# STATISTICAL ANALYIS PLAN (SAP)

## Study Details:

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| Protocol Version | 1.0 | Protocol Date | 27-FEB-2017 |

## SAP Version Control:

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# Contents

# 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 (S+N internal Safety team) |
| CE | Conformité Européene |
| CIP | Clinical Investigation Plan |
| CRF | Case Report Form(s) |
| CRO | Contract Research Organization |
| CV | Curriculum Vitae |
| DevD | Device Deficiency(ies) |
| CTAS | CADENCE Total Ankle System |
| EC | Ethics Committee |
| FAAM | Foot and Ankle Ability Measure questionnaire. (ADL Subscale only) |
| FDA | Food and Drug Administration |
| FU | Follow-Up |
| GCP | Good Clinical Practice |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonisation |

| Abbreviation | Definition |
|---|---|
| IDE | Investigational Device Exemption |
| IEC | Independent Ethics Committee |
| IFU | Instructions for Use |
| IMDRF | International Medical Device Regulatory Forum |
| IRB | Institutional Review Board |
| ISO | International Organization for Standardizations |
| ITT | Intention to Treat Population |
| LOCF | Last Observation Carried Forward |
| NA or N/A | Not Applicable |
| N (or n) | Total Sample Size (or subgroup sample size) |
| PP | Per-protocol Population |
| PROM | Patient Reported Outcome Measures |
| PROMIS | PROMIS Physical Function – Mobility Item Bank v1.2 |
| QoL | Quality of Life |
| S+N | Smith+Nephew Orthopedics |
| SADE | Serious Adverse Device Effect(s) |
| SAE | Serious Adverse Event(s) |
| SAF | Safety Population |
| SAP | Statistical Analysis Plan |
| SF-36v2 | Short Form-36 Version 2 Health Survey |
| TFL | Tables, Figures and Listing |
| USADE | Unanticipated Serious Adverse Device Effect(s) |
| VAS | Visual Analogue Scale |

# 2 INTRODUCTION

The following Statistical Analysis Plan (SAP) details the statistical considerations, including the data analysis methods, for the Study Protocol T-CTAS-002. 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 post-market, prospective, non-randomized, multi-center, international, open-label single-arm post approval clinical evaluation of the CADENCE Total Ankle System (CTAS) for use in primary ankle joint replacement. Patients will be followed for 10 years post implant with assessments at baseline, surgery then 6 weeks, 3 and 6 months, 1/2/5 and 10 years post implant. The primary objective is the 2-year implant survivorship.

| | Screen Baseline | Surgery | 6-week (± 2-week) | 3-month (± 2-week) | 6-month (± 1-month) | 1-year (± 2-months) | 2-year (± 2-months) | 5-year (± 5-months) | 10-year (± 5-months) |
|---|---|---|---|---|---|---|---|---|---|
| Inclusion/Exclusion/Consent | X | | | | | | | | |
| Baseline Demographics | X | | | | | | | | |
| Medical History and Diagnosis | X | | | | | | | | |
| Operative Evaluation | | X | | | | | | | |
| Follow-up Visit | | | X | X | X | X | X | X | X |
| Ankle VAS Pain Assessment | X | | X* | X | X | X | X | X | X |
| SF-36v2 | X | | | X | X | X | X | X | X |
| FAAM (ADL subscale only) | X | | | X | X | X | X | X | X |
| PROMIS | X | | | X | X | X | X | X | X |
| Concomitant Medication | X | | X | X | X | X | X | X | X |
| Protocol Deviations | X | X | X | X | X | X | X | X | X |
| Adverse Events | X | X | X | X | X | X | X | X | X |
| Study Completion/Exit | | If required | If required | If required | If required | If required | If required | If required | X |
| **Study required x-rays** | | | | | | | | | |
| A/P | X | | X** | X | X | X | X | X | X |
| Lateral Neutral | X | | X** | X | X | X | X | X | X |
| Dorsiflexion (ROM) | X | | X** | X | X | X | X | X | X |
| Plantarflexion (ROM) | X | | X** | X | X | X | X | X | X |
| Intraoperative Fluoroscopy | | X*** | | | | | | | |

* Non-weight bearing only

** Per Surgeon Discretion (Weight-bearing may not be recommended at this time)

*** Immediately prior to device insertion, a lateral fluoroscopy image of the ankle is required to be collected

VAS – Visual Analogue Scale
SF-36v2 - SF-36v2® Health Survey
FAAM – Foot and Ankle Mobility Measure, the Activities of Daily Living (ADL) subscale
PROMIS – Physical Function – Mobility Item Bank v1.2

# 4 STUDY OBJECTIVES

This study will evaluate the long-term performance and safety data for the CTAS when used for primary arthroplasty in patients with primary arthritis (e.g. degenerative disease), secondary arthritis (e.g. post-traumatic, avascular necrosis, if minimally 2/3 of the talus is preserved), and systemic arthritis of the ankle (e.g. rheumatoid arthritis, hemochromatosis).

