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STATISTICAL ANALYSIS PLAN (SAP)

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1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse Device Effect(s)
ADL	Activities of Daily Living
AE	Adverse Event(s)
ANOVA	Analysis of Variance
AP	Anteroposterior
CAPA	Corrective and Preventative Action
CE	Conformité Européene
CI	Confidence Interval (s)
CIP	Clinical Investigation Plan
CoC	Ceramic-on-ceramic
CoP	Ceramic-on-polyethylene
CRF	Case Report Form(s)
CRO	Contract Research Organization
CV	Curriculum Vitae
DevD	Device Deficiency(ies)
DFU	Diabetic Foot Ulcer

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Abbreviation	Definition
DVT	Deep Vein Thrombosis
EC	Ethics Committee
EQ-5D	EuroQol 5D
FAS	Full Analysis Set
FDA	Food and Drug Administration
FJS	Forgotten Joint Score
FU	Follow-Up
GCP	Good Clinical Practice
HHS	Harris Hip Score
HOOS	Hip Disability and Osteoarthritic Outcome Score
HRA	Health Research Authority
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IEC	Independent Ethics Committee
IFU	Instructions for Use
IRB	Institutional Review Board
ISO	International Organization for Standardizations
ITT	Intention to Treat Population
LOCF	Last Observation Carried Forward
NA or N/A	Not Applicable
KOOS	Knee Disability and Osteoarthritic Outcome Score
KSS	Knee Society Score
MoM	Metal-on-metal
MoP	Metal-on-polyethylene

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Abbreviation	Definition
N (or n)	Total Sample Size (or subgroup sample size)
NHS	National Health Service
NIH	National Institutes of Health
NIHR	National Institute for Health Research
NSAE	Non-Serious Adverse Event(s)
PI	Principal Investigator
PP	Per-protocol Population
PRO	Patient Reported Outcomes
PROM	Patient Reported Outcome Measure
PU	Pressure Ulcer
QoL	Quality of Life
S+N	Smith & Nephew Inc.,/T. J. Smith & Nephew Ltd./Smith+Nephew Orthopedics/insert applicable Sponsor
SADE	Serious Adverse Device Effect(s)
SAE	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
TFL	Tables, Figures and Listing
THA	Total Hip Arthroplasty
THP	Total Hip Prosthesis
TKA	Total knee Arthroplasty
TKP	Total Knee Prosthesis
Tx	Treatment
UKS	Unicompartmental Knee System
UNI	Unicompartmental

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Abbreviation	Definition
USADE	Unanticipated Serious Adverse Device Effect(s)
VLU	Venous Leg Ulcer
WOMAC	The Western Ontario and McMaster Universities Arthritis Index
XLPE	Cross-Linked Polyethylene

2 INTRODUCTION

The following Statistical Analysis Plan (SAP) details the statistical considerations, including the data analysis methods, for the Study Protocol number 17-4049-03 dated 14-APR-2020. Related documents to this SAP are the Study Protocol, Case Report Form (CRF), and Tables, Figures and Listings (TFL) Templates Shells.

3 STUDY DESIGN

This is a retrospective/prospective, open-label single cohort, multicenter study to collect relevant clinical data on 147 knees with unicompartmental degeneration of the knee, in which the Journey UNI UKS was previously implanted.
Data from eligible subjects will be recorded from the subject's medical record onto case report forms (CRFs) with the exception of Patient-Reported Outcomes (PROs) per section 12.1.
Approximately 10 clinical sites in the United States and Canada will enroll 147 knees that meet the study criteria.
Two prospective follow-up clinical assessments will be performed. The first will occur 36 (± 12) months postoperatively and the second will occur 60 (± 12) months postoperatively.

4 STUDY OBJECTIVES

To assess the safety and effectiveness of the JOURNEY UNI UKS in subjects with unicompartmental degeneration of the knee who previously had the JOURNEY UNI UKS implanted, and to test non-inferiority of the cumulative percent implant survival compared to a literature reference rate of 91.7% (Australian Orthopaedic Association [AOA] National Joint Replacement Registry Annual Report 2015)[1] at 5 years.

4.1 Primary Objective(s)

Not specified in protocol.

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4.2 Secondary Objective(s)

Not specified in protocol.

