STATISTICAL ANALYIS PLAN (SAP)

Study Details:

Protocol Version	2.0	Protocol Date	27-May-2013

SAP Version Control:

SAP Status	Final, Version 1.0, 05-Oct-2023
Previous Version Number, Date	N/A

Name and Title	Signature and Date / DocuSign Stamp
Yueming Shi Statistician, Bayesian Statistics (Statistician)	DocuSigned by: Yueming Shi Signer Name: Yueming Shi Signing Reason: I am the author of this document Signing Time: 31-Jan-2024 | 19:43:38 GMT 21B94D7EDD60456CBB43BBC136D9B217
Jay Jantz Director of Global Biostatistics & Data Sciences (Head of Global Biostatistics)	DocuSigned by: Jay Jantz Signer Name: Jay Jantz Signing Reason: I approve this document Signing Time: 01-Feb-2024 | 00:27:33 GMT B7D37248838E4CACAE11E7E55198A88D

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1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse Device Effect(s)
ADL	Activities of Daily Living
AE	Adverse Event(s)
ANCOVA	Analysis of Covariance
ASES	American Shoulder and Elbow Surgeons Shoulder Score
CRF	Case Report Form(s)
DevD	Device Deficiency(ies)
DF99	Datafax Safety Database
EC	Ethics Committee
EQ-5D	EuroQol 5D
FAS	Full Analysis Set
FDA	Food and Drug Administration
FU	Follow-Up
ITT	Intention to Treat Population
LOCF	Last Observation Carried Forward
LSMean	Least Squares Mean
NA or N/A	Not Applicable
N (or n)	Total Sample Size (or subgroup sample size)

Abbreviation	Definition
NSAE	Non-Serious Adverse Event(s)
PP	Per-protocol Population
QoL	Quality of Life
S+N	Smith+Nephew Orthopedics
SADE	Serious Adverse Device Effect(s)
SAE	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SAF	Safety Analysis Set
TFL	Tables, Figures and Listing
USADE	Unanticipated Serious Adverse Device Effect(s)
VAS	Visual Analog Scale
WOOS	Western Ontario Osteoarthritis of the Shoulder index

2 INTRODUCTION

The following Statistical Analysis Plan (SAP) details the statistical considerations, including the data analysis methods, for the Study Protocol version 2, 27-May-2013. Related documents to this SAP are the Study Protocol, Case Report Form (CRF), and Tables, Figures and Listings (TFL) Templates Shells.

3 STUDY DESIGN

The study is a post market, multi-centre prospective, non-randomized, non-comparative, open investigation.

4 STUDY OBJECTIVES

4.1 Primary Objective

The primary objective is to determine success of the PyroTITAN™ HRA Shoulder Prosthesis as defined by no revisions, no device related complications requiring surgical replacement and freedom from chronic dislocation.

4.2 Secondary Objectives

The secondary objectives of this investigation are to evaluate the functionality, and radiographic performance of the PyroTITAN™ HRA Shoulder prosthesis.

5 STUDY ENDPOINTS

5.1 Primary Endpoint

The primary endpoint is a composite endpoint for clinical success.

Clinical requirements for success will be evaluated at 24, 60 and 120 months:

- Device remains implanted
- Absence of device-related complications requiring surgical replacement, removal, or augmentation of components
- Freedom from chronic dislocation

5.2 Secondary Endpoint(s)

To demonstrate postoperative functionality and radiographic performance at 2, 3, 4, 5, 8 and 10 years post treatment, as compared with pre-treatment results through:

- ASES Score improvement
- Patient satisfaction
- VAS Pain
- WOOS
- Constant Score
- EQ-5D Quality of Life Questionnaire

Radiographic and MRI requirements for success at the different time points:

- No evidence of device failure, specifically progressive migration or implant loosening
- Anatomic alignment is a criterion that may be included in the definition of success in some investigations

5.3 Exploratory Endpoint(s)

To demonstrate postoperative functionality at 2, 3, 4, 5, 8 and 10 years post treatment, as compared with pre-treatment results through:

- Range of motion

5.4 Safety Endpoint(s)

Adverse Events including, but not limited to:

- Infection
- Loss of fixation
- Breakage
- Dislocations
- Revisions

6 STATISTICAL CONSIDERATIONS

6.1 Determination of Sample Size

The following is the sample size justification taken from the study protocol V2, 27-May-2013:

The original sample size in this study was 150 enrolled subjects. Additional proof testing and improvements in the device inspection process were employed during the study, at which time it was determined that an additional cohort of subjects was necessary. We are now comparing a cohort of subjects enrolled after these changes to the original cohort of subjects.