## 4.1 Primary Objective(s)

To evaluate 2-year implant survivorship in patients who receive the CTAS when used for primary ankle arthroplasty. Implant survivorship is defined as absence of device removal or revision of one or more of the implant component(s).
NOTE: Revision does not involve other joint-involving procedures that are termed reoperations (such as gutter debridement and peri-prosthetic joint-involving surgeries that are considered additional procedures (such as subtalar joint arthrodesis, ligamentous release or plication, Achilles tendon lengthening, etc.).

## 4.2 Secondary Objective(s)

To evaluate 5-year and 10-year survivorship, and relative changes in pain, functionality, patient satisfaction, radiographic performance, and quality of life scores at all visits as compared to pre-operative scores including:

- PROMIS Physical Function – Mobility Item Bank v1.2 (PROMIS)
- Foot and Ankle Ability Measure questionnaire (FAAM) (ADL Subscale only)
- Ankle Visual Analog Scale (VAS) pain assessment
- Short Form-36 Version 2 Health Survey (SF-36v2)
- Total ROM (degrees plantarflexion and dorsiflexion)

Imaging Objectives:
X-ray imaging will be used in this study to evaluate the radiographic performance of the device in support of a portion of the secondary endpoints of the study. Specifically, the following qualitative and quantitative parameters will be evaluated:

- Device migration
- Device subsidence
- Device tilting
- Device condition
- Radiolucency at 10 lateral and 10 AP zones
- Osteolysis

- Heterotopic ossification
- Adverse bony changes
- Sclerosis
- ROM.

# 5 STUDY ENDPOINTS

## 5.1 Primary Endpoint(s)

Rate of survivorship of the CTAS as established by obtaining information on revision or implant removal over time. Survivorship success at 2 years is defined as absence of device removal or revision of one (or more) of the implant component(s).

## 5.2 Secondary Endpoint(s)

Implant survivorship:

- Rate of the survivorship of the CTAS at the 5 and 10-year follow-up visit is defined as absence of device removal or revision.

Clinical Assessment:

- Relative change compared to pre-surgery (baseline) values for:
  - PROMIS
  - FAAM (ADL Subscale only)
  - VAS pain assessment
  - SF-36v2.

Radiographic Assessment:

- Radiographic success is defined as absence of implant radiolucency, subsidence, tilting and/or migration defined as no evidence of radiolucency >4 mm in more than 3 zones and of subsidence or tilting >4 degrees, or migration > 4mm.

## 5.3 Safety Endpoint(s)

Safety Evaluation:

- Rate of all device and/or procedure related AEs, SAEs (related to device and/or procedure) or SAEs considered by the position as related to the study condition or the lower limbs and all subsequent surgical interventions.

# 6 STATISTICAL CONSIDERATIONS

## 6.1 Determination of Sample Size

This post-market descriptive study will include 60 patients. No formal justification has been given in Protocol v1.0.

## 6.2 Randomisation

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

## 6.3 Interim Analysis

Two interim analyses will be conducted, when all patients have completed the 2 and then the 5 year visits. For each interim, complete tables and listings will be generated containing all study data up to each of the interim timepoints.

# 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): This is defined as subjects implanted with the CTAS. This will be the population used in all analyses of survivorship, radiographic assessments, protocol deviations and adverse events.
- Intention to Treat population (ITT): The ITT is a subset of subjects in the SAF analysis population who have at least one postoperative assessment with any of the PROMs (Patient Reported Outcome Measures) or other performance indices. This population will be used for efficacy endpoints (i.e., PROMIS, VAS Pain, FAAM, SF-36).
- Per-Protocol Population (PP): The PP population is a subset of the ITT analysis population who do not have significant protocol deviations that would warrant exclusion and who satisfy all enrolment eligibility 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).

