Statistical Analysis Plan (SAP)

Comparison of Alignment achieved using Single-Use versus Reusable Instrumentation in Total Knee Arthroplasty (TKA): A Prospective, Non-Randomized Multi-center Investigation ("Attune TKA SUI Alignment Study")

Protocol Version: B

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SAP Revision: 1.0
SAP Revision Date: 05/06/2019

Revision History

Revision Number	Revision Date (DD/MM/YYYY)	Reasons for Revision

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List of Abbreviations

AE	Adverse Event
AP	Anteroposterior
CI	Confidence Interval
CIP	Clinical Investigational Plan
CR	Cruciate Retaining
FB	Fixed Bearing
FM	Distal Femoral Varus-valgus
HKA	Hip-Knee-Ankle
MedDRA	Medical Dictionary for Regulatory Activities
OR	Operating Room
PS	Posterior Stabilizing
RP	Rotating Platform
RUI	Reusable Instrumentation
SAP	Statistical Analysis Plan
SD	Standard Deviation
SUI	Single-use Instrumentation
TKA	Total Knee Arthroplasty
TM	Proximal Tibial Varus-valgus

1 Study Design

This study is designed as a prospective, comparative, sequential, non-randomized, multi-center, controlled clinical investigation. Randomization will not be utilized in this study in order to isolate and learn if there are changes in Operating Room (OR) efficiency with Single-Use Instrumentation under normal operating room procedures.

There will be 4 centers worldwide that will recruit a total of 88 Subjects: 44 treatment [Single-Use Instrumentation, (SUI)] and 44 control [Reusable Instrumentation, (RUI)]). A complete description of the methods for determining sample size is contained in Section 7. The recruitment goal will be to evenly distribute enrollment across the four sites; therefore, it is expected that each site will enroll 22 Subjects (11 Control followed sequentially by 11 Treatment Subjects).

- The **Control group** will consist of 44 Subjects, 11 per site and the surgical procedure for these Subjects will be performed using Reusable Instruments (RUI).
- The **Treatment group** will consist of 44 Subjects, 11 per site and the surgical procedure for these Subjects will be performed using Single Use Instruments (SUI).

For a given site, either Cruciate Retaining (CR) or Posterior Stabilizing (PS) configurations will be used; consistent with their standard of care. Within a given CR site, the Investigator may choose to implant either the CR Fixed Bearing (FB) or CR Rotating Platform (RP) configurations. Similarly, within a given PS site, the Investigator may choose to implant either the PS FB or PS RP configurations.

One surgeon at each site will complete all RUI and SUI surgical cases including the learning curve cases. No Sub-Investigators will be permitted to perform surgery to avoid possible confounding issues with varying surgical process. All sites will have previously completed their learning curve cases with the ATTUNE Primary Implant implanted using RUI prior to enrolling the first patient. Then after the completion of all RUI study cases, a series of learning curve cases will be permitted for the use of SUI. The duration of the SUI learning curve is anticipated to be approximately 5 cases and is at the discretion of the Principal Investigator. These early cases that are within the learning curve will not be enrolled into this study at each site.

The study is designed to assess mechanical axis alignment, component alignment, safety, operating room efficiency and surgeon satisfaction achieved using the two instrumentation systems. The primary, secondary, and exploratory objectives are presented below.

1.1 Primary Objective

To determine whether the mechanical axis alignment achieved with SUI instrumentation is non-inferior to the alignment achieved with RUI instrumentation. Mechanical axis alignment is defined as the line drawn from the center of the femoral head through the center of the knee and ankle and will be measured from weight bearing long-leg (51") Anteroposterior (AP) radiographs, taken approximately 90 days post-op (when subject has reached full knee extension) and read by an independent radiographic reviewer.

1.2 Secondary Objectives

- To compare alignment achieved with SUI vs. RUI of individual components in the frontal and sagittal planes, specifically: distal femoral varus-valgus (FM), proximal tibial varus-valgus (TM), femoral component flexion and tibial slope.
- To compare the type and frequency of adverse events, from the time of surgery through to withdrawal of a subject or the end of the study (includes serious adverse events, and device and/or procedure-related adverse events), between the SUI and RUI instrument groups.

1.3 Exploratory Objectives

- To compare SUI and RUI operating room times from OR set-up through OR clean down as detailed in the Clinical Investigational Plan (CIP) Table 8-3.
- To determine whether SUI provides opportunity to reduce the incidence of minor procedural obstacles during the time in the OR.
- To compare Surgeon satisfaction of SUI instrumentation to RUI instrumentation.

