STATISTICAL ANALYSIS PLAN (SAP)

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1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse Device Effect(s)
ADL	Activities of Daily Living
AE	Adverse Event(s)
AEMB	Adverse Event Monitoring Board
ANOVA	Analysis of Variance
ASES	American Shoulder and Elbow Surgeons
CI	Confidence Interval
CM	Constant-Murley
CRF	Case Report Form(s)
DevD	Device Deficiency(ies)
EQ-5D	EuroQol 5D
FAS	Full Analysis Set
FU	Follow-Up
ITT	Intention to Treat Population
LOCF	Last Observation Carried Forward
MCID	Minimal Clinically Important Difference
MRI	Magnetic Resonance Imaging
NA or N/A	Not Applicable

Abbreviation	Definition
N (or n)	Total Sample Size (or subgroup sample size)
NST	Non Self-Tapping
PEEK	Polyether Ether Ketone
PK	PEEK
PP	Per-protocol Population
QoL	Quality of Life
RG	REGENESORB
S+N	Smith & Nephew Inc.
SADE	Serious Adverse Device Effect(s)
SAE	Serious Adverse Event(s)
SANE	Single Assessment Numeric Evaluation
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SD	Standard Deviation
ST	Self-Tapping
TFL	Tables, Figures and Listing
USADE	Unanticipated Serious Adverse Device Effect(s)
VAS	Visual Analog Scale

2 INTRODUCTION

The following Statistical Analysis Plan (SAP) details the statistical considerations, including the data analysis methods, for the Study Protocol HEALICOIL.KNOTLESS.2019.12. Related documents to this SAP are the Study Protocol, Case Report Form (CRF), and Tables, Figures and Listings (TFL) Templates Shells.

3 STUDY DESIGN

This is a prospective, multi-center, non-randomised clinical trial. The study is divided into 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 the HEALICOIL Knotless REGENESORB Non Self-Tapping subgroup.

	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)

4 STUDY OBJECTIVES

4.1 Primary Objective(s)

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

4.2 Secondary Objective(s)

The secondary objectives are:

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

5 STUDY ENDPOINTS

5.1 Primary Endpoint(s)

The primary endpoint is clinical success rate at 6 months post-operative, where failure is defined as the need for a second repair procedure. The second repair procedure will be a repair of the original rotator cuff repair and/or biceps tenodesis from the index procedure.

5.2 Secondary Endpoint(s)

All endpoints to be collected and analysed 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)

- Single Assessment Numeric Evaluation (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 subgroup)
- 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

5.3 Safety Endpoint(s)

- 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

6 STATISTICAL CONSIDERATIONS

6.1 Determination of Sample Size

The sample size for this study is precision based and not based on statistical power considerations, thus no formal statistical hypothesis is formulated. With an estimated clinical success rate (absence of second repair procedure) of 91% for each HEALICOIL Knotless variant and a corresponding 95% exact confidence interval between 80% and 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=80

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

Table 1: Enrolment 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 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.

6.2 Randomisation

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

6.3 Interim Analysis

An interim analysis will be done on all HEALICOIL Knotless REGENESORB NST and HEALICOIL Knotless REGENESORB ST patients that have completed their 6 month follow up. Any available 12-month data at the point of data extraction will also be summarised and included.

7 STATISTICAL ANALYSIS

7.1 General

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

Where data summaries are specified, categorical and ordinal variables will be summarized with frequencies and percentages. Continuous variables will be summarized with the following summary statistics: number of observations, mean, median, standard deviation, minimum and maximum values.

All analyses will be performed in SAS 9.4 (or later).