With an expected attrition rate of 10% per annum, this will yield an evaluable sample size of 52 shoulders at ten years ($150 * 0.9^{10} = 52.3$, where 0.9 or 90% is the number expected to be retained from one year to the next). Based on past experience, we may obtain clinical follow-up on this number of shoulders, but we may obtain radiographic follow-up on as few as two-thirds of these shoulders (about 35 shoulders). This remaining number of evaluable shoulders with clinical and radiographic follow-up is adequate to establish a reliable ten-year survival estimate of survival for hemi arthroplasty (Dorey and Amstutz, 1986).

For the new cohort, the sample size is calculated based on the non-inferiority of the study device. The success rate for the study device is 96.1% from the original population and is used as reference rate. Therefore, for a conservative success rate of 96.1% of the study device is used in the study. The non-inferiority margin δ of -0.033 is chosen in the study. 212 subjects are required to achieve 100(1 – β) % =80% power to detect non-inferiority at the Significance level of α = 0.05. To account for 10% lost to follow-up, the total number of additional subjects is 237. Therefore, the estimated enrolment for the study will be 387 subjects.

6.2 Randomisation

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

6.3 Interim Analysis

A 5-year interim analysis will be carried out for this study.

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 subject populations will be used for the statistical analysis of this study.

- **Full analysis set population (FAS)**, following Intention to Treat principle including all subjects who are enrolled into the study.
- **Per-Protocol Population (PP)**, including all subjects in the full analysis set who have no significant protocol deviations and met the inclusion/exclusion criteria.
- **Per-Protocol Population 1(PP1)**, including all subjects in the full analysis set who have no significant protocol deviations and met the inclusion/exclusion criteria. This is the original cohort of subjects in the study who were enrolled prior to the additional proof testing and improvements in device inspection process. This population will be used for supporting analysis of the primary endpoint.
- **Per-Protocol Population 2(PP2)**, including all subjects in the full analysis set who have no significant protocol deviations and met the inclusion/exclusion criteria. This is the additional cohort of subjects who were enrolled after the additional proof testing and improvements in device inspection process. This population will be used for supporting analysis of the primary endpoint.

- **Safety Population (SAF)**, including all subjects who have received any study treatment.

All safety analyses will utilise the SAF Population. All non-safety related endpoints will be analysed using both the FAS and PP analysis populations.

7.3 Handling of Missing, Incomplete and Repeat Data

Data will be analysed as observed in the study database.

7.4 Derived Data

Analysis populations

- Flag for inclusion in the SAF population
- Flag for inclusion in the ITT population
- Flag for inclusion in the PP population
- Flag for inclusion in the PP1 population
- Flag for inclusion in the PP2 population

Visit dates

- Pre-Operative visit within - 180 to -1 day window
- 3 month follow up within 1 - 120 day window
- 6 month follow up within 30 day window
- 12 month follow up within 60 day window
- 24 month follow up within 60 day window
- 36 month follow up within 90 day window
- 48 month follow up within 90 day window
- 60 month follow up within 90 day window
- 96 month follow up within 90 day window
- 120 month follow up within 90 day window

Demographics

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

Surgery Details

- Surgical Time = End time of Operation – Start time of operation
- Time to discharge = Date of discharge – Date of Surgery

Primary Endpoint

- Binary variable for clinical success (device survival), 1 if all the following are true and 0 if any is false:
    A. Device remains implanted.
    B. Absence of device-related complications requiring surgical replacement, removal, or augmentation of components.
    C. Freedom from chronic dislocation.

