STATISTICAL ANALYSIS PLAN (SAP)

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Revision History

Document Version	Changes Made	Document Date
0.1	Original	21 September 2016
0.2	Added Section 8 per FDA's request and insert Modified to Harris Hip Score (pg 12)	04 October 2016
0.3	Updated the following items to correspond to what is presented in the study protocol: • Document headers/footers • Abbreviations • Visit Schedule and Visit Windows • Change references to "Harris Hip Score" to "Modified Harris Hip Score" • Details of how radiographs should be taken and where they will be submitted • Clarification of "enrolled set" • Preoperative and Postoperative Procedures Patient Disposition at preoperative, operative, and post-operative visits will be presented for the Enrolled cohort only. Change in how missing data is handled with regard to categorical summary statistics. This was changed to use all non-missing data and is now consistent with how missing data is treated in the continuous summary statistics. Clarification of data to be considered in the final analysis, to note that "lost to follow-up due to revisions" will be considered. Updates to definitions of Adverse Events to match study protocol, which are based on ISO 14155:2011	29 June 2017
1.0	Administrative changes were made to make the SAP consistent with the study protocol. Due to the number of administrative changes, the detailed list of changes is captured in an Addendum to this document.	22 June 2018

Document Version	Changes Made	Document Date
2.0	Added provisions for missing data due to COVID-19 visit restrictions, as well as specifics surrounding the patient accountability calculations to determine impact of COVID-19-related missing data.	28 Jul 2022
3.0	Issued on S+N current SAP standard template resulting in minor changes to section numbers and order, content remains unchanged: • 1. Introduction to 2 Introduction • 2 Study Objectives changed to 4 Study Objectives • 3.3 Sample size justification to 6.1 • 3.4 Randomization and blinding to 6.2 • 3.5 Efficacy endpoints to 5 Study Endpoints • 4 Statistical Analysis moved to 7 Statistical Analysis • 5.1 Subject enrollment and disposition to 7.6 • 5.2 Protocol violations to 7.7 • 5.3 Demographic and baseline characteristics to 7.5 • 6.1 Analysis of primary endpoint to 7.10 • 6.2 Analysis of secondary efficacy endpoints to 7.11 • 7 Evaluation of Safety to 7.13 • 8 Additional Analyses to 7.14 Other Data Summaries • 9 Planned Reporting to 6.3 Interim Analysis Content change: • 7.6 Disposition Data: additional detail provided and terminology updated to match FDA Annual Progress Report 2022/2023 Section 3.1 • 7.6 Additional screening/enrollment summaries included for Ct.gov purposes • 7.14 Addition of propensity scoring • 7.14 Addition of exploratory analysis on radiographic findings	30 October 2023
4.0	• Section 7.6 – Clarity on the dates to be reported per site • Section 7.14 – Clarifying reason for propensity scoring as supportive evidence to primary analysis • Section 7.14 – Defining the predictor variables to be used in the logistic regression analysis	21 November 2023

Document Version	Changes Made	Document Date
	• Section 7.14 – Clarification that Standardized mean differences will be used. • Section 7.14 – Updated details around radiographic findings	
5.0 (DRAFT)	Section 5.1: • Updated to reflect amendment to protocol 6.0 and clarification of the primary endpoint Section 7.10: • Updated to reflect amendment to protocol 6.0 and clarification of the primary endpoint • Inclusion of margin from 6.1 Sample Size Section 7.14: • Removal of propensity scoring between the US / EU studies as per FDA letter 29Nov2023 • As per FDA letter 29Nov2023, addition of propensity scoring between United Kingdom National Joint Registry (UK NJR) and: 1. US Study 2. EU Study • Removal of Radiographic Findings • Addition of evaluation of relationship cup inclination with mHHS pain scores	20 December 2023
5.1 (DRAFT)	Sections 5.1, 7.10, 7.14: • Addition of "Mild" pain from HHS to accompany "no acetabular cup inclination changes greater than 4 degrees from baseline when accompanied by "Mild", "Moderate", "Marked" or "Disabled" mHHS pain score."	17 January 2024
5.2	Section 7.14: • As per FDA request, removal of all propensity score analyses between US Study and UK NJR, and EU Study to UK NJR.	19 January 2024

