STATISTICAL ANALYIS PLAN (SAP)

Study Details:

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1. List of Abbreviations

Abbreviation	Definition
AE	Adverse Event(s)
ANOVA	Analysis of Variance
HHS	Harris Hip Score
HOOS	Hip Disability and Osteoarthritic Outcome Score
ITT	Intention to Treat Population
LOCF	Last Observation Carried Forward
N (or n)	Total Sample Size (or subgroup sample size)
PP	Per-protocol Population
SAE	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
TFL	Tables, Figures and Listing

2. Introduction

The following Statistical Analysis Plan (SAP) details the statistical considerations, including the data analysis methods, for the Study Protocol 2011-ODHH166. Related documents to this SAP are the Study Protocol, Case Report Form (CRF), and Tables, Figures and Listings (TFL) Templates Shells.

3. Study Design

Prospective, consecutive series, non-randomised, multicenter study evaluating the Safety and Effectiveness of a New Hard-on-Hard Total Hip Replacement System in Patients with Non-inflammatory Arthritis with a Standard THA Metal Ion Control Group.

Schedule of Assessments

Schedule	Preop	Op	DC	3 mo ± 4 wks	6 mo ± 4 wks	1 yr ± 4 wks	2 yr ± 6 wks	5yr -2 wks+ 180 days	6yr ± 90 days	7yr ± 90 days	8yr ± 90 days	9yr ± 90 days	10yr ± 180 days	Unscheduled
Days	-	-	-	64-120	155-211	338-394	689-773	1812 - 2006	2101 - 2281	2466 - 2646	2831 - 3019	3196 - 3376	3471 - 3831	-
Inclusion/Exclusion	√	-	-	-	-	-	-	√	-	-	-	-	-	-
Informed Consent	√	-	-	-	-	-	-	√	-	-	-	-	-	-
Demographics/Med History	√	-	-	-	-	-	-	-	-	-	-	-	-	-
Clinical Evaluation (HHS)	√[a]	-	-	√[a]	√[a]	√[a]	√[a]	√	-	√	-	-	√	√[a]
Radiography	√[a]	-	√[a]	√[a]	√[a]	√[a]	√[a]	√		√			√	√
Metal Ion Testing (Whole Blood)	√	-	-	√	√	√	√	√	-	√	-	-	√	√
HOOS Subject Questionnaire	√[a]	-	-	√[a]	√[a]	√[a]	√[a]	√	-	√	-	-	√	√[a]
Adverse Events	-	√	√	√	√	√	√	√	√	√	√	√	√	√
End of Study	-	-	-	-	-	-	-	-	-	-	-	-	√[c]	-
Retrospective Demographics/Med History Data Collection[b]	√	√	√	√	√	√	√	-	-	-	-	-	-	-
Retrospective Clinical Evaluation (HHS)[b]	√			√	√	√	√							
Retrospective HOOS[b]	√			√	√	√	√							
Retrospective Adverse Event Data Collection[b]	√	√	√	√	√	√	√	-	-	-	-	-	-	-
Retrospective Radiography Data Collection[b]	√	√	√	√	√	√	√	-	-	-	-	-	-	-

a - For Investigational subjects only
b - Control subjects only
c - An end of study form will be completed for all subjects at the 10 year visit if not completed prior

4. Study Endpoints

4.1 Primary Endpoints

The primary endpoints for this study are:

- Device-Related Revisions
- Adverse Events
- Metal Ion levels in whole blood [Cobalt (Cr), Chronium (Cr), Nickle (Ni), Titanium (Ti), Zirconium (Zr), Niobium (Nb), Molybdenum (Mo), Vanadium (V) and Aluminium (Al)].

4.2 Secondary Endpoints

The secondary endpoints for this study are:

- The Harris Hip Score (HHS)
- Hip Disability and Osteoarthritis Outcome Scores (HOOS)
- Radiographic Success, including the assessment of bone loss, radiolucencies, subsidence, and heterotopic ossification as compared to the preoperative radiograph.
- Health Economic Data
    - Surgical blood loss
    - Length of hospital stay
    - Operative time
    - Re-hospitalizations

5. Statistical Considerations

5.1 Determination of Sample Size

A total of 25 subjects were enrolled in the study (20: ODH-ODH and 5 controls). All patients completing the 2 year primary follow up were invited to participate in the extension phase of the study. No justification for the sample size was provided.

