STATISTICAL ANALYIS PLAN (SAP)

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Contents

1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse Device Effect
ADL	Activity limitations daily living
AE	Adverse Event(s)
ASADE	Anticipated Serious Adverse Device Effect
CI	Confidence Interval
CRF	Case Report Form
DC	Discharge
DevD	Device Deficiency(ies)
FAS	Full Analysis Set
FU	Follow-Up
HHS	Harris Hip Score
HOOS	Hip Disability and Osteoarthritic Outcome Score
ISO	International Organization for Standardisation
LSLV	Last Subject Last Visit
MAR	Missing at Random
MMRM	Mixed Model Repeated Measure
N/A	Not Applicable
NICE	National Institute for Clinical Excellence
ODEP	Orthopaedic Data Evaluation Panel
OP	Operative
PP	Per-protocol Population

Abbreviation	Definition
QoL	Quality of Life
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
TFL	Tables, Figures and Listing
UCLA	University of California, Los Angeles
USADE	Unanticipated Serious Adverse Device Effect
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 R3H01/02/01/2017 version 2.0/BNA. Related documents to this SAP are the Study Protocol, Case Report Form (CRF), and Table, Figure and Listing (TFL) Template Shells. This SAP is also an amendment to the previous finalized versions 1.0 and 2.0.

3 STUDY DESIGN

This is a multicenter prospective observational post-market clinical follow-up study that includes 512 patients who had a total hip replacement with the R3 Acetabular System and either cemented or cementless hip stem. The schedule of events is provided in Table 1.

Table 1. Study schedule of events

Study Activity	Preop	Op	DC	3M (+/- 14d)	1Y (+/- 2m)	3Y (+/- 3m)	5Y (+/- 6m)	7Y (+/- 6m)	10Y (+/- 6m)
Inclusion/Exclusion	X								
Informed Consent	X								
Demographics/Med History	X								
Harris Hip Score	X			X	X	X	X	X	X
UCLA	X			X	X	X	X	X	X
HOOS	X			X	X	X	X	X	X
Radiograph Evaluation			X		X*	X	X	X	X
Operative		X							
Discharge			X						
Adverse Events		X	X	X	X	X	X	X	X

* Full pelvic overview

4 STUDY OBJECTIVES

The objective of this study is to determine the long-term safety and effectiveness of the R3 Acetabular System by analysing the clinical, radiographic responses and the adverse event rates for

patients undergoing primary total hip arthroplasty using the R3 Hip System (R3 Acetabular System). The study hypothesis is as follows: implant survivorship (Kaplan-Meier) (revision for any reason) of the R3 cup is at least 97% at 3 years, 95% at 5 years, 93% at 7 years, and 90% at 10 years follow-up.

5 STUDY ENDPOINTS

5.1 Primary Endpoint

The primary endpoint is implant survivorship at 10 years postoperatively.

5.2 Secondary Endpoint

Secondary endpoints include the following:

- Implant survivorship of the acetabular/cup at 10 years postoperatively
- Modified Harris Hip Score (mHHS)
- Hip disability and Osteoarthritis Outcome Score (HOOS)
- University of California, Los Angeles (UCLA) Rating
- Radiographic evaluation
- Patient Satisfaction

5.3 Safety Endpoints

The safety endpoints are as follows:

- Incidence of Adverse Events by International Organization for Standardization (ISO) classifications
- Incidence of AEs by severity,
- Incidence of AEs by relationship to study device,
- Incidence of serious adverse events (SAEs),
- Incidence of Serious Adverse Device Effects (SADEs),
- Incidence of Unanticipated Serious Adverse Device Effects (USADEs),
- Incidence of Anticipated Serious Adverse Device Effects (ASADEs),
- Incidence of procedure-and or device related events,

- Listing of revisions and components revised.

6 STATISTICAL CONSIDERATIONS

6.1 Determination of Sample Size

The target enrollment during this study was 500 patients however 512 subjects have been enrolled. This number of patients leads to representative results with a greater precision of the survival rates, i.e. small confidence intervals.

The sample size is large enough to satisfy pseudo-regulatory requirements set-forth in individual European countries such as the Orthopaedic Data Evaluation Panel[1] (ODEP) and the National Institute for Clinical Excellence (NICE) requirements[2]. According to the ODEP criteria for categorizing products in relation to NICE's long-term benchmarks for hip replacements, a level A study (strongest evidence) requires an initial cohort of 500 patients or more.

