STATISTICAL ANALYIS PLAN (SAP)

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Contents

1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse Event
BMI	Body Mass Index
CRF	Case Report Form
DevD	Device Deficiency
ISO	International Organization for Standardizations
KOOS	Knee Disability and Osteoarthritic Outcome Score
KSS	Knee Society Score
N (or n)	Total Sample Size (or subgroup sample size)
QoL	Quality of Life
S+N	Smith & Nephew Inc.,/T. J. Smith & Nephew Ltd./Smith+Nephew Orthopedics
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAF	Safety Population
TFL	Table, Figure and Listing
TKS	Total knee System
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

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2 INTRODUCTION

This statistical analysis plan (SAP) is written to specify the details of the statistical analyses for the Legion Primary Total Knee System (TKS) study with protocol ID: 10-4042. This SAP composition is based on version 3.0 of the protocol dated 01 February 2011 and its accompanying case report forms (CRFs). The contents of this SAP and of its accompanying shell mockups will serve as guideline for the programming of all tables, figures and listings (TFLs) that would summarize the data.

3 STUDY DESIGN

This is a prospective, consecutive series, multi-center clinical study of the LEGION™ TKS. The study design will facilitate the assessment of the safety and effectiveness profiles of the LEGION™ TKS in subjects with degenerative knee disease requiring primary total knee replacement.

Subjects who consent to participate in this study and who satisfy the study's inclusion will be enrolled. Up to 138 subjects will be enrolled at a maximum of 8 investigational sites, with an expectation of 18 subjects (up to a maximum of 28 subjects) enrolled at each site. Table 1 displays the study's schedule of events.

Table 1. Schedule of events

Study Activity	Preop	O/D	3 mo (± 2	1 yr (± 3 mo)	2 yr (± 6 mo)	3 yr (± 1 yr)	5 yr (± 1 yr)	7 yr (± 1 yr)	10 yr (± 1 yr)
Inclusion/exclusion Form	X	-	-	-	-	-	-	-	-
Informed Consent	X	-	-	-	-	-	-	-	-

Demographics/ Med History Form	X	-	-	-	-	-	-	-	-
Clinical KSS/KOOS	X	-	X	X	X	X	X	X	X
Operative/Discharge Form	-	X	-	-	-	-	-	-	-
Radiograph Analysis	-	X	X	X	X	X	X	X	X
Adverse Event Form	-	†	†	†	†	†	†	†	†
End of Study/Exit Form	-	-	†	†	†	†	†	†	†

† This form should be completed when necessary.

4 STUDY OBJECTIVES

The objective of this study is to establish the safety and efficacy of the LEGION™ Primary Total Knee System at each postoperative time point.

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5 STUDY ENDPOINTS

5.1 Primary Endpoint

- Cumulative percent survival.

5.2 Secondary Endpoints

- Surgical and device related adverse events,
- Knee Society Score (KSS),
- Knee Osteoarthritis Outcome Score (KOOS) and
- Radiographic evaluation.

5.3 Exploratory Endpoints

Not applicable.

5.4 Safety Endpoints

- Overall summary of AEs,
- Incidence of AEs by severity,
- Incidence of AEs by relationship to study device,
- Incidence of AEs that led to discontinuation,
- Incidence of AEs by outcome,
- Incidence of serious adverse events (SAEs) by relationship to study device,
- Incidence of adverse device effects (ADEs)
- Incidence of serious adverse device effects (SADE)
- Incidence of unanticipated serious adverse effects (USADEs), and
- Incidence of unanticipated adverse device effects (UADEs) and.
- International Organization for Standardizations (ISO) AEs

6 STATISTICAL CONSIDERATIONS

6.1 Determination of Sample Size

The sample size estimate for this study was calculated to determine the non-inferiority of the study device to a literature-specified reference proportion using a non-inferiority margin, $\delta>0$.

Based on this, the following hypotheses was postulated:

H_0 (null): $\pi 0 - \pi \geq \delta$

H_a (alternate): $\pi 0 - \pi < \delta$

where π is the cumulative percent survival of study device, $\pi 0$ is the literature-specified reference percent survival and δ=0.07.