Contents

1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse Device Effect(s)
AE	Adverse Event(s)
AP	Anteroposterior
ASA	American Society of Anaesthesiologists

Abbreviation	Definition
CRF	Case Report Form(s)
DOD	Biolox delta ceramic-on-ceramic
EC	Ethics Committee
FDA	Food and Drug Administration
mHHS	Modified Harris Hip Score
ICF	Informed Consent Form
IRB	Institutional Review Board
OUS	Outside of the United States
PAS	Post-Approval Study
PMA	Premarket Approval
ROM	Range of Motion
SADE	Serious Adverse Device Effect(s)
SAE	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SMD	Standardized Mean Difference
UK NJR	UK National Joint Registry
USADE	Unanticipated Serious Adverse Device Effect(s)

2 INTRODUCTION

Smith & Nephew Orthopaedics is the Sponsor of a prospective, multicenter, non-randomized, clinical outcomes study of the R3 Acetabular System in patients with degenerative hip disease in Europe. The study design included an evaluation of the performance of a Biolox delta ceramic-on-ceramic cohort using the R3 delta Ceramic Acetabular System in patients undergoing primary total hip arthroplasty. The R3 Biolox delta Ceramic Acetabular System has been commercially available outside the United States (OUS) since 2008 and this study satisfied post-market surveillance requirements in Europe. Clinical data from this European post-market study was used to support a Premarket Approval (PMA) application that was submitted to the US Food and Drug Administration (FDA) on August 20, 2015. The clinical data submitted in the PMA application (PMA cohort) included subject follow-up to the 3-year postoperative interval. Approval was sought for the R3 delta Ceramic Acetabular System based upon the PMA cohort clinical data. The PMA (P150030) was reviewed by the FDA and approved on October 17, 2016. The R3 delta Ceramic Acetabular System is commercially available in the United States. A condition of the FDA approval was that Smith & Nephew Orthopaedics was required to sponsor a post-approval study (PAS) of the R3 delta Ceramic Acetabular System in the United States to address any concerns regarding differences in the US and European patient populations. This study is being conducted to comply with FDA requirements that Smith & Nephew Orthopaedics sponsor a post-market study of the R3 delta Ceramic Acetabular System in the US.

3 STUDY DESIGN

3.1 General Design and Plan

This is a post-market, prospective, multicenter, observational study to collect clinical and radiological data from 183 subjects undergoing primary total hip arthroplasty with the R3 delta Ceramic Acetabular System.

Total study duration for study participants will be 3 years with follow-up visits planned prior to hospital discharge, and at 3 months, 1 year, 2 years and 3 years postoperative. Subjects will be enrolled at up to 10 sites in the United States.

3.2 Visit Schedule and Visit Windows

The intervals and schedule of evaluations are provided in the following table.

Study Activity	Pre-operative	Intraoperative (Day 0)	Discharge	3 mo (+/- 2 wks.)	1 yr (+/- 2 mo)	2 yr (+/- 2 mo)	3 yr (+/- 2 mo)
Inclusion/exclusion	X						
Informed consent	X						
Demographics	X						
Operative Data Collection		X					
Discharge Data Collection	X		X				
Modified Harris Hip Score	X			X	X	X	X
X-rays[1]: AP pelvis, AP hip, lateral hip			X	X	X	X	X
Adverse Event Assessments		X	X	X	X	X	X
Concomitant Medications, Procedures		X	X	X	X	X	X
Telephone Follow Up[2]				*	*	*	*
End of Study/Exit	*	*	*	*	*	*	*

* As needed
[1] see Appendix II- Radiographic Evaluation Protocol
[2] As needed please refer to Protocol Section 6.5 (Telephone Follow-Up)