The baseline and disposition tables will be given for all three populations. The survivorship, radiographic assessment, safety and protocol deviation tables will be given for the SAF set. The PROM tables will be given for both the ITT and PP analysis sets.

## 7.3 Handling of Missing, Incomplete and Repeat Data

The primary analysis on implant survivorship will be based on survival analysis with missing data treated as censored.

If a variable is not mentioned in this section then no missing data imputation will be performed and the value will remain as missing. Where missing data imputation is used, two separate analyses will be performed; observed data analysis and missing data imputation data analysis.

## 7.4 Derived Data

Analysis Populations

- Indicator for inclusion in the SAF, ITT and PP populations

Protocol Deviations

- Indicator for visit out of visit window

| Visit | Target Visit Day (Visit Data – Surgery Date)+1 | Visit Window |
|---|---|---|
| Surgery | 0 | 0 |
| 6 weeks (±2 weeks) | 42 | 28-56 |
| 3 months (±2 weeks) | 90 | 76-104 |
| 6 months (±1 month) | 186 | 155-217 |
| 1 year (±2 months) | 365 | 303-427 |
| 2 years (±2 months) | 730 | 668-792 |
| 5 years (±5 months) | 1,825 | 1,670-1,980 |
| 10 years (±5 months) | 3,650 | 3,495-3,805 |

*based on 31 days in month, 365 in year

Demographics

- BMI [kg/m$^2$] = $weight\ [kg]$ / $(height\ [cm]/100)^2$

Duration

- Duration between surgery and each study visit calculated as
  Study Visit$_n$ = Date of visit$_n$ – Date of surgery
- Operative duration = End time – start time
- Tourniquet duration = End time – start time
- Hospital stay = Hospital operative discharge date – operative surgery date

PROMIS: Physical Function Mobility

- A higher score indicates more mobility
- Each of the 15 items is scored on a 5-point Likert scale (5 to 1) from 'without any difficulty / not at all' to 'unable to do/cannot do'. The score total will range from 15 to 75 and will be transformed to percentage scores.
- PROMIS Mobility Percentage Score = (score from 15 items – 15 ) / 60 x 100

FAAM: ADL score

- Each of the 21 items is scored on a 5-point Likert scale (4 to 0) from 'no difficulty at all' to 'unable to do'. Item score totals will range from 0 to 84 for the ADL subscale and will be transformed to percentage scores. Higher scores represent higher levels of function for each subscale, with 100% representing no dysfunction.
- ADL Percentage Score = score from 21 items / 84 x 100
- For the most valid results it is suggested that scores for the FAAM ADL be generated only when patients completed 90% or more of the items (19 of 21 for the ADL) for the assessment

SF-36

1. Scoring the RAND 36-Item Health Survey is a two-step process:
    - Precoded numeric values will be recoded per the scoring key given in Table 1. Note, all items are scored such that a high value defines a more favourable health state, and each item is scored on a 0 – 100 range.
    - Items in the same scale will then be averaged to create the 8 scale scores. Table 2 lists the items forming each scale.
    - A count of the number of items answered within each scale, by patient and visit will be calculated. If for each patient and visit >50% of items are missing then the average will not be calculated.

Table 1. Recoding items

| **Item Numbers** | **Change original response category *** | **To recorded value of:** |
|---|---|---|
| 1, 2, 6, 8, 9 (a-i) | 1 → | 100 |
| | 2 → | 75 |
| | 3 → | 50 |
| | 4 → | 25 |
| | 5 → | 0 |
| 3 (a-j) | 1 → | 0 |
| | 2 → | 50 |
| | 3 → | 100 |
| 7 | 1 → | 100 |
| | 2 → | 80 |
| | 3 → | 60 |
| | 4 → | 40 |
| | 5 → | 20 |
| | 6 → | 0 |
| 4 (a-d), 5 (a-c), 10, 11 (a-d) | 1 → | 0 |
| | 2 → | 25 |

| | | |
|---|---|---|
| | 3 → | 50 |
| | 4 → | 75 |
| | 5 → | 100 |

** Precoded response choices as printed in the questionnaire*

Table 2. Averaging items to form scales

| Scale | Number of items | After recoding per Table 1, average the following items | Component Score |
|---|---|---|---|
| Physical functioning | 10 | 3 (a-j) | Physical |
| Role limitations due to physical health | 4 | 4 (a-d) | Physical |
| Role limitations due to emotional problems | 3 | 5 (a-c) | Mental |
| Energy/fatigue | 4 | 9(a,e,g,i) | Mental |
| Emotional well-being | 5 | 9(b,c,d,f,h) | Mental |
| Social functioning | 2 | 6, 10 | Mental |
| Pain | 2 | 7, 8 | Physical |
| General health | 5 | 1 11(a,b,c,d) | Physical |

