analyses

All safety endpoints will be summarized using the safety population.

Adverse Events

The number of subjects reporting: adverse events, serious 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 total number of device deficiencies and the number of patients reporting a device deficiency will be summarized and presented. The number of intra-operative device deficiencies will also be summarized.

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

10.6 Interim Analyses

An interim analysis will be done on all HEALICOIL Knotless REGENESORB NST and HEALICOIL Knotless REGENSORB ST patients that have completed their 6 month follow up.

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. With an estimated clinical success rate of 91% for each HEALICOIL Knotless variant and a corresponding 95% confidence interval between 80% and 100%, enrolling between 60 and 80 subjects per variant would provide probability greater than 90%. Enrolling between 60 and 80 subjects per variant would provide probability greater than 90%.

HEALICOIL Knotless PEEK patients: Minimum N=60, Maximum N=80

HEALICOIL Knotless REGENESORB patients: Minimum N=60, Maximum N=80

Enrollment distribution will ensure that all variants are represented in the patient population:

Table 11-1: Enrollment Distribution

HEALICOIL Knotless Suture Anchor	Minimum	Maximum
HEALICOIL Knotless PEEK ST	30	40
HEALICOIL Knotless PEEK NST	30	40
HEALICOIL Knotless RG ST	30	40
HEALICOIL Knotless RG NST	30	40

The statistical plan will provide a detailed approach of the statistical analysis that will be conducted on two independent groups: the HEALICOIL Knotless PEEK anchor group (2 variants, 60-80 patients) and the HEALICOIL Knotless REGNESORB anchor group (2 variants, 60-80 patients).

Furthermore, the 30-40 HEALICOIL Knotless RG NST variant patients will undergo double row repair and will be followed up for a longer duration (24 months) to support claims on long-term resorption of the REGENESORB material.

12 ADVERSE EVENTS AND DEVICE DEFICIENCIES

12.1 Definitions (ISO/DIS 14155:2018)

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

Table 12.1-1: Categories of Adverse Event

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

12.1.1 Adverse Event

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

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

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

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

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

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

12.1.2 Adverse Device Effect

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

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

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

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

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

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

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

12.1.3 Related Serious Adverse Events and Serious Adverse Device Effects

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

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

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

12.1.4 Anticipated/Unanticipated Serious Adverse Device Effect

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

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

Potential Adverse Effects listed in the HEALICOIL Knotless IFUs include:

- Loss of fixation or pull out of suture anchors can occur
- Mild inflammatory reaction
- Foreign body reaction
- Infection, both deep and superficial
- Allergic reaction

This list is not exhaustive. Please check Instructions For Use for a full list of adverse effects which are known to occur (anticipated) with HEALICOIL Knotless devices. Adverse Effects, including those listed above, are only ASADEs if the event is considered serious, as outlined in 11.1.3.

For HEALICOIL Knotless Self-Tapping devices: titanium alloys contain elements that may stimulate allergic hypersensitive response by the immune system. These elements are titanium, aluminium, and vanadium (Ti, Al, and V). When sensitivity is anticipated, appropriate preoperative testing should be conducted.

12.1.5 Severity

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

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

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

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

12.1.6 Device Deficiency

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

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

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

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

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

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

12.2 AE Coding Dictionary

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

12.3 Reporting procedures

AE of any kind and DD will be recorded in the applicable CRF and source notes. The Investigator will evaluate all AE for relationship to the device and procedure, seriousness, and severity (if applicable). DD will be evaluated for potential to cause SADE. The following timescales should be followed for the AE/DD information to be submitted/entered into the CRF and reported to the Sponsor or designee (see figure 12.3-1 and 12.3-2):

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

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

For ADE and DD, 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/IEC of adverse events according to the IRB/IEC 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 ISF Sponsor Contact Information Sheet to report SAE, unanticipated SADE, anticipated SADE, and DD.