4.3 Exploratory Objective(s)

Not specified in protocol.

5 STUDY ENDPOINTS

5.1 Primary Endpoint(s)

Implant survival 5 years postoperatively.

5.2 Secondary Endpoint(s)

Effectiveness

- 2011 Knee Society Score (KSS) at Pre-operative, 6-month, 1-year, 3-year, and 5-year visit.
- The EuroQoL Five Dimensions Five Levels Questionnaire (EQ-5D-5L) at Pre-operative, 6-month, 1-year, 3-year, and 5-year visit.
- Self-Administered Patient Satisfaction Survey (SAPSS) for Primary Hip and Knee Arthroplasty at 6-month, 1-year, 3-year, and 5-year visit.
- Forgotten Joint Score (FJS) at Pre-operative, 6-month, 1-year, 3-year, and 5-year visit.

Safety

- Radiographic findings

5.3 Exploratory Endpoint(s)

Not applicable.

5.4 Safety Endpoint(s)

All adverse events (AEs) including device-related (as indicated by the Investigator) adverse events (AE)
Device Deficiencies

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6 STATISTICAL CONSIDERATIONS

6.1 Determination of Sample Size

This study will screen and consent until 147 knees from approximately 10 sites have been enrolled. The study is intended to test for non-inferiority in the percentage of revision-free survival at 5 years recorded during the study compared to existing literature. The 2015 AOA Annual Report records the revision-free survival for unicompartmental knees at 5 years as 91.7%.
Using a non-inferiority margin of 8%, a sample size of 125 subjects will provide at least 80% power at the 5% significance level using exact binomial methods. To allow for a 15% attrition and drop-out rate, a total of 147 knees will be enrolled.
Subjects that are screened and consented to participate in the study but later withdraw consent before Visit 2 will not count towards the estimated sample size; these subjects will be replaced.

6.2 Randomisation

Not applicable.

6.3 Interim Analysis

No interim analyses are planned 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.

For data summaries, categorical and ordinal variables will be summarized using frequency and percent. Continuous variables will be summarized using characteristics such as number of observations, mean, median, standard deviation, minimum and maximum values.

Kaplan-Meier product limit estimates will be used to estimate the implant survivorship at 3 years (36 months) and 5 years (60 months). Thus, revision of one or more components for any reason is the event of interest and will be classified and subsequently defined as failure. A knee that is prematurely discontinued or a subject who dies prior to the occurrence of an event will be censored on the date of this discontinuation (for his/her contributory knees). A subject who completes the study at 5 years without an event will have their enrolled knee(s) censored on the date of study completion.

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All analyses will be performed in SAS 9.4 (or later) and/or R 4.0 (or later).

7.2 Analysis Populations

- Safety (SAF) population - All subjects who have received study treatment. This population will be used for the analyses of all safety endpoints and radiographic findings endpoint. This population will also be used for secondary analysis for the primary endpoint.
- Intent to Treat (ITT) population: All subjects who received study treatment and have any post-baseline data. This population will be used for the primary analysis of all effectiveness endpoints.
- Per protocol (PP) population - All subjects in the ITT population who do not deviate significantly from the protocol and who satisfy the pre-specified inclusion/exclusion criteria of the study. This population will be used to as secondary analysis for effectiveness endpoints.

7.3 Handling of Missing, Incomplete and Repeat Data

No data imputation will be performed for the study.

7.4 Derived Data

Age

- Age (in years) = (Operative Date)-(Date of Birth)

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)

Time to Revision

- Time to revision (in months) = (Revision Date – Operative Date)/30.4375.

Change from pre-operative to post-operative visits

Change from pre- to post-operative visit will be calculated as follows:

$$\text{Post} - \text{operative value}_{visit\ n} - \text{Pre} - \text{operative value}_{(Visit\ 1)}, \quad where\ n = 2,3,4, \ldots.$$

SAPSS

The SAPSS is a questionnaire/instrument designed to be used in conjunction with other clinical measures and functional health status instruments to evaluate the results of hip and knee arthroplasty. The instruments used to obtain these data are as follows:

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- Patients' overall satisfaction with surgery,
- Extent of pain relief,
- Ability to perform home or yard work, and
- Ability to perform recreational activities.