2. Changes from baseline to each post-baseline visit for each of the 8 health scales will be derived as:

$$\text{Index value}_{visit\ n} - \text{Index value}_{visit\ 1}, \quad where\ n = \text{x, x, x} \ldots$$

3. The Physical Component Score will be calculated as an average of the 4 following scale scores (transformed scores from Table 2): physical functioning, role limitations due to physical health, pain and general health
4. The Mental Component Score will be calculated as an average of the 4 following scale scores (transformed scores from Table 2): role limitations due to emotional problems, energy/fatigue, emotional well-being and social functioning.
5. For the Physical and Mental Component Scores, changes from baseline (<Define which visit is baseline>) to each post-baseline visit will be derived as:

$$\text{Index value}_{visit\ n} - \text{Index value}_{visit\ 1}, \quad where\ n = \text{x, x, x} \ldots$$

PROM questionnaires (PROMIS, FAAM, VAS)

- Changes from baseline to each post-baseline visit for each of the PROM questionnaires will be derived as:

$$\text{Index value}_{visit\ n} - \text{Index value}_{visit\ 1}, \quad where\ n = \text{x, x, x} \ldots$$

Radiographic Success at each visit:

- Defined as absence of implant radiolucency, subsidence, tilting, migration defined as no evidence of radiolucency >4 mm in more than 3 zones and of subsidence or tilting >4 degrees, or migration > 4mm
- No if:
    1. ≥3 of the 20 radiolucency zones = 3 (i.e.>4mm in width), OR
    2. device tilting = 1 (present), OR
    3. device subsidence (tibial OR talar) = 3 (i.e. >4mm), OR
    4. device migration (tibial OR talar) = 3 (i.e.>4mm).
- Otherwise radiographic success = Yes (and assessments taken place)
- 'Unable to assess' if all radiographic measures 'unable to assess'

Implant survivorship success at each visit:

- Yes if intact or re-operation or supplementary fixation
- No if revised or removed.

Patient level implant Survival Time (months):

- For a patient that completes the study without a failure event: (final study assessment/point of contact – operative date)/30.4375
- For implant failure (failure date – operative date)/30.4375
- NB 30.4375=365.25/4

Patient level implant Survival Censor:

- For a patient that completes the study without a failure event: Yes
- For implant failure: No

<u>Adverse Events</u>

- Investigator events do not receive a classification and so S+N classify events as follows:
    - ADE if the relationship to the study device and/or the relationship to the study procedure is possibly/probably/related
    - SAE if the event is serious
    - SADE if it is an ADE which is also serious
    - USADE if it is a 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 (Adverse Event Monitoring Board) 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 |
| USADE | SADE | USADE |

## 7.5 Baseline Data

Demographics
Patient demographics including age, gender, weight, height and body mass index (BMI) will be summarised.

Nicotine use will be summarised, including duration for current/former smokers.

Patient's current work status will be summarised (with dates since last worked provided in the Listings).

Medical History

The patient's affected side and weight bearing status will be summarised.
Presenting symptoms of pain (including duration since earliest symptoms), loss of motion and strength will be summarised.

The primary study diagnosis will be summarised along with any previous lower extremity surgical interventions (details of which to be provided in the Listings).

Any pre-operative medical conditions will be summarised along with body systems and whether ongoing.

The FAAM, VAS, PROMIS and SF-36 baseline summaries will be included in the secondary variable tables along with all study visits.

Operative Evaluation

The duration of operation and tourniquet use will be summarised.

The surgery type, whether adjunctive procedures were performed (and type), whether secondary procedures were performed (and type) will be summarised. Whether cement was used (and type), whether any additional topical agents were used during surgery (details in Listings).

Whether the CTAS device was implanted in the patient, and if any intra-operative complications occurred will be summarised.

Length of hospital stay will be summarised.

## 7.6 Disposition Data

The number of patients that enter the study, the number of patients that attend each study visit and the number of patients in each analysis set will be summarised.

The number of patients that have discontinued treatment and reasons for withdrawal will be summarised.