6.2 Randomisation

Not applicable.

6.3 Interim Analysis

Not applicable as LSLV has been performed.

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 are the analysis populations used in summarizing all tables:

Safety Analysis Population (SAF)
This will include all subjects (Hips) enrolled and implanted with the study device in the study.

Full Analysis Set (FAS)
The FAS population will include all subjects (Hips) in the SAF with at least one postoperative assessment on any of the Patient Reported Outcome Measures (PROMs).

Per Protocol (PP) Population
The PP population will include all subjects (Hips) in FAS, who have no significant protocol deviations and satisfy all study eligibility criteria and the inclusion/exclusion criteria. Significant protocol deviations leading to removal from the PP population will be determined and finalized prior to the final analyses at 10 years. The final assignment of a subject to the PP population will be established after all protocol deviations have been reviewed and evaluated. Subjects excluded from the PP will be documented/listed together with their reason(s) for exclusion.

7.3 Handling of Missing, Incomplete and Repeat Data

For the primary endpoint, subjects with hips that are prematurely discontinued from the study due to death or loss to follow-up would be censored on the last known date on-study.

Specific instructions for handling missing PROMs is described in Section 7.4. If ≥ 10% of postoperative UCLA, HOOS or HHS scores at more than 2 of the postoperative follow-up time points are missing, only their observed data will be summarized using the change from preoperative to each postoperative time point as the endpoints of interest.

7.4 Derived Data

Body Mass Index (BMI)

- BMI = {(Weight in kg)/(Height in m)^2}, if units are in kg for weight and m for height OR;
- BMI = {(Weight in lbs)x703.07))/(Height in inches)^2}, if units are in lbs for weight and inches for height (Adjustments made to formula to standardize BMI unit to kg/m^2).

Change from baseline

Change from baseline (preoperative) scores to postoperative time points (i.e. Visit$_i$) for all pertinent endpoints would be calculated at follow-up visits as follows:
Postoperative visit$_i$ score – preoperative score.

Hip Disability and Osteoarthritis Outcome Score (HOOS)

The HOOS consists of 3 subscales; Pain, Stiffness and Function in daily living (ADL). Five standardized answer options are given and each question gets a score from 0 to 4. The detailed information is showed in Table 2. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) for each subscale will be calculated as:

HOOS pain = 100 – AVERAGE (P1:P5)* 100/4
HOOS Stiffness = 100 – AVERAGE (S4:S5)* 100/4
HOOS ADL = 100 – AVERAGE (A1:A17)* 100/4

Table 2 HOOS Domain Questionnaire and Scores

HOOS Item #	HOOS Items (Individual item scores 0-4, with None = 0; Mild = 1; Moderate = 2; Severe = 3; Extreme = 4)
Pain (score range 0-20)	
P1	Walking on a flat surface?
P2	Going up or down stairs?
P3	At night while in bed?
P4	Sitting or lying?
P5	Standing upright?
Stiffness (score range 0-8)	
S4	Severity of stiffness after first wakening in the morning?
S5	Severity of stiffness after sitting/lying/resting later in the day?
ADL (score range 0-68)	
A1	Descending stairs?
A2	Ascending stairs?

A3	Rising from sitting?
A4	Standing?
A5	Bending to floor/pick up an object?
A6	Walking on flat surface?
A7	Getting in/out of car?
A8	Going shopping?
A9	Putting on socks/stockings?
A10	Rising from bed?
A11	Taking off socks/stockings?
A12	Lying in bed?
A13	Getting in/out of bath/shower?
A14	Sitting?
A15	Getting on/off toilet?
A16	With heavy domestic duties?
A17	With light domestic duties?

If there are some missed answers, then the following rule will be followed.

1. For each subscale, if there are at least 50% of the items are answered, then we will calculate the subscale mean score as showed in Table 3.
2. For each subscale, if more than 50% of items are missed, then we will not calculate subscale mean score.
3. Subscale scores will be calculated independently, i.e. if a particular subscale is not valid, the results from the other subscale will still be calculated if available.

Table 3 Number of items needed for each subscale

SubDomain	# of items need to for calculation subscale mean score
Pain	3
Stiffness	1
ADL	9

Modified Harris Hip Score (HHS)

The mHHS includes a modification to the Harris Hip Score: the "Distance Walked" section of the Harris Hip Score was modified to replace the number of blocks with actual distances since the term "blocks" is not commonly used as a measurement of distance in Europe.