Figure 12.3-1: Evaluation and Reporting of AE

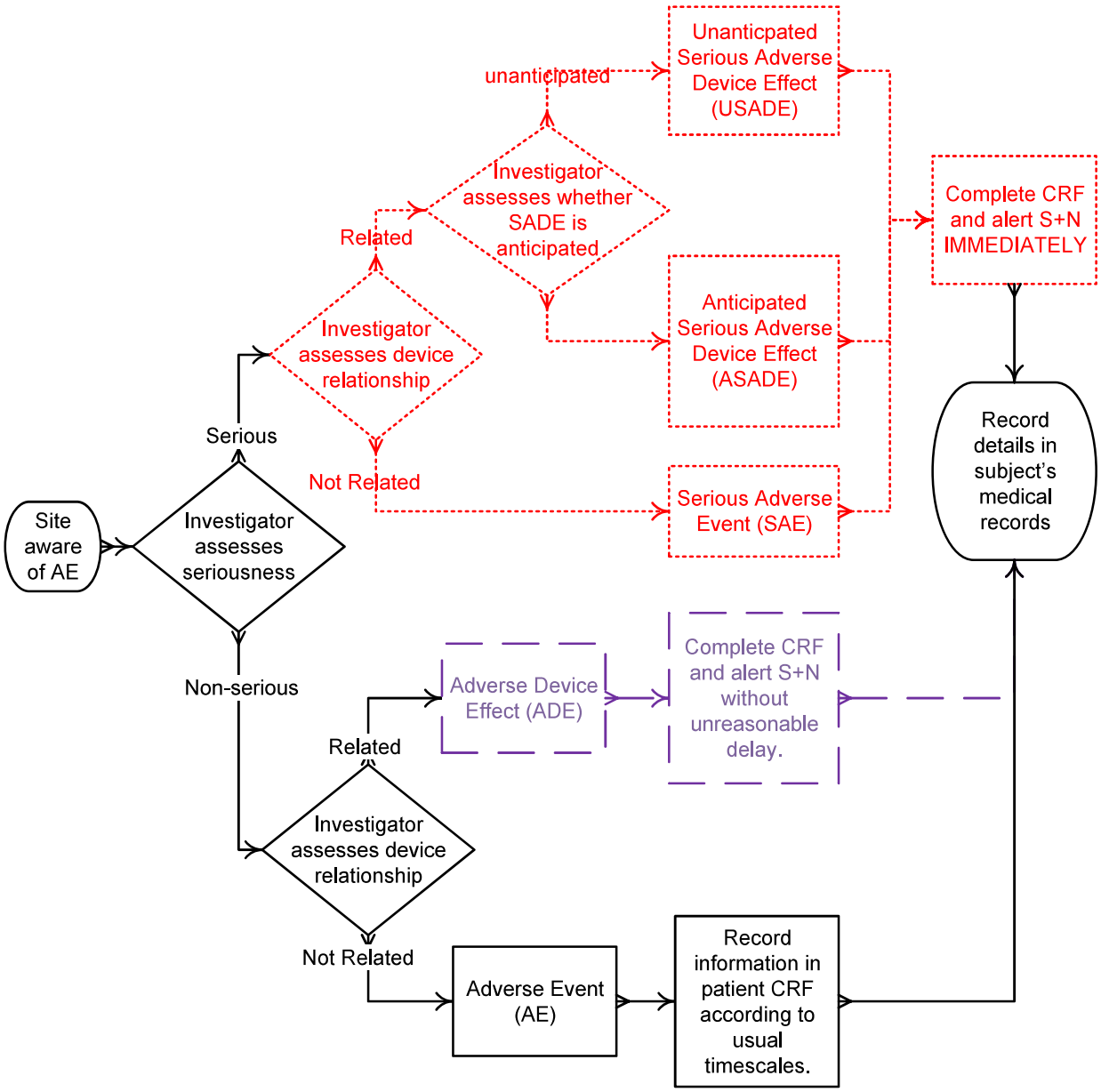
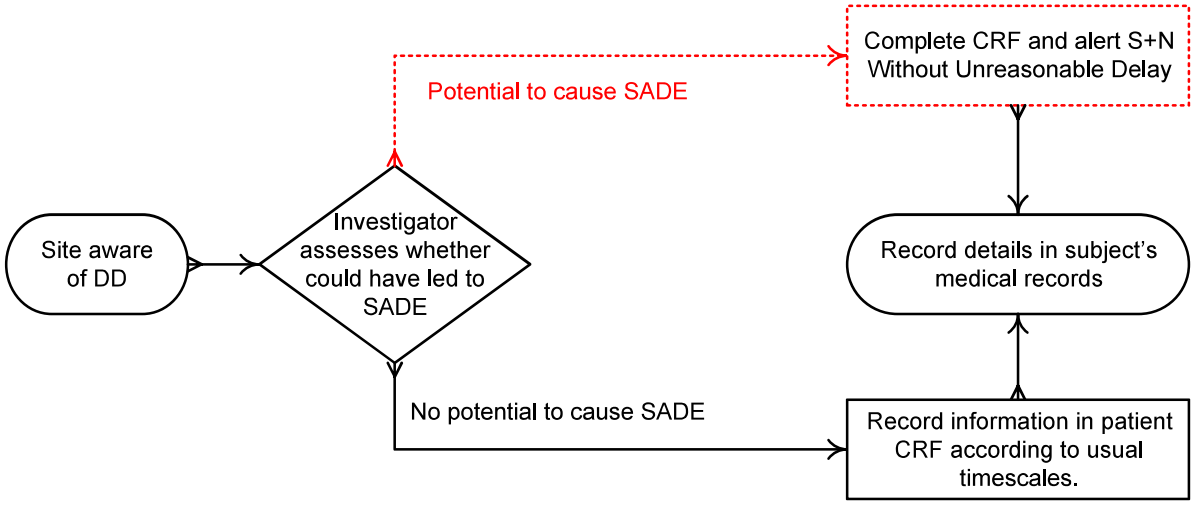