7.2 Analysis Populations

The following analysis populations will be used for this study:

- Safety population (SAF), including all subjects who have received the study device.
- Full Analysis Set (FAS), following Intention to Treat principle, is a subset of subjects in the SAF analysis population who have attended at least one post-surgery assessment.
- Per-Protocol population (PP), including all subjects in the full analysis set who have no significant protocol deviations and met the inclusion/exclusion criteria. Significant protocol deviations will include but not only restricted to subjects enrolled who do not satisfy the study entry eligibility criteria, the use of excluded medication, poor compliance, loss to follow up and missing data. All other significant deviations will be formally classified on a case-by-case basis prior to the final study database lock (or point of data extract for interim analyses).

All baseline disposition and demographic tables will be produced for all three analysis populations. The survivorship, radiographic assessment, safety and protocol deviation tables will be given for the SAF population. PRO tables will be provided for both the FAS and PP populations.

7.3 Handling of Missing, Incomplete and Repeat Data

Not applicable.

7.4 Derived Data

<u>Analysis populations</u>

- Flag for inclusion in the SAF population
- Flag for inclusion in the FAS population
- Flag for inclusion in the PP population

<u>Visit dates</u>

- 6 month follow up within 30 day window
- 12 month follow up within 30 day window
- 24 month follow up within 60 day window

ASES
The score is derived using the following equation:

> *ASES score[1] = [(10 – VAS pain score) x 5] + [(5/3) x Cumulative functional questions score].*

The VAS Pain score refers to the question "Intensity of pain" and ranges from 0 to 10.

There are 10 functional questions: put on a coat, sleep on the affected side, wash back/do up bra, managing toileting, comb hair, reach a high shelf, lift 10lbs above shoulder, throw a ball overhand, usual work, usual sport.

Assign the response to each functional question a score as follows:

- Unable to do = 0
- Very difficult to do = 1
- Somewhat difficult = 2
- Not difficult = 3

To calculate the cumulative functional questions score, sum the responses to the 10 questions (each response is worth a maximum of 3 points, maximum possible functional score of 30).

Calculate the ASES score for each visit, as well as the change from baseline score to each visit (score at post-op visit minus score at baseline).

A MCID flag will be created which will be 1 if the change from baseline score is greater than or equal to 6.4[2], and 0 otherwise.

Similarly, the change from baseline to each visit will be calculated for the VAS Pain score. A MCID flag will be created which will be 1 if the change from baseline score is greater than or equal to 2.4[3-5], and 0 otherwise.

SANE
Change from baseline to each visit will be calculated (score at post-op visit minus score at baseline).

A MCID flag will be created which will be 1 if the change from baseline score is greater than or equal to 16.9[6], and 0 otherwise.

Constant-Murley

The Constant-Murley score is derived using the following equation:

> *Constant-Murley score[7] = [VAS pain score (0-15) + Cumulative ADL score (0-20) + Cumulative mobility score (0-40) + Maximum strength score (0-25)]*

The VAS Pain score refers to the question "Indicate the highest pain level you have experienced in your shoulder during ordinary activities within the last 24 hours" and ranges from 0 to 15.

Calculate cumulative ADL score as follows (maximum 20 points):

- Is your sleep disturbed by your shoulder?
  - Undisturbed sleep (2 points)
  - Occasional disturbance (1 point)
  - Every night (0 points)
- How much of your normal daily work does your shoulder allow you to perform?
  - 0-3 (4 points)
  - 4-6 (3 points)
  - 7-9 (2 points)
  - 10-12 (1 point)
  - 13-15 (0 points)
- How much of your normal recreational activity does your shoulder allow you to perform?
  - 0-3 (4 points)
  - 4-6 (3 points)
  - 7-9 (2 points)
  - 10-12 (1 point)
  - 13-15 (0 points)
- To which level can you use your hand comfortably?
  - Below the waist (0 points)
  - Up to waist (2 points)
  - Up to xiphoid (4 points)
  - Up to neck (6 points)
  - Up to top of head (8 points)
  - Above head (10 points)

Calculate cumulative mobility score as follows (maximum 40 points):

- Movement flexion
  - 0-30 (0 points)
  - 31-60 (2 points)
  - 61-90 (4 points)