Table 4 displays the algorithms used for scoring each of the 10 items (components) of the mHHS as well as the domains (pain, function, AoD and ROM) of the mHHS and total mHHS.

Table 4. modified Harris Hip Score (HHS) scores per item and domain

Item	Original Response	Likely scores per Item	Domains (Range of Scores)
Pain	None or ignores it	44	**Pain Domain (0 to 44)**
	Slight, minimal, no compromise in activities	40	
	Mild pain, no effect on average activities, rarely moderate pain with unusual activity; may take aspirin	30	
	Moderate pain; tolerable but makes concessions to pain. Some limitation of ordinary activity or work. May require occasional pain medication stronger than aspirin	20	
	Marked pain, serious limitation of activities	10	
	Totally disabled, crippled, pain in bed, bedridden	0	
Limp	None	11	**Function Domain (0 to 47)**
	Slight	8	
	Moderate	5	**{Sum of all items within subdomain}**
	Severe	0	
Support	None	11	
	Single cane for long walks	7	
	Single cane most of the time	5	
	One crutch	3	
	Two canes	2	
	Two crutches or not able to walk	0	
Distance walked	Unlimited	11	
	Six blocks	8	
	Daily shopping	5	
	Indoors only	2	
	Bed and chair only	0	
Sitting	Comfortably in ordinary chair	5	
	On a high chair for 30 minutes	3	
	Unable to sit comfortably in any chair	0	

Public transportation	Yes, possible	1	
	No, unable	0	
Stairs	Normally without using a railing	4	
	Normally using a railing	2	
	In any manner	1	
	Unable to do stairs	0	
Socks/Shoes	With ease	4	
	With difficulty	2	
	Unable	0	
Range of Motion (ROM)	Flexion = FLEX+EXT-FLEX_ZERO	N/A	
	Movement = ABD+ADD-ABD_ZERO	N/A	
	Rotation = ER+IR-ER_ZERO	N/A	
ROM subscore	Flexion+Movement+Rotation		**Range of Motion Domain (0 to 5))**
	0 to 29	0	
	30 to 59	1	
	60 to 99	2	
	100 to 159	3	
	160 to 209	4	
	≥ 209	5	
Leg Length Difference (in mm)	None	N/A	
	Ipsilateral longer (LL_DIF_LONG)	N/A	
	Ipsilateral shorter (LL_DIF_SHORT)	N/A	
Absence of Deformity (AOD)	IF (FLEX_ZERO = . OR FLEX_ZERO < 31) AND (ABD_ZERO = . OR ABD_ZERO < 11) AND (ER_ZERO = . OR ER_ZERO < 11) AND LL_DIF_LONG < 33 AND LL_DIF_SHORT < 33 THEN AODScore = 4	0 or 4	**Absence of Deformity Domain (0 to 4)**
Total HHS		Sum of all domain scores per subject	Sum of all domain scores per subject

Note: The maximum possible score for the HHS is 100.

7.5 Baseline Data

The following preoperative, operative and demographic variables would be summarized using descriptive characteristics for continuous[1] or categorical[2] data as appropriate:

- Age[1] (in years),
- Sex[2] (males or females),
- Height[1] (in cm),
- Weight[1] (in kg),
- BMI[1]
- Primary diagnosis[2],
- Charnley classification[2]
- Surgical history ipsilateral[2]
- ASA Physical Status[2]
- Head, Size, Neck Length, Inlay Material, Inlay[2]
- Surgical Approach[2]

Variables summarized will not only be restricted to the above listed but all variables deemed pertinent and obtainable preoperatively and operatively.

7.6 Disposition Data

Hip accountability will be summarized by study visit (see Table 1 for visit schedule) for the number of hips that are theoretically due, subjects who died, hips that were revised, hips terminated from the study for any reason. Additional information will include but not limited to number of subjects presenting at each visit, number of hips expected at each visit and follow up rate.

7.7 Protocol Deviations

A listing of all protocol deviations encountered on-study will be summarized.

7.8 Multiplicity

No adjustments for multiplicity are planned for this study.

7.9 Analysis of Primary Endpoint

The Kaplan-Meier survival estimate would be used to estimate implant survivorship. 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+1)/30.4375.