Items are classified into a 4-point Likert scale with response categories consisting of "Very satisfied, "Somewhat satisfied", "Somewhat dissatisfied" and "Very dissatisfied".

FJS

The FJS-12 is a PROM that assesses joint awareness during the activities of daily living. The FJS-12 comprises of 12 questions with a 5-point Likert response format (0 to 4), where 0 = Never; 1 = Almost Never; 2 = Seldom; 3 = Sometimes and; 4 = Mostly. The 12 questions that joint awareness is based on are as follows:

- Night Symptoms
- Sitting
- Walking
- Bathing
- Travelling
- Stairs
- Walking uneven ground
- Rising
- Standing
- Housework/Gardening
- Walking/Hiking
- Favorite Sport

An overall score based on the sum of all 12 responses (minimum of 0 and maximum of 48) is computed and transformed linearly into a 0 to 100 score. The higher the transformed score the greater is the ability of the subject to forget about the affected/replaced knee during activities of daily living.

European QoL (EQ-5D-5L)

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The classification system of the EQ-5D-5L is comprised of five dimensions, namely mobility, self-care, usual activities, pain/discomfort and anxiety/depression with each of the dimensions having five levels: "no problem" (level 1), "slight problems" (level 2), "moderate problems" (level 3), "severe problems" (level 4), and "extreme problems" (level 5). Hence, the system defines 3125 (5^5) health states ranging from 11111 to 55555 (i.e. the best possible health state to the worst possible health state).

- The individual domain responses on each of the 5 dimensions will be combined based on the levels scored combining the domains to form a 5-digit number in the form XXXXX (where X is 1-5) describing the respondent's health state as previously described. The EQ-5D-5L index value will be derived by using the vendor supplied calculator in Microsoft Excel to convert each 5-digit EQ-5D-5L profile.
- The second part of the EQ-5D-5L consists of a 20-centimeter vertical VAS ranging from 0 to 100. It records the respondent's self-rated health where the 'Best imaginable health state' is scored as 100 and 'Worst imaginable health state' scored as 0.

<u>KSS Endpoints</u>

The KSS comprises information on Objective Knee Indicators (range 0 to over 100 points), Patient Satisfaction (range 0-40), Patient Expectation (range 0-15), and Functional Activities (range 0-100). The KSS endpoints are derived from a series of questions that relate to everyday activities. More elaborate information for deriving the KSS endpoints are described in the publication by Scuderi et al[2]. However, an abbreviated description of the KSS endpoints used in the study is described in this SAP.

- *Objective Knee Score (Completed by Physician/Surgeon)*
- The objective score allows for more than 100 points in patients with greater than 125° of flexion and a stable painless knee as outlined below.
  - "Alignment" allows for a maximum of 25 points and is determined on a weight-bearing AP radiograph measuring the femoral-tibial (Anatomic) axis.
  - "Instability" allows for a maximum of 25 points for a knee that is stable in the coronal and saggital axis.

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- "Joint Motion" allows one point for each 5° of joint motion with a potential for greater than 25 points to be assigned for patients with greater than 125° of motion. There are deductions for flexion contracture and extension lag.
- "Instability" has a maximum allowable point allocation of 25+.
- "Symptoms" category contains two 10-level scales, ranging from "none" to "severe" for each patient to rate pain encountered when walking on level ground and on stairs/inclines. For this, a patient starts with 10 points on each scale for a painless knee with deductions of up to 10 points deductions as indicated by the patient's response on each pain scale. There is an additional question regarding how "normal" the knee feels to the patient. The maximum allowable point is 25.

Patient Expectations and Satisfaction (Completed by Patient)

- "Patient Expectations" is a three-question fifteen-point scale that is collected pre-operatively and post-operatively. The pre-operative questions reflect a patient's opinion on the extent to which s/he expects that the operation will improve his/her knee pain, and the ability to perform activities of daily living and recreational activities.
- The post-operative patient expectations questions reflect the extent to which the outcome after the operation has met the patient's pre-operative expectations with respect to pain and function.
- Patient satisfaction is a five question 40 point scale that is collected preoperatively and at each follow-up visit.