A will be determined through absence of a removal/ revision
B will be determined through assessment of complications forms
C will be determined through assessment of Adverse Events

- Duration to intervention = Date of surgical intervention – Date of surgery

VAS Pain and Satisfaction
Calculate the change from baseline VAS pain and VAS satisfaction scores to each visit (score at post-op visit minus score at baseline).

ASES[1]
The score is derived using the following equation:

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

The pain score is copied from the VAS Form, which asks the subject to rate pain on a scale of 0mm no pain, to 100mm worst possible pain. This 100mm score will be converted to cm for the purposes of the ASES score calculation, by dividing by 10. This means the range of the VAS pain score will be 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).

WOOS [3]
There are 19 questions, each question is answered on a visual analogue scale ranging from 0 to 100. The questions are divided into four domains: Physical symptoms (max score 600), sports and work (max score 500), lifestyle (max score 500) and emotions (max score 300). The overall score ranges from 0 to 1900, with 1900 being the worst. For ease of interpretation, scores are converted to a percentage of the maximum score for each domain and overall [(score/max score)*100].

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

Constant-Murley[2]
The Constant-Murley score is derived using the following equation:

> *Constant-Murley score = [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 occupation or daily living limited by your shoulder?
  - No (4 points)
  - Moderate limitation (2 point)
  - Severe limitation (0 points)
- Is your leisure and recreational activities limited by your shoulder?
  - No (4 points)
  - Moderate limitation (2 point)
  - Severe limitation (0 points)
- Is your night sleep disturbed by your shoulder?
  - No (2 points)
  - Sometimes (1 point)
  - Yes (0 points)
- State to what level you can use your arm for painless, reasonable activities?
  - Waist (2 points)
  - Xiphoid (4 points)
  - Neck (6 points)
  - Head (8 points)
  - Above head (10 points)

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

- Forward flexion
  - 0-30 (0 points)
  - 31-60 (2 points)
  - 61-90 (4 points)
  - 91-120 (6 points)
  - 121-150 (8 points)
  - ≥151 (10 points)
- 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 (4 points)
  - Hand to top of head, elbow forward (6 points)
  - Hand to top of head, elbow back (8 points)
  - Full elevation (10 points)
- Internal rotation
  - Lateral thigh (0 points)
  - Buttock (2 points)
  - Lumbosacral junction (4 points)
  - Waist (6 points)
  - 12th 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, 4th attempt, 5th 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).

<u>EQ-5D</u>
Create flag for the country to be used to derive EQ-5D-3L (Country code - site ID: AU - 401, 402; GB - 403; FR - 404; SE - 406).

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 "EQ-5D-3L Crosswalk Index Value Calculator" [4].

Change from baseline (Pre-Operative visit) to each post-baseline visit in EQ-5D-3L index value will be derived as:

$$\text{Index value}_{visit\ n} - \text{Index value}_{visit\ 1}, \quad where\ n = 1,2,3 \ldots,10$$

Separate dimension responses should be derived using LOCF values as specified in section 7.3. These values should be used to calculate an LOCF version of the EQ-5D-3L Index value as above. The change from baseline in this value would then also be calculated in the same way as above.

EQ VAS

Change from baseline to each post-baseline visit in EQ VAS score will be derived as:

$$\text{EQ VAS}_{visit\ n} - \text{EQ VAS}_{visit\ 1}, \quad where\ n = 1,2,3 \ldots,10$$

An LOCF version of EQ VAS should be calculated as specified in section 7.3. The change from baseline for this variable will also be calculated as above.

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 RAVE. 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 "related" if the relationship if rated as possible/probable/definite to the Device and/or procedure from the investigator assessment, otherwise it will be classified as "not related".
- 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
USADE	SADE	USADE

7.5 Baseline Data

The following data is to be summarised at baseline. If any baseline data is to be summarised together with later visit data then the analysis will be described in the relevant endpoint section and not in this section.