3.2.1 Visit 1: Pre-Operative Visit

Information will be collected on the study population prior to device implantation. Demographic factors including age, gender and primary diagnosis will be obtained.
Procedures to be completed at the pre-operative visit:

- confirm informed consent and inclusion/exclusion criteria are met
- assign a subject ID
- collect data per case report form (CRF) completion guidelines, including demographic data, mHHS, Charnley Classification, ASA score (American Society of Anesthesiologists), and prior hip surgery.
- Perform all study procedures per study schematic

3.2.2 Visit 2: Intraoperative to Hospital Discharge

Information on the operative procedure for each subject including surgical approach, component size and device identifier, surgical time, and intraoperative blood loss will be obtained. Additionally, length of hospital stay and discharge to home or any other institution will be recorded. Any adverse events (complications) occurring from the time of study device implant and prior to discharge will be collected and recorded on the appropriate CRF.

Patients will have radiographs taken after implantation (before discharge from the hospital) to establish a baseline. All study radiographs (Anteroposterior (AP) pelvis, AP hip, and lateral hip) should be acquired according to the Image Acquisition Protocol and will be transmitted to the central imaging vendor for independent review.

3.2.3 Visit 3: Postoperative

Postoperative follow-up visits will occur at 3 months (+/- 2 weeks), 1 year (+/- 2 months), 2 years (+/- 2 months) and 3 years (+/- 2 months) postoperative. Subjects will be evaluated using the modified Harris Hip Score (mHHS) that was used in the original European post-market surveillance study. The mHHS includes a modification to the "Distance Walked" section of the Harris Hip Score to add distances to the choices available, such as indicating the number of blocks as a defined distance since the term "blocks" is not commonly used as a measurement of distance in Europe.

AP and lateral radiographs will be taken at these postoperative visits. All study radiographs (AP pelvis, AP hip, lateral hip) should be acquired according to the Image Acquisition Protocol. X-rays will be transmitted to the central imaging vendor for independent review. Radiographs will be evaluated by an independent evaluator according to the Smith & Nephew Radiographic Evaluation Protocol.

Procedures to be completed at the postoperative visits:

- perform study procedures per study schematic
- perform required X-rays (see Appendix II for subject positioning details)
- transmit X-rays to the central imaging vendor
- obtain and record any adverse events (AEs) occurring from the time of study device implantation
- collect data per CRF completion guidelines

3.2.4 Telephone Follow-Up

If subjects are unable to return for follow-up visits to the Investigator's office, they may be contacted by telephone to assess their status. Subjects will be asked whether the device is in place or has been revised and asked whether any adverse events related to the study hip device have occurred since the last visit.

In addition, the patient portion of mHHS (all data except for Range of Motion (ROM), Trendelenburg and Leg Length Difference) will be collected during this Telephone Follow-Up Assessment [1,2]. Note that if the subject later returns for a follow-up visit to the Investigator's office during the same interval as a telephone follow-up visit, the complete mHHS will be collected and included in the analyses in lieu of the patient portion.

The proposal to collect the patient portion of the mHHS data by telephone interview, and to use these data in lieu of the full mHHS when necessary, is justified based on the clinical study that has been published in the Journal of Telemedicine and Telecare in 2005[2] which confirms that there is overall no statistical difference between in-office complete mHHS and telephone patient portion mHHS assessments. Note that 'mHHS' in this study refers to a modification in how the "distance walked" question is asked, to make it more relevant for the European study population. However, in the article[2], 'mHSS' refers to the patient portion of the HHS without ROM, Trendelenburg and Leg Length Difference, as these cannot be collected remotely. Removal of the ROM and deformity components gives a maximum score of 91, which is multiplied by a factor of 1.1 in order to derive a total score out of 100. The published study showed that the differences between the complete HHS and the patient portion of the HHS are not statistically significant or clinically relevant, and thus the patient portion can be used for routine follow-up assessment of patients who have undergone total hip replacement[2].