Figure12.3-2: Evaluation and Reporting of DD



12.4 Unblinding of Investigational Product

Not Applicable

12.5 Follow-up of Subjects with Adverse Events

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

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

12.5.1 Ongoing Adverse Events at Study Discontinuation

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

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

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

13 INVESTIGATOR OBLIGATIONS

The Principal Investigator will comply with the commitments outlined in the in the Statement of Investigator, provided by the Sponsor/within the Clinical Trial Agreement, and with Good Clinical Practice (GCP), and all applicable regulatory requirements as outlined in Appendix 22.5 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 Contract Research Organization

S+N will use Medical Metrics Inc (MMI) to conduct an independent evaluation of the imaging to assess treatment performance and outcomes to include:

- Characterize tendon thickening and REGENESORB material resorption at 6 months and 24 months in the HEALICOIL Knotless REGENESORB NST subgroup
- To characterize the MRI tendon re-tear rates at 6 months and 24 months in the HEALICOIL Knotless REGENESORB NST subgroup

14.2 Site Qualification Visit

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

14.3 Site Initiation Visit

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

14.4 Interim Monitoring Visit

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

14.5 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.

14.6 Close-Out Visit

A study close-out visit will be performed by the Sponsor or designee to retrieve and account for all remaining clinical data and to resolve outstanding queries. During study close-out, the monitor will review investigator files to ensure required documents and records are on file, confirm the disposition of any other ancillary items used for the study, and review regulatory requirements

regarding records retention and IRB/IEC reporting requirements. When no subjects have been included, a remote close-out visit may be conducted.

15 PROTOCOL DEVIATIONS

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. Protocol deviations reported by the Investigator or discovered during monitoring visits will be compiled in a Protocol / GCP Deviation Log (TMP-CD-31-02 Protocol/GCP Deviation Log). Significant and/or recurrent protocol/GCP deviations will be documented on a protocol deviation form (TMP-CD-31-01 Protocol/GCP Deviation) including identified root cause and, as necessary, appropriate corrective and preventive actions will be put in place and signed off by the study personnel.

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

16 PROTOCOL AMENDMENTS

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

17 CONFIDENTIALITY OF THE STUDY

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

18 STATEMENTS OF COMPLIANCE

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

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

19 END OF STUDY

The end of study is considered the last visit of the last subject undergoing treatment in the study. It is expected to last 36 months.

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 all subjects including 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.

20 PUBLICATION POLICY
20.1 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.

20.2 Data Sharing

Smith+Nephew is committed to upholding the highest ethical and legal standards involved in conducting clinical trials. Smith+Nephew, therefore, supports the data sharing requirements of The International Committee of Medical Journal Editors (ICMJE) published on the 6th June 2017. In accordance, Smith+Nephew will consider requests to share individual (de-identified) participant data that underlie the results of any interventional clinical trial, as presented from the 1st July 2018 within an ICMJE associated journal. Requests made by researchers who provide a methodologically sound proposal will be considered. Requests may include data that underlie results presented in text, tables, figures, and appendices, together with data dictionaries. Availability of these data will begin nine months and end 36 months after article publication. Data supplied may only be used by the researcher(s) named in the approved research proposal for the purposes of achieving the aims

of the analyses specified therein. All proposals should be directed to datasharing.gcs@smith-nephew.com. To gain access, data requestors will need to sign a data access agreement.