Study duration and the duration between surgery and each visit will be summarised.

Details of the dates that the first patient was screened, first patient enrolled and the last patient completed will be provided.

## 7.7 Protocol Deviations

The frequency of protocol deviations along with the number of patients experiencing each will be summarised. It will be indicated in the Listings where a deviation led to an exclusion from any analysis populations.

## 7.8 Multiplicity

No adjustments for multiplicity are planned for this study.

## 7.9 Analysis of Primary Endpoint(s)

Implant survivorship is defined as absence of device revision or removal.

The implant survivorship rate will be summarized by the number and percentage of patients that have implant survivorship at their 2 year visit. A 95% exact confidence interval for the proportion will be presented using the Clopper-Pearson method.[5]

## 7.10 Analysis of Secondary Endpoint(s)

Implant survivorship

The cumulative implant survivorship status will be summarised by visit.

The cumulative proportion of implant survivorship at 5 and 10 years will be summarised by the number and percentage of survivorship together with 95% exact confidence intervals calculated using the Clopper-Pearson method.

If feasible, Kaplan-Meier survival graphs will be displayed to graphically illustrate implant survivorship over the study duration.
Time to device revision will be the endpoint of interest to estimate the implant survivorship. Implant survival time (in months) is computed as: (Event Date – Operative Date)/30.4375. Implanted patients that continue until study completion without an on-study revision will be censored at their last known date of participation in the study. Any premature patient discontinuation from study due to a patient's death or any other reason will be censored on the date of this discontinuation. A patient who is lost to follow-up will be censored at the patient's last known contact date.

Patient Reported Outcome Measure: PROMIS – Physical Function – Mobility

The PROMIS Mobility score will be summarised at all study visits including baseline.

The absolute reduction from baseline to each study visit will be summarised.

Paired T-tests will be used to compare baseline values to each post-operative visit, p-values and 95% confidence intervals will be presented.

Patient Reported Outcome Measure: VAS Pain Assessment

A higher VAS score indicates a higher level of pain.

Pain whilst resting and pain during activity will each be summarised at all study visits including baseline (at the 6 week visit there will be no pain during activity collected).

The absolute reduction, in both pain VAS scores, from baseline to each study visit will be summarised.

Paired T-tests will be used to compare baseline values to each post-operative visit, p-values and 95% confidence intervals will be presented.

Patient Reported Outcome Measure: FAAM (ADL only)

The FAAM score will be summarised at all study visits including baseline (use derived not from database).

The absolute reduction from baseline to each study visit will be summarised.

Paired T-tests will be used to compare baseline values to each post-operative visit, p-values and 95% confidence intervals will be presented.

Patient Reported Outcome Measure: SF-36 v2

The SF-36 is a widely used health-related quality-of-life measure; the version presented here is the RAND 36-Item health Survey v2.0. The survey asks 36 questions covering eight health concepts: Physical Functioning (10 items), Bodily Pain (2 items), Role Limitations due to Physical (4 items) or Emotional (3 items) Problems, Emotional Well-Being (5 items), Social Functioning (2 items), Energy/Fatigue (4 items) and General Health Perceptions (5 items). It also includes a single item that provides an indication of perceived change in health.

The patient responses to each of the 8 health scale scores (continuous), the Physical and Mental Component scores (continuous), and the single item indicating perceived change (categorical) will be summarized at all study visits.
The change in the 8 health scale scores, and Physical and Mental Component scores between baseline and all post-baseline study visits will also be summarised.

Paired T-tests will be used to compare baseline values to each post-operative visit (Physical and Mental Component scores only), p-values and 95% confidence intervals will be presented.

Radiographic Assessment

The following qualitative endpoints will be summarised at all study visits: device migration (tibial and talar), device subsidence (tibial and talar), device tilting, device condition, radiolucency (10 lateral zones and 10 AP zones), osteolysis (tibial and talar), heterotopic ossification, adverse bony changes and sclerosis.
When summarising the qualitative endpoints the number of patients 'unable to assess'/'not required'/'not applicable' will also be given.

The ankle dorsiflexion (deg), the ankle plantarflexion (deg) and the tibiotalar range of motion (derived, deg) will be summarised at all study visits.

Radiographic success (as defined in derived variables) will be summarised at all study visits.

## 7.11 Analysis of Safety Endpoint(s)

All safety analyses and summaries will be conducted using the Safety Population).