4 STUDY OBJECTIVES

The study objective is to confirm that the safety and effectiveness of the R3 Biolox delta Ceramic Acetabular System in the US population is consistent with the effectiveness and safety profile shown in the European study (PMA cohort).

[1] Range of Motion, Trendelenburg and Leg Length Difference must be determined in person by clinically trained site staff to collect these data points in a reliable and clinically accurate manner.
[2] Sharma, et al. "Use of telephone interviews to follow up patients after total hip replacement." Journal of Telemedicine and Telecare Volume 11 Number 4 2005

5 STUDY ENDPOINTS

5.1 Primary Endpoint(s)

The primary endpoint is overall study success at 3 years postoperative. Success is defined the same way it was in the PMA cohort, to allow comparison. The primary endpoint will be analyzed using the exact binomial test. Overall success is defined as:

- No component revision,
- Modified Harris Hip Score (mHHS) of at least 80 points, and
- No radiographic failure, defined as:
  No radiolucencies greater than 2 mm in 50% or more in any of the cup or stem zones, no femoral or acetabular subsidence greater than or equal to 5 mm from baseline, and no acetabular cup inclination changes greater than 4 degrees from baseline when accompanied by "Mild", "Moderate", "Marked" or "Disabled" mHHS pain score.

In the event that the need for remote visits due to COVID-19 significantly impacts the primary endpoint, the following additional analyses will be performed to allow inclusion of as many study subjects as possible in the analysis:

(1) An alternative analysis in which overall success will consist of components that can be remotely collected via telephone, and will be defined as:
   - No component revision,
   - Patient portion of the Modified Harris Hip Score (mHHS), as described in Section 3.2.4**Error! Reference source not found.**, of at least 80 points.

(2) An alternative analysis that allows for post-three-year data to be used in place of missing or incomplete three-year visits ("rollback").

5.2 Secondary Endpoint(s)

Secondary endpoints include clinical assessments of pain and function using the modified Harris Hip Score, radiographic findings, and implant survivorship.

5.3 Exploratory Endpoint(s)

There are no exploratory endpoints for this study.

5.4 Safety Endpoint(s)

Adverse events and device deficiencies, noted by study staff and reported by the subject, and occurring from the time of study device implantation through to study completion should be recorded on the appropriate CRFs.

6 STATISTICAL CONSIDERATIONS

6.1 Determination of Sample Size

The primary objective of this study is to confirm that the safety and effectiveness of the R3 Biolox delta Ceramic Acetabular System in the US population is consistent with the effectiveness and safety profile shown in the European study (PMA cohort). The primary endpoint is overall study success at 3 years postoperative. Secondary endpoints include clinical assessments of pain and function, radiographic findings, and implant survivorship.

Overall success (as defined in the section entitled "Primary endpoint") in the PMA Cohort was found to be 86.4% at 3 years postoperative for the Biolox delta ceramic-on-ceramic (DOD) treatment group. It is expected that the overall success for the DOD US Cohort is similar to the overall success for the DOD PMA Cohort (European data).

Statistical Hypotheses:

H_0: π_{DOD} -0.864 ≤ δ

H_a: π_{DOD} -0.864 > δ

Where,

π_{DOD} = Overall Success of DOD US

1-sided alpha error = 5%

Power of the test = 80%

δ=-0.08

The minimum sample size required for hypothesis testing: 146 DOD US subjects. The total sample size after adjustment for lost-to-follow-up (20%) is 183 DOD subjects. Sample size was calculated assuming use of an Exact Binomial test[3].

[3] https://support.sas.com/documentation/cdl/en/statug/63962/HTML/default/viewer.htm#statug_power_a0000000996.htm

6.2 Randomization

This is a non-randomized device trial.