- *Functional Score (Completed by Patient)*

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- The functional score is composed of the four subgroups and has a maximum score of 100 as follows:

  - "Walking and Standing" has a maximum value of 30 points with deductions for the use of walking aids and supports.

  - "Standard Activities" has a maximum of 30 points and evaluates "standard" activities of daily living. Patients can also respond if they never participate in the activities. Patients who respond "I never do this" receive zero points for that activity.

  - "Advanced Activities" has a maximum of 25 points and evaluates function in performing more vigorous activities ranging from climbing a ladder or step-stool to running. Patients can also respond if they never participate in the activities. Patients who respond "I never do this" receive zero points for that activity.

  - "Discretionary Activities" has a maximum of 15 points and allows patients to select the three activities that they consider most important to them personally from a group of seventeen recreational and exercise activities. Patients who do not participate in any of the discretionary activities will have a functional knee score that is limited to 85 points. The discretionary activities do not need to be identical in the pre-operative and post-operative period.

<u>Adverse Events</u>

AE form and the corresponding follow-up form will be combined, and the latest entry will be accessed by the internal AEMB for seriousness and relatedness.

Investigator events do not receive a classification and so S+N classify events as follows:

- An event will be classified as an ADE if the relationship to the study device and/or the relationship to the study procedure is possibly/definitely
- 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

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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 demographic and/or baseline variables whose information is available either at the pre-operative or at the operative visits will be summarized using descriptive characteristics for continuous[1] or categorical[2] data as follows:

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- Age[1] (in years),
- Sex[2] (males or females),
- Race[2],
- Bilateral status (i.e. unilateral or bilateral)[2],
- Weight[1] (in kg),
- Height[1] (in cm),
- Body mass index (BMI)[1],
- Primary diagnosis[2],
- Duration of surgery (in minutes)[1],
- Use of prophylactic antibiotic[2],
- Deep vein thrombosis (DVT) prophylaxis given[2] ,
- Incision length[2],
- Total tourniquet time[1],
- Total blood loss[1],
- Blood loss prevention method[2].
- Compartment replacement[2] and
- Use of the NAVIO robotic-assisted surgical system[2]

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Age will further be summarized categorically by stratifying into: < 60 years versus ≥ 60 years. BMI will also be summarized categorically by stratifying into: < 30 kg/m^2 versus ≥ 30 kg/m^2.

7.6 Disposition Data

A table will be provided summarising number of subjects and number of knees.

Subject (and knee) disposition will be summarized after completion of the study using frequency (n) and percentage (%) of subjects (or knee) who completed and who did not complete the study. For those who did not complete the study, the primary reason for discontinuation will additionally be summarized.

The number of knees that enter the study, and the number of knees with follow up information will be provided by visit:

- Theoretically due: number enrolled and implanted with study device
- Deaths: cumulative number of subjects that died prior to the study visit
- Revisions / failures: cumulative number of subjects that revised/failed prior to the study visit
- Cumulative terminations: terminated from study other than from revision or death
- Expected = theoretical due – cumulative (deaths + revisions + termination)
- Actual = actual number of subjects at follow up visit
- Follow up = actual / expected x 100.

The number of subjects that have discontinued from the study and reasons for withdrawal will be summarised.

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

Screening and enrolment summary: For each centre/site, dates that the first subject was screened/enrolled and the last subject completed will be provided, duration (site, 1st enrolled – final subject exit), together with number of subjects enrolled and number of subjects completed 5 year visit.

7.7 Protocol Deviations

A listing of deviations encountered during the study will be listed. The frequency of protocol deviations will be summarized along with the number of subjects experiencing each.

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7.8 Measurement of Treatment Compliance

Not applicable.

7.9 Multiplicity

No adjustments for multiplicity are planned for this study.

7.10 Analysis of Primary Endpoint(s)

The primary endpoint is 5-year revision-free survival. The proportion of subjects who do not have implant failure by the 5-year time point will be presented along with the 95% confidence interval for the proportion, to be calculated using exact binomial methods.
Non-inferiority will be assessed using a margin of 8% against the percentage of revision-free survival at 5 years recorded during the study, compared to existing literature. The 2015 AOA Annual Report records the revision-free survival for unicompartmental knees at 5 years as 91.7%. The hypothesis test will be as following:

H0: $\theta \leq \theta_0 -$ NI vs

H1: $\theta > \theta_0 -$ NI

Where θ is the proportion of subjects with revision-free survival at 5 years for the new treatment with exact binomial methods, θ_0 is the 91.7% benchmark from the 2015 AOA Annual Report, and NI (Non-Inferiority Margin) is the 8% margin set for non-inferiority. The hypothesis test will be evaluated with exact binomial method, and the null hypothesis will be rejected with a p-value less than 0.05.