  - 91-120 (6 points)
  - 121-150 (8 points)
  - ≥151 (10 points)
- Movement abduction
  - 0-30 (0 points)
  - 31-60 (2 points)
  - 61-90 (4 points)
  - 91-120 (6 points)
  - 121-150 (8 points)
  - ≥151 (10 points)
- External rotation – check all that apply
  - Hand behind head, elbow forward (2 points)
  - Hand behind head, elbow back (2 points)
  - Hand to top of head, elbow forward (2 points)
  - Hand to top of head, elbow back (2 points)
  - Full elevation (2 points)
- Internal rotation
  - Lateral thigh (0 points)
  - Behind the buttock (2 points)
  - Sacroiliac joint (4 points)
  - Waist (6 points)
  - 12th thoracic vertebra (8 points)
  - Interscapular (10 points)

Calculate maximum strength score as follows (maximum 25 points):
If strength has been measured in kilograms, convert it to pounds by multiplying by 2.2.
Maximum strength score (in pounds) = max(1st attempt, 2nd attempt, 3rd attempt)

Calculate the CM score for each visit, as well as the change from baseline score to each visit (score at post-op visit minus score at baseline).

A MCID flag will be created which will be 1 if the change from baseline score is greater than or equal to 10.4[8], and 0 otherwise.

<u>EQ-5D-3L</u>
Index Score[9]:

- The individual dimension responses on a scale of 1-3 will be combined in the order: Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression to form a 5-digit EQ-5D-3L profile in the form XXXXX (where X is 1-3) describing the respondent's health state.

- An EQ-5D-3L index value will be derived per subject by matching the 5-digit profile to the correct country and index value on the vendor supplied calculator. All sites in this study are in the US.

Calculate the EQ-5D-3L index score for each visit, as well as the change from baseline score to each visit (score at post-op visit minus score at baseline).

Similarly, the change from baseline to each visit will be calculated for the VAS health score.

Adverse events

Adverse events are recorded by the Investigator and then reviewed by the Adverse Events Monitoring Board (AEMB) at Smith + Nephew and documented in the Safety Notification Tracker. The most stringent classification will be presented and reported. Investigator assessments will be provided in listings.

Investigators do not classify events, S+N use the Investigator assessment to classify the event as follows:

- An event will be classified as an ADE if the event is related to the study device and/or procedure
- An event will be classified as an SAE if the event is serious
- An event will be classified as an SADE if it is an ADE which is also serious
- An event will be classified as a USADE if it is an SADE which is also unanticipated
- Otherwise, the event will be a non-device, non-procedure related, non-serious AE

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

Due to system updates, checks need to be performed to ensure the most stringent classification is being reported. When comparing Investigator assessments (classifications as above) with AEMB classifications, the most stringent classification should be reported as follows:

Investigator assessment	**AEMB classification**	**Most stringent**
AE	SAE	SAE
SAE	AE	SAE
AE	ADE	ADE
ADE	AE	ADE
ADE	SADE	SADE
SADE	ADE	SADE
SAE	SADE	SADE

SADE	SAE	SADE
SADE	USADE	USADE

7.5 Baseline Data

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

7.6 Disposition Data

The number of subjects that entered the study and attended each of the follow up visits will be presented as count and percentage.

The number of subjects that completed the study, the number of withdrawals prior to completion and reasons for withdrawal will be presented.

The study duration of all subjects will be summarised using descriptive statistics for continuous variables.

Dates of first subject first visit and last subject last visit will be reported.

7.7 Protocol Deviations

Protocol deviations will be discussed during data review and the reasoning for a patient's inclusion/exclusion in each of the analysis populations will be documented. The frequency of protocol deviations will be summarized along with the number of subjects experiencing each. A listing will be provided of all protocol deviations.

7.8 Multiplicity

No adjustments for multiplicity are planned for this study.