6.3 Interim Analysis

An interim data release will occur at the midpoint of the study, 2.5 years after study initiation. The interim data release will be comprised of data regarding secondary endpoints. In addition, an interim report will be provided to the Agency annually, which will include summaries of the current data in the study.

7 STATISTICAL ANALYSIS

7.1 General

Categorical variables will be summarized with the number and percent of subjects in each group. Continuous variables will be summarized with the mean, standard deviation, median, minimum, and maximum values. 95% confidence intervals will be calculated for the primary and secondary endpoints.

All data collected in the CRF will be presented in the listings.

7.2 Analysis Populations

7.2.1 Screened Set

Subjects considered potential candidates for the study based on pre-screening will sign an IRB/EC approved Informed Consent Form (ICF) prior to any study activities. The Investigator or delegated study research staff may then complete the first study visit with the subject.

7.2.2 Enrolled set

Every subject that receives the study device will be considered enrolled in the study and included in the Enrolled set. If a subject has provided consent and completed screening, and for any reason does not receive the study device, the subject will not be considered enrolled in the study.

7.2.3 Software

SAS® v9.2 or above will be used to analyze the data.

7.3 Handling of Missing, Incomplete and Repeat Data

When data are being summarized, only the non-missing values will be evaluated for computing summary statistics.

In general, partial dates will be imputed as follows:

- if only the day is missing, the first day of the month will be assumed;
- if the day and the month are missing, January 1st will be assumed;
- if a date is completely missing or unknown and the visit is not indicated on the CRF, the data will not be included in a specific time window for analysis. Note that all AEs will be included regardless of whether the date is missing or incomplete.

When subjects do not attend an in-office study visit and a telephone visit is conducted instead, the data from telephone visit will be used for analyses wherever possible.

When the patient misses the final (3 year) visit but is able to return the office at a later date, the additional mHHS and radiographic data that were not collected during the telephone visit will be collected and used for the final analyses at 3 years.

7.4 Derived Data

Not applicable.

7.5 Baseline Data

Demographic data including age, gender, race, and primary diagnosis will be obtained at the preoperative visit.

The demographic and baseline characteristics will be summarized using descriptive statistics for the Enrolled set.

7.6 Disposition Data

Patient accounting will be presented according to the recommendations in the FDA guidance entitled "Clinical Data Presentations for Orthopedic Device Applications".

- **Actual A (in window)**: Hips with all data (Adverse Event/Revision Assessment, modified Harris Hip Score and radiographic evaluation) at the relevant visit, in the window time frame.

- **Actual A**: Hips with all data (Adverse Event/Revision Assessment, modified Harris Hip Score and radiographic evaluation) at the relevant visit (includes hips with visits out of the interval window).
- **Actual B**: Hips who returned to the office with any data (Adverse Event/Revision Assessment, modified Harris Hip Score or radiographic evaluation) at the relevant visit.
- **Actual Modified B**: Hips with any data (Adverse Event/Revision Assessment, modified Harris Hip Score, radiographic evaluation, or telephone visit) at the relevant visit, including hips unable to return for follow-up visits that were contacted by telephone for determination of patient satisfaction and device survival.
- **Theoretical**: Number of hips that would have reached the beginning of the study window associated with each visit if all subjects returned.
- **Deaths**: Cumulative number of subjects that died during or prior to the upper window limit of the study visit.
- **Failures**: Cumulative number of hips that failed (revision) during or prior to the upper window limit of the study visit.
- **Expected**: Theoretical hips minus the number of deaths and revisions.
- **Follow-up Rate**: Actual/Expected*100

Patients discontinued from the study prematurely will be presented, with a breakdown of the reasons for discontinuation as reported in the CRF.

Due to subject visit restrictions associated with COVID-19 pandemic, it is expected that Protocol Deviations will occur that may affect the subject accountability rates. In particular, radiographic data and data that can only be collected at the office follow up are likely to be missing or out of window. However, the telephone survey will ensure that most of the key information needed for the primary analysis at the 3-year follow-up visit is collected. Additionally, every effort will be made to gather radiographic data and the complete HHS at a later time when an in-person visit was not completed within the 3-year window.