2 Treatment Assignment

Treatment assignment is described in Section 1.

3 Randomization and Blinding Procedures

Neither randomization nor blinding will be implemented in this study.

4 Interval Windows

Data collected throughout the study will be assessed for compliance with the protocol-specified visit schedule. Three windows are defined based on the number of days prior to or after surgery, Day 0. Visits conducted within the intervals shown in Table 4-1 will be assessed for compliance with the protocol. If multiple visits fall into the same interval, the result closest to the target study day will be used in analysis. All safety data will be included in the Safety analysis.

Table 4-1 Interval Windows

STUDY VISIT	Target Study Day	Lower Bound Day	Upper Bound Day
Pre-Op	-90	-180	0
Surgery	0		0
Immediately Post-op	15	1	29
3 Month	90	30	150

5 Levels of Significance

Only the primary endpoint analysis in this study is prospectively powered and will be conducted with a 1-sided independent means t-test with an alpha of $\alpha = 0.05$. Confidence intervals and p-values may be provided for demographic or baseline comparisons, or for other secondary and tertiary endpoints, but these are all deemed to be exploratory. Unless otherwise stated, these confidence intervals will be 2-sided 95% confidence intervals. Because these endpoint analyses are deemed to be exploratory, there will be no adjustment of significance levels because of testing multiple hypotheses. No labeling claims will therefore be made based on these exploratory findings.

6 Analysis Sets

The determination of subjects to be excluded from the Per Protocol Set will be based on study team review of noncompliance and will be documented separately. The original CIP was written to exclude subjects who had a major protocol deviation, but such deviations may be about study compliance and not necessarily about the scientific integrity of the data. Analysis set definitions from the CIP and those slightly revised definitions per this SAP appear below.

6.1 CIP Analysis Set Definitions

Consented/Enrolled Population: All cases consented to participate in this study.
Safety Population: All cases that received the Attune device and the assigned instruments were used.
Per Protocol Population: All cases from the Safety Population that did not have major protocol violations.

6.2 Modified Analysis Set Definitions

Consented/Enrolled Set: All subjects who consented to participate in the study.
Safety Set: All subjects who received an ATTUNE device.
Note: If the treatment instrumentation used for the tibial and femoral cuts differ, the subject will be included in the instrumentation group used for the distal femoral cut. If both SUI and RUI were used for a single cut (tibial or femoral), the subject will be included in the first used instrumentation group. The Safety Set will be used to present results for Demographic, Exploratory Endpoints, and Adverse Events.
Per Protocol Set: All Safety Set subjects for whom a single instrumentation type was used and who had no protocol noncompliance evaluated which presents serious risk for the validity or integrity of the clinical trial data and/or regulatory acceptability of the sponsor/study/site; safety or well-being of the subject at risk. The Per Protocol Set will be used to present analyses of the primary and secondary endpoints.

7 Sample Size Justification

The primary endpoint of the difference in group means for the absolute value of mechanical axis alignment will be tested for non-inferiority using a 2-sample t-test and a non-inferiority margin of 1.5° when comparing alignment results obtained using single use instruments to those of reusable instruments. The sample size was established to provide 95% power for a 1-sided test of non-inferiority with α = 0.05 using a pooled standard deviation (SD) of 1.870°. This estimated SD was obtained from a previous DePuy Study (ID # 04023). A sample size of 35 per group was obtained to provide 95% power with a 1-sided alpha of 0.05 and 1:1 treatment allocation. The final sample size was inflated by at least 20% to 44 per group to account for attrition and possible problems with radiographic image quality.

8 Analyses to be Conducted

8.1 General Conventions

Study data will be tabulated for all subjects in the target analysis population using SAS v9.3 or higher. Planned tabulations are described below and table, figure, and listing shells are provided separately (see Appendix for file name).

Standard descriptive summaries for continuous data include the number of subjects with nonmissing data (n), mean, SD, median, minimum, and maximum values. For categorical data, the count and percentage will be provided. Percentages will be based on the number of subjects without missing data.

When there is a need to test the significance of a difference between groupings of comparisons of SUI versus RUI which result in a p-value or confidence interval, a t-test will be conducted for continuous variables, and Fishers' Exact Test will be used for categorical variables.

8.2 Disposition of Study Subjects

An overall summary of the number of subjects who were (or had): Enrolled, Enrolled but not treated, in the Safety Analysis Set, in the Per Protocol Set, withdrew before study completion, and who completed the study will be tabulated for all sites combined. A listing will be created for completion status and will include columns for all of the items included in the summary table.