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22 APPENDICES
22.1 Protocol Amendment 2

22.1.1 General Purpose

Version 2.0 of the protocol was amended to 3.0 primarily to reflect a simplification of the pre-operative imaging requirements for subjects in the Regenesorb NST cohort. Clarifications were also made to the process of enrolling subjects and entering their data into EDC. Details of ancillary products were added. Height, weight, smoking status and diabetes status have been added to the required data to be collected.

22.1.2 Rationale

Version 2.0 of the protocol required investigators to take on the responsibility for confirming that the pre-operative MRIs for RG NST subjects met the sequence requirements listed in inclusion criterion #2. Investigators expressed some concern that they were not imaging experts and did not feel confident confirming MRIs met inclusion criteria. In protocol version 3.0 this was addressed so that an external imaging vendor would make these pre-operative image eligibility decisions. Sites are now required to submit pre-operative images to an imaging vendor who will return a response within 3 business days, either accepting or rejecting images. Furthermore, the list of acceptable pre-operative sequences has been expanded so that more MRIs will make it through the eligibility assessment. Acceptable sequences are listed in the Image Acquisition Protocol.

Protocol v2.0 was not clear on whether screened subjects should be assigned a study ID number. Version 3.0 addresses this by confirming that all subjects who sign a consent form must be entered into the database and given a study ID. This will allow the sponsor to capture details of screen failure should subjects fail to meet eligibility prior to surgery or intraoperatively.

22.1.3 Effect on Study Status

At the time of the amendment, only one patient has been consented. The impact is therefore likely to be positive and will make the screening and enrollment process simpler and more expedient for patients in the RG NST group.

The update to the screening and subject ID assignment workflow should not impact the study; it should make the enrollment process simpler and allow for more fulsome oversight.

22.1.4 Details

Section	Current Text 02/Oct/2020 Version 2.0	Revised Text 25/Feb/2020 Version 3.0
Section 2, Synopsis	Has a pre-operative standard of care MRI within 6 months of surgery containing the following sequences: a. Sat T2 FS: Oblique Sag T2-weighted Fat Saturation Spin Echo (oriented perpendicular to the scapula), with TE > 70 ms, **AND** b. Cor T2 FS: Oblique Cor T2-weighted Fat Saturation Spin Echo (oriented parallel to the scapula), with TE > 70 ms, **AND** c. Sag T1: Oblique Sag T1-weighted Spin Echo (oriented perpendicular to the scapula); **OR** d. Willing and able to undergo an additional study specific pre-operative MRI according to the study Imaging Protocol if the above criteria is not met **OR** e. **MRI not required; subject not in HEALICOIL RG NST subgroup**	2. Has a pre-operative MRI collected within 6 months of surgery which meets one of the following criteria: a. MRI collected as standard-of-care has been submitted to external imaging vendor and confirmed as acceptable OR b. If standard-of-care images are unavailable or considered unacceptable by external imaging vendor, subject must undergo an additional study-specific pre-operative MRI, confirmed as acceptable by external imaging vendor OR c. MRI not required; subject not in HEALICOIL Knotless RG NST subgroup
Section 4.4 moved to Section 12.1.4	Potential Adverse Effects listed in the IFUs include: • Loss of fixation or pull out of suture anchors can occur Rotator Cuff Tendon Repair • Mild inflammatory reaction • Foreign body reaction • Infection, both deep and superficial • Allergic reaction For HEALICOIL Knotless Self-Tapping devices: titanium alloys contain elements that may stimulate allergic hypersensitive response by the immune system. These elements are titanium, aluminium, and vanadium	Potential Adverse Effects listed in the IFUs include: • Loss of fixation or pull out of suture anchors can occur Rotator Cuff Tendon Repair • Mild inflammatory reaction • Foreign body reaction • Infection, both deep and superficial • Allergic reaction For HEALICOIL Knotless Self-Tapping devices: titanium alloys contain elements that may stimulate allergic hypersensitive response by the immune system. These elements are titanium, aluminium, and vanadium This list is not exhaustive. Please check Instructions For Use for a full list of adverse effects which are known to occur (anticipated) with HEALICOIL Knotless devices. Adverse Effects, including those listed above, are only ASADEs if the event is considered serious, as outlined in 11.1.3.