To present a thorough assessment of hip accountability, the following information will be included in the annual reports and final study report:

(1) The typical accountability table that has been presented in each annual report will be presented, using the same rules for inclusion in each category (i.e. $Actual^{A}$, $Actual^{Awithinwindow}$, $Actual^{B}$, $Actual^{Mod.\ B}$).

(2) Final 3-year accountability, which will include telephone visit data (or full HHS if available) plus out-of-window radiographic data as allowable for "complete data" ($Actual^{Awithinwindow}$,and $Actual^{A}$), and telephone visit data alone as allowable for other accountability categories including $Actual^{B}$ and $Actual^{Mod.\ B}$.

(3) A listing of deviations and missed/out of window visits that result from the COVID-19 pandemic.

Screening failures and patients discontinued from the study prematurely will be presented with a breakdown of the reasons for discontinuation as reported in the CRF.

Screening and enrolment summary: For each centre/site, dates that the first subject was screened/enrolled (first subject, first visit) and the last subject completed (last subject, last visit) will be provided, duration (site, 1st enrolled – final subject exit), together with number of subjects enrolled and number of subjects completed 3 year visit. Dates of all visits will be provided in the report listings.

7.7 Protocol Deviations

A protocol deviation is an instance of failure, intentionally or unintentionally, to follow the requirements of the protocol. Protocol deviations include but are not limited to: deviations from inclusion/exclusion criteria, endpoint variable criteria, and missed study visits or visits outside the window. Protocol deviations due to COVID will be tracked.

Protocol deviations will be classified as major protocol deviation and minor protocol deviation.

Major and minor protocol deviations will be summarized.

7.8 Measurement of Treatment Compliance

Not applicable.

7.9 Multiplicity

Not applicable, no adjustments for multiplicity are planned for this study.

7.10 Analysis of Primary Endpoint(s)

The primary endpoint is overall study success at 3 years postoperative. Success is defined the same way it was in the PMA cohort, to allow comparison. Overall success is defined as:

- No component revision,
- Modified Harris Hip Score (mHHS) of at least 80 points, and
- No radiographic failure, defined as:
  No radiolucencies greater than 2 mm in 50% or more in any of the cup or stem zones, no femoral or acetabular subsidence greater than or equal to 5 mm from baseline, and no acetabular cup inclination changes greater than 4 degrees from baseline when accompanied by "Mild", "Moderate", "Marked" or "Disabled" mHHS pain score.

All subjects in the enrolled population with evaluable data at 3 years postoperative will be considered for analysis. Subjects lost to follow up due to revision at any point up to the end of the three-year visit window will be considered as failures.

A one-sided analysis using the exact binomial model will be used to analyze success rate against the success rate of the PMA cohort of 86.4%, with 8% margin (as per Sample Size Section 6.1).

As mentioned in Section 7.14 additional analyses will be performed to accommodate inclusion of as many study subjects as possible in the analysis.

7.11 Analysis of Secondary Endpoint(s)

Secondary endpoints include clinical assessments of pain and function using the modified Harris Hip Score, radiographic findings, and implant survivorship. These assessments will be summarized using descriptive statistics at postoperative visits. No analyses are planned.

7.12 Analysis of Exploratory Endpoint(s)

There are no exploratory endpoints for this study.

7.13 Analysis of Safety Endpoint(s)

The number of AEs, SAEs, USADEs, Reoperation and Revisions, and the number and the percentage of patients experiencing AEs, SAEs, USADEs will be presented for the enrolled set.

The number of AEs and the number and the percentage of patients with at least one AE will be presented for AEs and SAEs.

The number and the percentage of patients with at least one AE will be presented by severity, seriousness, device relatedness and procedure relatedness.

Adverse event definitions are shown below and are as per the study protocol.