8.3 Demographic and Baseline Characteristics

Descriptive statistics will be displayed using the subjects in the Safety and the Per Protocol Analysis Populations for:

- Age at consent (in years);
- Gender;
- Race;
- Ethnicity;
- Height (cm);
- Weight (kg);
- BMI (kg/m^2) calculated as (Weight in kilograms)/(Height in meters)^2;
- Primary Diagnosis;
- Configuration type (Cruciate Retaining or Posterior Stabilizing);
- Breakdown of Fixed Bearing and Rotating Platform configurations within CR and PS.

Preoperative demographics and baseline characteristics will be compared to determine whether differences exist between treatment groups. Operative details including the type of components implanted, configuration type, and breakdown of FB and RP configurations within CR and PS will be presented without formal comparison.

8.4 Primary and Secondary Endpoint(s) and Associated Hypotheses

8.4.1 Primary Endpoint(s) and Associated Hypotheses

The primary endpoint is absolute value of the mechanical axis alignment. The mechanical axis alignment is defined as the angle between the line drawn from the center of the femoral head through the center of the knee and line drawn from the knee center to the ankle center. Mechanical axis alignment will be measured from weight bearing long-leg (51") Anteroposterior (AP) radiographs, taken approximately 90 days post-op (when Subject has reached full knee extension, within 5 degrees) and read by an independent radiographic reviewer.

The mechanical axis alignment will be calculated from the Hip-Knee-Ankle (HKA) angle provided by the independent radiographic evaluations as:

Mechanical Axis Alignment = HKA Angle – 180.

The primary endpoint will be the absolute value of this Mechanical Axis Alignment result. Descriptive statistics for the primary endpoint will be presented by time point and treatment group.

The primary endpoint analysis will be to determine whether the mean alignment achieved with SUI instrumentation is non-inferior to the mean alignment achieved with RUI instrumentation. The non-inferiority margin was set at 1.5° based on clinical judgement as it was considered the maximum non-meaningful difference between instrumentation systems.

The null (H_o) and alternate (H_A) hypotheses are as follows:

H_o: $\mu_{SUI} \geq \mu_{RUI} + 1.5^o$
H_A: $\mu_{SUI} < \mu_{RUI} + 1.5^o$,

where μ_{RUI} is the mean of the absolute values (hereafter, "absolute") of mechanical axis alignment angle for Subjects being operated upon using reusable instruments

(RUI), and μ_{SUI} is the mean of the absolute mechanical axis alignment angle of Subjects being operated upon using single use instruments (SUI).

8.4.2 Secondary Endpoints and associated hypotheses

The secondary endpoints are designed to further compare alignment achieved with SUI to that of RUI based on radiographs taken approximately 90 days post-op. The following secondary endpoints will be assessed:

- Difference in means (SUI-RUI) of the distal femoral varus-valgus (FM) angle,
- Difference in means (SUI-RUI) of the proximal tibial varus-valgus (TM) angle,
- Difference in means (SUI-RUI) of the femoral component flexion angle,
- Difference in means (SUI-RUI) of the tibial slope,
- Difference in means (SUI-RUI) of the raw mechanical axis alignment angle.

The calculations of these endpoints from the independent radiographic evaluations is as follows:

1. Distal femoral varus-valgus angle: The result from the independent radiographic evaluations will be used without change.

2. Proximal tibial varus-valgus angle: The result from the independent radiographic evaluations will be used without change.

3. Femoral component flexion angle:

    a. For CR configuration, the femoral component flexion angle to be used in the analysis = 95 – the femoral component flexion result provided in by the independent radiographic evaluation.

    b. For PS configuration, the femoral component flexion angle to be used in the analysis = 77 – the femoral component flexion result provided in by the independent radiographic evaluation.

4. Tibial slope: the tibial slope to be used in the analysis = 90 – the tibial slope result provided by the independent radiographic evaluation.

5. Raw mechanical axis alignment angle: The raw mechanical axis alignment angle will be calculated from the Hip-Knee-Ankle (HKA) angle provided by the independent radiographic evaluations as:

Mechanical Axis Alignment = HKA Angle – 180.

Descriptive statistics for the secondary endpoints will be presented by time point and treatment group.

For each of the above endpoints, an exploratory two sample, 2-sided t-test will be conducted to test (H_o) versus alternate (H_A) at the $\alpha = 0.05$ level:

H_o: $\mu_{SUI} = \mu_{RUI}$
H_A: $\mu_{SUI} \neq \mu_{RUI}$, where μ_{SUI} is the mean of the angle/slope for Subjects treated with SUI and μ_{RUI} is the mean of the angle/slope for Subjects treated with RUI.