With an α (Type I error) = 0.05 and power, Type II error, β = 0.2 i.e. Statistical Power = 80%, sample size, n was calculated using the following formula (Chow et al, 2003):

$$n = \frac{(z_\alpha + z_\beta)^2[\pi(1-\pi)]}{(\pi - \pi_0 - \delta)^2}$$

The cumulative percent survival for the study device is unknown for this population, but there is no reason to believe that it would be less than the reference rate. Therefore, a conservative success rate of 93.1% for the study device was assumed at 10 years. Thus, 96 subjects will be required to detect non-inferiority of the study device. Assuming further that 30% of subjects enrolled will be lost to follow up by the end of 10 years, a sample size of at least 138 subjects was to be enrolled in this study.

6.2 Randomisation

Not applicable.

6.3 Interim Analysis

Not applicable.

7 STATISTICAL ANALYSIS

7.1 General

Smith+Nephew's Global Biostatistics group will conduct the statistical analysis for this study. Unless otherwise stated, 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.

7.2 Analysis Populations

The "Safety" population (SAF) will be used as the analysis population for summarizing all data. This is defined as all knees (or subjects) enrolled into the study and who were implanted with the study device.

7.3 Handling of Missing, Incomplete and Repeat Data

Missing value imputation would be carried out on KSS endpoints. According to instructions for the derivation of the KSS endpoints, in an event that there are fewer than 50% missing responses within a domain, imputation with values equal to the average of all of the other items in the same domain would be used (KSS User Manual, 2012).

7.4 Derived Data

Age

- Age (in years) = INT{(Operative Date)-(Date of Birth)+ 1/365.25}

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 + 1)/30.4375

Change from pre-operative to post-operative visits

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

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

Knee Society Score (KSS) Endpoints

The Knee Society Score (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 (2012). 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.
  - "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)*

- 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.

Knee Osteoarthritis Outcome Score (KOOS)

Each item (question) that is used for scoring the KOOS is rated on a scale of 0 to 4 as follows:

- 0 = None; 1 = Mild; 2 = Moderate; 3 = Severe and; 4 = Extreme.

A minimum of 50% of all items for each subscale of the KOOS will be responded to before a subscale score is derived. Table 2 thus indicates for each subscale, the minimum number of items to be scored for a KOOS subscale endpoint to be calculated.

Table 2. Minimum number of items required and algorithms for a KOOS subscale score.

Subdomain	Minimum number of Items needed for calculation of subdomain score	Algorithms for subdomain scoring
Pain (P1 – P9)	5	$100 - \frac{\text{Mean Score (P1 – P9) x 100}}{4}$
Symptoms and Stiffness (S1 – S7)	4	$100 - \frac{\text{Mean Score (S1 – S7) x 100}}{4}$
Function, daily living (A1 – A17)	9	$100 - \frac{\text{Mean Score (A1 – A17) x 100}}{4}$
Sports and recreational activities (SP1 – SP5)	3	$100 - \frac{\text{Mean Score (SP1 – SP5) x 100}}{4}$
Quality of Life (QoL) (Q1 – Q4)	2	$100 - \frac{\text{Mean Score (Q1 – Q4) x 100}}{4}$

Each subscale is scored independently at each visit. The mean score of the individual items of each subscale are calculated and divided by 4. A score of 100 indicates that by that visit the subject has no problems while a score of 0 is indicative of severe problems on each of the subscale scores.

7.5 Baseline Data

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

- Age[1] (in years),
- Sex[2] (males or females),
- Bilateral Status[2] (unilateral or bilateral),
- Body Mass Index (BMI)[1]

Age will additionally be categorically summarized into ≤ 60 years versus >60 years while BMI will further be summarized into ≤ 30 kg/m^2 versus >30 kg/m^2.