7.9 Analysis of Primary Endpoint(s)

Success rate will be summarised by the number and percentage of patients that have not 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.

Success rate will be presented by group (PEEK or REGENESORB).

Additionally, success rate will be presented by variant (ST/NST) and primary diagnosis (rotator cuff repair and/or biceps tenodesis), separately for PEEK and REGENESORB.

The primary endpoint analysis will be conducted on the safety population.

7.10 Analysis of Secondary Endpoint(s)

All summaries will be provided overall by group (PEEK or REGENESORB) and will be further broken down for each subgroup (PEEK ST, PEEK NST, RG ST, RG NST) as appropriate. All 24 month summaries will only be for the RG NST subgroup.

Repair failure rate
Repair failure rate at 12 and 24 months will be summarised 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 that we do not know the outcome for). A 95% exact confidence interval for the proportion will be presented using the Clopper-Pearson method.

Additionally, repair failure rate will be presented by variant (ST/NST) and primary diagnosis (rotator cuff repair and/or biceps tenodesis), separately for PEEK and REGENESORB.

If the data allows, a Kaplan-Meier analysis will be presented, where a second repair procedure is the event of interest.

ASES
Although the ASES standardised form contains both physician assessment and patient self-evaluation section, only the VAS pain and 10 functional questions (for the index arm) are used to calculate the ASES score.

ASES questionnaires that are incomplete for the questions used for scoring at the baseline visit will not be included in the analyses.

The highest possible score is 100. Minimal clinically important difference (MCID) for the ASES is 6.4[2] points for patients undergoing rotator cuff repair.

Pain in the index shoulder will be assessed using the VAS pain score from the ASES. The scale ranges from 0cm to 10cm, where 0 represents no pain and 10 represents worst pain. For outcomes involving the ASES VAS pain score, the MCID will be 2.4[3-5]cm.

The ASES score and ASES VAS pain score 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. A paired sample t-test will be used to test changes in the scores from baseline to each post-operative visit. If the t-test assumptions are not met then a Wilcoxon Signed Rank test will be considered.

The MCID will be used to determine the clinical importance of the mean difference between visits. The criteria for determining clinical importance of the mean difference will be as follows:

- If the confidence interval of the mean difference is completely above the MCID, the difference is considered "clinically significant"
- If the confidence interval of the mean difference contains the MCID, the difference is considered "possibly clinically significant"
- If the confidence interval of the mean difference is completely below the MCID, the difference is considered "not clinically significant"

The assessment of clinical importance will be reported along with the confidence intervals for each outcome. Additionally, we will provide a summary of the proportion of patients who achieved the MCID.

<u>SANE</u>

The SANE is a simple, single-question, patient-based shoulder function assessment tool with a score range from 0% to 100%, with 100% being considered normal. The MCID for the SANE is 16.9[6] points.

The SANE 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. A paired sample t-test will be used to test changes in the scores from baseline to each post-operative visit. If the t-test assumptions are not met, then a Wilcoxon Signed Rank test will be considered. MCID will be presented as described in the ASES section above.

Constant-Murley

The CM score consists of 4 domains: pain, activities of daily living (ADL), movement and power/strength. Pain and 3 items under ADL are participant reported while all other items are assessed by an examiner.

The pain item is a VAS where 0cm indicates no pain and 15cm indicates intolerable pain, and is assigned a maximum of 15 points. The ADL component is assigned a maximum of 20 points with 2 items scored using a VAS and 2 items scored using a Likert scale. The movement section is assigned a maximum of 40 points, and evaluates four active range of motions, receiving 1-10 points each. Finally, the strength component is given a maximum of 25 points and requires the use of a dynamometer. Scoring is calculated from the highest score of 3 attempts – the patients 'best score'.

Constant-Murley score questionnaires that are incomplete for the questions used for scoring at the baseline visit will not be included in the analyses.