Section 6.1.3	No ancillary products will be provided.	There are two ancillary products provided for the conduct of this study. All sites will be provided with at least one Manual Muscle Tester (MMT), often referred to as a dynamometer, packaged in a Pelican type storage case. MMTs are ergonomic devices used to objectively quantify muscle strength. Additionally, all sites will be provided with at least one long-arm isometric goniometer which is used to measure joint range of motion. Both devices are required to complete the Constant-Murley score at the pre-op and follow-up visits. There are required ancillary products for the conduct of the study, which are a hand-held Manual Muscle Tester (MMT) with a Pelican Type Storage Case and a goniometer. The MMT is an ergonomic device used to objectively quantify muscle strength (Lafayette Hand-held Dynamometer User Instructions, page 2). The device is provided to the sites in a sturdy case for device protection during shipping and storage. A long-arm isometric goniometer is required. These instruments allow for the precise measurements of angels, which helps the clinician to measure joint range of motion.
Section 9.1.2	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 should not be assigned subject numbers, but their demographic information must be captured in the appropriate CRF with the reason for screen failure specified.	NOTE: All subjects who sign an informed consent form must be assigned a study number and have demographic information recorded. Consented subjects who fail to meet all inclusion and exclusion criteria will be considered a screen fail and an End of Study CRF must be completed. The inclusion/exclusion CRF must also be updated to indicate which criterion has not been met. Subjects who are consented but have not received one of the study devices are not considered enrolled.
Section 9.1.2	Obtain written informed consent from the subject as detailed in Section 7.5 ----- Do not proceed until consent has been obtained -----	**p.42, section 8.1.2/3** 1. Obtain written informed consent from the subject as detailed in Section 6.5 ----- Do not proceed until consent has been obtained -----

	2. Screen the subject for protocol inclusion/exclusion criteria 3. Obtain demographic information and medical history, including information on all concomitant medications/therapies 4. Assign the subject a study number and instruct the subject on treatment procedures. 5. Compete the Screening and Enrollment Log 6. Obtain baseline Patient Reported Outcomes (PROs): ASES, Constant-Murley, SANE, EQ-5D-3L 7. Collect pre-operative standard of care MRI or perform an additional study specific pre-operative MRI according to the study Imaging Protocol per inclusion criterion #2. (For HEALICOIL Knotless REGENESORB NST subjects). 8. Complete Pre-Operative Visit CRFs 9. Subjects will be instructed to return to the treatment facility for the Treatment/Operation Visit 2 in ≤ 60 days.	**2. Add new subject into EDC into assign an ID** 3. Screen the subject for protocol inclusion/exclusion criteria **4. Obtain demographic information and medical history. Record height, weight, smoking status and history of diabetes** 5. Compete the Screening and Enrollment Log 6. Obtain baseline Patient Reported Outcomes (PROs): ASES, Constant-Murley, SANE, EQ-5D-3L **7. Collect pre-operative standard of care MRI and submit to imaging vendor for qualification. If images are not available or submitted images are unacceptable perform an additional study specific pre-operative MRI; see Image Acquisition Protocol for sequences to be used (For HEALICOIL Knotless** REGENESORB NST subjects ONLY). 8. Complete Pre-Operative Visit CRFs 9. Subjects will be instructed to return to the treatment facility for the Treatment/Operation Visit 2 in ≤ 60 days. **10. Complete End of Study form, if applicable**
Section 9.1.3	Record device identification information for the anchors (e.g., Unique Device Identifier, Lot Number, Serial Number, Catalogue Number), suture type used with HEALICOIL Knotless PEEK and HEALICOIL Knotless REGENESORB anchors, and position of anchors.	Record device identification information for the anchors (e.g., Unique Device Identifier, Lot Number, Serial Number, Catalogue Number), suture type used with HEALICOIL Knotless PEEK and HEALICOIL Knotless REGENESORB anchors, and position of anchors.
Section 9.1.9	Discontinued subjects are those who voluntarily discontinue participation, who are withdrawn for reasons of safety or use of prohibited concomitant treatments, who are lost to follow-up, or who have missed 2 study visits or fail to complete the 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).	Discontinued subjects are those who: voluntarily discontinue participation; are withdrawn for reasons of safety; are lost to follow-up; have missed 2 study visits; undergo a surgical procedure not listed in the protocol; or receive non-study devices or study devices in an incompatible combination as listed in the inclusion criteria. Where possible, a full Exit Visit should be completed for all subjects who discontinue the study early. Where consent is withdrawn, the date and any reason given for discontinuation should be captured, at a minimum (see Section 6.8).