Screening

- Baseline demographics: age (years); gender and dominant side
- Baseline Vital Signs: height (cm); weight (kg); BMI(kg/m2)
- Medical history/ Primary Diagnosis/ Presenting symptoms
- Concomitant Medications/ Medical Conditions

Operative Details

- Surgical details (Operative side, operative time, estimate blood loss, patient transfusion, bone grafting, cement use, stability upon implantation)
- Walch Classification
- Glenoid reshaping
- Surgical approach
- Treatment of Bicep tendon
- Intraoperative complications
- Time to discharge

7.6 Disposition Data

- The number of subjects screened.
- The number of subjects attending each study visit will be summarised with the dates of first subject first visit and last subject last visit inserted into the footnote.
- Reason for study completion

7.7 Protocol Deviations

The frequency of protocol deviations will be summarized along with the number of subjects experiencing each.

7.8 Multiplicity

No adjustments for multiplicity are planned for this study.

7.9 Analysis of Primary Endpoint(s)

A composite endpoint for Clinical success (device survival) is defined as a binary variable (1/0) (1 if all the following are true and 0 if any is false):

A. Device remains implanted.
B. Absence of device-related complications requiring surgical replacement, removal, or augmentation of components.
C. Freedom from chronic dislocation.

The primary endpoint is the clinical success (device survival) rate at 10-years.
The study hypothesis is to test whether the 10-year survival (i.e., clinical success) rate in the investigational PyroTITAN HRA group is non-inferior to the reference rate at 96.1%. This study will be considered successful if the upper bound of the two-sided 95% confidence interval for the success rate difference (reference – study survival rate) is less than the non-inferiority margin of 3.3%.

The primary non-inferiority hypothesis is formulated as:

$\mathbf{H_0: P_0 - \delta \geq P_T}$
$\mathbf{H_a: P_0 - \delta < P_T}$

The variables are defined as follows:
P_T = 120-month success rate in the PyroTitan HRA group
P_0 = Reference success rate from original population
H_0 = Null hypothesis

H_a = Alternative hypothesis that that the success rate in the investigational group is non-inferior to the reference rate
δ = Non-inferiority margin pre-specified to be 3.3%.

The survival rate (the clinical success rate) will be calculated and the associated 95% exact confidence interval presented. If the upper 95% confidence limit is greater than the reference rate minus the non-inferiority margin (96.1 – 3.3 = 92.8%) then non-inferiority of the observed rate to the reference rate to within a 3.3% margin can be concluded.

Additionally, survival rate (the clinical success rate) and the associated 95% exact confidence interval at 2 and 5 years will be calculated and presented.

If data allows, time-to-event curves for device survival will be estimated using the Kaplan- Meier technique. For analysis of device survival, those lost to follow up or withdrawn from the study for reasons other than device revision or removal will be regarded as censored observations.

The primary analysis of this endpoint is to be carried out using the FAS population. The same analysis will be carried out on the PP population as supporting analyses.

As an additional analysis, the primary endpoint will be summarised for PP1 and PP2 populations in order to compare the cohort of subjects enrolled after the device changes to the original cohort of subjects.

7.10 Analysis of Secondary Endpoint(s)

ASES
ASES Scores range from 0 to 100 with a score of 0 indicating a worse shoulder condition and 100 indicating a better shoulder condition.

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

The ASES 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 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.

VAS Pain

VAS Pain scores range from 0 to 100, with higher VAS score indicates a higher level of pain.
VAS Pain will be summarised at each study visit and the absolute change in VAS scores, from baseline to each study visit 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.

VAS Satisfaction

VAS Satisfaction scores range from 0 to 100, withhigher VAS score indicates a higher level of satisfaction.
VAS Satisfaction will be summarised at each study visit. As there is no baseline assessment of VAS satisfaction no analysis for change over time will be planned.

WOOS

There are 19 questions, each question is answered on a visual analogue scale ranging from 0 to 100. The questions are divided into four domains: Physical symptoms (max score 600), sports and work (max score 500), lifestyle (max score 500) and emotions (max score 300). The overall score ranges from 0 to 1900, with 1900 being the worst. For ease of interpretation, scores are converted to a percentage of the maximum score for each domain and overall [(score/max score)*100].

The WOOS score for each domain and overall will be derived for each patient at each visit and summary statistics will be presented. Change from baseline scores per domain and overall to each post-operative visit will also be presented.
A paired sample t-test on the overall WOOS score 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.