In addition, the distributions of the raw values (showing both positive and negative results, where appropriate) associated with these endpoints will be summarized as categorical variables (n, %) in 1-degree increments, and the relative frequencies will be graphed by treatment group for the following measurements:

- Absolute mechanical axis alignment angle;
- Distal femoral varus-valgus (FM) angle;
- Proximal tibial varus-valgus (TM) angle;
- Femoral component flexion angle;
- Tibial slope angle; and
- Raw mechanical axis alignment angle.

Additionally, a third analysis will be conducted to present the number of surgeries achieving the Mechanical Axis Alignment within 3 degrees of target (i.e., ±3 degrees

of 0) at 3 Months post-operative. These results will be presented categorically (n, %) by treatment group and by site (i.e., surgeon).

8.4.3 Additional Endpoints (Primary, Safety, or Exploratory)

Surgeon Satisfaction

Surgeon satisfaction with the performance of SUI and RUI instrumentation will be assessed on a four-point scale (1=Strongly Dissatisfied, 2=Dissatisfied, 3=Satisfied, 4=Strongly Satisfied) for the following:

- Distal femoral resection instrumentation;
- Proximal tibial resection instrumentation; and
- All ATTUNE TKA instrumentation.

For each of the three satisfaction questions above, analysis will be conducted two ways:

(1) Summarizing the response to each question as a categorical variable: The tally and percent of times that each response was indicated. This will be summarized overall and by site.

(2) Dichotomizing the response to determine “Adequate Surgeon Satisfaction” then summarizing by treatment group with counts and percentages. Adequate Surgeon Satisfaction will be derived as “Yes” for responses: “Satisfied” and “Strongly Satisfied” and “No” for responses: “Strongly Dissatisfied” and “Dissatisfied”. Binomial exact 95% CI will be provided for the proportions and fisher’s exact test will be implemented to test the difference between treatment groups.

For each site (surgeon), a line graph will be generated which displays surgeon satisfaction (y-axis) for the site’s first through last case (x-axis).

OR Efficiency

Exploratory analyses will be conducted to see if SUI improves OR efficiency compared to conventional (RUI) instruments. Specifically, the following durations will be assessed comparatively between treatment groups and stratified by site:

- OR Set-up Time: Set-up Stop Time – Set-up Start Time;
- Anesthesia Time: Anesthesia Stop Time – Anesthesia Start Time;
- Surgery Time: Surgical Stop Time – Surgical Start Time;
- Clean-Down Time: Clean Down Stop Time – Clean Down Start Time;
- Total Time: Clean Down Stop Time – Set-up Start Time.

For each of the OR Efficiency endpoints defined above, analysis will be conducted by summarizing the endpoint as a continuous result (n, mean, SD, median, min, max, 95% CI) and presenting results by treatment group. In this analysis, 2 sample t-tests will be used to assess the difference in the mean response between treatment groups.

Procedural Delays

The incidence of procedural obstacles (i.e., Staff change-over, Holes in blue wrap, Late staff, Missing instrument(s), Missing implants, Patient delay, Prolonged anesthesia, Prolonged surgery, Scrub nurse not familiar with instruments, or Other) will be summarized for both treatment groups.

For each site (surgeon), a listing of procedural obstacles will be generated which presents the procedural obstacles for the site's first through last case.

8.5 Safety Analyses

For this study, only serious AEs and those AEs related or possibly related to either the device and/or the procedure are to be reported to the Sponsor (Please see Figure 9-1 in the CIP). AEs were collected from the time of surgery forward and coded by MedDRA v17.0.

An adverse event overview table will be provided and will include both the number of events (n) and the number and percentage (n, %) of subjects with 1 or more event in the following categories:

- Serious,
- Definitely, probably, or possibly device-related,
- Definitely, probably, or possibly procedure-related,
- Operative site,
- Systemic,
- Intra-operative (AE with onset on the day of surgery), and
- Post-operative (AE with onset after the date of surgery).

In addition, all adverse events will be listed.

8.6 Handling of Missing Data

No missing data methods will be implemented to account for missing data.

8.7 Sensitivity Analyses

The analysis of the primary endpoint will be repeated using all subjects in the Safety Population with available data to determine the robustness of the study outcome.

9 Data Monitoring Committee (DMC)

No DMC is required for this study.

Appendix: Tables, Listings and Graphs Shells

The document that contains the tables, listings and graphs shells is entitled Study 10002 Table Figure and Listing Shells.

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