5.2 Randomisation

No randomization took place for this study. Instead Subjects who refuse ODH-ODH enrollment were asked to participate in the control group.

5.3 Interim Analysis

Interim analyses will be conducted post-operatively after all subjects have completed 5 year and 7 years visits. The focus of these analyses will be on safety and efficacy.

6. Statistical Analysis

6.1 General

Smith & Nephew's Global Biostatistics group will conduct the statistical analysis for this study. Unless otherwise stated, all statistical significance tests conducted 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).

6.2 Analysis Populations

The following analysis populations will be used for this study:

- **Safety Population (SAF):** Including all subjects who have enrolled in the study and received the study treatment. This population will be used for analysis of safety data including the primary endpoints.
- **Intention to treat population (ITT):** following Intention to Treat principle including all subjects enrolled into the study, this does not include those who only provide retrospective data. This population will be used for the primary analysis of secondary endpoints.
- **Per-Protocol Population (PP):** including all subjects in the ITT, who have no significant protocol deviations and who meet the inclusion/exclusion criteria. This population will be used as a secondary analysis of secondary endpoints.

6.3 Handling of Missing, Incomplete and Repeat Data

- **Revision data** - If a subject has a revision at any point during the study, for purposes of calculating the revision rate by a particular visit then the fact that a revision has occured will be carried forward to all the following visits.
- **HHS/ HOOS –** If any individual HHS/ HOOS responses are missing at a post-baseline visit then the data will be input from the previous assessment using the Last Observation Carried Forward (LOCF) method. If baseline is the only previous data point then no implementation methods should be used, baseline data should not be carried forward. If all HHS/ HOOS responses are missing at a post-baseline visit (including if a subject has discontinued from the study) then all missing dimension scores should be carried forward using the LOCF method as above, with no carrying forward of baseline values.

6.4 Derived Data

<u>Analysis Populations</u>

- Indicator for inclusion in SAF
- Indicator for inclusion in the ITT

- Indicator for inclusion in the PP

Demographics, Baseline Data and Disposition Data

- $\text{Age} = (\text{Date of preop visit} - \text{date of birth})/365.25$

  Note: Round down to the nearest whole number.
- $\text{Body Mass Index (BMI)}[\text{kg/m}^2] = \text{weight}\,[\text{kg}] * (\text{height}\,[\text{cm}]/100)^2$
- Baseline is considered as the Pre-Op visit.
- Indicator for bilateral subject.

Revision Data

- Any subject classified as lost-to-follow-up, deceased or withdrawn will be censored in the survival analysis on the date which it occurs. If a device-related revision occurs this will be considered a device failure. If none of the above occur before the end of the study the subject will be censored on end of study visit/ date of interim analysis.

HHS

- Total HHS score will be calculated as per the specific version instructions.
- Absolute change in Total HHS Score = Score at visit – Score at baseline (pre-op).

HOOS

- HOOS domain scores will be calculated as per the specific version instructions
- Absolute change in HOOS domain Score = Score at visit – Score at baseline (pre-op).

6.5 Baseline Data

Baseline data to be summarised for all populations:

- Operated Side (Left/ Right/ Bilateral)
- Demographics (to be summarised by subjects) - age, sex, height, weight, BMI, ethnicity

- Medical History - Primary Diagnosis, other co-morbidites, tobacco and alcohol use
- Operative data – Surgical approach, total operative/ anesthesia time, total blood loss, bone graft used, antibiotic prophylaxis used, DVT prophylaxis used, head reducer used, drains used, cables or wires used,

6.6 Disposition Data

The following disposition data will be summarised for all populations

- Number of subjects/ hips in each analysis population (present both if any bilateral subjects are enrolled)
- The number of subjects/ hips that attend each study visit.
- Reason for study discontinuation
- The dates of first subject first visit and last subject last visit will be included as a footnote

6.7 Protocol Deviations

All protocol deviations will be listed including the deviation date, description of the deviation and whether this led to the subject being removed from the PP population.