Adverse Events

Adverse event table summaries will be provided using the most stringent classification from Investigator and Adverse Event Monitoring Board (AEMB). Both Investigator and AEMB classifications will be provided alongside the most stringent classification in the Listings.

The number of events and the number of patients reporting: adverse events (AE), serious adverse events (SAE), adverse device effects (ADE), serious adverse device effects (SADE) and unanticipated serious adverse device effects (USADE) will be summarised.

In addition, AEs will be summarised by: severity; the relationship to the study device, relationship to study procedure; outcome and duration of adverse events at trial discontinuation.

Adverse Events will be coded by the S+N safety team using the International Medical Device Regulators Forum (IMDRF) terminology and coding system. Coded AEs will be summarised descriptively and provided in the Listings.

## 7.12 Other Data Summaries

Patient's weight and weight bearing status will be summarised by visit (including baseline).

Nicotine use will be summarised at all follow up visits, whether the patient participated in physical therapy, whether the patient was using any supplemental ankle support, ankle mobilization status, type of support and current work status will be summarised at all follow up visits.

How satisfied the patient was with their surgical treatment, and whether they would recommend the same treatment to a friend with the same condition will be summarised at all post-baseline visits.

## 7.13 Changes in Analysis Methods Specified in the Protocol

The study protocol section 7.3.1 details an interim analysis will be conducted after all patients had completed the 2 year assessment. The Publication Policy Section 14 states the intention of the study is to publish all results after review and analysis of 2 year (short-term), 5 year (mid-term) and 10 year (long term). Hence two interim analyses are required (after all patients complete the 2 and 5 year assessments).

Clarification of patient analysis populations.

# 8 REFERENCES

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| Signer Events | Signature | Timestamp |
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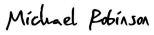
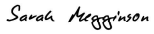
| Michael Robinson<br>michael.robinson@smith-nephew.com<br>Senior Statistician II<br>Smith & Nephew<br>Security Level: Email, Account Authentication (Required) |  <br>Signature Adoption: Pre-selected Style<br>Signature ID:<br>0E27C33E-B434-41FB-820C-99CBC38E7E89<br>Using IP Address: 216.222.214.6<br><br>With Signing Authentication via DocuSign password<br>With Signing Reasons (on each tab):<br>I approve this document | Sent: 29-Nov-2022 \| 14:36<br>Viewed: 01-Dec-2022 \| 15:48<br>Signed: 01-Dec-2022 \| 15:50 |
| **Electronic Record and Signature Disclosure:**<br>Not Offered via DocuSign | | |
| Sarah Megginson<br>sarah.megginson@smith-nephew.com<br>Biostatistics/Data Analyst 3<br>Smith & Nephew<br>Security Level: Email, Account Authentication (Required) |  <br>Signature Adoption: Pre-selected Style<br>Signature ID:<br>AB606B91-C10B-4190-9D3E-0B2F7B357742<br>Using IP Address: 216.222.208.4<br><br>With Signing Authentication via DocuSign password<br>With Signing Reasons (on each tab):<br>I am the author of this document | Sent: 29-Nov-2022 \| 14:36<br>Viewed: 29-Nov-2022 \| 14:36<br>Signed: 29-Nov-2022 \| 14:37 |
| **Electronic Record and Signature Disclosure:**<br>Not Offered via DocuSign | | |

| In Person Signer Events | Signature | Timestamp |
|---|---|---|

| Editor Delivery Events | Status | Timestamp |
|---|---|---|

| Agent Delivery Events | Status | Timestamp |
|---|---|---|

| Intermediary Delivery Events | Status | Timestamp |
|---|---|---|

| Certified Delivery Events | Status | Timestamp |
|---|---|---|

| Carbon Copy Events | Status | Timestamp |
|---|---|---|

| Witness Events | Signature | Timestamp |
|---|---|---|

| Notary Events | Signature | Timestamp |
|---|---|---|

| Envelope Summary Events | Status | Timestamps |
|---|---|---|
| Envelope Sent | Hashed/Encrypted | 29-Nov-2022 \| 14:36 |
| Certified Delivered | Security Checked | 29-Nov-2022 \| 14:36 |
| Signing Complete | Security Checked | 29-Nov-2022 \| 14:37 |
| Completed | Security Checked | 01-Dec-2022 \| 15:50 |

| Payment Events | Status | Timestamps |
|---|---|---|