The score ranges from 0 to 100 points, with a higher score indicating better shoulder function. The MCID for the Constant-Murley is 10.4[8] points.

The CM score 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. A paired sample t-test will be used to test changes in the scores from baseline to each post-operative visit. If the t-test assumptions are not met then a Wilcoxon Signed Rank test will be considered. MCID will be presented as described in the ASES section above.

EQ-5D-3L

The EQ-5D-3L is a standardized measure of health status developed by the EuroQol Group and provides a simple measure of general health. The EQ-5D-3L descriptive system contains 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. The subject is asked to answer a question on each dimension on a scale comprising of 3 levels: no problems (1), some problems (2), and extreme problems (3). This decision results in a 1-digit number expressing the level selected for that dimension. The digits for the 5 dimensions can be combined in the order shown above to form a 5-digit profile (e.g. 11111 describes no problems in any dimension). This can then be cross-referenced using vendor provided calculator against the country of the Investigator site to come up with an index value describing the respondent's health state. Higher index values indicate better health and lower index values describe worse health.

The subject responses to each dimension (categorical) and the overall EQ-5D-3L index values (continuous) will be summarised at all study visits. The change in the index value between baseline

and all post-operative visits will also be summarised. A paired sample t-test will be used to test changes in the scores from baseline to each post-operative visit. If the t-test assumptions are not met, then a Wilcoxon Signed Rank test will be considered.

Additionally, the EQ-5D-3L has a VAS component which records the subjects self-rated health on a scale of 0-100.

The subject responses (continuous) will be summarised at all study visits. Change from baseline to each post-operative visit will also be presented. A paired sample t-test will be used to test changes in the scores from baseline to each post-operative visit. If the t-test assumptions are not met then a Wilcoxon Signed Rank test will be considered.

Imaging
MRIs are conducted on the RG NST group only. 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 summarised appropriately for categorical or continuous variables by an external imaging vendor. Results will be provided in a separate report that will be incorporated into the CSR.

7.11 Analysis of Safety Endpoint(s)

All safety endpoints will be summarised using the safety population.

Adverse events
The number of events and the number of subjects reporting: adverse events (AEs), serious adverse events (SAEs), adverse device effects (ADEs), serious adverse device effects (SADEs), and unanticipated serious adverse device effects (USADEs) will be summarised. This will be presented separately for REGENESORB and PEEK.

Adverse event table summaries will be provided using the most stringent classification from Investigator and Sponsor. Both Investigator and Sponsor classifications will be provided alongside the most stringent classification in the Listings
In addition, AEs will be summarised by Investigator assessment: frequency, severity, anticipated/unanticipated, relationship to device and procedure; treatment and surgical intervention details (type, reason), outcome and duration of adverse events at trial discontinuation will be summarised.
A listing will be provided which details subject number, variant (RG ST, RG NST, PK ST, PK NST), AE description, start date, end date/ongoing, classification, severity, seriousness, relationship to

device, relationship to procedure, anticipation, actions taken, outcome and whether study participation was discontinued due to the event.

Device deficiencies
The number of device deficiencies will be summarised by REGENESORB and PEEK. A listing of device deficiency details will be provided and will include variant (RG ST, RG NST, PK ST, PK NST).

7.12 Other Data Summaries

Not applicable.

7.13 Changes in Analysis Methods Specified in the Protocol

The primary endpoint in protocol v3.0 dated 25Feb2021 is repair failure rate at 6 months. In this SAP, the primary endpoint has been updated to success rate to be consistent with the sample size calculations. Success rate will be the primary analysis in this study and a brief explanation of what this means in terms of failure will be provided in the Clinical Study Report.

This SAP has been up versioned to V2 with the purpose of reflecting changes on the MCID values of SANE score and EQ-5D-3L index, reference for SANE MCID was updated and EQ-5D-3L index MCID was deleted due to the lack of a specific value for rotator cuff repair and biceps tenodesis.

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