The primary endpoint will be analysed using the ITT population as the primary analysis population while the safety population and per protocol population will be used for its sensitivity analysis.
A Kaplan-Meier survival graph will be generated (using the ITT population) to support the results of the implant survivorship.

7.11 Analysis of Secondary Endpoint(s)

Efficacy

- The 2011 KSS endpoints (Objective knee score, Patient satisfaction, Patient expectation, and Functional activities) will be summarized using descriptive statistics for continuous variables. For each of the KSS endpoints, changes from preoperative to postoperative visits will be made. In

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order to account for correlation between bilateral knees belonging to a subject, repeated measures Analysis of Variance (ANOVA) or Analysis of Covariance (ANCOVA) will be carried out with knee identification as the repeated term in the model. Covariates such as but not restricted to age, sex, weight, and race may be added to and then subsequently retained in the model if such covariates are found to significantly ($p<0.10$) impactful on the KSS outcome. Visit will be included as a factor in the model. Contrast statements comparing Least Square (LS) means obtained at each visit from the model between the postoperative visits and the preoperative visit as well as the corresponding 95% CIs will be estimated.

- For each of the five EQ-5D-5L indices (Mobility, Self-care, Usual activities, Pain/discomfort and Anxiety/depression) the proportion of patients with problems at pre-operative and post-operative time points will be summarized. Additionally shift tables from pre-operative to post-operative time points will be summarized. Index values obtained from the use of the EQ-5D-5L will be summarized at the preoperative and postoperative visits. Changes from the preoperative visit to postoperative visits will be summarized. The Wilcoxon signed rank test will be used to test for any differences between pre-operative and post-operative scores.
- The FJS will be summarized using descriptive statistics for continuous variables at the preoperative and postoperative visits. Changes from the preoperative to the postoperative visits will similarly be summarized. The Wilcoxon signed rank test will be used to test for any differences between pre-operative and post-operative scores.
- The SAPSS will be summarized at post-operative time points using descriptive summary statistics for categorical variables i.e. frequency (n) and percentage (%).

<u>Safety</u>

Following endpoints will be analysed with the SAF population:

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- The presence of the radiographic observations implant loosening, stress shielding, implant loosening/migration, periprosthetic fractures and wear of articulating surfaces of replacement components will be summarized as counts (n) and percentages (%) by visit at pre-operative and post-operative visits.
- The presence of radiolucent lines by zone (femoral, anterior ML and lateral ML) and visit (pre-operative visit and post-operative visits) will be summarized as counts (n) and percentages (%). The cumulative sum of dimensions (mm) of all radiolucent lines by zone will be summarized using descriptive statistics for continuous variables.

7.12 Analysis of Exploratory Endpoint(s)

Not applicable.

7.13 Analysis of Safety Endpoint(s)

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

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

In addition, AEs will be summarised by: frequency, severity, anticipated/unanticipated, relationship to device and procedure; treatment and surgical intervention details (type, reason), outcome and duration of adverse events at trial discontinuation will be summarised.

All safety analysis will be performed using the SAF analysis population.

Device Deficiencies

The number of device deficiencies, and the number with potential to cause an SAE will be summarised.

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7.14 Other Data Summaries

Not applicable.

7.15 Changes in Analysis Methods Specified in the Protocol

The following secondary endpoint from the protocol was moved to safety endpoint in the SAP: Device-related (as indicated by the Investigator) adverse events (AE)

8 REFERENCES

1. Australian Orthopedic Association, https://aoanjrr.sahmri.com/en/annual-reports-2015.
2. Scuderi GR, Bourne RB, Noble PC, Benjamin JB, Lonner JH, Scott WN. The new Knee Society Knee Scoring System. Clin Orthop Relat Res. 2012 Jan; 470 (1):3-19.

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