Implanted hips 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 hip discontinuation from study due to a subject's death or any other reason will be censored on the date of this discontinuation. A subject who is lost to follow-up will be censored at the subject's last known contact date. The Cumulative proportion of implant survivorship at 36 months (3-year), 60 months (5 years), 84 months (7 years) and 120 months (10 years) will be estimated and displayed accordingly. These Kaplan-Meier estimates will be provided with their corresponding two-sided 95% Confidence Intervals (CIs). If feasible, Kaplan-Meier survival graphs will be displayed to graphically illustrate implant survivorship over the study duration.

For the a-priori protocol-specified hypothesis, if the lower bound of 95% two-sided CIs at 3 years, 5 years, 7 years and 10 years are not less than 97%, 95%, 93% and 90% respectively, then we conclude that implant survivorship of the R3 cup is at least 97% at 3 years. 95% at 5 years, 93% at 7 years, and 90% at 10 years follow-up respectively.

The primary endpoint analysis will be performed on the FAS population. As sensitivity analysis, the same analysis will be performed on the PP population.

7.10 Analysis of Secondary Endpoints

- HOOS sub-scores, HHS (and the its subscores) and UCLA would be summarized using descriptive summary characteristics for continuous variables at the preoperative and all postoperative time points. Changes from the preoperative (baseline) to subsequent postoperative visit(s) would also be summarized using descriptive statistics for continuous

variables. Mixed Model Repeated Measures (MMRM) with a missing at random (MAR) assumption to account for the pattern of missing longitudinal data would be used to analyze the Patient Reported Outcome Measures (PROMs) to compare the scores between the preoperative and postoperative visit time points. The model will include fixed effect term for visit. The Kenward Rogers denominator degrees of freedom would be used coupled with a specification for an unstructured covariance matrix. The test of any of the comparisons between the preoperative and postoperative visits will be concluded to be statistically significant if $p < 0.05$. Model-based Means or Least Square (LS) Means for all visits as well as the differences between each postoperative versus the preoperative visit and their 95% two-sided Confidence Intervals (CI) would be presented. Should greater than 10% of any of the PROMs data on at least at two of the postoperative timepoints be missing, MMRM would not be used.

- For radiographic findings, patient satisfaction and Trendelenburg, descriptive summary statistics for categorical variables such as frequency (n) and percentage (%) will be presented by visit.

The secondary endpoint analysis will be performed only on the FAS population.

7.11 Analysis of Safety Endpoints

An overall summary AE table that would summarize as number (n) and percentages (%), the overall incidence according to subjects (and hips) with at least one AE; subjects (and hips) with at least one AE by worst severity (mild, moderate, or severe), by worst outcome (resolved, ongoing/unresolved, death or removal/revision of components), worse relatedness to device, SAEs, ADEs, SADEs, ASADEs and, USADEs. Classification of AEs would also be summarized using ISO classifications. A data listing with all AEs (and their classifications) reported on-study will be presented. Finally, the incidence of device-and/or procedure related AE by their type will be presented too.

7.12 Additional Analysis

Type of R3 bearing would be classified into meaningful subgroups by the Clinical Strategy team using Head/Inlay/Inlay Material available in the database. Implant survivorship would subsequently be summarized exploratorily for each of the classified subgroup of the R3 bearing (head/inlay: i.e. Biolox delta ceramic-on-ceramic, Biolox forte ceramic-on-ceramic, Oxidized zirconium-on-

crosslinked polyethylene, Ceramic-on-crosslinked polyethylene, Metal-on-crosslinked polyethylene and Metal-on-metal) using Kaplan-Meier survival methods as described in Section 7.9.

The analysis population for these analyses would be the FAS population.

7.13 Other Data Summaries

Not applicable.

7.14 Changes in Analysis Methods Specified in the Protocol

The protocol-specified hypothesis is now more carefully elucidated in this SAP.

The primary analysis population of the primary endpoint is now specified to the based on the FAS population.

After consultation between key study stakeholders, it was determined that the additional COVID-related analyses previously included in SAP final version 1.0 would be of negligible-to-no impact on the results and therefore this is removed from this amendment.

Additional exploratory analysis of the primary endpoint by head/inlay material was added on request by Clinical Strategy.

8 REFERENCES

1. ODEP criteria for categorizing data in relation to NICE's benchmarks. *Orthopaedic Data Evaluation Panel*. 2005.
2. NICE. Guidance on the selection of prostheses for primary total hip replacement. *Technology Appraisal Guidance No. 2. National Institute for Health and Clinical Excellence*. 2000.

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