6.8 Multiplicity

No adjustments for multiplicity are planned for this study.

6.9 Analysis of Primary Endpoints

All primary endpoints are assessed using the safety population

6.9.1 Device-Related Revisions

The Kaplan-Meier product limit survival estimates will be presented at 6-months, 2-years, 5-years, 7-years and 10-years post-op along with the associated 95% confidence intervals. The event of interest will be device-related revisions. Subjects who do not have device-related revision will be censored either at the time-point being analysed i.e. 5-years at the 5-year interim analysis etc. or at the time they discontinue from the study for

any other reason i.e. lost to follow-up. This analysis will be presented by treatment (control/ R3 ODH-ODH).

The Kaplan Meier Survival plot will also be presented at 12 months both overall and by device type.

6.9.2 Adverse Events

The total number of adverse events of all classifications will be summarised by treatment and overall along with the number and proportion of subjects experiencing an adverse event of any type.

The above will also be summarised by seriousness, severity, relationship to study device/ procedure and outcome.

The frequency of ADEs and SADEs that occurred between each study visit will be presented along with the total for the overall study. The number of subjects recording each will also be presented.

6.9.3 Metal Ion Analysis

Metal ion levels (Co, Cr, Ni, Ti, Zr, Nb, Mo, V and Al) will be summarised as a continuous variable at 6 months, 2 years, 5 years, 7 years and 10 years post-operatively.
As well as the summary above, the proportion of subjects with each metal ion level ≥ 7 parts per billion (ppb) will be presented at each study visit.

6.10 Analysis of Secondary Endpoint(s)

All secondary endpoints are assessed primarily using the ITT population and the PP population will be used for a secondary analysis.

The analysis of HHS and HOOS will be performed on observed data as well as with LOCF imputed data.

6.10.1 The Harris Hip Score (HHS)

Where HHS data has been collected it will be summarised using descriptive statistics at baseline, 6-months, 2 years, 5 years, 7 years and 10 years visits by treatment and overall.

The change from baseline in HHS score as derived in section 6.4 will also be summarised at the same study visits by treatment and overall.

Paired t-tests will be used to test for a difference in the change from baseline HHS score for each treatment separately from baseline to 5-years, 7-years and 10-years. The differences will be presented along with the associated 95% confidence intervals. If the assumptions of the t-test is violated then the Wilcoxon signed rank test will be used instead with Hodges-Lehmann estimates of the median difference and 95% confidence interval reported.

A sensitivity analysis will be carried out in the same way as described above however using the data as it is recorded without LOCF methods applied.

6.10.2 Hip Disability and Osteoarthritis Outcome Scores (HOOS)

HOOS consists of 5 subscales; pain, other symptoms, function in daily living, function in sport and recreation, and hip related quality of life. Five possible responses are allowed for each question and each answer equates to a score of 0 to 4. Points equating to the responses for each subcategory are added together and normalized to a maximum total score of 100.

Where HOOS data has been collected the subscales will be summarised using descriptive statistics at baseline, 6-months, 2 years, 5 years, 7 years and 10 years visits by treatment and overall.

The change from baseline in HOOS subscale scores as derived in section 6.4 will also be summarised at the same study visits by treatment and overall.

Paired t-tests will be used to test for a difference in the change from HOOS subscale scores for each treatment separately from baseline to 5-years, 7-years and 10-years. The differences will be presented along with the associated 95% confidence intervals. If the assumptions of the t-test is violated then the Wilcoxon signed rank test will be used instead with Hodges-Lehmann estimates of the median difference and 95% confidence interval reported.

A sensitivity analysis will be carried out in the same way as described above however using the data as it is recorded without LOCF methods applied.

6.10.3 Radiographic Success

Radiographic findings including the assessment of bone loss, radiolucencies, subsidence, and heterotopic ossification as compared to the preoperative radiograph will be summarised by treatment and overall at baseline, 6-months, 2 years, 5 years, 7 years and 10 years.

6.10.4 Health Economic Data

The following health economic data will be summarised by treatment and overall:

- Surgical blood loss
- Length of hospital stay
- Operative time
- Re-hospitalizations