Constant Murley Score

The CM score consists of 4 domains: pain (15 points), activities of daily living (ADL) (20 points), movement (40 points) and power/strength (25 points). Strength score is calculated as the highest score of the 3 attempts.

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 total score is calculated as the sum of each score from the 4 domains and ranges from 0 to 100 points, with a higher score indicating better shoulder function.

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 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.

EQ-5D Quality of Life Questionnaire

The EQ-5D-3L is a standardised 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, 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 (i.e. 11111 describes no problems in any dimension). This can then be cross-referenced using vendor provided "EQ-5D-3L Crosswalk Index Value Calculator"[4] against the country of the investigator site (Country code - site ID: AU - 401, 402; GB - 403; FR - 404; SE - 406) 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 summarized at all study visits. The change in the index value between baseline and all post-baseline study visits will also be summarised.

EQ-5D-3L index value will be assessed using repeated measures ANCOVA model, with the change from baseline index value as the dependent variable. As a minimum the model will contain terms for visit (repeated term) and baseline index value. The following terms will be added to the model using a stepwise selection procedure with an F-value to attain a significance level of 0.1: site, primary diagnosis and BMI. The p-value for the type III effects of all fixed effects terms included in the final model will be presented. The Least Square Mean (LSMean) change in EQ-5D-3L index value between baseline and all post-baseline study visits will be presented with the associated 95% confidence interval and p-value.

If the data does not satisfy the assumptions of an ANCOVA model then an appropriate non-parametric analysis will be considered such as Wilcoxon Signed Rank Test, with the Hodges-Lehmann estimate of the median change in index value presented along with the associated 95% confidence interval.

EQ VAS

The EQ visual analogue scale (EQ VAS) records the subject's self-rated health on a vertical, visual analogue scale (VAS).

The subject responses to EQ VAS scores (continuous) will be summarized at all study visits. The change in EQ VAS score between baseline and all post-baseline study visits will also be summarised.

EQ VAS will be assessed using repeated measures ANCOVA model, with the change from baseline in EQ VAS as the dependent variable. As a minimum the model will contain terms for visit (repeated term) and baseline EQ VAS. The following terms will be added to the model using a stepwise selection procedure with an F-value to attain a significance level of 0.1: site, primary diagnosis and BMI. The p-value for the type III effects of all fixed effects terms included in the final model will be presented. The Least Square Mean (LSMean) change in EQ VAS between baseline and all post-baseline study visits will be presented with the associated 95% confidence interval and p-value.

If the data does not satisfy the assumptions of an ANCOVA model then an apporpriate non-parametric analysis will be considered such as Wilcoxon Signed Rank Test, with the Hodges-Lehmann estimate of the median change in EQ VAS presented along with the associated 95% confidence interval.

Radiographic success (X-Ray and MRI)
Radiographic analysis will be performed by a third-party vendor (Medial Metrics Inc.) under a separate SAP.

7.11 Analysis of Exploratory Endpoint(s)

Range of Motion
Summary statistics for both passive and active range of motion on the operative shoulder will be given as continuous variables for:

- Forward elevation
- External rotation (Arm comfortably at side)
- External rotation (Arm at 90° abduction)
- Internal rotation (Highest posterior anatomy reached with thumb)
- Internal rotation (Arm in abduction)
- Cross-body adduction (Antecubital fossa to opposite acromion)
- Abduction

7.12 Analysis of Safety Endpoint(s)

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.

Events will be summarised by the AE/SAE/ADE/SADE/USADE classifications derived from the Investigator assessment of the event. In the case of disagreements, a separate summary of event classifications made by the Sponsor will also be provided.

In addition, AEs will be summarised by; severity (intensity), relationship to study device, relationship to procedure, outcome and duration of adverse event at trial discontinuation.

A listing will be provided which details subject number, 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.

7.13 Other Data Summaries

Not Applicable

7.14 Changes in Analysis Methods Specified in the Protocol

- The 5-year interim analysis was not specified in the protocol however it has been added to allow for the 2 and 5 year data to be published.

8 REFERENCES

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