7.6 Disposition Data

The disposition of subjects (knees) will be summarized as using accountability of clinical follow-up of the subjects' knee from the preoperative, operative through the 10 year postoperative follow-up. Information that will be summarized in this table will include but not only restricted to theoretically due, revisions, terminations, expected knees at visit, not yet overdue at visit and knees evaluated at visit.

7.7 Protocol Deviations

A listing of cumulative protocol deviations encountered on-study will be presented for each subject (and/or knee) with deviations.

7.8 Measurement of Treatment Compliance

Not applicable.

7.9 Multiplicity

Not applicable.

7.10 Analysis of Primary Endpoint

- Kaplan-Meier product limit survival estimates will be used to estimate implant (device) survivorship, S(t) where S(t) is the proportion of knees without an implant revision at time t. Time to implant revision is the endpoint of interest in the determination of implant survivorship. The cumulative proportion of knees with implant survivorship at 3 months, 12 months (1 year), 24 months (2 years), 36 months (3 years), 60 months (5 years), 84 months (7 years) and 120 months (10 years) will be estimated and displayed accordingly. Knees that are still on-study without a revision will be censored on that date of database lock. A prematurely discontinued knee from study as a result of death or for any other reason will be censored on the discontinuation date. A subject lost to follow-up prior to the database lock will have the contributory knee censored on the last known contact date. Kaplan-Meier estimates for implant survivorship will be presented with the corresponding two-sided 95% Confidence Intervals (CIs). Kaplan-Meier survival graphs will also be displayed.

- A listing of subjects with revised implants and the components revised would be provided.
- The Kaplan-Meier product limit estimates will further be presented after stratifying by age group, BMI group and gender.

7.11 Analysis of Secondary Endpoints

- Surgical and device-related AEs will be summarized using numbers (n) and percentages. The count of episodes for each of these events will also be presented.
- All KSS and KOOS scores will be summarized by visit (preoperative to 10 years) using descriptive statistics for continuous variables. Changes from preoperative to all postoperative visits will additionally be summarized (except for KSS expectation).
- For radiographic evaluations, the proportion of knees with evaluations performed will be summarized. Of those knees with radiographic evaluations performed the proportion of knees with radiolucent lines observed within the femoral zone, tibial ML zone, tibial AP zone and the patellar zone will be summarized. Additionally among knees with radiolucent lines, the number of zones with radiolucent lines present will be summarized using descriptive summary characteristics for continuous variables. The cumulative sum of radiolucent lines will also be summarized using descriptive statistics for continuous variables.
- The proportion of knees evaluated with periosteal hypertrophy, implant loosening, osteolysis or subsidence will be summarized.
- The proportion of knees with patellar problems such as dislocation, abnormal placement or subluxation will be summarized.

7.12 Analysis of Exploratory Endpoints

Not applicable.

7.13 Analysis of Safety Endpoints

- An overall summary AE table that would summarize as number (n) and percentages (%), the overall incidence according to knees with at least one AE; knees with an AE by worst

relationship to study device; knees with at least one AE with an involvement with a study knee; knees with at least one AE by worst severity (mild, moderate, or severe); knees with at least one AE by worst outcome and; knees with any AE that led to discontinuation from study.

- Other events that will be summarized within the overall summary AE table include SAEs, ADEs, SADEs, UADEs and USADEs. These tables will also include the cumulative episodes of events encountered.
- ISO tables will be summarized as appropriate.
- An AE listing will be provided which would display these AE characteristics by study knee as well as systemic AEs.

7.14 Other Data Summaries

Not applicable.

7.15 Changes in Analysis Methods Specified in the Protocol

The protocol-specified analysis of the primary endpoint was planned to be inferentially performed using a non-inferiority approach. This study is now being terminated early, thus, the primary endpoint will only be descriptively summarized.

8 REFERENCES

1. Chow SC, Shao J, Wang H. (2003). Sample size calculation in clinical research. Dekker, New York.
2. The 2011 Knee Society Knee Scoring System: Licenced User Manual, 2012, http://www.kneesociety.org/ web/2011%20KSS%20User%20Manual FINAL 12-2012.pdf.

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