Section 9.2	Magnetic Resonance Imaging (MRI) will be used to determine tendon thickening and anchor absorption/replacement by bone at 6 and 24 months. MRI will was be used to determine tendon retear rate at 6 months and 24 months. Refer to Imaging Protocol for assessment details. The subject's standard of care pre-operative MRI will be collected to determine their baseline. The pre-operative MRI must be within 6 months of surgery and contain the following sequences: • Sat T2 FS: Oblique Sag T2-weighted Fat Saturation Spin Echo (oriented perpendicular to the scapula), with TE > 70 ms, AND • Cor T2 FS: Oblique Cor T2-weighted Fat Saturation Spin Echo (oriented parallel to the scapula), with TE > 70 ms, AND • Sag T1: Oblique Sag T1-weighted Spin Echo (oriented perpendicular to the scapula). If the subject's pre-operative MRI does not meet the above criteria then an additional study specific pre-operative MRI will be performed according the study Imaging Protocol and collected to determine their baseline.	Magnetic Resonance Imaging (MRI) will be used to determine tendon thickening and anchor absorption/replacement by bone at 6 and 24 months in the RG NST variant only. MRI will be used to determine tendon re-tear rate at 6 months and 24 months. Refer to Imaging Protocol for assessment details. The subject's standard of care pre-operative MRI will be collected to determine their baseline. If a pre-operative standard-of-care MRI is available it must be submitted to the study imaging vendor for qualification. The vendor will provide a response to sites within 3 days confirming if the images are: acceptable, suboptimal or unacceptable. If MRI is unavailable or considered unacceptable an additional study-specific MRI must be performed. Only subjects with an acceptable pre-operative MRI will be able to proceed with surgery and receive a Healicoil Knotless Regensorb NST device. 6 month and 24 month MRI images must be obtained using the post-operative sequences listed in the Image Acquisition Protocol
Section 22.3	[none] – new section created in v3.0	Sites will be provided with a dynamometer for use in the Constant-Murley assessment. This has been labelled by Smith & Nephew and calibrated by the supplier. Dynamometers must be calibrated once per year and sites should work with the sponsor to return devise approaching calibration expiry. Calibrated replacement devices will be provided.
Figures	Figure 8.1-1	This figure has been deleted as it is an exact copy of 9.1-1. It is therefore redundant and likely to cause confusion.
Other	Figure 9.1-1, Sections 9.1.2 & 9.1.3	The option to complete an end-of-study form was entered for these visits as it is possible subjects may screen fail at these time points.
Other	Section numbering	Due to formatting issues many of the section numbers and references to sections or tables were incorrect. These have been fixed.

22.1.5 Approval/Notification

The redlined amended protocol 3.0 will be submitted to central and local IRBs for approval depending on site requirements.

22.2 Instructions for Use

Refer to the Instruction for Use supplied with this product.

22.3 Equipment and Special Instructions

Sites will be provided with a dynamometer for use in the Constant-Murley assessment. This has been labelled by Smith & Nephew and calibrated by the supplier. Dynamometers must be calibrated once per year and sites should work with the sponsor to return devise approaching calibration expiry. Calibrated replacement devices will be provided.

22.4 Health Economic Outcome Measures/Quality of Life measures

Using the EQ-5D-3L questionnaire the following secondary outcomes will be collected:

- Mobility
- Self-care
- Activities
- Pain/discomfort
- Anxiety/depression

EQ-5D-3L scores will be recorded pre-operatively, at 6 and 12 months for HEALICOIL Knotless PEEK ST and NST and REGENESORB ST subgroups and at 6, 12 and 24 months for the HEALICOIL Knotless REGENESORB NST subgroup.

22.5 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.

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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 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. 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.

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You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
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To advise Smith Nephew - Sub of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at kate.drysdale@smith-nephew.com and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

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To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to kate.drysdale@smith-nephew.com and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

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