7.13.1 Adverse Event (AE)

An 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 study medical device.

This definition includes but is not limited to:

- events related to the study device
- events related to the procedures involved

7.13.2 Serious Adverse Event (SAE)

A SAE is an adverse event that:

- resulted in death,
- was life threatening (at the time of the event); or
- resulted in hospitalization (initial or prolonged); or
- resulted in a disability or permanent damage (a significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life); or
- resulted in a congenital anomaly or birth defect; or
- required medical or surgical intervention to preclude permanent impairment of a body function or prevent permanent damage to a body structure; or
- does not fit the other outcomes above but may jeopardize the subject and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.

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

7.13.3 Adverse Device Effect (ADE)

An ADE is an adverse event related to the use of an investigational medical device.

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
- any event resulting from use error or from intentional misuse of the investigational medical device.

7.13.4 Serious Adverse Device Effect (SADE)

A SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

7.13.5 Unanticipated Serious Adverse Device Effect (USADE)

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects.

7.13.6 Device Deficiency

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling.

7.13.7 Assessment of Adverse Event Severity

The Investigator will assess and categorize AEs as mild, moderate, or severe based on the following definitions:

- Mild: the subject is aware of the sign or symptom, but finds it easily tolerated. The event is of little concern to the subject and/or little clinical significance. The event is not expected to have any effect on the subject's overall health or well-being.

- Moderate: the subject has discomfort enough to cause interference with or change in usual activities. The event is of some concern to the subject's health or wellbeing and may require medical intervention and/or close follow-up.
- Severe: the adverse event interferes considerably with the subject's usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or well-being. The event is likely to require medical intervention and/or close follow-up and may be incapacitating or life threatening. Hospitalization and treatment may be required.

7.13.8 Assessment of Adverse Event Relationship to Device and Procedure

All adverse events (AE) are assessed for relatedness to the study device and study procedure based upon the following definitions:

- Unrelated: the event is clearly not related to the study device or study procedure
- Possible: the event may or may not be related to the study device or study procedure. A relationship cannot be ruled out.
- Definite: the event is clearly related to the study device or study procedure.

7.14 Other Data Summaries

Subgroup analyses of the primary endpoint based upon race will be conducted. Descriptive summaries of these analyses, for each racial subgroup, will be provided.

Due to the COVID-19 pandemic, it is expected that restrictions on in-office visits may cause out of window in-office follow-up visits and result in missing or out of window data such as mHHS and radiographic endpoints. To evaluate whether there is a significant difference in the mean mHHS for subjects who use the patient portion of mHHS and the mean for subjects who use the overall mHHS, the following additional analysis will be performed:

- A comparison of total mHHS scores (including RoM assessments) from subjects who completed an in-person visit compared to scores from subjects who completed the telephone visit at the 3-year follow-up visit. This will be tested using an independent sample t-test.

Radiographic Findings

At the 3 year postoperative endpoint, the frequency of subjects will be tabulated for mHHS pain component by whether subjects show a >4 degree change in acetabular cup inclination angle from baseline. The relationship between whether subjects showed pain as "Mild", "Moderate", "Marked" or "Disabled" (from mHHS pain score) and those with a greater than 4 degree change in acetabular cup angle inclination from baseline will be compared using Fisher's Exact test.

7.15 Changes in Analysis Methods Specified in the Protocol

Not applicable

8 REFERENCES

1. Range of Motion, Trendelenburg and Leg Length Difference must be determined in person by clinically trained site staff to collect these data points in a reliable and clinically accurate manner.

2. Sharma, et al. "Use of telephone interviews to follow up patients after total hip replacement." Journal of Telemedicine and Telecare Volume 11 Number 4 2005

3. https://support.sas.com/documentation/cdl/en/statug/63962/HTML/default/viewer.htm#statug_power_a0000000996.htm

4. Medical Metrics Inc (2020) R3 Delta and ODH Studies: Interpreting Acetabular Cup Inclination [White paper].